Diabetes in pregnancy

Management of diabetes and its complications from preconception to the postnatal period

NICE guideline NG3

Methods, evidence and recommendations

Wednesday February 25th, 2015

December 2020: NICE's original guidance on diabetes in pregnancy was published in 2015. It was updated in 2018 and 2020. See the [NICE website](#) for the guideline recommendations and the evidence reviews for the 2020 updates. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2018 or 2020.

Final

Commissioned by the National Institute for Health and Care Excellence

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1 Introduction

This section was updated in 2015

Since the publication of the Diabetes in Pregnancy guidance in 2008 there have been several developments that have prompted this update.

Firstly, there have been new studies on the diagnosis and treatment of gestational diabetes (GDM). The landmark Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (The HAPO Study Cooperative Research Group, 2008) demonstrated a continuous relationship between glycaemia and adverse pregnancy outcome in a global population of women without gestational diabetes. This led to the publication of consensus guidelines on the definition of gestational diabetes that have been adopted by the World Health Organization (WHO). The new definition would diagnose many more women with gestational diabetes and has been the subject of wide debate. However, no cost benefit analysis of the new guidance had been undertaken and this was thought to be a priority for this guideline update.

Secondly, new trials of interventions in gestational diabetes have been published and the existing treatment guidance clearly needed updating as a result.

Next, newer technologies of metabolic monitoring of blood glucose, such as continuous glucose monitoring and blood ketones, needed evaluating in the context of diabetic pregnancy. Moreover, the role of glycated haemoglobin (HbA1c) in the diagnosis and management of diabetic pregnancy remained controversial and was a high priority from stakeholders in the scoping process.

Other topics that were selected for review were the evidence for the role of specialist (multidisciplinary) teams, the blood glucose targets before and during pregnancy, and the timing and best test for the diagnosis of continuing glucose intolerance in women after delivery.

There are many topics that were not covered but, where possible, the existing recommendations have been updated where they were incorrect or out of date.

1.1 2008 Guideline

1.1.1 Diabetes in pregnancy

Diabetes is a disorder of carbohydrate metabolism that requires immediate changes in lifestyle. In its chronic forms, diabetes is associated with long-term vascular complications, including retinopathy, nephropathy, neuropathy and vascular disease. Approximately 650 000 women give birth in England and Wales each year,[1] and 2–5% of pregnancies involve women with diabetes.[2,3,20] Pre-existing type 1 diabetes and pre-existing type 2 diabetes account for 0.27% and 0.10% of births, respectively.[2] The prevalence of type 1 and type 2 diabetes is increasing. In particular, type 2 diabetes is increasing in certain minority ethnic groups (including people of African, black Caribbean, South Asian, Middle Eastern and Chinese family origin).[2] There is a lack of data about the prevalence of gestational diabetes, which may or may not resolve after pregnancy. The clinical experience of the guideline development group (GDG) suggests that the average prevalence in England and Wales is approximately 3.5% (the precise figure varies from region to region, depending on factors such as ethnic origin, with certain minority ethnic groups being at increased risk; see Section 4.1). Approximately 87.5% of pregnancies complicated by diabetes are, therefore, estimated to be due to gestational diabetes, with 7.5% being due to type 1 diabetes and the remaining 5% being due to type 2 diabetes.

Diabetes in pregnancy is associated with risks to the woman and to the developing fetus.[4,5] Miscarriage, pre-eclampsia and preterm labour are more common in women with pre-existing diabetes. In addition, diabetic retinopathy can worsen rapidly during pregnancy. Stillbirth,

congenital malformations, macrosomia, birth injury, perinatal mortality and postnatal adaptation problems (such as hypoglycaemia) are more common in babies born to women with pre-existing diabetes.

This clinical guideline contains recommendations for the management of diabetes and its complications in women who wish to conceive and those who are already pregnant. The guideline builds on existing clinical guidelines for routine care during the antenatal, intrapartum and postnatal periods. It focuses on areas where additional or different care should be offered to women with diabetes and their newborn babies.

1.1.2 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[6] This clinical guideline concerns the management of diabetes and its complications from preconception to the postnatal period. It has been developed with the aim of providing guidance on:

- preconception information
- diagnosis and management of gestational diabetes
- glycaemic control in the preconception, antenatal and intrapartum periods
- changes to medications for diabetes and its complications before or during pregnancy
- management of diabetic emergencies (for example, hypoglycaemia and ketoacidosis) and diabetic complications (such as retinopathy) during pregnancy
- the timetable of antenatal appointments to be offered to women with diabetes
- timing and mode of birth (including induction of labour, caesarean section, analgesia and anaesthesia, and the use of steroids for fetal lung maturation)
- initial care of the newborn baby
- management of diabetes and its complications during the postnatal period.

1.1.3 Areas outside the remit of the guideline

- This guideline does not address:
- aspects of routine antenatal, intrapartum and postnatal care that apply equally to women with or without diabetes
- aspects of routine care for women with diabetes that do not change during the preconception, antenatal, intrapartum or postnatal periods
- advice about contraceptive methods for women with diabetes
- management of morbidity in newborn babies of women with diabetes beyond initial assessment and diagnosis.

1.1.4 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England, Wales and Northern Ireland, in particular:

- healthcare professionals involved in the care of women with diabetes and their newborn babies (including general practitioners (GPs), nurses and midwives, obstetricians, diabetes physicians and neonatal paediatricians)
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health, trust and care-home managers
- women with diabetes and their families.

A version of this guideline for women with diabetes and the public is available from the NICE website (www.nice.org.uk/CG063publicinfo) or from NICE publications on 0845003 7783 (quote reference number N1485).

1.1.5 Other relevant documents

The National Collaborating Centre for Women's and Children's Health (NCC-WCH) was commissioned by the National Institute for Health and Clinical Excellence (NICE) to establish a multi-professional and lay working group (the GDG) to develop the guideline. The membership of the GDG was determined by the NCC-WCH and NICE, and included the following:

- two obstetricians
- two diabetes physicians
- two diabetes specialist midwives
- a diabetes specialist nurse
- a GP
- a neonatal paediatrician
- two patient/carer representatives.

Staff from the NCC-WCH provided methodological support for the guideline development process by undertaking systematic searches, retrieving and appraising the evidence, health economic modelling and writing successive drafts of the guideline. The neonatal paediatrician appointed to the GDG at the beginning of the development process resigned in October 2007 due to ill health and was replaced by another neonatal paediatrician.

During the development of the guideline, the GDG identified a need for expert advice in relation to obstetric analgesia and anaesthesia, diabetic retinopathy and data relating to pregnancy in women with pre-existing diabetes held by the Confidential Enquiry into Maternal and Child Health (CEMACH), which covers England, Wales and Northern Ireland. Expert advisers were appointed by the GDG to advise on each of these issues, although they were not involved in the final decisions regarding formulation of recommendations.

All GDG members' and external advisers' potential and actual conflicts of interest were recorded on declaration forms provided by NICE and are presented in Appendix B. The forms covered personal pecuniary interests (including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry), personal non-pecuniary interests (including research interests), personal family interests (including shareholdings) and non-personal pecuniary interests (including funding from the healthcare industry for research projects and meetings). The GDG chair and NCC-WCH project director considered all the declarations and concluded that none of the declared interests constituted a material conflict of interest that would influence the recommendations developed by the GDG.

Organisations with interests in the management of diabetes and its complications from preconception to the postnatal period were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process. The process of stakeholder registration was managed by NICE. The different types of organisations that were eligible to register as stakeholders included:

- national patient and carer organisations that directly or indirectly represent the interests of women with diabetes and their families before and during pregnancy
- national organisations that represent the healthcare professionals who provide services for women with diabetes before and during pregnancy
- companies that manufacture the preparations or products used in the management of diabetes in pregnancy

- providers and commissioners of health services in England, Wales and Northern Ireland
- statutory organisations such as the Department of Health and the Welsh Assembly Government
- research organisations that have done nationally recognised research in relation to the topics covered in the guideline.

1.1.6   Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including the following NICE guidance.

- Clinical guidelines
  - o Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults[7]
  - o Type 2 diabetes: the management of type 2 diabetes[8] (to replace separate guidelines on blood glucose, blood pressure and blood lipids, renal disease and retinopathy)*
  - o Antenatal care: routine care for the healthy pregnant woman[9] (the section of the antenatal care guideline that addresses screening for gestational diabetes has been developed in parallel with the development of this guideline; see Chapter5).
  - o Intrapartum care: care of healthy women and their babies during childbirth[10]
  - o Postnatal care: routine postnatal care of women and their babies[11]
  - o Induction of labour[12] (this diabetes in pregnancy guideline replaces the part of the induction of labour guideline that relates to women with diabetes) plus
  - o Caesarean section.[13]
- Technology appraisals (TAs)
  - o Guidance on the use of continuous subcutaneous insulin infusion for diabetes[14]
  - o Guidance on the use of glitazones for the treatment of type 2 diabetes[15]
  - o Guidance on the use of long-acting insulin analogues for the treatment of diabetes
  - o insulin glargine[17]
  - o Guidance on the use of patient-education models for diabetes.[18]
- Public health guidance
  - o oImproving the nutrition of pregnant and breastfeeding mothers and children in low-income households.[19]

The guideline also complements and updates the National Service Framework (NSF) for diabetes.[20]

1.1.7   Guideline methodology

This guideline was developed in accordance with the NICE guideline development process outlined in the 2005 technical manual[21] and the 2006 and 2007 editions of the NICE guidelines manual.[22,23] Table 1 summarises the key stages of the guideline development process and which version of the process was followed at each stage.

1.1.7.1   Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. The clinical questions are presented in Appendix B of the original guideline. Additionally, stakeholder organisations

were invited to submit evidence for consideration by the GDG provided it was relevant to the topics included in the scope and of equivalent or better quality than evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases via the 'Ovid' platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), and PsycINFO (1967 onwards). The most recent search conducted for the three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects) was undertaken in Quarter 1, 2007. Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches, although publications in languages other than English were not appraised. Both generic and specially developed methodological search filters were used appropriately.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

Towards the end of the guideline development process, searches were updated and re-executed, thereby including evidence published and included in the databases up to 21 March 2007.

Table 1: Stages in the NICE guideline development process and the versions followed at each stage

Stage	2005[21]	2006[22]	2007[23]
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution, etc.)	✓		
Forming and running the guideline development group	✓		
Developing clinical questions	✓		
Identifying the evidence		✓	
Reviewing and grading the evidence		✓	
Incorporating health economics		✓	
Making group decisions and reaching consensus			✓
Linking guidance to other NICE guidance			✓
Creating guideline recommendations			✓
Developing clinical audit criteria			✓
Writing the guideline			✓
Validation (stakeholder consultation on the draft guideline)			✓
Declaration of interests[a]	✓	✓	✓

Evidence published after this date has not been included in the guideline. This date should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed, are provided on the accompanying CD-ROM.

1.1.7.2 Appraisal and synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[24–30] and classified using the established hierarchical system presented in Table 2. This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study was assigned a quality rating coded as '++', '+' or '−'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs; EL = 1++) or an individual RCT (EL = 1+). Studies of poor quality were rated as '−'. Usually, studies rated as '−' should not be used as a basis for making a recommendation, but they can be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL = 2). A level of evidence was assigned to each study appraised during the development of the guideline.

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the effectiveness (accuracy) of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated or quoted where possible (see Table 3).

Table 2: Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias 1− Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Table 3: '2 x 2' table for calculation diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Test positive	a (true positive)	b (false positive)	a+b
Test negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d=N (total number of tests in study)
Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d)			

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting accuracy of diagnostic tests. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy of evidence that takes into account the various factors likely to affect the validity of these studies (see Table 4).[22]

Clinical evidence for individual studies was extracted into evidence tables (provided on the accompanying CD-ROM) and a brief description of each study was included in the guideline text. The body of evidence identified for each clinical question was synthesised qualitatively in clinical evidence statements that accurately reflected the evidence. Quantitative synthesis (meta- analysis) was not performed for this guideline because there were no clinical questions for which sufficient numbers of similar studies were identified to merit such analysis.

1.1.7.3 Specific considerations for this guideline

Where the evidence supports it, the guideline makes separate recommendations for women with pre-existing diabetes (type 1 diabetes, type 2 diabetes and other forms of diabetes, such as maturity-onset diabetes of the young)[31] and gestational diabetes.

The term 'women' is used in the guideline to refer to all females of childbearing age, including young women who have not yet transferred from paediatric to adult services.

For this guideline, the effectiveness of interventions has been assessed against the following outcome domains.

- Neonatal outcomes
  - miscarriage, stillbirth, neonatal or infant death
  - congenital malformation
  - macrosomia, small for gestational age (SGA), low birthweight
  - shoulder dystocia, birth trauma (bone fracture, nerve palsy)
  - admission to intensive care unit, high-dependency unit, special care unit or transitional care unit
  - hypoglycaemia, respiratory distress, sepsis, transient heart failure, resuscitation, jaundice, hypocalcaemia, polycythaemia, hypoxic ischaemic encephalopathy, impairment of neurodevelopment.
- Maternal outcomes
  - preterm birth
  - mode of birth (spontaneous vaginal, instrumental, caesarean section)
  - mode of infant feeding
  - maternal health-related quality of life (validated questionnaire)
  - maternal satisfaction with experience of pregnancy and birth
  - perineal trauma, wound healing
  - maternal death

- maternal obstetric complications (haemorrhage, infection, thrombosis, admission to intensive care unit, incontinence)
- maternal diabetic complications (glycaemic control (glycosylated haemoglobin; HbA1c), hypoglycaemic episodes, diabetic ketoacidosis (DKA), retinopathy, nephropathy, macrovascular disease)
- development of type 2 diabetes.

CEMACH has conducted a three-part enquiry programme relating to diabetes in pregnancy. The programme, which started in 2002, focused on pre-existing diabetes (type 1 and type 2 diabetes; i.e. gestational diabetes was excluded). The three parts of the programme were:

- a survey of diabetes maternity services, which assessed the quality of maternity service provision against standards set out in the NSF for diabetes[20,32]

- a descriptive study of 3808 pregnancies followed until 28 days after birth in women with pre- existing diabetes who booked or gave birth between 1 March 2002 and 28 February 2003[32]

- a national confidential enquiry of demographic, social and lifestyle factors and clinical care in 442 pregnancies complicated by pre-existing diabetes.[33]

Results from the CEMACH diabetes in pregnancy programme were considered systematically by the GDG alongside other evidence and particularly as an indicator of current clinical practice.

Table 4: Levels of evidence for studies of the accuracy of diagnostic tests

Level	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:

- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case-control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

1.1.7.4 Health economics considerations

The aims of the economic input to the guideline were to inform the GDG of potential economic issues relating to the management of diabetes and its complications from preconception to the postnatal period, and to ensure that recommendations represented cost-effective use of healthcare resources.

The GDG prioritised a number of clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. A systematic search for published economic evidence was undertaken for these questions. For economic

evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation.[34] Reviews of the very limited relevant published economic literature are presented alongside the clinical reviews or as part of appendices detailing original economic analyses (see below).

Health economic considerations were aided by original economic analysis undertaken as part of the development of the guideline where robust clinical effectiveness data were available and UK cost data could be obtained. For this guideline the areas prioritised for economic analysis were:

- self-management programmes for women with diabetes who are planning a pregnancy (see Appendix N)
- treatment for gestational diabetes (see Appendix N) – this was addressed through a unified analysis of screening, diagnosis and treatment for gestational diabetes involving joint work with the NICE antenatal care GDG

NOTE for 2015 update: The health economic analysis fo the cost-effectiveness of screening, diagnosis and treatment of gestional diabetes has been mostly updated by the analysis in Chapter 9. This 2008 economic analysis is included in Appendix N to reflect its relavence to recommendations made in Section 4.2, risk factors for gestional diabetes.

- screening for congenital malformations (see Appendix N)
- monitoring fetal growth and wellbeing (see Section 5.9.3)
- criteria for admission to a neonatal intensive care unit (NICU) or special care unit (see Section 7.1.5).

The results of each economic analysis are summarised briefly in the guideline text. Detailed descriptions of the methods used for assessing the cost-effectiveness of self-management programmes are presented in Appendix C. The methods used for assessing the cost-effectiveness of screening, diagnosis and treatment for gestational diabetes are presented in Appendix D and those for assessing the cost-effectiveness of screening for congenital cardiac malformations are described in Appendix E.

1.1.7.5 GDG interpretation of the evidence and formulation of recommendations

For each clinical question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree clinical and cost-effectiveness evidence statements. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared. In areas where no substantial clinical research evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost-effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer their clinical questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified nine key priorities for implementation (key recommendations), which (in accordance with the criteria specified in the NICE guidelines manual[23]) were those recommendations expected to have the biggest impact on care and outcomes for pregnant women with diabetes and their babies in the NHS as a whole. The key priorities were selected using a variant of the nominal group technique. Each GDG member submitted an electronic form indicating their top five recommendations in order of priority. The GDG members' votes were collated and a shortlist of priority recommendations

was obtained by including all recommendations that had been voted for by at least one GDG member. The shortlisted recommendations were discussed at subsequent GDG meetings, and the final selection was made by retaining the recommendations that had received most votes and distilling the important issues contained in some long recommendations into more succinct recommendations.

The GDG also identified five key priorities for research (again using criteria set out in the NICE guidelines manual), which were the most important research recommendations, again using a variant of the nominal group technique. Each GDG member submitted an electronic form indicating their top five research recommendations in order of priority. The GDG members' votes were collated and a shortlist of priority recommendations was obtained using the same criteria that were used to shortlist recommendations for clinical care. The shortlisted recommendations were discussed at subsequent GDG meetings, and the final selection was made by retaining the recommendations that had received most votes.

1.1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 4 years from the date of publication. Reviewing may begin earlier than 4 years if significant evidence that affects guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

In this revised reprint, the information on the therapeutic indications, contraindications and use in pregnancy and lactation of medicines used in diabetes management and retinal assessment (specifically insulins, the oral hypoglycaemic agents metformin and glibenclamide, and tropicamide) has been corrected to follow the relevant summaries of product characteristics (SPCs) (July 2008). Changes have been made to the recommendations in Sections 2.2 and 3.6 and to the footnotes of recommendations in Sections 2.2, 3.6, 4.3 and 8.1. Footnotes have been deleted from recommendations in Sections 2.2, 3.6, 3.10, 4.3, 5.3 and 5.4

1.1.9 Stakeholder involvement in the guideline development process

Registered stakeholder organisations were invited to comment on the scope of the guideline during the scoping stage of development and on the evidence and recommendations in the validation stage (see Section 1.2.6).

The GDG carefully considered and responded to all of the comments received from stakeholders during the consultation periods. The comments and responses, which were reviewed independently by a guideline review panel convened by NICE, are published on the NICE website.

1.2 2015 guideline update development methodology

1.2.1 Introduction

This guidance was commissioned by NICE and developed in accordance with the guideline development process outlined in the 2009 and 2012 editions of The Guidelines Manual. Table 5 summarises the key stages of the guideline development process and which version of the process was followed for each stage.

Table 5: Stages in the NICE guideline development process and versions of The Guidelines Manual followed at each stage

Stage	2009 version	2012 version
Scoping the guideline (determining what the guideline would and would not cover)	✓	
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution etc)	✓	

Stage	2009 version	2012 version
Forming and running the guideline development group	✓	
Developing review questions	✓	
Identifying the evidence		✓
Reviewing and grading the evidence		✓
Assessing cost effectiveness		✓
Making group decisions and reaching consensus		✓
Linking guidance to other NICE guidance		✓
Creating guideline recommendations		✓
Developing clinical audit criteria		✓
Writing the guideline		✓

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the guideline development group throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from http://www.nice.org.uk/About/Who-we-are/Policies-and-procedures/NICE-equality-scheme.

1.2.2 Developing review questions and protocols and identifying evidence

The scope for this guideline (see Appendix A) outlines the main areas where guidance is needed. The guideline development group formulated review questions based on the scope and prepared a protocol for each review question (see Appendices C and D). These formed the starting point for systematic reviews of relevant evidence.

Published evidence was identified by applying systematic search strategies (see Appendices) to the following databases: Medline (1946 onwards), Embase (1974 onwards) and 4 Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment [HTA] database). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED). The Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1980 onwards) was searched for selected topics only. Where possible, searches were limited to English-language only. Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, all searches were updated and re-executed within 6 to 8 weeks of the start of the stakeholder consultation to ensure the reviews were up-to-date. This process was completed by June 2014.

1.2.3 Reviewing and synthesising evidence

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see http:/www.gradeworkinggroup.org/index.htm), a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low or very low if factors listed above are not addressed adequately.

For issues of diagnosis, the highest possible level of evidence is a controlled prospective observational study (a cohort study or case-control study), and a body of evidence based on

This section was updated in 2015

such studies would have an initial quality rating of high, which might be downgraded to moderate, low or very low, depending on the factors listed above. A retrospective observational study and a body of evidence based on such studies would have an initial quality rating of moderate, which might be downgraded to low or very low, or upgraded to high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was optimal.

Some studies were excluded from the guideline reviews after obtaining copies of the corresponding publications (see Appendix G) because they did not meet inclusion criteria specified by the guideline development group in the review protocols (see Appendix D). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H).

The body of evidence identified for each review question was reviewed and synthesised according to the GRADE approach and presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings for each outcome (relative and absolute effect sizes and associated confidence intervals [CIs]).

The review questions were judged on a number of outcomes. The justification for using these outcomes was based on their relevance to the populations covered by the guideline and consensus among members of the guideline development group. Outcomes included those that would confer benefit to the woman or her baby, as well as unwanted effects of treatment that would be important to reduce to a minimum. The outcomes used across the whole guideline are listed below. When assessing the effectiveness of a particular intervention in each review, appropriate information about the effect on one or more primary outcomes was sought.

Maternal outcomes used to judge review questions were:

- worsening of retinopathy and/or nephropathy
- incidence of dyslipidaemia
- glycaemic control measured by HbA1c values
- venous thromboembolic disease
- arterial thromboembolic disease
- hypertension
- maternal mortality
- preterm birth
- non-routine hospital contact or assessment for ketosis including phone contact
- hospital admission for diabetic ketoacidosis
- maternal satisfaction
- hypoglycaemic episodes
- spontaneous miscarriage
- acceptability/take up of targets, testing regimen or treatment
- pre-eclampsia
- mode of birth (spontaneous vaginal, operative vaginal, caesarean section [elective or emergency])

This section was updated in 2015

- need for additional treatment for gestational diabetes, such as diet, oral hypoglycaemic agents or insulin
- severe hypoglycaemic episodes
- maternal complications of delivery
- incidence of gestational diabetes and of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes in women postnatally
- accuracy in detecting gestational diabetes and IFG, IGT or diabetes in women postnatally.

Neonatal outcomes used to judge review questions were:

- stillbirth, perinatal and neonatal death
- neonatal intensive care unit length of stay greater than 24 hours
- admission to neonatal intensive care unit (NICU)
- neonatal hypoglycaemia
- neonatal hyperinsulinaemia or hyper C-peptideaemia
- any congenital abnormality, regardless of gestational age
- large for gestational age
- macrosomia
- shoulder dystocia (with and without consequences for the baby such as trauma, neuromuscular injury)
- initiation of breastfeeding (when started and exclusivity).

In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating).
- Limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up; these can reduce the quality rating).
- Inconsistency of effects across studies (this can reduce the quality rating).
- Indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating).
- Imprecision (this can reduce the quality rating).
- Other considerations (including large magnitude of effect, evidence of a dose–response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The GRADE approach covers studies of treatment effectiveness. However, it is less well established for studies reporting accuracy of diagnostic tests. All studies were assessed for limitations using methodology checklists available in the NICE Guidelines Manual 2012 including the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) methodology checklist to assess quality of diagnostic studies

Within the GRADE system it is necessary to predetermine values for minimum important differences in outcomes. For categorical outcomes the GRADE default of ± 0.25 for risk ratios and odds ratios was used. For continuous outcomes, the guideline development group was asked to predefine minimally important differences (the smallest difference between treatments that healthcare professionals or patients think is clinically beneficial). However, the group was unable to agree these, so continuous variables were graded based on a statistically derived minimum important difference (See Cochrane Handbook, Section 7.7.3.8). The minimally important differences derived for continuous outcomes are noted in

Appendix I. A dichotomous outcome result was considered precise if the confidence interval for the point estimate was below a threshold of 0.75, was between 0.75 and 1.25 or was above 1.25. If the confidence interval crossed either of the 0.75 or 1.25 thresholds the result was considered as seriously imprecise and downgraded. If the confidence interval crossed

This section was updated in 2015

both thresholds, the result was considered as very seriously imprecise and downgraded by 2 grades. Continuous outcomes were downgraded if the confidence interval for the mean or mean difference crossed the line of no effect and the minimally important difference (50% of the combined standard deviation of the 2 groups at baseline).

Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or means with standard deviations (SDs). For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity and likelihood ratios for positive and negative test results (LR+ and LR−, respectively) were calculated or quoted where possible (see Table 6).

Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled risk ratios (RRs), pooled odds ratios (ORs) or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies), the effect sizes reported in the included studies were presented for each individual study.

Table 6: '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d=N (total number of tests in study)

1.2.4 Assessing cost effectiveness

The aims of the health economic input to the guideline were to inform the guideline development group of potential economic issues relating to diabetes in pregnancy, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The guideline development group prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. A single global systematic search for published economic evidence was undertaken to cover all clinical questions in the guideline. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature are presented in the health economics chapter (Chapter 9).

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for possible economic analysis were:

- first trimester screening for glucose intolerance
- screening for gestational diabetes at 24–28 weeks
- diagnostic thresholds for gestational diabetes
- treatment of gestational diabetes

This section was updated in 2015

- the effectiveness of continuous glucose monitoring
- specialist teams for pregnant women with diabetes
- the gestational age-specific risk of intrauterine death and optimal timing of birth
- postnatal testing and optimal timing after pregnancy.

However, it was not possible to undertake original analyses for all these areas. In some areas the clinical evidence was such that modelling was not needed to aid recommendations. For other areas it was possible to make an assessment as to likely cost effectiveness without recourse to a model.

A model was developed to assess several alternative diagnostic thresholds for gestational diabetes. It was also possible to use this model to compare NICE risk factor screening against a policy of universal screening. Patient level data was also used to compare the cost effectiveness of NICE risk factor screening against other biochemical screening tests.

1.2.5   Evidence to recommendations

This section was updated in 2015

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the guideline development group to agree short clinical (and, where appropriate, cost effectiveness) evidence statements which were presented alongside the evidence profiles. Statements summarising the group's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified, the guideline development group considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on group consensus in relation to the likely cost effectiveness implications of the recommendations. The group also identified areas where evidence to answer review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The guideline development group identified 10 'key priorities for implementation' (key recommendations) and 5 high priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on the care of women with diabetes before, during and after pregnancy and their babies, and outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE Guidelines Manual). The priority research recommendations were selected in a similar way.

1.2.6 Stakeholder involvement

This section was updated in 2015

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The guideline development group carefully considered and responded to all comments received from stakeholder organisations. The comments and responses were reviewed by NICE in accordance with the NICE guideline development process.

1.2.7 Specific considerations for this guideline

This section was updated in 2015

Selected searches were limited by date to 2005 onwards in order to capture evidence published since the searches for the previous guideline were completed; where searches were limited by date this is indicated in the protocols (see Appendix D).

Where the guideline development group agreed that the study populations or interventions for a question could contain some degree of heterogeneity this was initially set at a threshold of 33% – for example where some participants were women with complications of pregnancy rather than a healthy, uncomplicated pregnancy (as per the guideline scope) – and then discussed with the group on a question by question basis for relevance. This is noted in any relevant protocol where it applies, along with any further specifications.

The country of study and ethnicity characteristics of the study population (where available) were recorded in the 'Other considerations' column of the GRADE profiles as the guideline development group wanted to assess the relevance of study populations to England and Wales and because it is recognised that women of some ethnicities have a higher risk of developing gestational diabetes. Where relevant, the group commented on the ethnicity of study populations in the Evidence to recommendations (under 'Other considerations').

Outcomes are reported in GRADE profiles as identified as priority outcomes by the guideline development group during review protocol development. Where no evidence was found for priority outcomes, data is reported for other proxy or similar outcomes agreed as relevant by the guideline development group chair.

For reviews of diagnostic or predictive accuracy of tests the following terms and thresholds (Jaeschke et al., 1994) were used to define the usefulness of the test:

Sensitivity and specificity:

- High: 90% and above
- Moderate: 75% to 89.9%
- Low: 74.9% or below

Positive likelihood ratio:

- Very useful: more than 10
- Moderately useful: 5 to 10
- Not useful: less than 5

Negative likelihood ratio:

- Very useful: 0 to 0.1
- Moderately useful: 0.1 to 0.5
- Not useful: more than 0.5

Correlation coefficients:

- High correlation: r-value of 0.6 to 1.0 (or −0.6 to −1.0)
- Moderate correlation: r-value of 0.4 to 0.59 (or −0.4 to −0.59)
- Low correlation: r-value of 0.2 to 0.39 (or −0.2 to −0.39)
- Very low or no correlation: r-value of 0 to 0.19 (or 0 to −0.19)

1.3 Schedule for updating the 2015 guideline

NICE is currently reviewing its schedule for guideline updates. For the most up-to-date information about the guideline review schedule, please see the latest version of the NICE manual available from the NICE website.

1.4 Explaining the changes in the partial update of the 2015 guideline

This guideline partially updates and replaces NICE clinical guideline Diabetes in pregnancy (CG63, published 2008).

New and updated recommendations have been included on many topics.

Recommendations are marked to indicate the year of the last evidence review:
- [2008] if the evidence has not been updated since the original guideline
- [2008, amended 2015] if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation
- [new 2015] if the evidence has been reviewed and the recommendation has been added or updated
- [2015] if the evidence has been reviewed but no change has been made to the recommended action.

It has not been possible to update all recommendations in this update of the guideline. Areas for review and update were identified and prioritised through the scoping process and stakeholder feedback. Areas that have not been reviewed in this update may be addressed in 2 years' time when NICE next considers updating this guideline. NICE is currently considering setting up a standing update committee for diabetes, which would enable more rapid update of discrete areas of the diabetes guidelines as and when new and relevant evidence is published.

2 Summary of recommendations and care pathway

Note that glibenclamide was removed from recommendations in the 2020 guideline update. See the current recommendations at www.nice.org.uk/guidance/NG3

Update 2015
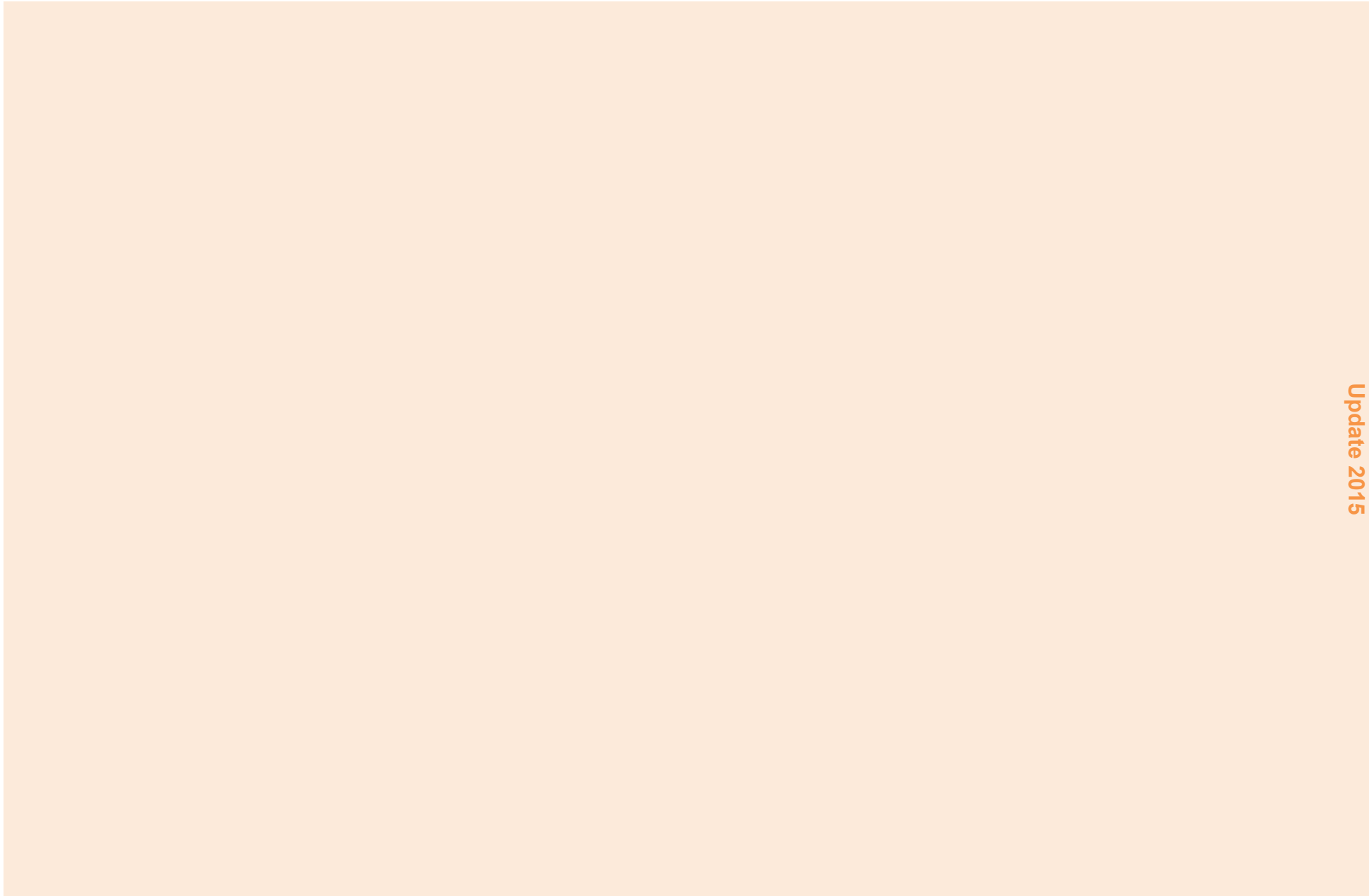
2.1.1 Intrapartum care

The current recommendations can be found at www.nice.org.uk/guidance/ng3

2.1.2 Postnatal care

The current recommendations can be found at www.nice.org.uk/guidance/ng3

2.1 Key research recommendations

The following research recommendations have been identified as priorities.

2.2.1 Preconception care for women with diabetes: insulin pump therapy and continuous glucose monitoring

What are the roles of insulin pump therapy(continuous subcutaneous insulin infusion) and continuous glucose monitoring in helping women with diabetes to achieve blood glucose targets before pregnancy?

Why this is important

Babies born to women with diabetes have a high risk of having congenital malformations and this risk is greater if blood glucose control is poor around the time of conception. However, lowering the risk to that of women without diabetes would require normalisation of blood glucose levels, and this is difficult to achieve without increasing the risk of serious hypoglycaemia.

Insulin pump therapy and continuous glucose monitoring have been shown to reduce both blood glucose levels and rates of hypoglycaemia in the non-pregnant population, but it is uncertain if this holds true before conception and in early pregnancy. There is therefore an urgent need to test the effectiveness and acceptability of these technologies in women with diabetes who are planning pregnancy. This would be best undertaken in a randomised controlled trial of women with diabetes who are trying to conceive. Women would be allocated to receive either conventional care (self-monitoring of blood glucose and insulin adjustment) or insulin pump therapy and continuous glucose monitoring.

2.2.2 Testing for gestational diabetes

This section was updated in 2015

When should testing for gestational diabetes take place – in the first or second trimester?

Why this is important

Conventionally, testing for gestational diabetes takes place in the second trimester. Intervention has been shown to improve outcomes for women diagnosed with gestational diabetes. However, maternal age and obesity are increasing, and some women (especially those from populations with a high incidence of type 2 diabetes) enter pregnancy with undiagnosed type 2 diabetes, but may not be tested for diabetes until the second trimester. This exposes the woman and the fetus to risks resulting from early and prolonged maternal hyperglycaemia. It is presumed that this is associated with increased morbidity. UK population studies are needed to establish the incidence of glucose intolerance in women in the first trimester. Well-designed randomised controlled trials are needed to establish if testing, diagnosis and intervention in the first rather than the second trimester improves maternal, fetal and neonatal outcomes, including fetal hyperinsulinaemia.

2.2.3 Barriers to achieving blood glucose targets before and during pregnancy

What are the barriers that women experience to achieving blood glucose targets?

Why this is important

It is vital for normal fetal development in the first trimester that women with pre-existing diabetes achieve good blood glucose control both before and during pregnancy. Good control also helps to prevent macrosomia and other complications in the third trimester in women with pre-existing or gestational diabetes. Whereas many women manage to achieve blood glucose targets, a proportion of women continue to find it difficult to do so. A number of factors could be involved, such as health beliefs, a poor understanding of the importance of good blood glucose control, an inability to be able to comply with a demanding regimen of blood glucose testing up to 7 times a day, and the need to adjust insulin dosage. A better understanding of the barriers in this cohort of women is needed so that healthcare professionals can work to overcome them. Robust qualitative studies are needed to explore these barriers, with the aim of improving blood glucose control and fetal outcomes in pregnancy for women with pre-existing diabetes and women with gestational diabetes.

2.2.4 Risk of fetal death for women with diabetes

How can fetuses at risk of intrauterine death be identified in women with diabetes?

Why this is important

Unexpected intrauterine death remains a significant contributor to perinatal mortality in pregnant women with diabetes. Conventional tests of fetal wellbeing (umbilical artery Doppler ultrasound, cardiotocography and other biophysical tests) have been shown to have poor sensitivity for predicting such events. Alternative approaches that include measurements of erythropoietin in the amniotic fluid and MRI spectroscopy may be effective, but there is currently insufficient clinical evidence to evaluate them. Well-designed randomised controlled trials that are sufficiently powered are needed to determine whether these approaches are clinically and cost effective.

2.2.5 Postnatal treatment for women diagnosed with gestational diabetes

Are there effective long-term pharmacological interventions to prevent the onset of type 2 diabetes that can be recommended postnatally for women who have been diagnosed with gestational diabetes?

Why this is important

Gestational diabetes is one of the strongest risk factors for the subsequent development of type 2 diabetes: up to 50% of women diagnosed with gestational diabetes develop type 2 diabetes within 5 years of the birth. There are some data suggesting that changes in diet and exercise, with or without metformin, can prevent type 2 diabetes developing in non-pregnant middle-aged people with glucose intolerance, but there are no studies specifically in women with a past history of gestational diabetes. There is thus an urgent need to investigate what interventions may delay or prevent type 2 diabetes developing in this high-risk population of women. Undertaking a formal randomised controlled trial involving long-term outcomes is often not feasible in practice. However, it would be possible to have a quasi-randomised study comparing 2 populations of women with similar demographic profiles who had gestational diabetes. One population would be encouraged at their annual check to follow a specific diet and exercise regime and those in the other population would not. The incidence of the development of type 2 diabetes in the 2 groups at 5, 10 and 20 years would be compared.

2.2   Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

b   care.

The current recommendations can be found at www.nice.org.uk/guidance/ng3

2.3   Care pathway

The pathway for this guideline can be found at the following link:

https://pathways.nice.org.uk/pathways/diabetes-in-pregnancy

3 Preconception care

3.1 Outcomes and risks for woman and baby

3.1.1 Description of the evidence

No specific searches were undertaken for this section of the guideline. The evidence is drawn from publications identified in searches for other sections.

3.1.2 How diabetes affects pregnancy

Women with type 1 and type 2 diabetes have an increased risk of adverse pregnancy outcomes, including miscarriage, fetal congenital anomaly and perinatal death.[2] [EL = 3]

Factors associated with poor pregnancy outcome (defined as a singleton baby with a major congenital anomaly born at any gestational age and/or a baby who died between 20 weeks of gestation and 28 days after birth) in women with type 1 and type 2 diabetes have been documented in the final report of the CEMACH diabetes in pregnancy programme.[33] [EL = 3–4]

aternal social deprivation is associated with poor pregnancy outcome for women with type 1 or type 2 diabetes (odds ratio (OR) [1,2], 95% confidence interval (CI) 1.1 to 1.4), but ethnicity (Black, Asian or Other Ethnic Minority group) is not (OR 0.9, 95% CI 0.5 to 1.5).[33] [EL = 3–4] This differs from the general maternity population in which both factors are associated with poor pregnancy outcomes.[32] [EL = 2+]

Women with pre-existing complications of diabetes are more likely to have a poor pregnancy outcome (OR 2.6, 95% CI 1.3 to 4.9) than women without. [33] [EL = 3–4] However, nephropathy (OR 2.0, 95% CI 1.0 to 4.2), recurrent hypoglycaemia (OR 1.1, 95% CI 0.7 to 1.7) and severe hypoglycaemia (OR 1.3, 95% CI 0.7 to 2.3) during pregnancy were not associated with poor pregnancy outcome. Antenatal evidence of fetal growth restriction was associated with poor pregnancy outcome (OR 2.9, 95% CI 1.4 to 6.3), but antenatal evidence of fetal macrosomia was not (OR 0.8, 95% CI 0.5 to 1.3).

Certain social and lifestyle factors have also been shown to be associated with poor pregnancy outcome:[33] unplanned pregnancy (OR 1.8, 95% CI 1.0 to 2.9), no contraceptive use in the 12 months prior to pregnancy (OR 2.3, 95% CI 1.3 to 4.0), no preconception folic acid (OR 2.2, 95% CI 1.3 to 3.9), smoking (OR 1.9 95% CI 1.2 to 3.2), sub-optimal approach of the woman to her diabetes prior to pregnancy (OR 4.9, 95% CI 2.7 to 8.8) and sub-optimal approach of the woman to her diabetes during pregnancy (OR 3.9, 95% CI 2.5 to 6.1). However, a body mass index (BMI) of at least 30 kg/m² was not associated with poor pregnancy outcomes (OR 1.1, 95% CI 0.6 to 1.9). [EL = 3–4] The importance of planning pregnancy and the role of contraception is considered further in Sections 3.2 and 3.3. Diet and dietary supplements are considered further in Section 3.4.

A lack of local glycaemic control targets (OR 2.0, 95% CI 1.0 to 3.8) and sub-optimal glycaemic control before and during pregnancy were also associated with poor pregnancy outcome (preconception OR 3.9, 95% CI 2.2 to 7.0; first trimester OR 3.4, 95% CI 2.1 to 5.7; after first trimester OR 5.2, 95% CI 3.3 to 8.2).[33] [EL = 3–4]

Specific diabetes care risk factors, maternity care risk factors and postnatal care risk factors were also identified in the CEMACH final report.[33] [EL = 3–4] These issues are discussed in Chapters 5 (diabetes care during pregnancy and antenatal care for women with diabetes), 6 (intrapartum care) and 8 (postnatal care for women with diabetes).

Update 2015

3.1.3   How pregnancy affects diabetes

Pregnancy can affect the control and complications of diabetes. There is increased frequency of hypoglycaemia and decreased hypoglycaemia awareness during pregnancy. Nausea and vomiting in pregnancy can disrupt blood glucose control and severe nausea and vomiting (hyperemesis gravidarum) in women with diabetes can lead to ketoacidosis (see Section 5.1).

Pregnancy is associated with progression of diabetic retinopathy (see Section 5.6. Progression of retinopathy is more likely in women with more severe retinopathy, poor glycaemic control and hypertension (see Sections 5.6 and 5.7).

Pregnancy may accelerate progression to end-stage renal disease in women with moderate to advanced diabetic nephropathy (see Section 5.7).

General anaesthesia in women with diabetes leads to a high risk of hypoglycaemia and a higher rate of Mendelson syndrome due to the higher resting gastric volume compared to women without diabetes (see Section 6.2).

3.1.4   Ethnicity

The CEMACH descriptive study found that maternal ethnic origin of pregnant women with type 1 and type 2 diabetes (considered together) was not significantly different to the general maternity population of England, which reports 80.3% White, 5.8% Black (Black Caribbean, Black African and Black Other), 10.5% Asian (Indian, Pakistani and Bangladeshi) and 3.4% Chinese and other ethnic background. However, a much higher proportion of women with type 2 diabetes were of Black, Asian or Other Ethnic Minority origin compared to women with type 1 diabetes (48.5% versus 8.5%).[2] [EL = 3]

The CEMACH data suggested that ethnicity is not associated with poorer pregnancy outcome for women with type 1 or type 2 diabetes (Black, Asian or Other Ethnic Minority group, OR 0.9, 95% CI 0.5 to 1.5). However, women from ethnic minority groups are more likely to develop gestational diabetes (see Section 4.2). They are also more likely to have unplanned pregnancies and less likely to have a measure of long-term glycaemic control in the 6 months before pregnancy (see Section 3.10).[33] [EL = 3–4]

The CEMACH data for England showed that in women of white ethnic origin there was a clear increase in the number of women with type 2 diabetes with increasing quintile of social deprivation (6.8% in least and 45.1% in most-deprived quintile). This trend was not statistically significant in women of white ethnic origin with type 1 diabetes (18.3% in least-deprived quintile and 21.9% in most-deprived quintile). For women of Black or Other Ethnic Minority origin, this association was stronger and seen in women with type 1 diabetes (4.7% in least-deprived quintile and 35.6% in most-deprived quintile) and type 2 diabetes (3.4% in least-deprived quintile and 59.4% in most-deprived quintile).[2] [EL = 3]

3.1.5   Evidence statement

Women with pre-existing type 1 and type 2 diabetes have an increased risk of adverse pregnancy outcomes, including miscarriage, fetal congenital anomaly and perinatal death. The following factors are associated with adverse pregnancy outcome: maternal social deprivation, unplanned pregnancy and lack of contraceptive use in the 12 months prior to pregnancy, lack of preconception folic acid, smoking, sub-optimal approach of the woman to her diabetes before or during pregnancy and sub-optimal glycaemic control before or during pregnancy, antenatal evidence of fetal growth restriction, pre-existing diabetes complications, lack of local glycaemic control targets, lack of discussion of diabetes-specific issues related to alcohol intake, lack of discussion of fetal risks in diabetic pregnancy, lack of a baseline retinal examination in the 12 months before pregnancy and sub-optimal preconception care (excluding glycaemic control). [EL = 3–4]

Pregnancy can affect glycaemic control in women with diabetes, increasing the frequency of hypoglycaemia and hypoglycaemia unawareness, and the risk of ketoacidosis. General anaesthesia in women with diabetes can also increase the risk of hypoglycaemia. The progression of certain complications of diabetes, specifically diabetic retinopathy and diabetic nephropathy, can be accelerated by pregnancy.

3.1.6 Existing guidance

The standard set by the NSF for diabetes[20] in relation to diabetes in pregnancy was for the NHS to develop, implement and monitor policies to empower and support women with pre-existing

Diabetes and women with gestational diabetes to optimise pregnancy outcomes. The NSF stated that maternity care should ensure that all pregnant women have a positive experience of pregnancy and childbirth, and that they should receive care that promotes their physical and psychological wellbeing and optimises the health of their babies. The NSF highlighted that maternity care for women with diabetes may be perceived as highly 'medicalised' with a tendency towards intervention in labour and birth and that this could make the experience negative or frightening. It was suggested that keeping women with diabetes and their partners fully informed and involved in decision making would help to ensure that their experience of pregnancy and childbirth would be a positive one.

3.1.7 From evidence to recommendations

As no systematic searches were conducted for this section of the guideline, the GDG's recommendations are based on its consensus view of what information should be offered to women with pre-existing diabetes before pregnancy to support and explain its substantive recommendations regarding management options before, during and after pregnancy, both in terms of maternity care and management of diabetes during these periods and to reinforce the recommendations of the NSF for diabetes.

3.1.8 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.1.9 Research recommendations

There were no research recommendations relating to the information that should be offered about outcomes and risks for the woman and the baby.

3.2 The importance of planning pregnancy and the role of contraception

3.2.1 General advice

3.2.2 Description of the evidence

No specific searches were undertaken for this section of the guideline. The evidence is drawn from publications identified in searches for other sections.

The CEMACH diabetes in pregnancy programme provides data on current practice in England, Wales and Northern Ireland in relation to planning pregnancy, use of contraception and preconception counselling in women with type 1 and type 2 diabetes.[33] [EL = 3–4]

The CEMACH descriptive study found 38.2% of women with type 1 diabetes and 24.8% of women with type 2 diabetes had pre-pregnancy counselling documented.[2] A pre-pregnancy glycaemic test in the 6 months before pregnancy was recorded for 40% of the women with

type 1 diabetes and 29.4% of the women with type 2 diabetes. [EL = 3]

The CEMACH enquiry reported that pre-pregnancy counselling included a discussion about:

- glycaemic control in 51% of women with poor pregnancy outcome and 56% with good pregnancy outcome
- diet in 42% of women with poor pregnancy outcome and 48% with good pregnancy outcome
- contraception in 19% of women with poor pregnancy outcome and 36% with good pregnancy outcome
- retinopathy in 30% of women with poor pregnancy outcome and 39% with good pregnancy outcome
- nephropathy in 23% of women with poor pregnancy outcome and 25% with good pregnancy outcome
- hypertension in 22% of women with poor pregnancy outcome and 28% with good pregnancy outcome
- alcohol intake in 20% of women with poor pregnancy outcome and 25% with good pregnancy outcome
- need for increased pregnancy surveillance in 54% of women with poor pregnancy outcome and 62% with good pregnancy outcome

- fetal risks in 42% of women with poor pregnancy outcome and 58% with good pregnancy outcome
- the increased chance of induction of labour for 32% of women with poor pregnancy outcome and 51% with good pregnancy outcome
- the increased possibility of caesarean section for 39% of women with poor pregnancy outcome and 53% with good pregnancy outcome.

Note that poor pregnancy outcome was defined as a singleton baby with a major congenital anomaly who gave birth at any gestation and/or a baby who died from 20 weeks of gestation up to 28 days after birth. Good pregnancy outcome was defined as a singleton baby without a congenital anomaly who survived to day 28 after birth.

The CEMACH enquiry found an association between poor pregnancy outcome and a lack of discussion of diabetes-specific issues related to alcohol intake (OR 2.5, 95% CI 1.1 to 5.4), lack of discussion of fetal risks in diabetic pregnancy (OR 2.9, 95% CI 1.1 to 8.2), lack of a baseline retinal examination in the 12 months before pregnancy (OR 2.3, 95% CI 1.2 to 4.5) and assessment of sub-optimal preconception care (excluding glycaemic control; OR 5.2, 95% CI 2.7 to 10.1).[33] [EL = 3–4]

However, the CEMACH enquiry found no association between poor pregnancy outcome and a lack of contraceptive advice before pregnancy (OR 1.7, 95% CI 0.8 to 3.5), lack of discussion about diet (OR 1.8, 95% CI 0.8 to 4.1), poor glycaemic control (OR 1.2, 95% CI 0.5 to 2.5), retinopathy (OR 1.1, 95% CI 0.6 to 2.3), nephropathy (OR 0.8, 95% CI 0.4 to 1.7), hypertension (OR 1.1, 95% CI 0.5 to 2.3), lack of discussion of increased diabetes surveillance (OR 1.7, 95% CI 0.6 to 4.5), increased pregnancy surveillance (OR 1.5, 95% CI 0.6 to 4.0), increased risk of induction of labour (OR 2.2, 95% CI 1.0 to 4.9) or possible caesarean section (OR 2.4, 95% CI 1.0 to 5.8), lack of dietetic review before pregnancy (OR 1.2, 95% CI 0.7 to 2.1), lack of a baseline test of renal function (OR 2.0, 95% CI 0.9 to 4.3) or assessment of albuminuria (OR 1.5, 95% CI 0.8 to 2.8).[33] [EL = 3–4]

As noted in Section 3.1, social and lifestyle factors, such as unplanned pregnancy and lack of contraceptive use in the last 12 months, are associated with poor pregnancy outcome. In the general maternity population, 42% of women did not plan their last pregnancy. The CEMACH enquiry found 51% (72/141) of the women with poor pregnancy outcome and 38% (55/144) of the women with good pregnancy outcome were documented as having not planned their last pregnancy (OR 1.8, 95% CI 1.0 to 2.9).33 [EL = 3–4] Sixty-six percent (71/108) of the women with poor pregnancy outcome and 45% (54/121) of the women with good pregnancy outcome were not documented as using any type of contraception in the 12 months before conception (OR 2.3, 95% CI 1.3 to 4.0).

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that 38% (32/84) of women with type 2 diabetes and 40% (50/121) of women with type 1 diabetes were documented as having not planned their last pregnancy compared with 42% in the general maternity population. Contraceptive use in the 12 months prior to pregnancy was lower in women with type 2 diabetes (32%) compared with women with type 1 diabetes (59%, P = 0.001).[33] [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that there was no difference between women with type 1 or type 2 diabetes with regard to whether they had a test for glycaemic control in the 12 months prior to pregnancy (83% versus 81%, P = 0.66).33 Women with type 1 diabetes were more likely to have sub-optimal preconception glycaemic control (75%) than women with type 2 diabetes (60%) (P = 0.013). [EL = 3–4]

There are advantages to the woman and baby in planning pregnancy. Optimising glycaemic control before conception and in the first few weeks of pregnancy is of prime importance.

Poor glycaemic control before pregnancy and in early pregnancy is associated with congenital malformations and miscarriage (see Section 3.7).

The CEMACH enquiry found that a greater number of women with poor pregnancy outcomes (69%) compared with women with good pregnancy outcome (50%) were not documented as having commenced folic acid supplementation before pregnancy (adjusted OR 2.2, 95% CI 1.3 to 3.9).[33] Only 32% (33/103) of women taking folic acid were on the high dose (5 mg/day). [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported there was no difference between the number of women with type 1 diabetes and those with type 2 diabetes who were documented as having commenced folic acid supplementation in the 12 months before pregnancy (45% [32/71] of women with type 2 diabetes and 49% [54/110] of women with type 1 diabetes, P = 0.6).[33] [EL = 3–4]

Women with diabetes are at an increased risk of having a baby with a neural tube defect. Women with diabetes who are planning to get pregnant are recommended to supplement their diet with folic acid until 12 weeks of gestation (see Section 3.4).

Some medications used to treat complications of diabetes can increase the risk of congenital malformation if used in the early stages of pregnancy. These medications include angiotensin-converting enzyme (ACE) inhibitors used to treat hypertension and nephropathy, angiotensin-II receptor blockers (ARBs) (also known as angiotensin-II receptor antagonists) used to treat hypertension and statins used to treat elevated cholesterol. These medications should be discontinued before pregnancy to reduce the risk of congenital malformations and safe alternative medications should be prescribed if appropriate (see Section 3.8).

Because of the importance of planning future pregnancies in women with diabetes, it is recommended that information and advice about contraception and the importance of planned pregnancy is offered to the women with diabetes in the postnatal period (see Section 8.2).

Since development of the fetal organs occurs during the first 3 months of pregnancy and good glycaemic control in the preconception period and the first trimester of pregnancy decreases the risk of congenital anomaly and miscarriage (see Sections 3.5, 6, 7),[35,36] planning pregnancy is particularly important for women with diabetes. However, women with diabetes are less likely to plan pregnancy than women without diabetes and young women with diabetes lack awareness of the importance of planning pregnancy and the role of preconception care[33,10].

3.2.3 Evidence statement

Women with pre-existing diabetes who have preconception care and advice involving a discussion of glycaemic control, diet, contraception, retinopathy, nephropathy, hypertension, alcohol intake, the need for increased pregnancy surveillance, fetal risks, the chance of induction of labour and caesarean section have better pregnancy outcomes than women who do not have preconception care and advice.

Development of the fetal organs occurs in the first 3 months of pregnancy, and so good glycaemic control and avoidance of medications that could harm the developing fetus should be established before discontinuing contraception.

3.2.4 From evidence to recommendations

As no systematic searches were conducted for this section of the guideline, the GDG's recommendations are based on its consensus view of what information should be offered to women with diabetes in relation to planning pregnancy and the role of contraception to

support and explain its substantive recommendations regarding management options before, during and after pregnancy.

3.2.5   Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.3   Oral contraception

This section was updated in 2015

3.3.1   Review questions

What is the effectiveness of oral oestrogen-containing contraceptives in women with diabetes compared with women without diabetes?

What is the effectiveness of oral progestogen-containing contraceptives in women with diabetes compared with women without diabetes?

3.3.2   Introduction

The objectives of these review questions were to determine:

- Whether the use of oral contraceptives in women with diabetes is as effective in preventing pregnancy as in both women without diabetes using this form of contraception and women with diabetes using other forms of contraception.
- Whether their use is associated with increased risks in women with pre-existing diabetes, especially those with vascular complications of diabetes.

Women with either type 1 or type 2 diabetes will be considered.

Two types of oral contraceptives were investigated by the reviews: those containing oestrogen and progestogen (also known as 'combined' oral contraceptives); and those containing only progestogen (also known as 'progestogen-only' oral contraceptives). The 2 review questions were addressed using a single search for evidence.

The scope for the guideline update specifies that the guideline will address the role of oral contraceptives by looking for studies that compare contraception use in women with diabetes with contraceptive use in women without diabetes.

The guideline development group agreed that the evidence identified in the searches for the above questions should also be used to evaluate the contraceptive effectiveness and risk of adverse effects of using oral contraceptives in women with diabetes compared with women with diabetes using other forms of contraception, or compared with women with diabetes using no contraception. The group members were aware that there was likely to be a limited number of studies on this topic and thus they took the decision to include all studies to maximise the chance they would be able to answer the review research questions.

3.3.3   Description of included studies

Eight studies were included in the review (Ahmed et al., 2005; Diab and Zaki, 2000; Garg et al., 1994; Grigoryan et al., 2006; Klein et al., 1990; Petersen et al., 1995; Skouby et al., 1986; Tanis et al., 2001).

This review was conducted in two parts: the first compared women with diabetes using oral contraceptives with women without diabetes using oral contraceptives; and the second compared women with diabetes using oral contraceptives with women with diabetes using other forms of contraception or no contraception.

Women with diabetes using oral contraceptives compared with women without diabetes using oral contraceptives

For the comparison of women with diabetes using oral contraceptives and women without diabetes using oral contraceptives, 2 studies (1 prospective observational study and 1 case-control study) were identified for inclusion (Ahmed et al., 2005; Tanis et al., 2001). The prospective observational study (Ahmed et al., 2005) involved 92 women, of whom 22 were using oral contraceptives and therefore of interest in these review questions. The majority of the women in the diabetes group had type 1 diabetes (11/12 women) but the type of oral contraceptives being used was not reported. During the study, the women received a hypertension drug, but it is not clear whether the women had pre-existing vascular complications or not. Only the baseline characteristics of the women were relevant to the current review, and so the pre-drug administration data are presented here as a prospective observational study. The case-control study (Tanis et al., 2001) involved 1173 women, of whom 446 were using combined oral contraceptives containing 30 micrograms of ethinyl estradiol and therefore of interest in these review questions. The study did not report the type of diabetes in the included women.

Women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives

For the comparison of women with diabetes using oral contraceptives and women with diabetes not using oral contraceptives, 6 studies (2 prospective randomised trials, 2 prospective observational studies and 2 prospective case-control studies) were identified for inclusion (Diab and Zaki, 2000; Garg et al., 1994; Grigoryan et al., 2006; Klein et al., 1990; Petersen et al., 1995; Skouby et al., 1986).

Two studies compared combined oral contraceptives with no oral contraceptives (Garg et al., 1994; Petersen et al., 1995). Another study compared oral contraceptives with no oral contraceptives, but did not specify whether the women were using combined or progestogen-only oral contraceptives (Klein et al., 1990). One study compared combined oral contraceptives with an intrauterine contraceptive device (Diab and Zaki, 2000). One study compared women using different types of oral contraceptives and reported separate results for the use of combined oral contraceptives and progestogen-only oral contraceptives (Skouby et al., 1986). One study compared combined oral contraceptives with an intrauterine contraceptive device and with women not using contraception (Grigoryan et al., 2006). The smallest study consisted of 27 women (Skouby et al., 1986) and only 1 study included more than 100 women (Klein et al., 1990). In 1 study, 30% of the women participating changed to a different treatment group after 6 months (Skouby et al., 1986).

In 1 study a comparison of mean outcomes across groups was presented (Garg et al., 1994). In 4 studies, mean changes in outcomes from baseline within study groups are presented for various time points (Diab and Zaki, 2000; Grigoryan et al., 2006; Petersen et al., 1995; Skouby et al., 1986)

Guideline development group priority outcomes reported in the studies comparing women with diabetes using oral contraceptives with women with diabetes not using oral contraceptives were:

- worsening of retinopathy and/or nephropathy
- change in HbA1c
- incidence of dyslipidaemia
- hypertension.

The guideline development group priority outcomes that were not reported in the studies were:

- pregnancy rate

- venous thromboembolic disease
- arterial thromboembolic disease
- mortality.

3.3.4 Evidence profiles

The GRADE profiles for this review are presented in Table 7 to Table 14.

Table 7: GRADE profile for adverse outcomes of oral oestrogen-containing contraceptives and oral progestogen-containing contraceptives in women with type 1 or type 2 diabetes compared with women without diabetes

| Number of studies | Number of women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	With diabetes	Without diabetes	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Worsening of retinopathy and/or nephropathy											
Filtration fraction											
1 (Ahmed et al., 2005)	12	10	NA	MD 0.0 higher (0.0 to 0.1 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]
Glomerular filtration rate (ml·min^{-1}·1.73 m^{-2}; median of readings at 10, 5 and 0 minutes before administration of oral captopril[f])											
1 (Ahmed et al., 2005)	12	10	NA	MD 2 lower (21.1 lower to 17.1 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]
Microalbuminuria (%)											
1 (Ahmed et al., 2005)	6/9 (67%)	0/10 (0%)	RR 14.3 (0.8 to 271.1)[a]	NC	Low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[c,d,e]
Plasma renin activity (ng Ang I·ml^{-1}·hour^{-1})											
1 (Ahmed et al., 2005)	12	10	NA	MD 0.0 higher (0.4 lower to 0.4 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]
Renal plasma flow (ml·min^{-1}·1.73 m^{-2}; median of readings at 10, 5, and 0 minutes before administration of oral captopril[f])											
1 (Ahmed et al., 2005)	12	10	NA	MD 38 lower (105.7 lower to 29.7 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]
Urine sodium excretion rate (mmol/24 hours)											
1 (Ahmed et al., 2005)	12	10	NA	MD 2 lower (75.6 lower to 71.6 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	With diabetes	Without diabetes	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Urine protein excretion rate (mg/24 hours)											
1 (Ahmed et al., 2005)	12	10	NA	MD 89 higher (3.0 higher to 175.0 higher)[a]	Low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[c,d,e]
Change in HbA1c											
HbA1c (%)											
1 (Ahmed et al., 2005)	12	10	NC	NC	Low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	NC	Yes[c,d,e]
Fasting plasma glucose (mmol/l)											
1 (Ahmed et al., 2005)	12	10	NA	MD 3.9 higher (1.6 higher to 6.3 higher)[a]	Low	Observational	No serious risk of bias	No serious inconsistency	Serious indirectness[g]	No serious imprecision	Yes[c,d,e]
Arterial thromboembolic disease											
Myocardial infarction											
1 (Tanis et al., 2001)	5/7 (71%)	94/439 (21%)	RR 3.4 (2.0 to 5.5)[a]	514 more per 1000 (214 more to 964 more)[a]	Low	Case control	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[h,i]
Hypertension											
Mean arterial pressure (mmHg)											
1 (Ahmed et al., 2005)	12	10	NA	MD 4 lower (9.4 lower to 1.4 higher)[a]	Very low	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d,e]

MD mean difference, NA not applicable, NC Not calculable, RR risk ratio
a. Calculated by the NCC-WCH based on results reported in the paper
b. Confidence interval for the MD crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the 2 groups at baseline)
c. 11 of the 12 women in the diabetes group had type 1 diabetes
d. Conducted in the USA. Ethnicity of the participants was not reported.
e. The women included in the study used different types of oral contraceptives. The mean oestrogen content was 31.0 micrograms (SD 1.9) for women with diabetes and 30.5 micrograms (SD 2.1) for women without diabetes, and the mean progesterone content was 0.34 mg (SD 0.11) for women with diabetes and 0.36 mg (SD 0.12) for women without diabetes.
f. Administration of oral captopril is not relevant in this review question and the results reported are baseline measurements
g. Fasting plasma glucose is reported as a proxy for change in HbA1c as there were limited data reported for HbA1c

h. Conducted in the Netherlands. 94% of the myocardial infarction group and 93% of the control group were white. The ethnicity of the other participants was not reported. Type of diabetes not reported.

i. The dosage of oral contraceptives used was not reported, but the study only included women who used oral contraceptives containing 30 micrograms of ethinyl oestradiol

Table 8: GRADE profile for worsening of retinopathy and/or nephropathy in women with type 1 diabetes using oral contraceptives compared with women with type 1 diabetes not using oral contraceptives

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Using oral contraceptives	Not using oral contraceptives	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Worsening of retinopathy											
Worsening by 1 eye grade											
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives											
1 (Garg et al., 1994)	9/40 (23%)	8/39 (21%)	RR 1.1 (0.5 to 2.6)[a]	21 more per 1000 (from 103 fewer to 328 more)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	No serious indirectness[c]	Serious imprecision[d]	Yes[e, f]
Worsening by more than 1 eye grade											
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives											
1 (Garg et al., 1994)	8/40 (20%)	6/39 (15%)	RR 1.3 (0.5 to 3.4)[a]	46 more per 1000 (from 77 fewer to 369 more)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	No serious indirectness[c]	Serious imprecision[d]	Yes[e, f]
Mild to minimal diabetic retinopathy											
Oral contraceptives (type not reported) versus no oral contraceptives											
1 (Klein et al., 1990)	147/351 (42%)	88/214 (41%)	RR 1.0 (0.8 to 1.3)[a]	8 more per 1000 (from 82 fewer to 103 more)[a]	Very low	Observational	Very serious limitations[g]	No serious inconsistency[b]	Serious indirectness[h]	Serious imprecision[d]	Yes[e, i]
Moderate to severe retinopathy											
Oral contraceptives (type not reported) versus no oral contraceptives											
1 (Klein et al., 1990)	74/351 (21%)	43/214 (20%)	RR 1.1 (0.8 to 1.5)[a]	10 more per 1000 (from 50 fewer to 94 more)[a]	Very low	Observational	Very serious limitations[g]	No serious inconsistency[b]	Serious indirectness[h]	Serious imprecision[d]	Yes[e, i]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Using oral contraceptives	Not using oral contraceptives	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Proliferative retinopathy											
Oral contraceptives (type not reported) versus no oral contraceptives											
1 (Klein et al., 1990)	91/351 (26%)	52/214 (24%)	RR 1.1 (0.8 to 1.4)[a]	17 more per 1000 (from 49 fewer to 107 more)[a]	Very low	Observational	Very serious limitations[g]	No serious inconsistency[b]	Serious indirectness[h]	No serious imprecision	Yes[e, i]
Worsening of nephropathy											
Worsening of renal/microalbuminuria status											
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives											
1 (Garg et al., 1994)	5/41 (12%)	3/40 (8%)	RR 1.6 (0.4 to 6.4)[a]	47 more per 1000 (from 44 fewer to 403 more)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	No serious indirectness[c]	Serious imprecision[d]	Yes[e, f]
Microalbuminuria at baseline											
Oestrogen and progestogen combined oral contraceptives versus unspecified nonhormonal contraceptives											
1 (Petersen et al., 1995)	2/22 (9%)	3/20 (15%)	RR 0.6 (0.1 to 3.5)[a]	59 fewer per 1000 (from 134 fewer to 369 more)[a]	Very low	Case-control	Serious limitations[j]	No serious inconsistency[b]	Serious indirectness[k]	Serious imprecision[d]	Yes[l, m]
Microalbuminuria at 12 months											
Oestrogen and progestogen combined oral contraceptives versus unspecified nonhormonal contraceptives											
1 (Petersen et al., 1995)	2/22 (9%)	2/20 (10%)	RR 0.9 (0.1 to 6.2)[a]	9 fewer per 1000 (from 87 fewer to 521 more)[a]	Very low	Case-control	Serious limitations[j]	No serious inconsistency[b]	Serious indirectness[k]	Serious imprecision[d]	Yes[l, m]
Albumin excretion rate 20 to 200 micrograms/min											
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives											
1 (Garg et al., 1994)	10/43 (23%)	4/43 (9%)	RR 2.5 (0.9 to 7.4)[a]	140 more per 1000 (from 14 fewer to 592 more)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Serious indirectness[n]	Serious imprecision[d]	Yes[e, f]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Using oral contraceptives	Not using oral contraceptives	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Albumin excretion rate more than 200 micrograms/min											
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives											
1 (Garg et al., 1994)	0/43 (0%)	2/43 (5%)	RR 0.2 (0.0 to 4.1)[a]	37 fewer per 1000 (from 46 fewer to 142 more)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Serious indirectness[n]	Serious imprecision[d]	Yes[e, f]

NA not applicable, NC Not calculable, RR risk ratio

a. Calculated by the NCC-WCH based on results reported in the paper

b. Single study analysis

c. Study met population and outcome criteria specified in the review protocol

d. Confidence interval for the RR crosses the line of no effect (RR=1) and RR=0.75 and/or RR=1.25

e. Conducted in the United States of America. Ethnicity of the participants was not reported.

f. The dosages of oestrogen and/or progestogen in the oral contraceptives were not reported. However, all women were using low-dose preparations containing 0.05 mg or less of ethinyl oestradiol (or mestranol) and a progestin

g. Attempts were not made within the design or analysis to balance the comparison groups for potential confounders, and participants were not blinded. It is unclear whether the groups were comparable at baseline, received the same care apart from taking oral contraceptives, or whether clinicians were blinded to treatment allocation or other confounding factors.

h. Data does not reflect a worsening of retinopathy, only the degree of retinopathy at the time of data collection

i. The dosages of oestrogen and/or progestogen in the oral contraceptives were not reported.

j. The main potential confounders were not identified or taken into account in the design and analysis of the study

k. Data does not reflect a worsening of nephropathy, only the number of women with microalbuminuria at the time of data collection

l. Conducted in Denmark. Ethnicity of the participants was not reported.

m. The women received 30 micrograms ethinyl oestradiol and 75 micrograms gestodene

n. Data do not reflect a worsening of nephropathy, only the number of women with an albumin excretion rate in the specified range at the time of data collection

Table 9: GRADE profile for change in HbA1c in women with type 1 diabetes using oral contraceptives compared with women with type 1 diabetes not using oral contraceptives (single time point data)

Number of studies	Number of women	Mean Value (%)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		Oral contraceptives group	No oral contraceptives group	Relative (95% confidence interval)	Absolute (95% confidence interval)							
HbA1c (%)												
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives												
1 (Garg et al., 1994)	43 in each group	12.0 (SD 2.0)	12.0 (SD 2.0)	NA	Mean difference 0.0 (0.9 lower to 0.9 higher)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Serious indirectness[c]	No serious imprecision	Yes[d,e]

NA not applicable, NC Not calculable, SD standard deviation
a. Calculated by the NCC-WCH based on results reported in the paper
b. Single study analysis
c. Data does not reflect a change in HbA1c, only the HbA1c value at the time of data collection
d. Conducted in the United States of America. Ethnicity of the participants was not reported.
e. The dosages of oestrogen and/or progestogen in the oral contraceptives were not reported. However, all women were using low-dose preparations containing 0.05mg or less of ethinyl oestradiol (or mestranol) and a progestin

Table 10: GRADE profile for change in HbA1c in women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives (multiple time point data)

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
From baseline to 2 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	9.5 (SD 0.7)	8.2 (SD 0.3)	NA	Mean difference 1.3 lower (0.8 lower to 1.8 lower)[a]	Moderate	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[e, f, g]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Skouby et al., 1986)	10	8.6 (SD 0.7)	9.4 (SD 0.6)	NA	Mean difference 0.8 higher (0.2 higher to 1.4 higher)[a]	Moderate	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[e, f, h]
1 (Skouby et al., 1986)	9	9.1 (SD 0.5)	9 (SD 0.5)	NA	Mean difference 0.1 lower (0.4 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[e, f, j]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	8.9 (SD 0.5)	7.4 (SD 0.9)	NA	Mean difference 1.5 lower (0.8 lower to 2.2 lower)[a]	Moderate	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[e, k]
From baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	10	7.5 (SD 0.3)	7.6 (SD 0.2)	NA	Mean difference 0.1 higher (0.1 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.5 (SD 0.3)	7.6 (SD 0.5)	NA	Mean difference 0.1 higher (0.2 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	12	7.5 (SD 0.3)	7.6 (SD 0.2)	NA	Mean difference 0.1 higher (0.1 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	10	7.7 (SD 0.4)	7.8 (SD 0.5)	NA	Mean difference 0.1 higher (0.3 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.6 (SD 0.5)	7.5 (SD 0.6)	NA	Mean difference 0.1 lower (0.3 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	9	7.3 (SD 0.4)	7.4 (SD 0.6)	NA	Mean difference 0.1 higher (0.4 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	11	7.8 (SD 0.3)	7.7 (SD 0.8)	NA	Mean difference 0.1 lower (0.6 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	11	7.5 (SD 0.7)	7.7 (SD 0.4)	NA	Mean difference 0.2 higher (0.3 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
No contraception												
Women with type 1 or type 2 diabetes												
1 (Grigoryan et al., 2006)	40	7.7 (SD 0.6)	7.5 (SD 0.3)	NA	Mean difference 0.2 lower (0.4 lower to 0.0 higher)[a]	Moderate	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[m, q]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
From baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	9.5 (SD 0.7)	9.1 (SD 0.7)	NA	Mean difference 0.4 lower (1.1 lower to 0.3 lower)[a]	Moderate	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[e, f, g]
1 (Skouby et al., 1986)	10	8.6 (SD 0.7)	8.8 (SD 0.4)	NA	Mean difference 0.2 higher (0.3 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[e, f, h]
1 (Skouby et al., 1986)	9	9.1 (SD 0.5)	9.1 (SD 0.5)	NA	Mean difference 0 (0.5 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[e, f, j]
1 (Grigoryan et al., 2006)	10	7.5 (SD 0.3)	7.4 (SD 0.2)	NA	Mean difference 0.1 lower (0.3 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.5 (SD 0.3)	7.4 (SD 0.4)	NA	Mean difference 0.1 lower (0.4 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	12	7.5 (SD 0.3)	7.4 (SD 0.4)	NA	Mean difference 0.1 lower (0.4 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	10	7.7 (SD 0.4)	7.6 (SD 0.7)	NA	Mean difference 0.1 lower (0.6 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.6 (SD 0.5)	7.7 (SD 0.3)	NA	Mean difference 0.1 higher (0.2 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	9	7.3 (SD 0.4)	7.5 (SD 0.5)	NA	Mean difference 0.2 higher (0.3 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	8.9 (SD 0.5)	9.5 (SD 0.9)	NA	Mean difference 0.6 higher (0.1 lower to 1.3 higher)[a]	Low	Randomised trial	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[e, k]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	11	7.8 (SD 0.3)	7.9 (SD 0.2)	NA	Mean difference 0.1 higher (0.1 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	11	7.5 (SD 0.7)	7.5 (SD 0.7)	NA	Mean difference 0.0 (0.6 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
No contraceptives												
Women with type 1 or type 2 diabetes												
1 (Grigoryan et al., 2006)	40	7.7 (SD 0.6)	7.7 (SD 0.5)	NA	Mean difference 0.0 (0.3 lower to 0.3 higher)[a]	Moderate	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[m, q]
From baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	10	7.5 (SD 0.3)	7.6 (SD 0.6)	NA	Mean difference 0.1 higher (SD 0.4 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.5 (SD 0.3)	7.6 (SD 0.3)	NA	Mean difference 0.1 higher (0.1 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	12	7.5 (SD 0.3)	7.6 (SD 0.6)	NA	Mean difference 0.1 higher (0.3 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	10	7.7 (SD 0.4)	7.5 (SD 0.4)	NA	Mean difference 0.2 lower (0.6 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.6 (SD 0.5)	7.4 (SD 0.5)	NA	Mean difference 0.2 lower (0.6 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Grigoryan et al., 2006)	9	7.3 (SD 0.4)	7.6 (SD 0.3)	NA	Mean difference 0.3 higher (0.1 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	11	7.8 (SD 0.3)	7.5 (SD 0.6)	NA	Mean difference 0.3 lower (0.7 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	11	7.5 (SD 0.7)	7.6 (SD 0.4)	NA	Mean difference 0.1 higher (0.4 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
No contraceptives												
Women with type 1 and type 2 diabetes												
1 (Grigoryan et al., 2006)	40	7.7 (SD 0.6)	7.6 (SD 0.7	NA	Mean difference 0.1 higher (0.4 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[m, q]
From baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 8.2 (IQR NR)	Median 8.4 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[r]	No serious inconsistency[c]	No serious indirectness[d]	NC[s]	Yes[e, t]
1 (Grigoryan et al., 2006)	10	7.5 (SD 0.3)	7.5 (SD 0.4)	NA	Mean difference 0.0 (0.3 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Grigoryan et al., 2006)	14	7.5 (SD 0.3)	7.5 (SD 0.6)	NA	Mean difference 0.0 (0.4 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	12	7.5 (SD 0.3)	7.5 (SD 0.4)	NA	Mean difference 0.0 (0.3 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	10	7.7 (SD 0.4)	7.6 (SD 0.3)	NA	Mean difference 0.1 lower (0.4 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, n]
1 (Grigoryan et al., 2006)	14	7.6 (SD 0.5)	7.5 (SD 0.7)	NA	Mean difference 0.1 lower (0.6 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, o]
1 (Grigoryan et al., 2006)	9	7.3 (SD 0.4)	7.4 (SD 0.7)	NA	Mean difference 0.1 higher (0.5 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[f, m, p]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 diabetes												
1 (Grigoryan et al., 2006)	11	7.8 (SD 0.3)	7.8 (SD 0.7)	NA	Mean difference 0.0 (0.5 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]
Women with type 2 diabetes												
1 (Grigoryan et al., 2006)	11	7.5 (SD 0.7)	7.4 (SD 0.3)	NA	Mean difference 0.1 lower (0.6 lower to 0.4 more)[a]	Low	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[i]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 8.5 (IQR NR)	Median 8.2 (IQR NR)	NA	Median difference 0.3 lower (NC)[a]	Very low	Case-control	Serious limitations[r]	No serious inconsistency[c]	No serious indirectness[d]	NC[s]	Yes[e]
No contraceptives												
Women with type 1 or type 2 diabetes												
1 (Grigoryan et al., 2006)	40	7.7 (SD 0.6)	7.5 (SD 0.2)	NA	Median difference 0.2 lower (0.4 lower to 0.0)[a]	Moderate	Randomised trial	Serious limitations[l]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision	Yes[m, q]

IQR interquartile range, NA not applicable, NC not calculable, NR not reported, SD standard deviation

a. Calculated by the NCC-WCH based on results reported in the paper

b. It is unclear whether an appropriate method of randomisation was used, whether there was adequate concealment of allocation to groups, whether comparison groups received the same care apart from the use of oral contraceptives, whether participants were blinded, and whether clinicians were blinded.

c. Single study analysis

d. Study met population and outcome criteria specified in the review protocol

e. Conducted in Denmark. Ethnicity of the participants was not reported.

f. Different groups of women are presented from the same study for the same outcome as they received different dosages of oestrogen and/or progestogen

g. These women received 35 micrograms ethinyl E2 (EE2) and 500 micrograms of norethindrone

h. These women received 4 mg of 17β-oestradiol (E2), 2 mg of oestradiol and 3 mg of norethindrone

i. Confidence interval for the MD crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the group at baseline and N months)

j. These women received a combination of 30 micrograms of EE2 + 50 micrograms of levonorgestrel for the first 6 days, 40 micrograms of EE2 + 75 micrograms of levonorgestrel for the next 5 days, and 30 micrograms of EE2 + 125 micrograms of levonorgestrel during the last 10 days for each treatment cycle

k. These women received 300 micrograms of norethindrone

l. It is unclear whether an appropriate method of randomisation was used, whether there was adequate concealment of allocation, whether the groups were comparable at baseline, whether the groups received the same care apart from the type of contraception used, whether participants and/or clinicians were kept blind to the type of contraceptive they were using, whether investigators were kept blind to important confounding and prognostic factors.

m. Conducted in Russia. Ethnicity of the participants was not reported.

n. These women received 30 micrograms ethinylestradiol and 150 micrograms desogestrel

o. These women received 20 micrograms ethinylestradiol and 150 micrograms desogestrel

p. These women received 30 micrograms ethinylestradiuol and 75 micorgrams gestodene

q. It was not reported how many of these women had type 1 and how many of these women had type 2 diabetes

r. The main potential confounders were not identified or taken into account in the design and analysis of the study

s. Confidence intervals for the median difference could not be calculated and so imprecision could not be calculated
t. 30 micrograms ethinyl oestradiol and 75 micrograms gestodene

Table 11: GRADE profile for incidence of dyslipidaemia in women with type 1 diabetes using oral contraceptives compared with women with type 1 diabetes not using oral contraceptives (single time point data)

Number of studies	Number of women	Mean Value (%)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		Oral contraceptives group	No oral contraceptives group	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Cholesterol (mmol/l)												
Oestrogen and progestogen combined oral contraceptives versus no oral contraceptives												
1 (Garg et al., 1994)	43 in each group	4.8 (SD 0.9)	4.6 (SD 0.7)	NA	Mean difference 0.1 higher (0.2 lower to 0.5 higher)[a]	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Very serious indirectness[c]	Serious imprecision[d]	Yes[e, f]

NA not applicable, SD standard deviation
a. Calculated by the NCC-WCH based on results reported in the paper
b. Single study analysis
c. Data do not reflect a change in incidence of dyslipidaemia, only the cholesterol value at the time of data collection. Cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia
d. Confidence interval for the MD crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the group at baseline and N months)
e. Conducted in the United States of America. Ethnicity of the participants was not reported.
The dosages of oestrogen and/or progestogen in the oral contraceptives were not reported. However, all women were using low-dose preparations containing 0.05 mg or less of ethinyl estradiol (or mestranol) and a progestin

Table 12: GRADE profile for incidence of dyslipidaemia in women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives (multiple time point data)

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Total cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 4.9 (IQR NR)	Median 4.6 (IQR NR)	NA	Median difference 0.3 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 5.4 (IQR NR)	Median 5.2 (IQR NR)	NA	Median difference 0.2 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	NC[e]	Yes[f]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 4.9 (IQR NR)	Median 4.6 (IQR NR)	NA	Median difference 0.3 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f, g]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.4 (SD 0.8)	5.1 (SD 0.9)	NA	Mean difference 0.4 lower (0.9 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[j]	Yes[k, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.8 (SD 0.1)	5.5 (SD 0.2)	NA	Mean difference 0.4 lower (0.9 lower to 0.2 lower)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	No serious imprecision	Yes[k]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 5.4 (IQR NR)	Median 5.1 (IQR NR)	NA	Median difference 0.3 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives –oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 4.9 (IQR NR)	Median 4.7 (IQR NR)	NA	Median difference 0.2 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f, g]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.4 (SD 0.8)	5.3 (SD 0.8)	NA	Mean difference 0.1 lower (0.6 lower to 0.4 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[j]	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.8 (SD 0.1)	5.4 (SD 0.6)	NA	Mean difference 0.4 lower (0.6 lower to 0.1 lower)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	No serious imprecision	Yes[k]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 5.4 (IQR NR)	Median 5.3 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f]
Baseline to 9 months												
Oral contraceptives –oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.4 (SD 0.8)	5.2 (SD 0.8)	NA	Mean difference 0.2 lower (0.7 lower to 0.3 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[j]	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	5.8 (SD 0.1)	5.7 (SD 0.6)	NA	Mean difference 0.1 lower (0.4 lower to 0.1 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[j]	Yes[k]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 12 months	Median 4.9 (IQR NR)	Median 4.5 (IQR NR)	NA	Median difference 0.4 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline , 19 at 12 months	Median 5.4 (IQR NR)	Median 5.1 (IQR NR)	NA	Median difference 0.3 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	NC[e]	Yes[f]
HDL cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 1.4 (IQR NR)	Median 1.4 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 1.6 (IQR NR)	Median 1.7 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f]
Baseline to 2 months												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	1.4 (SD 0.1)	1.6 (SD 0.1)	NA	Mean difference 0.2 higher (from 0.1 higher to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[f, n, o]
1 (Skouby et al., 1986)	10	1.5 (SD 0.1)	1.4 (SD 0.1)	NA	Mean difference 0.2 lower (from 0.3 lower to 0.1 lower)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[f, n, p]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Skouby et al., 1986)	9	1.5 (SD 0.1)	1.6 (SD 0.1)	NA	Mean difference 0.1 higher (0.0 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	1.2 (SD 0.1)	1.2 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[f, r]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 1.4 (IQR NR)	Median 1.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f, g]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.4 (SD 0.4)	NA	Mean difference 0.3 higher (0.1 higher to 0.5 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.1 (SD 0.3)	NA	Mean difference 0.1 higher (0.1 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[k]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 1.6 (IQR NR)	Median 1.8 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 1.4 (IQR NR)	Median 1.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f, g]
1 (Skouby et al., 1986)	10	1.4 (SD 0.1)	1.5 (SD 0.1)	NA	Mean difference 0.1 higher (0.0 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	1.5 (SD 0.1)	1.3 (SD 0.1)	NA	Mean difference 0.2 lower (0.3 lower to 0.1 lower)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[f, n, p]
1 (Skouby et al., 1986)	9	1.5 (SD 0.1)	1.5 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[f, n, q]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.4 (SD 0.4)	NA	Mean difference 0.3 higher (0.1 higher to 0.5 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[k, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	1.2 (SD 0.1)	1.3 (SD 0.1)	NA	Mean difference 0.1 higher (0.0 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[f, r]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.2 (SD 0.3)	NA	Mean difference 0.1 lower (0.1 lower to 0.3 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[k]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 1.6 (IQR NR)	Median 1.7 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f]
Baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.5 (SD 0.4)	NA	Mean difference 0.4 higher (0.2 higher to 0.6 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	No serious imprecision	Yes[k, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.1 (SD 0.2)	1.1 (SD 0.2)	NA	Mean difference 0.0 (0.2 lower to 0.1 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[l]	Serious imprecision[j]	Yes[k]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 1.4 (IQR NR)	Median 1.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 1.6 (IQR NR)	Median 1.9 (IQR NR)	NA	Median difference 0.3 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[l]	NC[e]	Yes[f]
HDL cholesterol/total cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectnesss	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NC[e]	Yes[f]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 2 months												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	0.3 (SD 0.1)	0.2 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, r]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NCe	Yes[f, g]
1 (Skouby et al., 1986)	10	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	0.3 (SD 0.1)	0.3 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[s]	Serious imprecision[j]	Yes[f, r]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectnesss	NC[e]	Yes[f]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 0.3 (IQR NR)	Median 0.3 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 0.3 (IQR NR)	Median 0.4 (IQR NR)	NA	Median difference 0.1 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[s]	NC[e]	Yes[f]
HDL$_2$ cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.6 (IQR NR)	Median 0.7 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.9 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 3 months												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.6 (IQR NR)	Median 0.6 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.9 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 0.6 (IQR NC)	Median 0.7 (IQR NC)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 0.9 (IQR NC)	Median 0.9 (IQR NC)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 0.6 (IQR NR)	Median 0.5 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 0.9 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[t]	NC[e]	Yes[f]
Baseline to 1 month												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.8 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.8 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.8 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.8 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline , 19 at 6 months	Median 0.8 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline , 19 at 6 months	Median 0.8 (IQR NR)	Median 0.8 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline , 17 at 9 months	Median 0.8 (IQR NR)	Median 1.0 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline , 19 at 9 months	Median 0.8 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[u]	NC[e]	Yes[f]
LDL cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 3.2 (IQR NR)	Median 2.6 (IQR NR)	NA	Median difference 0.6 lower (NC)a	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 3.3 (IQR NR)	Median 3.2 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f]
Baseline to 2 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	3.1 (SD 0.3)	3.4 (SD 0.4)	NA	Mean difference 0.2 higher (0.1 lower to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	3.2 (SD 0.4)	3.0 (SD 0.3)	NA	Mean difference 0.2 lower (0.5 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	3.2 (SD 0.2)	3.2 (SD 0.3)	NA	Mean difference 0.1 lower (0.3 lower to 0.2 higher)a	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	No serious imprecision	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	3.3 (SD 0.2)	3.5 (SD 0.4)	NA	Mean difference 0.2 higher (0.1 lower to 0.5 higher)a	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, r]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 3.2 (IQR NR)	Median 2.6 (IQR NR)	NA	Median difference 0.6 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f, g]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.6 (SD 0.7)	3.3 (SD 0.8)	NA	Mean difference 0.2 lower (0.7 lower to 0.3 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.5 (SD 0.5)	3.3 (SD 0.7)	NA	Mean difference 0.2 lower (0.6 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 3.3 (IQR NR)	Median 3.2 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 3.2 (IQR NR)	Median 2.6 (IQR NR)	NA	Median difference 0.6 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Skouby et al., 1986)	10	3.1 (SD 0.3)	3.5 (SD 0.4)	NA	Mean difference 0.4 higher (0.0 lower to 0.7 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	3.2 (SD 0.4)	3.1 (SD 0.4)	NA	Mean difference 0.1 lower (0.4 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	3.2 (SD 0.2)	3.4 (SD 0.3)	NA	Mean difference 0.2 higher (0.1 lower to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, n, q]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.6 (SD 0.7)	3.0 (SD 1.0)	NA	Mean difference 0.6 lower (1.1 lower to 0.0 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k, g]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	3.3 (SD 0.2)	3.2 (SD 0.2)	NA	Mean difference 0.1 lower (from 0.3 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[f, r]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.5 (SD 0.5)	3.3 (SD 0.8)	NA	Mean difference 0.3 lower (0.7 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 3.3 (IQR NR)	Median 3.1 (IQR NR)	NA	Median difference 0.2 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f]
Baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.6 (SD 0.7)	2.8 (SD 0.7)	NA	Mean difference 0.8 lower (1.3 lower to 0.4 lower)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	3.5 (SD 0.5)	3.4 (SD 0.4)	NA	Mean difference 0.1 lower (0.4 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[v]	Serious imprecision[j]	Yes[k]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 3.2 (IQR NR)	Median 2.5 (IQR NR)	NA	Median difference 0.7 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 3.3 (IQR NR)	Median 2.9 (IQR NR)	NA	Median difference 0.4 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[v]	NC[e]	Yes[f]
VLDL cholesterol (mmol/l)												
Baseline to 1 month												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.4 (IQR NR)	Median 0.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.4 (IQR NR)	Median 0.4 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f]
Baseline to 2 months												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	0.6 (SD 0.1)	0.7 (SD 0.2)	NA	Mean difference 0.1 higher (0.0 lower to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, n, o]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Skouby et al., 1986)	10	0.5 (SD 0.1)	0.4 (SD 0.1)	NA	Mean difference 0.1 lower (0.2 lower to 0.0 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	0.6 (SD 0.1)	0.6 (SD 0.2)	NA	Mean difference 0.1 higher (0.1 lower to 0.2 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	0.6 (SD 0.1)	0.8 (SD 0.1)	NA	Mean difference 0.2 higher (0.1 higher to 0.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	No serious imprecision	Yes[f, r]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.4 (IQR NR)	Median 0.6 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.4 (IQR NR)	Median 0.4 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline , 19 at 6 months	Median 0.4 (IQR NR)	Median 0.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f, g]
1 (Skouby et al., 1986)	10	0.6 (SD 0.1)	0.9 (SD 0.1)	NA	Mean difference 0.3 higher (0.2 higher to 0.4 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	No serious imprecision	Yes[f, n, o]
1 (Skouby et al., 1986)	10	0.5 (SD 0.1)	0.4 (SD 0.1)	NA	Mean difference 0.1 lower (0.2 lower to 0.0 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	0.6 (SD 0.1)	0.5 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	0.6 (SD 0.1)	0.5 (SD 0.1)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[w]	Serious imprecision[j]	Yes[f, r]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 0.4 (IQR NR)	Median 0.4 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 0.4 (IQR NR)	Median 0.5 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 0.4 (IQR NR)	Median 0.4 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[w]	NC[e]	Yes[f]
Triglycerides (mmol/l)												
Baseline to 1 month												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.9 (IQR NR)	Median 1.0 (IQR NR)	NA	Median difference 0.1 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 1.0 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	1.3 (SD 0.2)	1.6 (SD 0.3)	NA	Mean difference 0.3 higher (0.1 higher to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[f, n, o]
1 (Skouby et al., 1986)	10	1.1 (SD 0.2)	0.9 (SD 0.1)	NA	Mean difference 0.1 lower (0.3 lower to 0.0 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	1.3 (SD 0.3)	1.4 (SD 0.4)	NA	Mean difference 0.1 higher (0.2 lower to 0.5 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	1.3 (SD 0.1)	1.7 (SD 0.3)	NA	Mean difference 0.4 higher (0.2 higher to 0.6 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[f, r]
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.9 (IQR NR)	Median 1.2 (IQR NR)	NA	Median difference 0.3 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f, g]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.4 (SD 0.2)	1.6 (SD 0.1)	NA	Mean difference 0.1 higher (0.0 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.5 (SD 0.2)	1.6 (SD 0.3)	NA	Mean difference 0.1 higher (0.1 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[k]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 1.0 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 19 at 6 months	Median 0.9 (IQR NR)	Median 1.1 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f, g]
1 (Skouby et al., 1986)	10	1.3 (SD 0.2)	1.9 (SD 0.3)	NA	Mean difference 0.6 higher (0.4 higher to 0.9 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[f, n, o]

| Number of studies | Number of women | Mean value | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Skouby et al., 1986)	10	1.1 (SD 0.2)	1.0 (SD 0.1)	NA	Mean difference 0.1 lower (0.3 lower to 0.0)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al986)	9	1.3 (SD 0.3)	1.1 (SD 0.2)	NA	Mean difference 0.2 lower (0.3 lower to 0.1 higher)[a]	Low	andomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[f, n, q]
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.4 (SD 0.2)	1.6 (SD 0.1)	NA	Mean difference 0.2 higher (0.1 higher to 0.3 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistencyc	Serious indirectnessx	No serious imprecision	Yesk, [g]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	1.3 (SD 0.1)	1.2 (SD 0.1)	NA	Mean difference 0.1 lower (0.2 lower to 0.0 higher)+	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[f, r]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.5 (SD 0.2)	1.5 (SD 0.2)	NA	Mean difference 0.0 (0.1 lower to 0.1 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[k]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 6 months	Median 1.0 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f]
Baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.4 (SD 0.2)	1.7 (SD 0.1)	NA	Mean difference 0.2 higher (0.2 higher to 0.3 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[x]	No serious imprecision	Yes[k, g]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	1.5 (SD 0.2)	1.5 (SD 0.2)	NA	Mean difference 0.0 (0.1 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[h]	No serious inconsistency[c]	Serious indirectness[x]	Serious imprecision[j]	Yes[k]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22 at baseline, 17 at 9 months	Median 0.9 (IQR NR)	Median 1.1 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f, g]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20 at baseline, 19 at 9 months	Median 1.0 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.1 lower (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[x]	NC[e]	Yes[f]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Free fatty acids (mmol/l)												
Baseline to 2 months												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	854.0 (SD 99.0)	996.0 (SD 112.0)	NA	Mean difference 142.0 higher (42.7 higher to 241.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	No serious imprecision	Yes[f, n, o]
1 (Skouby et al., 1986)	10	986.0 (SD 151.0)	814.0 (SD 100.0)	NA	Mean difference 172.0 lower (292.3 lower to 51.7 lower)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	No serious imprecision	Yes[f, n, p]
1 (Skouby et al., 1986)	9	594.0 (SD 61.0)	452.0 (SD 151.0)	NA	Mean difference 142.0 lower (257.1 lower to 26.9 lower)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	No serious imprecision	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	969.0 (SD 138.0)	1030.0 (SD 251.0)	NA	Mean difference 61 higher (141.4 lower to 263.4 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	Serious imprecision[j]	Yes[f, r]

Number of studies	Number of women	Mean value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 6 months												
Oral contraceptives - oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	10	854.0 (SD 99.0)	756.0 (SD 118.0)	NA	Mean difference 98.0 lower (200.0 lower to 4.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	Serious imprecision[j]	Yes[f, n, o]
1 (Skouby et al., 1986)	10	986.0 (SD 151.0)	1033.0 (SD 145.0)	NA	Mean difference 47.0 higher (92.1 lower to 186.1 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	Serious imprecision[j]	Yes[f, n, p]
1 (Skouby et al., 1986)	9	594.0 (SD 61.0)	761.0 (SD 105.0)	NA	Mean ifference 167.0 higher (81.2 higher to 252.8 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	No serious imprecision	Yes[f, n, q]
Oral contraceptives – progestogen only												
Women with type 1 diabetes												
1 (Skouby et al., 1986)	9	969.0 (SD 138.0)	783.0 (SD 123.0)	NA	Mean difference 186.0 lower (316.6 lower to 55.3 higher)[a]	Low	Randomised trial	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[y]	Serious imprecision[j]	Yes[f, r]
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 0.9 (IQR NR)	Median 0.9 (IQR NR)	NA	Median difference 0.0 (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[y]	NC[e]	Yesf, [g]

		Mean value		Effect								

Number of studies	Number of women	At baseline	At X months	Relative (95% confidence interval)	Absolute (95% confidence interval)	Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 0.9 (IQR NR)	Median 1.1 (IQR NR)	NA	Median difference 0.2 higher (NC)[a]	Very low	Case-control	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[y]	NC[e]	Yes[f]

HDL high density lipoprotein, IQR interquartile range, LDL low density lipoprotein, NA not applicable, NC not calculable, SD standard deviation, VLDL very low density lipoprotein

a. Calculated by the NCC-WCH based on results reported in the paper

b. The main potential confounders were not identified or taken into account in the design and analysis of the study

c. Single study analysis

d. Total cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

e. Confidence intervals for the median difference could not be calculated and so imprecision could not be calculated

f. Conducted in Denmark. Ethnicity of the participants was not reported.

g. Women received 30 micrograms ethinyl estradiol and 75 micrograms gestodene

h. No attempt was made within the design or analysis to balance the comparison groups for potential confounders. It is unclear whether clinicians were blinded to treatment exposure or to confounding prognostic factors.

i. Total cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

j. Confidence interval for the MD crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the group at baseline and N months)

k. Conducted in Egypt. Ethnicity of the participants was not reported. 17/20 (85%) women in the combined oral contraceptives group had type 1 diabetes and 3/20 (15%) had type 2 diabetes. 15/20 (75%) of women in the intrauterine contraceptive device group had type 1 diabetes and 5/20 (25%) had type 2 diabetes.

l. HDL cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

m. It is unclear whether an appropriate method of randomisation was used, whether there was adequate concealment of allocation to groups, whether comparison groups received the same care apart from the use of oral contraceptives, whether participants were blinded, and whether clinicians were blinded.

n. Different groups of women are presented from the same study for the same outcome as they received different dosages of oestrogen and/or progestogen

o. Women received 35 micrograms ethinyl E2 (EE2) and 500 micrograms of norethindrone

p. Women received 4 mg of 17β-estradiol (E2), 2 mg of estradiol, and 3 mg of norethindrone

q. Women received 30 micrograms of EE2 + 50 micrograms of levonorgestrel for the first 6 days, 40 micrograms of EE2 + 75 micrograms of levonorgestrel for the next 5 days, and 30 micrograms of EE2 + 125 micrograms of levonorgestrel during the last 10 days for each treatment cycle

r. Women received 300 micrograms of norethindrone

s. HDL cholesterol/total cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

t. HDL2 cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

u. HDL3 cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

v. LDL cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

w. VLDL cholesterol is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

x. Triglycerides is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

y. Free fatty acids is reported as a proxy for incidence of dyslipidaemia as there were no data reported for dyslipidaemia

Table 13: GRADE profile for hypertension in women with type 1 diabetes using oral contraceptives compared with women with type 1 diabetes not using oral contraceptives (single time point data)

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Using oral contraceptives	Not using oral contraceptives	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Diastolic blood pressure											
Borderline elevated systolic blood pressure (defined as systolic blood pressure above the 90th percentile for age on at least two separate visits) (after use of oral contraceptives for ≥ 1 year)											
1 (Garg et al., 1994)	12/43 (28%)	16/43 (37%)	RR 0.8 (0.4 to 1.4)[a]	93 fewer per 1000 (from 223 fewer to 145 more)	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Very serious indirectness[c]	Serious imprecision[d]	Yes[e, f]
Borderline elevated diastolic blood pressure (defined as diastolic blood pressure above the 90th percentile for age on at least two separate visits) (after use of oral contraceptives for ≥ 1 year)											
1 (Garg et al., 1994)	23/43 (54%)	23/43 (54%)	RR 1.0 (0.7 to 1.5)[a]	0 fewer per 1000 (from 177 fewer to 257 more)	Very low	Case-control	No serious limitations	No serious inconsistency[b]	Very serious indirectness	Serious imprecision[d]	Yes[e, f]

RR risk ratio
a. Calculated by the NCC-WCH based on results reported in the paper
b. Single study analysis
c. Diastolic blood pressure is reported as a proxy for hypertension as there were no data reported for hypertension. Data do not reflect a change in hypertension, only the mean diastolic blood pressure value at the time of data collection
d. Confidence interval for the RR crosses the line of no effect (RR=1) and RR=0.75 and/or RR=1.25
e. Conducted in the USA. Ethnicity of the participants was not reported.
f. The dosages of oestrogen and/or progestogen in the oral contraceptives were not reported. However, all women were using low-dose preparations containing 0.05 mg or less of ethinyl estradiol (or mestranol) and a progestin

Table 14: GRADE profile for hypertension in women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives (multiple time point data)

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Systolic blood pressure (mmHg)												
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	113.0 (SD 4.4)	112.0 (SD 4.1)	NA	Mean difference 1.0 lower (3.7 lower to 1.7 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	112.0 (SD 4.1)	110.0 (SD 2.2)	NA	Mean difference 2.0 lower (4.1 lower to 0.1 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g]
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	113.0 (SD 4.4)	112.0 (SD 2.3)	NA	Mean difference 1.0 lower (3.3 lower to 1.3 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	112.0 (SD 4.1)	111.0 (SD 3.1)	NA	Mean difference 1.0 lower (3.3 lower to 1.3 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	113.0 (SD 4.4)	112.0 (SD 3.3)	NA	Mean difference 1.0 lower (3.5 lower to 1.5 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	112.0 (SD 4.1)	111.0 (SD 2.2)	NA	Mean difference 1.0 lower (3.1 lower to 1.1 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[d]	Serious imprecision[e]	Yes[f, g]
Diastolic blood pressure (mmHg)												
Baseline to 3 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	73.5 (SD 1.3)	72.5 (SD 5.5)	NA	Mean difference 1.0 lower (3.6 lower to 1.6 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	74.5 (SD 5.1)	71.0 (SD 4.5)	NA	Mean difference 3.5 lower (6.6 lower to 0.4 lower)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	No serious imprecision	Yes[f, g]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Baseline to 6 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	73.5 (SD 1.3)	72.0 (SD 5.2)	NA	Mean difference 1.5 lower (3.9 lower to 0.9 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	74.5 (SD 5.1)	69.0 (SD 2.2)	NA	Mean difference 5.5 lower (8.0 lower to 3.0 lower)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	No serious imprecision	Yes[f, g]
Baseline to 9 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	73.5 (SD 1.3)	71.5 (SD 5.9)	NA	Mean difference 2.0 lower (4.7 lower to 0.7 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	Serious imprecision[e]	Yes[f, g, h]
Non-oral contraceptives – intrauterine contraceptive device												
Women with type 1 or type 2 diabetes												
1 (Diab et al., 2000)	20	74.5 (SD 5.1)	67.5 (SD 4.4)	NA	Mean difference 7.0 lower (10.1 lower to 3.9 lower)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	Serious indirectness[i]	No serious imprecision	Yes[f, g]

Number of studies	Number of women	Mean Value		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
		At baseline	At N months	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Arterial blood pressure (mmHg)												
Baseline to 12 months												
Oral contraceptives – oestrogen and progestogen combined												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	22	Median 90.0 (IQR NR)	Median 92.0 (IQR NR)	NA	Median difference 2.0 higher (NC)[a]	Very low	Case-control	Serious limitations[j]	No serious inconsistency[c]	Serious indirectness[k]	NCI	Yes[m, h]
Non-oral contraceptives – unspecified non-hormonal contraceptives												
Women with type 1 diabetes												
1 (Petersen et al., 1995)	20	Median 97.0 (IQR NR)	Median 94.0 (IQR NR)	NA	Median difference 3.0 lower (NC)[a]	Very low	Case-control	Serious limitations[j]	No serious inconsistency[c]	Serious indirectness[k]	NCI	Yes[m]

IQR interquartile range, NA not applicable, NC not calculable, SD standard deviation
a. Calculated by the NCC-WCH based on results reported in the paper
b. No attempt was made within the design or analysis to balance the comparison groups for potential confounders. It is unclear whether clinicians were blinded to treatment exposure or to confounding prognostic factors.
c. Single study analysis
d. Systolic blood pressure is reported as a proxy for hypertension as there were no data reported for hypertension
e. Confidence interval for the MD crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the group at baseline and N months)
f. 17/20 (85%) women in the combined oral contraceptives group had type 1 diabetes and 3/20 (15%) had type 2 diabetes. 15/20 (75%) of women in the intrauterine contraceptive device group had type 1 diabetes and 5/20 (25%) had type 2 diabetes.
g. Conducted in Egypt. Ethnicity of the participants was not reported.
h. Women received 30 micrograms ethinyl estradiol and 75 micrograms gestodene
i. Diastolic blood pressure is reported as a proxy for hypertension as there were no data reported for hypertension
j. The main potential confounders were not identified or taken into account in the design and analysis of the study
k. Arterial blood pressure is reported as a proxy for hypertension as there were no data reported for hypertension
l. Confidence intervals for the median difference could not be calculated and so imprecision could not be calculated
m. Conducted in Denmark. Ethnicity of the participants was not reported.

3.3.5 Evidence statements

3.3.5.1 Women with diabetes using oral contraceptives compared with women without diabetes using oral contraceptives

3.3.5.1.1 *Pregnancy rate*

None of the studies reported the pregnancy rate in women either with or without diabetes taking oral contraceptives.

3.3.5.1.2 *Worsening of nephropathy*

One study (n=22) reported that for women taking oral contraceptives, urine protein excretion rate was higher in women with type 1 and type 2 diabetes compared with women without diabetes (mean difference [MD] 89, 95% confidence interval [CI] 3.0 to 175.0; low quality evidence). There were no differences between women with type 1 and type 2 diabetes and without diabetes who were taking oral contraceptives for other measures of renal function including filtration fraction (MD 0.0; 95%, CI 0.0 to 0.1; very low quality evidence), glomerular filtration rate (MD −2, 95%, CI −21.1 to 17.1; very low quality evidence], microalbuminuria (relative risk [RR] 14.3, 95% CI 0.8 to 271.1), renal plasma flow (MD −38, 95% CI −105.7 to 29.7; very low quality evidence), plasma renin activity (MD 0, 95% CI −0.4 to 0.4, very low quality evidence) and urine sodium excretion rate (MD 2, CI −75.6 to 71.6; very low quality evidence)

3.3.5.1.3 *Indicator of glycaemic control*

One study (n=22) reported that for women taking oral contraceptives, fasting plasma glucose (FPG) was higher in women with type 1 and type 2 diabetes compared with women without diabetes (MD 3.9, 95% CI 1.6 to 6.3). The evidence for this outcome was of low quality.

3.3.5.1.4 *Arterial thromboembolic disease*

One study (n=466) of women taking oral contraceptives found that the risk of myocardial infarction was higher in women with diabetes compared with women without diabetes (RR 3.4, 95% CI 2.0 to 5.0; low quality evidence).

3.3.5.1.5 *Hypertension*

One study (n=22) reported that there was no difference in mean arterial pressure between women with type 1 and type 2 diabetes or without diabetes (MD −4, 95% CI −9.4 to 1.4; very low quality evidence).

3.3.5.1.6 *Other outcomes*

The studies did not report data on incidence of retinopathy, dyslipidaemia, venous thromboembolic disease or mortality.

3.3.5.1.7 *Subgroup analyses*

The studies did not report the data in such a way that subgroup analyses by type of diabetes, presence of pre-existing vascular diseases, dose of oestrogen and/or progestogen, age, body mass index (BMI) or smoking status could be conducted.

3.3.5.2 Women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives

Confidence intervals could not be calculated for all data, and so it was not possible to assess the statistical significance of all results.

3.3.5.2.1 *Pregnancy rate*

None of the studies reported the pregnancy rate in women with diabetes either taking oral contraceptives or not taking oral contraceptives.

3.3.5.2.2 *Worsening of retinopathy*

One study (n=79) found that there was no difference in the risk of worsening retinopathy for women with type 1 diabetes using combined oral contraceptives.

3.3.5.3 Women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives

Confidence intervals could not be calculated for all data and so it was not possible to assess the statistical significance of all results.

3.3.5.3.1 *Pregnancy rate*

None of the studies reported the pregnancy rate in women with diabetes either taking oral contraceptives or not taking oral contraceptives.

3.3.5.3.2 *Worsening of retinopathy*

One study (n=79) found that there was no difference in the risk of worsening retinopathy for women with type 1 diabetes using combined oral contraceptives compared with women using no oral contraceptives (worsening by 1 eye grade: RR 1.1, 95% CI 0.5 to 2.6; worsening by more than 1 grade: RR 1.3, 95% CI 0.5 to 3.4). One study (n=565) also reported no differences in the risk of mild to minimal diabetic retinopathy (RR 1.0, 95% CI 0.8 to 1.3), moderate to severe retinopathy (RR 1.1, 95% CI 0.8 to 1.5) or proliferative retinopathy (RR 1.1, 95% CI 0.8 to 1.4) when women with type 1 diabetes using combined oral contraceptives were compared with women with type 1 diabetes not using oral contraceptives. The quality of the evidence for these outcomes was very low.

3.3.5.3.3 *Worsening of nephropathy*

Two studies reported that there was no difference in the risk of worsening nephropathy when women with type 1 diabetes using combined oral contraceptives were compared with women using no oral contraceptives (worsening of renal/microalbuminuria status (RR 1.6, 95% CI 0.4 to 6.4, 1 study n=81), microalbuminuria at 12 months (RR 0.9, 95% CI 0.1 to 6.2, 1 study n=42), albumin excretion rate 20 to 200 micrograms/min (RR 2.5, 95% CI 0.9 to 7.4, 1 study n=86) and albumin excretion rate more than 200 micrograms/min (RR 0.2, 95% CI 0.0 to 4.1, 1 study n=86). The quality of the evidence for these outcomes was very low.

3.3.5.3.4 *HbA1c*

One study (n=86) found no difference in the mean HbA1c percentage value in women with type 1 diabetes using oral contraceptives compared with women with type 1 diabetes not using oral contraceptives (MD 0.0, 95% CI −0.9 to 0.9). The quality of the evidence was very low.

At 2 months from baseline

Evidence from one RCT (n=27) found no difference from baseline in mean HbA1c percentage value in women with type 1 diabetes who were taking a triphasic combined oral contraceptive (MD −0.1, 95% CI −0.4 to 0.6, n=9; low quality evidence) or a progestogen only oral contraceptive (MD −1.5, 95% CI −0.8 to 2.2, n=9; moderate quality evidence). Women with type 1 diabetes taking monophasic low dose oral contraceptives had a lower mean HbA1c percentage value at 2 months from baseline (MD −1.3, 95% CI −0.8 to −1.8, n=10; moderate quality evidence) and women with type 1 diabetes taking monophasic high

dose oral contraceptives had a higher HbA1c percentage value at 2 months (MD 0.8, 95% CI 0.2 to 1.4, n=10; moderate quality evidence).

At 3 months from baseline

One RCT (n=153) showed no difference from baseline in mean HbA1c percentage value in women with type 1 or type 2 diabetes taking combined standard dose (type 1: MD 0.1, 95% CI −0.1 to 0.3, n=10, low quality evidence; type 2: MD 0.1, 95% CI −0.3 to 0.5, n=10, low quality evidence), combined low oestrogen (type 1: MD 0.1, 95% CI −0.2 to 0.4, n=14, low quality evidence; type 2: MD −0.1, 95% CI −0.3 to 0.5, n=14, low quality evidence) or combined low progestogen oral contraceptives (type 1: MD 0.1, 95% CI −0.1 to 0.3, n=12, low quality evidence; type 2: MD 0.1, 95% CI −0.4 to 0.6, n=9, low quality evidence) or women who were using an intrauterine device (IUD) (type 1: MD −0.1, 95% CI −0.6 to 0.4, n=11, low quality evidence; type 2 MD 0.2, 95% CI −0.3 to 0.7 n=11, low quality evidence) or no contraception (type 1 or 2: MD −0.2, 95% CI −0.4 to 0.4, n=40, moderate quality evidence).

At 6 months from baseline

One RCT (n=27) found no difference from baseline in mean HbA1c percentage value in women with type 1 diabetes who were taking a monophasic high dose (MD 0.2, 95% CI −0.3 to 0.7, n=10; low quality evidence), a triphasic combined (MD 0.0, 95% CI −0.5 to 0.5, n=9; low quality evidence) or a progestogen only oral contraceptive (MD 0.6, 95% CI −0.1 to 1.3, n=9; low quality evidence). Women with type 1 diabetes taking monophasic low dose oral contraceptives had a lower mean HbA1c percentage value at 6 months from baseline (MD −0.4, 95% CI −1.1 to −0.3, n=10; moderate quality evidence).

A second RCT (n=153) showed no difference from baseline in mean HbA1c percentage value in women with type 1 or type 2 diabetes taking combined standard dose (type 1: MD −0.1, 95% CI −0.3 to 0.1, n=10, low quality evidence; type 2: MD −0.1, 95% CI −0.6 to 0.4, n=10, low quality evidence), combined low oestrogen (type 1: MD −0.1, 95% CI −0.4 to 0.2, n=14, low quality evidence; type 2: MD 0.1, 95% CI −0.2 to 0.4, n=14, low quality evidence) or combined low progestogen oral contraceptives (type 1: MD −0.1, 95% CI −0.4 to 0.2, n=12, low quality evidence; type 2: MD=0.2, 95% CI −0.3 to 0.7, n=9, low quality evidence) or women who were using an IUD (type 1: MD 0.1, 95% CI −0.1 to 0.3, n=11, low quality evidence; type 2: MD 0.0, 95% CI −0.6 to 0.6, n=11, low quality evidence) or no contraception (type 1 or 2: MD −0.0, 95% CI −0.3 to 0.3, n=40, moderate quality evidence).

At 9 months from baseline

One RCT (n=153) found no difference from baseline in mean HbA1c percentage value in women with type 1 or type 2 diabetes taking combined standard dose (type 1: MD 0.1, 95% CI −0.4 to 0.6, n=10, low quality evidence; type 2: MD −0.2, 95% CI −0.6 to 0.2, n=10, low quality evidence), combined low oestrogen (type 1: MD 0.1, 95% CI −0.1 to 0.3, n=14; low quality evidence, type 2: MD −0.2, 95% CI −0.6 to 0.2, n=14; low quality evidence) or combined low progestogen oral contraceptives (type 1: MD 0.1, 95% CI −0.3 to 0.5, n=12, low quality evidence; type 2: MD 0.3, 95% CI −0.1 to 0.7, n=9, low quality evidence) or women who were using an IUD (type 1: MD −0.3, 95% CI −0.7 to 0.1, n=11, low quality evidence; type 2: MD 0.1, 95% CI −0.4 to 0.6, n=11, low quality evidence) or no contraception (type 1 or 2: MD −0.1, 95% CI −0.4 to 0.6, n=40, low quality evidence).

At 12 months from baseline

One RCT (n=153) found no difference from baseline in mean HbA1c percentage value in women with type 1 or type 2 diabetes taking combined standard dose (type 1: MD 0.0, 95% CI −0.3 to 0.3, n=10, low quality evidence; type 2: MD −0.1, 95% CI −0.4 to 0.2, n=10, low quality evidence), combined low oestrogen (type 1: MD 0.0, 95% CI −0.4 to 0.4, n=14, low

quality evidence; type 2: MD −0.1, 95% CI −0.6 to 0.4, n=14, low quality evidence) or combined low progestogen oral contraceptives (type 1: MD 0.0, 95% CI −0.3 to 0.3, n=12, low quality evidence; type 2: MD 0.1, 95% CI −0.5 to 0.7, n=9, low quality evidence) or women who were using an IUD (type 1: MD −0.0, 95% CI −0.5 to 0.5, n=11, low quality evidence; type 2: MD −0.1, 95% CI −0.6 to 0.4, n=11, low quality evidence) or no contraception (type 1 or 2: MD −0.2, 95% CI −0.4 to 0.0, n=40, moderate quality evidence).

One case control study (n=42) did not provide clear evidence of a difference in mean HbA1c percentage value from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.2, 95% CI not calculable [NC]; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.3, 95% CI NC; very low quality evidence).

3.3.5.3.5 *Dyslipidaemia, total cholesterol (mmol/litre)*

One case control study (n=86) found no difference in mean total cholesterol when women with type 1 diabetes using oral contraceptives were compared with women with diabetes not using oral contraceptives (MD 0.1, 95% CI −0.2 to 0.5; very low quality evidence)

At 1 month from baseline

One case control study (n=42) did not provide clear evidence of a difference in mean total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.3, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.2, 95% CI NC; very low quality evidence).

At 3 months from baseline

One case control study (n=42) did not provide clear evidence of a difference in mean total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.3, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.3, 95% CI NC; very low quality evidence).

One observational study (n=40) found no difference from baseline in mean total cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.4, 95% CI −0.9 to 0.2; very low quality evidence), but did report a reduction in mean total cholesterol at 3 months in women using an IUD (MD −0.4, 95% CI −0.9 to −0.2; very low quality evidence)

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.4, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.1, 95% CI NC; very low quality evidence).

One observational study (n=40) found no difference from baseline in mean total cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.4, 95% CI −0.6 to 0.1; very low quality evidence), but did report a reduction in mean total cholesterol at 6 months in women using an IUD (MD −0.4, 95% CI −0.6 to −0.1; very low quality evidence)

At 9 months from baseline

One observational study (n=40) found no difference from baseline in mean total cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.2, 95% CI −0.7 to 0.3; very low quality evidence) or in women using an IUD (MD −0.1, 95% CI −0.4 to 0.1; very low quality evidence)

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.4, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.3, 95% CI NC; very low quality evidence).

3.3.5.3.6   *HDL cholesterol (mmol/litre)*

At 1 month from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean HDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.1, 95% CI NC; very low quality evidence).

At 2 months from baseline

One RCT (n=27) found mean HDL cholesterol was raised 2 months from baseline in women with type 1 diabetes who were taking a monophasic low dose oral contraceptive (MD 0.2, 95% CI 0.1 to 0.3, n=10; low quality evidence), but there was no difference from baseline in mean HDL cholesterol in those taking monophasic high dose (MD −0.2, 95% CI −0.3 to −0.1, n=10; low quality evidence), triphasic combined (MD 0.1, 95% CI 0.0 to 0.2, n=9; low quality evidence) or progestogen only oral contraceptives (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence).

At 3 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean HDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.1, 95% CI NC; very low quality evidence).

One observational study (n=40) reported a rise at 3 months from baseline in mean HDL cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD 0.3, 95% CI 0.1 to 0.5; very low quality evidence) but found no difference in mean HDL cholesterol in women using an IUD (MD 0.1, 95% CI −0.1 to 0.2; very low quality evidence)

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean HDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.1, 95% CI NC; very low quality evidence).

One RCT (n=27) found mean HDL cholesterol was reduced 6 months from baseline in women with type 1 diabetes who were taking a monophasic high dose oral contraceptive (MD −0.2, 95% CI −0.3 to −0.1, n=10; low quality evidence), but there was no difference from baseline in mean HDL cholesterol in those taking monophasic low dose (MD −0.1, 95% CI −0.0 to −0.2, n=10; low quality evidence), triphasic combined (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD 0.1, 95% CI 0.0 to 0.2, n=9; low quality evidence).

One observational study (n=40) reported an increase 6 months from baseline in mean HDL cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD 0.3, 95% CI 0.1 to 0.5; very low quality evidence), but found no difference in mean total cholesterol in women using an IUD (MD −0.1, 95% CI −0.1 to 0.3; very low quality evidence)

At 9 months from baseline

One observational study (n=40) reported an increase 9 months from baseline in mean HDL cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD 0.4, 95% CI 0.2 to 0.6; very low quality evidence), but found no difference in mean total cholesterol in women using an IUD (MD 0.0, 95% CI −0.2 to 0.1; very low quality evidence)

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.3, 95% CI NC; very low quality evidence).

3.3.5.3.7 *HDL cholesterol/total cholesterol (mmol/litre)*

At 1 month from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL cholesterol/total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

At 2 months from baseline

One RCT (n=27) found no difference from baseline in mean HDL cholesterol/total cholesterol in women with type 1 diabetes who were taking a monophasic low dose (MD 0.0, 95% CI −0.1 to 0.1, n=10; low quality evidence), monophasic high dose (MD 0.0, 95% CI −0.1 to 0.1, n=10; low quality evidence), triphasic combined (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence).

At 3 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL cholesterol/total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL cholesterol/total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

One RCT (n=27) found no difference from baseline in mean HDL cholesterol/total cholesterol in women with type 1 diabetes who were taking a monophasic low dose (MD 0.0, 95% CI −0.1 to 0.1, n=10; low quality evidence), monophasic high dose (MD 0.0, 95% CI −0.1 to 0.1, n=10; low quality evidence), triphasic combined (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence).

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL cholesterol/total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.1, 95% CI NC; very low quality evidence).

3.3.5.3.8 *HDL2 cholesterol (mmol/litre)*

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL2 cholesterol at 1, 3, 6 or 12 months from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (respective median differences: 0.0, 95% CI NC; 0.0, 95% CI NC; −0.1, 95% CI NC; 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (respective median differences: 0.0, 95% CI NC; −0.1, 95% CI NC; 0.0, 95% CI NC; 0.0, 95% CI NC; very low quality evidence).

3.3.5.3.9 *HDL3 cholesterol (mmol/litre)*

One case-control study (n=42) did not provide clear evidence of a difference in mean HDL3 cholesterol at 1, 3, 6 or 12 months from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (respective median differences: 0.0, 95% CI NC; 0.1, 95% CI NC; 0.1, 95% CI NC; 0.2, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (respective median differences: 0.0, 95% CI NC; 0.0, 95% CI NC; 0.0, 95% CI NC; 0.1, 95% CI NC; very low quality evidence).

3.3.5.3.10 *LDL cholesterol (mmol/litre)*

At 1 month from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean LDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.6, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.1, 95% CI NC; very low quality evidence).

At 2 months from baseline

One RCT (n=27) found no difference from baseline in mean LDL cholesterol in women with type 1 diabetes who were taking a monophasic low dose (MD 0.2, 95% CI −0.1 to 0.6, n=10; low quality evidence), monophasic high dose (MD −0.2, 95% CI −0.5 to 0.2, n=10; low quality evidence), triphasic combined (MD −0.1, 95% CI −0.3 to 0.2, n=9; low quality evidence) or

progestogen only oral contraceptives (MD 0.2, 95% CI −0.1 to 0.5, n=9; low quality evidence).

At 3 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean LDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.6, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.1, 95% CI NC; very low quality evidence).

One observational study (n=40) found no difference from baseline in mean LDL cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.2, 95% CI −0.7 to 0.3; very low quality evidence), but did report a reduction in mean total cholesterol at 6 months in women using an IUD (MD −0.2, 95% CI −0.6 to −0.2; very low quality evidence)

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean LDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.6, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.2, 95% CI NC; very low quality evidence).

One RCT (n=27) found no difference from baseline in mean LDL cholesterol in women with type 1 diabetes who were taking a monophasic low dose (MD 0.4, 95% CI 0.0 to 0.7, n=10; low quality evidence), monophasic high dose (MD −0.1, 95% CI −0.4 to 0.3, n=10; low quality evidence), triphasic combined (MD 0.2, 95% CI −0.1 to 0.4, n=9; low quality evidence) or progestogen only oral contraceptives (MD −0.1, 95% CI −0.3 to 0.1, n=9; low quality evidence).

One observational study (n=40) found no difference from baseline in mean LDL cholesterol in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.6, 95% CI −1.1 to 0.0; very low quality evidence) or in women using an IUD (MD −0.3, 95% CI −0.7 to −0.2; very low quality evidence)

At 9 months from baseline

One observational study (n=40) reported a reduction in mean LDL cholesterol at 9 months from baseline in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD −0.8, 95% CI −1.3 to −0.4; very low quality evidence), but no difference from baseline in women using an IUD (MD −0.1, 95% CI −0.4 to 0.2; very low quality evidence)

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean LDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference −0.7, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.4, 95% CI NC; very low quality evidence).

3.3.5.3.11 *VLDL cholesterol (mmol/litre)*

At 1 month from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean VLDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen

oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

At 2 months from baseline

One RCT (n=27) found no difference from baseline in mean VLDL cholesterol in women with type 1 diabetes who were taking monophasic low dose (MD 0.1, 95% CI 0.0 to 0.3, n=10; low quality evidence), monophasic high dose (MD −0.1, 95% CI −0.2 to 0.0, n=10; low quality evidence) or triphasic combined oral contraceptives (MD 0.1, 95% CI −0.1 to 0.2, n=9; low quality evidence) but reported a rise at 2 months from baseline in mean VLDL cholesterol in women using progestogen only oral contraceptives (MD 0.2, 95% CI 0.1 to 0.3, n=9; low quality evidence).

At 3 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean VLDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.2, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in VLDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

One RCT (n=27) reported an increase in mean VLDL cholesterol at 6 months from baseline in women with type 1 diabetes who were taking monophasic low dose oral contraceptives (MD 0.3, 95% CI 0.2 to 0.4, n=10; low quality evidence), but no difference in mean VLDL cholesterol in women in monophasic high dose (MD −0.1, 95% CI −0.2 to 0.0, n=10; low quality evidence), triphasic combined (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD 0.0, 95% CI −0.1 to 0.1, n=9; low quality evidence).

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean VLDL cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

3.3.5.3.12 *Triglycerides (mmol/litre)*

At 1 month from baseline

One case control study (n=42) did not provide clear evidence of a difference mean triglycerides from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.1, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.0, 95% CI NC; very low quality evidence).

At 2 months from baseline

One RCT (n=27) reported an increase in mean triglycerides at 2 months from baseline in women with type 1 diabetes who were using monophasic low dose (MD 0.3, 95% CI 0.1 to 0.5, n=10; low quality evidence) and progestogen only oral contraceptives (MD 0.4, 95% CI 0.2 to 0.6, n=9; low quality evidence), but no difference in mean triglycerides in women using monophasic high dose (MD −0.1, 95% CI −0.3 to 0.0, n=10; low quality evidence) or triphasic combined oral contraceptives (MD 0.1, 95% CI −0.2 to 0.5, n=9; low quality evidence).

At 3 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean triglycerides from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.3, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.1, 95% CI NC; very low quality evidence).

One observational study (n=40) found no difference from baseline in mean triglycerides in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD 0.1, 95% CI 0.0 to 0.2; very low quality evidence) or using an IUD (MD 0.1, 95% CI −0.1 to 0.2; very low quality evidence)

At 6 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean triglycerides from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.2, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.1, 95% CI NC; very low quality evidence)

One RCT (n=27) reported an increase in mean triglycerides at 6 months from baseline in women with type 1 diabetes who were using monophasic low dose oral contraceptives (MD 0.6, 95% CI 0.4 to 0.9, n=10; low quality evidence), but no difference in mean triglycerides in women using monophasic high dose (MD −0.1, 95% CI −0.3 to 0.0, n=10; low quality evidence), triphasic combined (MD −0.2, 95% CI −0.3 to 0.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD −0.1, 95% CI −0.2 to 0.0, n=9; low quality evidence)

One observational study (n=40) reported an increase in mean triglycerides at 6 months from baseline in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive (MD 0.2, 95% CI 0.1 to 0.3; very low quality evidence), but no difference in mean triglycerides in women using an IUD (MD −0.0, 95% CI −0.1 to 0.1; very low quality evidence)

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference in mean triglycerides from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.2, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −0.1, 95% CI NC; very low quality evidence).

3.3.5.3.13   *Free fatty acids (mmol/litre)*

At 2 months from baseline

One RCT (n=27) reported that mean free fatty acids were raised at 2 months from baseline in women with type 1 diabetes who were taking a monophasic low dose oral contraceptive

(MD 142.0, 95% CI 42.7 to 241.3, n=10; low quality evidence), were reduced in those taking monophasic high dose (MD −172.0, 95% CI −292.3 to −51.7, n=10; low quality evidence) and triphasic combined oral contraceptives (MD −142.0, 95% CI −257.1 to −26.9, n=9; low quality evidence) and that there was no difference in mean free fatty acids in those using progestogen only oral contraceptives (MD 61, 95% CI −141.1 to 263.4, n=9; low quality evidence).

At 6 months from baseline

One RCT (n=27) reported that mean free fatty acids were raised at 6 months from baseline in women with type 1 diabetes who were taking a triphasic combined oral contraceptive (MD 167.0, 95% CI 81.2 to 252.8, n=10; low quality evidence), but that there was no difference from baseline in women using monophasic low dose (MD −98.0, 95% CI −200.0 to 4.3, n=10; low quality evidence), monophasic high dose (MD 47.0, 95% CI −92.1 to −186.1, n=9; low quality evidence) or progestogen only oral contraceptives (MD −186.0, 95% CI −316.6 to 55.3, n=9; low quality evidence).

At 12 months from baseline

One case-control study (n=42) did not provide clear evidence of a difference mean total cholesterol from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 0.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference 0.2, 95% CI NC; very low quality evidence)

3.3.5.3.14 *Hypertension*

One case-control study (n=86) reported no difference in the risk of borderline elevated systolic (RR 0.8, 95% CI 0.4 to 1.4; very low quality evidence) or diastolic (RR 1.0, 95% CI 0.7 to 1.5; very low quality evidence) blood pressure when women with type 1 diabetes using oral contraceptives for over 1 year were compared with women with diabetes not using oral contraceptives.

Systolic and diastolic blood pressure (mmHg)

One observational study (n=40) found no difference at 3, 6 or 9 months from baseline in mean systolic blood pressure (respectively MD −1.0, 95% CI −3.7 to 1.7; MD −1.0, 95% CI −3.3 to 1.3; MD −1.0, 95% CI −3.5 to 1.5; very low quality evidence) or mean diastolic blood pressure (respectively MD −1.0, 95% CI −3.6 to 1.6; MD −1.5, 95% CI −3.9 to 0.9; MD −2.0, 95% CI −4.7 to 0.7; very low quality evidence) in women with type 1 or type 2 diabetes using a combined low progestogen oral contraceptive or in mean systolic blood pressure (respectively MD −2.0, 95% CI −4.1 to 0.1; MD −1.0, 95% CI −3.3 to 1.3; MD −1.0, 95% CI −3.1 to 1.1; very low quality evidence) in women using an IUD, although mean diastolic blood pressure was reduced from baseline at all timepoints for these women (respectively MD −3.5, 95% CI −6.6 to 0.4; MD −5.5, 95% CI −8.0 to −3.0; MD −7.0, 95% CI −10.1 to 3.9; very low quality evidence).

3.3.5.3.15 *Arterial blood pressure (mmHg)*

One case-control study (n=42) did not provide clear evidence of a difference in mean arterial blood pressure at 12 months from baseline in women with type 1 diabetes using a combined low progestogen oral contraceptive (median difference 2.0, 95% CI NC; very low quality evidence) or in women who were not using oral contraceptives (median difference −3.0, 95% CI NC; very low quality evidence).

3.3.5.3.16 *Other outcomes*

The studies did not report data on incidence of venous thromboembolic disease, arterial thromboembolic disease or mortality.

3.3.5.3.17 *Subgroup analyses*

It was not possible to examine the effect of the type of diabetes on most outcomes. It was only possible to examine the effect of the type of diabetes for the HbA1c outcome, and the type of diabetes in the women studied did not affect the significance of the results.

There were only limited data relating to the effect of the dosage of oestrogen and/or progestogen on most outcomes. In addition, studies that used a dose of more than 50 micrograms of ethinyloestradiol were excluded, further limiting the data available for a subgroup analysis by dose. There was no evidence that a particular dose of oestrogen and/or progestogen affected the outcomes more than another.

The studies did not report the data in such a way that subgroup analyses by presence of pre-existing vascular diseases, age, body mass index (BMI) or smoking status could be conducted.

3.3.6 Health economics profile

No published health economic evidence was identified addressing the cost effectiveness of oral oestrogen-containing or oral progestogen-containing contraceptives in women with diabetes compared with women without diabetes.

These questions were not prioritised for health economic analysis as a key focus of this review was to determine whether oral contraceptives involved additional risks in diabetic women to assess whether their use might be contraindicated in this population.

3.3.7 Evidence to recommendations

3.3.7.1 Relative value placed on the outcomes considered

3.3.7.1.1 *Women with diabetes using oral contraceptives compared with women without diabetes using oral contraceptives*

The guideline development group prioritised the following outcomes reported in the studies comparing women with diabetes using oral contraceptives and women without diabetes using oral contraceptives:

- worsening of retinopathy and/or nephropathy
- change in HbA1c
- arterial thromboembolic disease
- hypertension.

Outcomes that were not reported in the studies were:

- pregnancy rate
- incidence of dyslipidaemia
- venous thromboembolic disease
- mortality.

In terms of effectiveness, pregnancy rate was the most important outcome. However, although this was not reported in any of the studies, the guideline development group felt this was not surprising given the small numbers in each of those studies.

3.3.7.1.2 *Women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives*

The guideline development group placed an equal value on all of the outcomes, as they each contribute to morbidity and mortality.

3.3.7.2 Consideration of clinical benefits and harms

3.3.7.2.1 *Women with diabetes using oral contraceptives compared with women without diabetes using oral contraceptives*

Regrettably, none of the studies reported pregnancy rate, and so it was not possible to compare the effectiveness of hormonal oral contraceptives in women with diabetes and women without diabetes from the reported evidence.

The data show an increase in the prevalence of microalbuminuria and myocardial infarction at baseline in the 2 studies comparing the use of oral hormonal contraceptives in women with and without diabetes. However, the guideline development group felt that the reported differences were most likely to be a result of the diabetes, the small numbers of women included in the studies and the inclusion criteria for the selected studies, rather than the result of the use of oral hormonal contraceptives.

There were no data on the impact of the contraceptive pill on other major cardiovascular complications of diabetes.

Also it was not possible to explore whether oral hormonal contraceptives have different effects on women with different types of diabetes.

3.3.7.2.2 *Women with diabetes using oral contraceptives compared to women with diabetes not using oral contraceptives*

There was no evidence of deterioration in glycaemia as assessed by HbA1c in women using oral contraceptives based on 4 studies including a total of 206 women. There was also no evidence of an impact of oral contraceptive use on serum lipids, although there were fewer data.

The guideline development group was uncertain of the significance of the observed reduction in diastolic blood pressure in women using an intrauterine contraceptive device. This uncertainty was reinforced by the lack of any effect on systolic blood pressure.

None of the studies identified during the search reported pregnancy rate.

3.3.8 Consideration of health benefits and resource uses

This review did not identify any data on the effectiveness of either type of oral contraceptive in diabetic women although the guideline development group did not believe there was any reason to suppose that they would be any less effective than in a non-diabetic population. The group considered that the evidence did not suggest that either type of oral contraceptive was contraindicated in diabetic women. Therefore, the health benefits and resource use of either type of oral contraceptive are similar to a non-diabetic population and the group agreed that their use in this population could be recommended. .

3.3.9 Quality of evidence

3.3.9.1 Women with diabetes using oral contraceptives compared with women without diabetes using oral contraceptives

The quality of the evidence was rated as very low or low for all reported outcomes considered in the review. The contributing data were obtained from 1 prospective observational study and 1 case-control study.

The sample sizes in these studies were very small, making it very difficult to draw conclusions that may be relevant to the wider diabetes population. The studies were only short-term in length and so it is not clear what the potential long-term effects would be.

The case-control study recruited women with a myocardial infarction and matched controls, and so the rate of myocardial infarction may be higher in the study than in the general population. The study also did not report the baseline characteristics of the women who had been taking oral contraceptives separately from those who had not, and so it was not possible to judge whether the group of women with diabetes and the group of women without diabetes were comparable in terms of age and history of hypertension.

Finally, the studies reviewed did not always compare the outcomes for the combined versus the progesterone-only preparations, nor did they describe which type of oral contraceptive was being used by the women.

3.3.9.2 Women with diabetes using oral contraceptives compared with women with diabetes not using oral contraceptives

The quality of the evidence was rated as very low to moderate for the reported outcomes considered in the review. There were no studies in women who had pre-existing macrovascular disease. The contributing data were obtained from 2 prospective randomised trials, 2 prospective observational studies and 2 prospective case-control studies.

3.3.10 Other considerations

It was unfortunate that there were no data reporting the effectiveness of either type of oral contraceptive in preventing conception. Nevertheless, the guideline development group reasoned that there was no theoretical reason why diabetes should make the oral contraceptive less effective.

Furthermore, the group felt that the evidence that had been reviewed did not demonstrate a greater likelihood of the prioritised adverse outcomes.

Finally, the group was aware of the following guidance relating to the use of contraception in women with diabetes which influenced the final recommendations. In particular, they noted the potential impact of the progesterone-only oral contraceptive on glucose metabolism.

Although the guideline on long-acting reversible contraception does not contain recommendations on the use of oral contraceptives in women with diabetes, it does make the following recommendations regarding women with diabetes:

- Healthcare professionals should be aware that intrauterine device (IUD) use is not contraindicated in women with diabetes.
- Healthcare professionals should be aware that intrauterine system (IUS) use is not contraindicated in women with diabetes.
- Healthcare professionals should be aware that injectable contraceptives are not contraindicated in women with diabetes.
- Healthcare professionals should be aware that Implanon use is not contraindicated in women with diabetes.

The guideline development group considered that the risk factor information within the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC, 2009; revised 2010) should be considered when choosing contraception.

In women with type 1 or type 2 diabetes and with no vascular disease:

- The advantages of using combined oral contraceptives generally outweigh the risks. (Category 2)
- The advantages of using progestogen-only contraceptives generally outweigh the risks. Progestogen-only contraceptives may alter carbohydrate metabolism, but evidence is limited. (Category 2)
- In women with diabetes and nephropathy, retinopathy, neuropathy or other vascular disease:
  - The risks of using combined oral contraceptives generally outweigh the advantages, and in some cases the health risk of using combined oral contraceptives is unacceptable. (Category 3/4 – the category should be assessed according to the severity of the condition)
  - The advantages of progestogen-only contraceptives generally outweigh the risks. Some progestogen-only contraceptives may increase the risk of thrombosis, but this increase is substantially less than the increase seen with use of the combined oral contraceptive. (Category 2)

When multiple risk factors for cardiovascular disease exist (such as older age, smoking, diabetes), the risk of cardiovascular disease may increase substantially with the use of progestogen-only contraceptives, but these are outweighed by the advantages of using this form of contraceptive.

There may be changes in carbohydrate metabolism in women in the general population using progestogen-only contraception, but no effect on glycaemia as assessed by HbA1c was found in women with diabetes. However, there was no information supplied about changes in hypoglycaemic therapy which may have masked the effect of the drug on glucose metabolism.

3.3.11   Key conclusions

The guideline development group agreed with the conclusion of the guideline development group of the original guideline that avoiding an unwanted pregnancy was an important aspect of the care of a woman with diabtes.

There were no data on effectiveness, in terms of pregnancy rate, of oral hormonal contraceptives containing oestrogen and/or progestogen in women with diabetes compared with those without diabetes.

There were limited data on the relative benefits and risks of the combined compared to the progesterone-only oral contraceptive.

The group was reassured that there were no data suggesting a deleterious effect of oral contraception on glycaemic control, surrogate markers of future macrovascular risks such as hypertension and serum lipids, and microvascular complications. Therefore, it was felt that diabetes was not a contraindication in itself to the use of any form of oral contraception and the choice should be based upon baseline risk as assessed for women without diabetes and the woman's individual preference.

3.3.12   Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.3.13   Research recommendations

1. **What is the efficacy (measured by pregnancy rate) of oral oestrogen-containing contraceptives in women with diabetes compared with women without diabetes**

There are no data on efficacy, in terms of pregnancy rate, of oral hormonal contraceptives containing oestrogen and progestogen in women with diabetes compared to those without diabetes.

Why this is important

Women with diabetes need to make informed choices about their method of contraception. Pregnancy is a greater risk for them and for their infants, especially if their diabetic control is poor, compared with women without diabetes. There is the potential for there to be a difference in pregnancy rates. This could be for metabolic or pharmaco-dynamic reasons or because women with diabetes could be either more or less compliant with medication than women without diabetes. The age of the woman and the stage of her reproductive life may also be a significant difference between a diabetic and non-diabetic woman. In addition women with Type 1 diabetes may be different from women with Type-2 diabetes. Relevant study designs would include case-control, cohort or observational studies. Qualitative studies could compare diabetic and non-diabetic women's views about compliance and the importance of preventing pregnancy.

2. **What is the efficacy (measured by pregnancy rate) of oral progestogen-containing contraceptives in women with diabetes compared with women without diabetes?**

There are no data on efficacy, in terms of pregnancy rate, of oral hormonal contraceptives

containing oestrogen and progestogen in women with diabetes compared to those without diabetes.

Why this is important

Women with diabetes need to make informed choices about their method of contraception. Pregnancy is a greater risk for them and for their infants, especially if their diabetic control is poor, compared with women without diabetes. There is the potential for there to be a difference in pregnancy rates. This could be for metabolic or pharmaco-dynamic reasons or because women with diabetes could be either more or less compliant with medication than women without diabetes. The age of the woman and the stage of her reproductive life may also be a significant difference between a diabetic and non-diabetic woman. In addition women with Type 1 diabetes may be different from women with Type-2 diabetes. Relevant study designs would include case-control, cohort or observational studies. Qualitative studies could compare diabetic and non-diabetic women's views about compliance and the importance of preventing pregnancy

3. **What are the long term effects of oral contraceptives in women with diabetes on glycaemic control and hypoglycaemic therapy (e.g. insulin dose? (epidemiological study)**

There are no data on adverse effects of oral hormonal contraceptives containing oestrogen and/or progestogen in women with diabetes on hypoglycaemic therapy compared to using other forms of contraception or no contraception. In addition it is not known if oral hormonal contraceptives have different long-term effects on women with different types of diabetes.

Why this is important

It is important to investigate whether taking oral contraception causes or exacerbates long term serious vascular disease in women with diabetes. The quality of the evidence examined for this review was rated as very low or low for all reported outcomes and the follow up periods did not exceed five years. The primary outcomes of interest would be mortality, myocardial infarction, venous thrombo-embolism and stroke and much longer follow up periods would be required to show significant clinical differences, if they exist. Relevant study designs would include cohort or case-control studies. It may be that there are existing data sets that could provide this information retrospectively.

4. **What is the difference in pregnancy outcome in women who have attended pre- conception care and those that have not?**

Why this is important

Several retrospective studies have shown that women with diabetes who self-select to attend preconception care have better pregnancy outcomes. However, women who attend pre- pregnancy counselling in previous studies have not been representative of the general antenatal population of women with diabetes. These women typically have fewer risk factors for adverse pregnancy outcomes and are more motivated. Randomised control trials are required to assess the effect of preconception care on pregnancy outcomes.

3.4 Diet, dietary supplements, body weight and exercise

3.4.1 Description of the evidence

3.4.1.1 Diet

The aims of dietary advice for women with diabetes who are planning a pregnancy are:

- optimisation of glycaemic control, avoiding large fluctuations of blood glucose, especially postprandial blood glucose, while avoiding ketosis and hypoglycaemia in women taking insulin
- provision of sufficient energy and nutrients to allow normal fetal growth while avoiding accelerated fetal growth patterns.[37]

Hyperglycaemia in early pregnancy is associated with congenital malformations and miscarriage (see Section 3.7). In later pregnancy it is implicated in accelerated fetal growth, stillbirth, and neonatal hypoglycaemia and hypocalcaemia (see Section 5).

Targeting postprandial hyperglycaemia is particularly important during pregnancy. Adjusting treatment to postprandial blood glucose levels is associated with better outcomes in women with type 1 diabetes or gestational diabetes than responding to fasting blood glucose (FBG) levels (see Sections 3.6, 4.5 and 5.2).

Dose Adjustment for Normal Eating (DAFNE) is an example of a structured education programme for people with type 1 diabetes in the UK (see below).

Low glycaemic index (GI) diets appear to reduce postprandial hyperglycaemia and women on low GI diets have been reported to have babies with lower birthweights compared with women on high GI diets (see Sections 3.4 and 5.4).

Exercise can help women with diabetes to lose weight and improve glycaemic control.

Folic acid supplementation reduces the prevalence of neural tube defects. Women with diabetes have an increased risk of neural tube defects, and there is no evidence that folic acid metabolism differs from that of women who do not have diabetes.

A meta-analysis was identified that compared the effect on HbA1c of low GI diets with that of high GI diets.38,39 The meta-analysis included 14 studies and 356 nonpregnant people (203 with type 1 diabetes and 153 with type 2 diabetes). The meta-analysis found that low GI diets reduced HbA1c by 0.43 percentage points (95% CI 0.72 to 0.13) over and above that produced by high GI diets. Taking HbA1c and fructosamine data together and adjusting for baseline differences, glycated proteins were reduced 7.4% more on the low GI diet than on the high GI diet (95% CI 8.8 to 6.0). [EL = 1++]

A prospective randomised study40 was performed in 15 women with glucose intolerance diagnosed early in the third trimester of pregnancy. The results showed that the mean plasma glucose concentrations of the diet-treated women were significantly greater than those of the controls (pregnant women with a normal glucose tolerance who ate according to appetite) at 10 a.m., 2 p.m. and 8 p.m. as compared with significantly lower in the insulin-treated group than the controls at 6 p.m., 2 a.m., 4 a.m. and 6 a.m. The mean 2 hour neonatal plasma glucose concentration of the diet-treated group was significantly higher than that of other groups. [EL = 1−]

Nausea and vomiting in pregnancy can disrupt blood glucose control (see Section 5.4).

3.4.1.2 Dietary supplements

Women with diabetes have an increased risk of having a baby with a neural tube defect (see Section 5.8).

The CEMACH enquiry found 69% (83/120) of the women with poor pregnancy outcome and 50% (66/131) of the women with good pregnancy outcome were documented as not having commenced folic acid supplementation before pregnancy (this is similar to the general maternity population), but only 33 women were on the 'high dose' (5 mg) of folic acid. Not commencing folic acid supplements prior to pregnancy led to an increased risk of poor pregnancy outcome (OR 2.2, 95% CI 1.3 to 3.9).[33] [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that 45% (32/71) of women with type 2 diabetes and 49% (54/110) of women with type 1 diabetes were documented as having commenced folic acid supplementation before pregnancy.[33] [EL = 3–4]

A case–control study compared folate metabolism in 31 pregnant women with diabetes to that in 54 pregnant women without diabetes.[39] The study found no significant differences for any measures of folate metabolism. [EL = 2+]

3.4.1.3 Body weight

Obesity is an independent risk factor for a number of adverse pregnancy outcomes including:[37]

- impaired glucose tolerance (IGT)
- hypertensive disorders
- caesarean section
- perinatal mortality
- macrosomia
- preterm birth
- congenital malformations. [EL = 2+]

A cohort study included 196 women with pre-existing diabetes and 428 women with gestational diabetes.41 After controlling for type of diabetes, maternal age, parity and obstetric history, the study found that, when compared with pre-pregnancy BMI less than 20 kg/m², pre-pregnancy BMI 30 kg/m² or more was independently associated with caesarean

section (OR 3.5, 95% CI 1.4 to 8.6) and preterm birth at less than 37 weeks of gestation (OR 5.1, 95% CI 1.4 to 18.6). Weight gain during pregnancy was independently associated with hypertensive disorders of pregnancy (OR 1.4, 95% CI 1.2 to 1.7) and large-for-gestational-age (LGA) babies (OR 1.3, 95% CI 1.1 to 1.6). [EL = 2++]

A prospective cohort study collected data on pre-pregnancy exposures and pregnancy outcome in 22 951 women (574 with diabetes, 1974 with a BMI 28 kg/m² or more).[42] There was no increased risk of major defects in the offspring of women without diabetes who were obese (relative risk (RR) 0.95, 95% CI 0.62 to 1.5) and no increased risk among women with diabetes who were not obese (RR 0.98, 95% CI 0.43 to 2.2). The offspring of women with diabetes and coexisting obesity were three times as likely to have a major defect (RR 3.1, 95% CI 1.2 to 7.6) than those of women without diabetes, suggesting that obesity and diabetes may act synergistically in the pathogenesis of congenital malformations. [EL = 2++]

A prospective population-based cohort study[43] of 1041 Latino mother–baby pairs assessed the combined influence of maternal weight and other anthropometric and metabolic characteristics on the birthweights of babies. The results showed that there was an increased risk of adverse maternal and infant outcomes associated with excessive maternal weight, weight gain and glucose intolerance. [EL = 2+]

A retrospective cohort study[44] examined the relationship between gestational weight gain and adverse neonatal outcomes among term babies (37 weeks of gestation or more). The results showed that the gestational weight gain above Institute of Medicine guidelines was common and associated with multiple adverse neonatal outcomes, whereas gestational weight gain below guidelines was only associated with SGA babies. [EL = 2−]

A prospective cohort study[45] evaluated the independent influence of pre-pregnancy BMI and glucose tolerance status on the presentation of diabetes-related adverse pregnancy outcomes in Spanish women. The results showed that pre-pregnancy maternal BMI exhibited a much stronger influence than abnormal blood glucose tolerance on macrosomia, caesarean section, pregnancy-induced hypertension and LGA newborns. [EL = 2++]

3.4.1.4 Exercise

Moderate exercise has been found to improve blood glucose control in women with gestational diabetes (see Section 4.5). No studies were identified in the population of pregnant women with pre-existing type 1 or type 2 diabetes.

A meta-analysis included six studies involving a total of 322 women with type 2 diabetes.[46] All studies compared dietary advice with dietary advice plus exercise. On average there was more weight loss in the dietary advice plus exercise groups. HbA1c decreased more in the women in the dietary advice plus exercise group than in those in the dietary advice group alone. Dietary advice plus exercise was associated with a statistically significant mean decrease in HbA1c of 0.9% at 6 months (95% CI 0.4 to 1.3) and 1% at 12 months (95% CI 0.4 to 1.5). [EL = 1++]

A Cochrane systematic review[47] aimed to evaluate the effect of exercise programmes alone or in conjunction with other therapies such as diet, compared with no specific programme or with other therapies, in pregnant women with diabetes on perinatal and maternal morbidity and mortality. The review found no significant difference between exercise and the other regimens in any of the outcomes evaluated. [EL = 1+]

3.4.2 Existing guidance

The NICE antenatal care guideline[9] recommends that healthy pregnant women (and those intending to become pregnant) should be informed that dietary supplementation with folic acid, before conception and up to 12 weeks of gestation, reduces the risk of having a baby with neural tube defects. The recommended dose is 400 micrograms per day for the general

maternity population. An Expert Advisory Group report issued by the Department of Health48 recommended that women with no history of neural tube defects should take 400 micrograms per day, whereas women with a history of neural tube defects should take a higher dose (5 mg per day).

NICE has developed public health guidance on maternal and child nutrition,[19] which aims to improve the nutrition of pregnant and breastfeeding mothers and children in low-income households. The guidance recommends that women with diabetes who may become pregnant and those who are in the early stages of pregnancy should be prescribed 5 mg of folic acid per day.

3.4.3 Evidence statement

Low GI diets reduce postprandial glycaemia

Obesity is a risk factor for a number of adverse perinatal outcomes. In cohort studies of women with gestational diabetes who are obese undergoing moderate calorie restriction, good outcomes were achieved without ketoacidosis.

Exercise can help women with diabetes to lose weight and improve glycaemic control.

Folic acid supplementation reduces the prevalence of neural tube defects. Women with diabetes have an increased risk of neural tube defects, and there is no evidence that folic acid metabolism differs from that of women who do not have diabetes.

3.4.4 From evidence to recommendations

A number of factors interact during pregnancy to influence glycaemic control including physiological changes during pregnancy, comorbidities, changes in lifestyle, insulin treatment and dietary factors.[37] It follows that dietary advice should be given on an individual basis from someone with appropriate training and expertise.

Given the evidence that obesity is linked to a number of adverse perinatal outcomes, women with diabetes who are obese and intending to become pregnant should be advised of the risks to their own health and that of their babies and encouraged to start a supervised weight reduction diet.

Folic acid is particularly important for women with diabetes planning a pregnancy because of the increased risk of congenital malformations, which include neural tube defects. At present there is no evidence to suggest that these women would benefit from a larger dose than is recommended for women who do not have diabetes. However, the GDG's view was that women with diabetes should take the higher dose of 5 mg per day, as for other women with increased risk of neural tube defects, when intending to become pregnant.

3.4.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.4.6 Research recommendations

There were no research recommendations relating to the information that should be offered about diet, dietary supplements, body weight and exercise.

3.5 Monitoring blood glucose and ketones in the preconception period

3.5.1 Blood glucose monitoring

3.5.1.1 Description of the evidence

The DCCT compared intensive treatment with conventional treatment where intensive treatment was a package of care that included self-monitoring of blood glucose at least four times a day and a monthly measurement of HbA1c.[70] The DCCT involved 1441 people with type 1 diabetes. The goal of intensive therapy was blood glucose concentrations as close to the non-diabetic range as possible. HbA1c was maintained at a significantly lower level in the intensive treatment group compared with the conventional treatment group (P < 0.0001).The mean ± SD value for all glucose profiles in the intensive therapy group was 8.6 ± 1.7 mmol/litre compared with 12.8 ± 3.1 mmol/ litre in the conventional therapy group (P < 0.001). The study found intensive therapy delayed the onset of complications of diabetes and slowed their progression. [EL = 1++]

The DCCT protocol required that women in the conventional treatment group change to intensive therapy while attempting to become pregnant and during pregnancy. An ancillary study compared pregnancy outcomes in 94 women originally assigned to intensive treatment with 86 women originally assigned to conventional treatment.[49] All women originally assigned to conventional treatment were changed to intensive treatment during pregnancy; 26 changed before conception and 60 changed after conception. The mean HbA1c at conception in the intensive treatment group was 7.4% ± 1.3% compared with 8.1% ± 1.7% in the conventional treatment group (P = 0.0001). Nine congenital malformations were identified, eight of which were in the conventional treatment group (P = 0.06). [EL = 2++]

3.5.1.2 Evidence statement

No studies were identified on how to monitor blood glucose and ketones in the preconception period. An RCT found that a package of care that included self-monitoring of blood glucose at least four times a day and a monthly measurement of HbA1c improved blood glucose control in people with type 1 diabetes and reduced the progression of complications of diabetes. An ancillary study found that the incidence of congenital malformations in the babies of women with type 1 diabetes was also reduced.

3.5.1.3 Recommendations

Recommendations for blood glucose monitoring are presented in Section 3.5.2.7.

3.5.2 Ketone monitoring

This section was updated in 2015

3.5.2.1 Review question

What is the effectiveness of blood ketone monitoring compared with urine ketone monitoring for women with type 1 or type 2 diabetes who are planning pregnancy?

3.5.2.2 Introduction

Ketones are derived from the breakdown of fat and can be used as a source of energy, for example during starvation. Ketones are usually present in very low concentrations in urine and blood in non-diabetic populations. The concentration of ketones in blood is normally less than 0.3 mmol/litre and they are usually undetectable by routine urine tests. Various factors can contribute to a raised concentration of ketones in the blood or urine including metabolic disorders (such as uncontrolled diabetes or weight loss), dehydration, low carbohydrate intake and individual variations in the threshold for ketonuria.

In someone with diabetes, increased ketone concentrations might indicate impending or established ketoacidosis (DKA). This serious condition can occur at relatively low blood glucose concentrations in pregnant women and requires urgent medical attention because of an increased risk of harm to the fetus. Although ketoacidosis is more common in women with type 1 diabetes, it has also been described in women with type 2 and gestational diabetes. Because DKA can profoundly compromise the wellbeing of both the woman and her baby (including maternal and fetal death), the 2008 guideline recommended that women with type 1 diabetes who are planning to become pregnant should be offered ketone testing strips and advised to test for ketonuria or ketonaemia if they become hyperglycaemic or unwell. In the absence of any evidence, this recommendation was based on a consensus of the guideline development group's knowledge and the best clinical practice at the time.

3.5.2.3 Description of included studies

No studies were identified that assessed how blood ketones should be monitored in the preconception period.

3.5.2.4 Health economics profile

No published health economic evidence was identified addressing the cost effectiveness of blood ketone monitoring compared with urine ketone monitoring for women with type 1 or type 2 diabetes who are planning pregnancy.

This question was not prioritised for health economic analysis as the guideline development group thought there were more important priorities for health economic analysis in the guideline.

3.5.2.5 Evidence to recommendations

3.5.2.5.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the following maternal outcomes for this review:

- preterm birth (birth before 37+0 weeks' gestation; take dichotomous or continuous data) in the subsequent pregnancy
- non-routine hospital contact or assessment for ketosis (ketonaemia or ketonuria, however defined), including phone contact
- hospital admission for diabetic ketoacidosis
- maternal satisfaction.

The group also prioritised the following fetal/neonatal (in the subsequent pregnancy) outcomes for this review:

- mortality - perinatal and neonatal death
- neonatal intensive care unit length of stay greater than 24 hours.

The outcomes chosen were considered to be clinically meaningful for the woman and baby, they could be reliably assessed in clinical research studies and were expected to be commonly reported in the evidence available for inclusion. The group decided to prioritise non-routine hospital contact or assessment for ketosis as an outcome because women with diabetes can be tested routinely for ketones outside pregnancy.

The group recognised that maternal mortality in association with diabetic ketoacidosis is a possibility but it agreed that it is a rare event in UK clinical settings, and so it was not prioritised for this review.

Shoulder dystocia was also acknowledged by the group as being an important outcome. However, the group recognised that its direct association with ketosis was unlikely and so this outcome was not prioritised for this review.

3.5.2.5.2 Consideration of clinical benefits and harms

The group recognised the potential health risk to future babies from high concentrations of ketones in blood or urine of diabetic women in the preconception period. Although high maternal ketone levels during pregnancy have not been proven conclusively to be dangerous to the fetus, neither have they have been proven to be harmless. The 2008 guideline assumed that there was a benefit in measuring ketones in women who are planning to become pregnant if they become hyperglycaemic or unwell. Also, this was consistent with NICE clinical guidance on type 1 diabetes which recommends monitoring blood or urine for the presence of ketones. The current guideline development group agreed with the previous guideline that there are potential benefits in the ability to measure blood ketones in women who are planning to become pregnant, especially if the woman is unwell or has very high blood glucose values. The group believed the benefits in terms of prompt recognition of DKA and its treatment were greater than the harms of unnecessary testing.

The group recognised that one of the main advantages of using a blood ketone test is that it can provide an accurate, convenient and timely assessment of ketosis. In contrast, urine testing only provides a qualitative measure of any ketosis over the preceding period since the woman last passed urine. (This is discussed at greater length in the Biochemical factors section below). Furthermore, it does not precisely correlate with blood ketone concentration which is more likely to reflect the severity of DKA. Finally, blood ketone levels increase before urine ketone levels, allowing an earlier identification of any metabolic deterioration.

In summary, the guideline development group felt that blood ketone tests give a specific value that more accurately reflects the level of ketosis and its severity. In theory this should lead to more timely recognition of DKA and earlier treatment.

3.5.2.5.3 Consideration of health benefits and resource uses

Although the guideline development group noted that blood testing strips are more expensive than those used for urine testing, and notwithstanding that a full health economic analysis was not undertaken for this guideline, the group was of the view that the convenience of undertaking blood testing for ketones (which can be performed at the same time as testing blood glucose levels and using the same device) would result in greater patient compliance than using urine testing strips. In turn this would lead to a more prompt response and treatment following an abnormal result which should result in a lower overall cost as suggested by a study in young people with type 1 diabetes (Laffel et al., 2006). In this study it was shown that the higher costs of blood ketone testing was offset by reduced treatment costs for DKA as a result of lower rates of hospitalisation.

The group noted that although blood ketone testing meters are not universally available for all diabetic patients, in general many patients with an increased risk of DKA (such as women with type 1 diabetes and unstable glucose control, and those on insulin pumps) would be issued with one.

However, the group did feel that, although DKA has been reported in people with type 2 diabetes, this was a relatively rare event. Thus they considered that any recommendation about ketone testing should be confined to women with type 1 diabetes. This would be in keeping with the type 2 diabetes guideline that does not recommend routine testing for ketones.

3.5.2.5.4 *Quality of evidence*

The group noted that no new evidence was found to establish which method is the most effective for monitoring ketones in women with type 1 and type 2 diabetes in the preconception period. In the absence of preconception-specific evidence, the guideline development group relied, in part, on consensus opinion and on their knowledge of current best clinical practice.

3.5.2.5.5 *Other considerations*

Practical issues

The guideline development group noted that for many patients with diabetes the convenience of testing blood for both glucose and ketones at the same time from a single capillary sample represented a distinct advantage of blood testing for ketones. Also, many people with diabetes (particularly the young) find urine testing inconvenient and unpleasant, and would rather avoid doing it.

Biochemical factors

Urine ketone testing strips are based on the nitroprusside reaction which primarily detects aceto-acetate and acetone. They are read visually, comparing the colour obtained with a colour coded chart, and do not require instrumentation for automatic reading. With this method the presence and quantity of ketones is reported subjectively either as 'negative', 'small', 'moderate' or 'large'.

Blood ketone testing strips measure beta-hydroxybutyric acid which is the predominant ketone body in ketoacidosis. The strip is read by a meter utilising a chemical process that does not require a colour chart and gives an accurate blood concentration. Moreover, blood beta-hydroxybutyric acid measurements are used to assess the severity of DKA and inform insulin and fluid replacement and help monitor the response to treatment.

The guideline development group noted that urine strips degrade over time and their accuracy is reduced after 6 months. In addition, urine strips can give a false-negative reading, either because: they have been exposed to the air for long periods; if the urine specimen is highly acidic; if the women is using certain prescription medicines (such L-DOPA metabolites); or if there are high levels of phenylketone.

Other guidelines in development

During the development process NICE established liaison between guideline development groups that were concurrently updating several diabetes guidelines (Type 1 diabetes in adults, Type 2 diabetes in adults, Diabetes in children and young people, and Diabetes in pregnancy) with the aim of aligning recommendations. As a consequence, the guideline development group for this guideline was aware that the guideline development groups for the guidelines on type 1 diabetes and diabetes in children and young people were recommending blood ketone testing rather than urine testing.

3.5.2.6 Key conclusions

Due to the lack of new evidence, the guideline development group, in part, used their knowledge and understanding of best clinical practice at the time to review the 2008 recommendation. The discussions and conclusions of the guideline development groups working on the guidelines on type 1 diabetes in adults and diabetes in children and young people were also noted and discussed. The guideline development group for this guideline agreed that because blood ketone testing can provide more accurate information about the severity of ketosis, as well as helping to monitor the response to therapy, it should be recommended in women with type 1 diabetes who are planning pregnancy if they become hyperglycaemic or unwell, in preference to urine ketone testing.

3.5.2.7 Recommendations
The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

3.5.2.8 Research recommendations

5. What is the relationship between pre-pregnancy glucose control and ketonaemia and the risk of miscarriage?

Why this is important

It is established that good glucose control pre-pregnancy reduces the risk of adverse pregnancy outcome, including congenital abnormalities and miscarriage, and that pooly controlled diabetes is associated with an increased risk of miscarriage. The role of ketonaemia on these risks is not known. Pregnancy is a state of accelerated ketosis, thus ketoanaemia is more likely to occur in pregnancy, and to occur at lower blood glucose levels. Ketonaemia could be a contributory factor to this risk of miscarriage. In the absence of evidence, women with type 1 diabetes are advised to test either their blood for ketones if they become hyperglycaemic or unwell, but it is not known if the avoidance of ketonaemia on a regular basis reduces early pregnancy loss. A prospective population based observational study should answer this question.

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x HbA1c values are reported in mmol/mol, using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardised HbA1c test. The equivalent values in %, using the Diabetes Control and Complications Trial (DCCT)-aligned HbA1c test, are reported in parentheses.

3.6 Target blood glucose values for women with type 1 or type 2 diabetes planning pregnancy

This section was updated in 2015

3.6.1 Review question

What are the target ranges for blood glucose in women with type 1 or type 2 diabetes who are planning pregnancy?

3.6.2 Introduction

The purpose of this review was to determine optimal targets for blood glucose control in women with type 1 or type 2 diabetes who are planning pregnancy. The search protocol for this question included randomised controlled trials (RCTs), systematic reviews and comparative observational studies. Non-comparative observational studies were to be included only if no comparative studies were identified. The same search was used to identify studies for this review and the reviews of target values for blood glucose pre-conception, target values for HbA1c pre-conception and during pregnancy and for blood glucose and HbA1c monitoring during pregnancy.

3.6.3 Description of included studies

No studies met the inclusion criteria for this review.

3.6.4 Health economics profile

No published health economic evidence was found addressing target ranges for blood glucose in diabetic women planning a pregnancy.

This was not prioritised for health economic analysis because although a target may affect the interventions and management used to assist a patient in achieving it, it does not incur an opportunity cost.

3.6.5 Evidence to recommendations

3.6.5.1 Relative value placed on the outcomes considered

The guideline development group identified 6 priority outcomes for this review. Maternal outcomes were:

- HbA1c (percentage) in the first trimester
- hypoglycaemic episodes before pregnancy or in the first trimester
- spontaneous miscarriage
- acceptability of targets.

Neonatal outcomes were:

- any congenital abnormality, regardless of gestational age
- mortality, defined as perinatal mortality (stillbirth and death up to 7 days after birth) and neonatal mortality (death up to 28 days after birth).

3.6.5.2 Consideration of clinical benefits and harms

The evidence considered in this chapter, chapter 5 and chapter 6 indicate that achieving low blood glucose values in pregnancy is associated with a lower incidence of adverse outcomes. For the preconception period, the guideline development group prioritised congenital malformations as the most important of these outcomes.

However, increased episodes of hypoglycaemia in the woman was another important outcome. The guideline development group noted that if pre-pregnancy target blood glucose values were recommended to be closer to those values recommended during pregnancy, this might represent a significant lowering of what was normal for women and may increase the risk of hypoglycaemia. This could be a prolonged problem in women who take time to conceive and as a result women may feel discouraged from engaging with pre-pregnancy care.

In addition, women with type 1 and type 2 diabetes may have microvascular disease that can worsen with rapid reduction in mean blood glucose levels. Diabetic retinopathy is one example of this. Older women with type 2 diabetes may have established or subclinical macrovascular disease that might pose a serious mortality risk as a result of any recurrent hypoglycaemia that may accompany intensification of insulin treatment. Also, women with long duration type 1 diabetes may have absolute or relative hypoglycaemia unawareness which would make them particularly vulnerable to severe hypoglycaemic episodes. Furthermore, many women considering pregnancy will have young children at home which would make hypoglycaemia a particular risk. Thus, a balance needs to be struck between the risk to the woman of hypoglycaemia and the benefit to the embryo in the first trimester, especially in terms of organogenesis.

It has been suggested that at least 60% of women do not plan for pregnancy. If the non-pregnancy target ranges for blood glucose were set significantly higher than the targets during pregnancy, then the above problems would be more likely.

3.6.5.3 Quality of evidence

No pregnancy specific evidence was available to inform recommendations.

3.6.5.4 Other considerations

The guideline development group was aware of the concurrent updating of other NICE diabetic guidelines and kept informed of their progess and developing recommendations. Specifically, they noted that the guideline development group of the guideline on type 1 diabetes in adults was planning to recommend a much lower range of target values than in the previous guideline with the aim of reducing the incidence of diabetic complications. Thus the guideline development group for this guideline felt that recommending the same target values would be reasonable.

Finally, the guideline development group highlighted that an individualised approach to blood glucose is still important and that targets needed to be discussed with the woman and adapted to her circumstances and whether she develops hypoglycaemic episodes.

3.6.6 Key conclusions

For these reasons and because no pre-pregnancy evidence was identified to directly inform a recommendation, the guideline development group decided to adopt the target values for type 1 diabetes recommended in the updated NICE clinical guideline on type 1 diabetes[y]. Many of these women would be likely to need insulin therapy before pregnancy in order to achieve those target values.

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[y]Because of a lack of evidence on plasma glucose targets for women with diabetes who are planning pregnancy, target ranges will be taken from the updated NICE guideline on type 1 diabetes (consultation 10 December 2014 to 4 March 2015). This recommendation will be replaced by one containing the target ranges when the type 1 diabetes guideline update is published (expected August 2015).

3.6.7 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.6.8 Research recommendations
This section was updated in 2015

Research into different levels of glycaemia before pregnancy is difficult if only because of the ethics of randomizing women to what may be considered to be inferior control. However, we could pose the following:

6. Achieving glycaemic targets pre-pregnancy – what can be done to help women achieve the best possible glycaemic control?

Why this important

The relationship between glycaemic control and adverse pregnancy outcome for women with pre-existing type 1 and 2 diabetes has been well documented. To optimise pregnancy outcome for both the woman and her offspring, women with pre-existing diabetes should be informed that good glycaemic control prior to pregnancy will reduce the risks of adverse pregnancy outcome such as miscarriage, congenital abnormality stillbirth and neonatal death.

Research is required to explore the barriers and facilitators for women accessing preconception care. Exploring the experiences of women who access preconception care and achieve the optimal blood glucose targets and those who do not achieve these goals. This will help gain an understanding from women the facilitators and barriers they experiences in trying to achieve their target blood glucose levels would highlight issues that could be addressed.

Investigating the knowledge and understanding of the importance of good glycaemic control from healthcare professionals caring for women with pre-existing diabetes may identify areas of service improvement that would assist women in their quest to achieve optimum blood glucose levels. It is anticpated that qualitative studies will be the best methodological approach for this research.

7. Achieving glycaemic targets pre-pregnancy – what are the barriers?

Why this is important

Preconception care is encouraged in women with type 1 and type 2 diabetes to establish optimal blood glucose control especially with the aim of reducing the incidence of congenital abnormalities. The specific additional measures recommended supporting that aim are starting Folic Acid 5mg and excluding teratrogenic medications. The NICE (2008) Diabetes in pregnancy Guideline recommended an HbA1c target of under 6.1% prior to trying for pregnancy. To achieve such a target women will need regular blood glucose monitoring (7-10 blood glucose tests per day) and run an increased risk of hypoglycaemia. Barriers may

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[z] Because of a lack of evidence on plasma glucose targets for women with diabetes who are planning pregnancy, target ranges will be taken from the updated NICE guideline on type 1 diabetes consultation (10 December 2014 to 4 March 2015). This recommendation will be replaced by one containing the target ranges when the type 1 diabetes guideline update is published (expected August 2015).

include a fear of hypoglycaemia and lack of time for frequent monitoring. Good quality qualitative studies are needed to identify potential barriers in women pre-pregnancy to enable health care professionals to encourage optimal control prior to pregnancy.

8. Achieving glycaemic targets pre-pregnancy – what is the role of the health care professional?

Why this is important

Preconception care should be offered to all women with pre-existing diabetes to establish optimal blood glucose control especially with the aim of reducing the incidence of congenital abnormalities. The specific additional measures recommended supporting that aim are starting Folic Acid 5mg and excluding teratrogenic medications. The NICE (2008) Diabetes in pregnancy Guideline recommended an HbA1c target of under 6.1% prior to trying for pregnancy. Women may need help from their health care professionals to achieve glycaemic targets in pregnancy. Glycaemic targets may seem unobtainable to some women whilst others may achieve target whilst experiencing frequent episodes of hypoglycaemia. The role of the healthcare professional may be different for individual women and could include that of educator, supporter, motivator or advocate. To develop a greater understanding of the role of the health care professional and how they can work with women to optimise control, qualitative studies are needed.

9. Achieving glycaemic targets pre-pregnancy – what is the role of telemedicine?

Why this is important

Telemedicine is used in a growing variety of applications and services to assist in the achievement of health goals. For women with pre-existing diabetes the use of such technology has the potential to assist women in achieving their blood glucose targets. The use of communications such as Skype allows for consultations with healthcare professionals over large geographical areas facilitating discussions related to the achievement of blood glucose levels and discuss issues surrounding tis. The use of applications associated with 'smart phone' technology may facilitate a two way exchange of biochemical information and appropriated advice. Research should be undertaken in the acceptability and understanding of the use of telemedicine by both women with pre exciting diabetes and healthcare professionals supporting women with these technologies. Exploring the use of telemedicine in primary care and specialist referral services would ascertain if these technologies are used and if so their efficacy technologies in remote patient monitoring. Ranodmised controlled trials of support using telemedicine versus conventional support for diabetic women before pregnancy together with health economic evaluation would be the best way of exploring the value of these new technologies.

10. What are the roles of insulin pump therapy (continuous subcutaneous insulin infusion) and continuous glucose monitoring in helping women achieve glucose targets pre pregnancy?

Babies born to women with diabetes have a high risk of having congenital malformations and this risk is greater if blood glucose control is poor around the time of conception. However, lowering the risk to that of women without diabetes would require normalisation of blood glucose levels, and this is difficult to achieve without increasing the risk of serious hypoglycaemia. Insulin pump therapy and continuous glucose monitoring have been shown to reduce both blood glucose levels and rates of hypoglycaemia in the non-pregnant population, but it is uncertain if this holds true before conception and in early pregnancy. There is therefore an urgent need to test the effectiveness and acceptability of these technologies in women with diabetes who are planning pregnancy. This would be best undertaken in a randomised controlled trial of women with diabetes trying to conceive.

Women would be allocated to receive either conventional care (self-monitoring of blood glucose and insulin adjustment) or insulin pump therapy and continuous glucose monitoring.

11. What is the long term impact for children born to women with different degrees of preconception glycaemic control?

Why this is important

There is good evidence that the degree of glycaemic control at the time of conception determines the risk of miscarriage and congenital malformations. While many of the glycaemic related malformations are incompatible with life others have long-term impact on future health and wellbeing. It is uncertain the extent, if any, the degree of glycaemic control preconception has on the future health and development of infants born without congenital malformations. The research would have to be a longitudinal population based study looking at development in childhood and beyond.

12. What is the experience for women with type 1 and type 2 diabetes going through preconception and pregnancy?

Why this is important

To really understand how best to support women with type 1 and 2 diabetes pre-pregnancy and pregnancy it is very important to develop a greater understanding of the lived experience of these women. This should enable healthcare professionals to provide sensitive, meaningful and effective care. These women have a higher risk adverse pregnancy outcomes if blood glucose levels are not controlled. Blood glucose levels need to be checked very frequently and acted on and it is the woman's responsibility of the women to manage this. A qualitative phenomenological study of women with type 1 and type 2 diabetes throughout their pre-pregnancy and pregnancy will provide a greater understanding of the issues faced by this group of women. On the basis of the results, services could be tailored to be beneficial to the needs of this group.

3.7 Target HbA1c values for women with type 1 or type 2 diabetes planning pregnancy

This section was updated in 2015

3.7.1 Review question

What is the target value for HbA1c in women with type 1 or type 2 diabetes who are planning pregnancy?

3.7.2 Introduction

The purpose of this review was to determine target values for HbA1c in women with type 1 and type 2 diabetes who are planning to become pregnant. The search for this study included randomised controlled trials (RCTs), systematic reviews and comparative observational studies. Non-comparative observational studies were to be included only if no comparative studies were identified. The same search was used to identify studies for this review and the reviews of target values for blood glucose pre-pregnancy, target values for HbA1c pre-pregnancy and during pregnancy and for blood glucose and HbA1c monitoring during pregnancy.

The original review question in the DiP 2008 guideline was 'What are the target ranges for blood glucose in the preconception period?' Studies that examined glycaemic control using blood glucose or HbA1c measurements were included as evidence in the chapter.

A more specific approach has been taken in this update. Four separate review questions have been stipulated to examine blood glucose or HbA1c measurements prior to conception and during pregnancy.

A total of 22 studies were included in the previous section on target values. The majority of these studies examined HbA1c and have been considered as part of this review or the corresponding 'during pregnancy' review and have been included or excluded as appropriate according to the protocols.

3.7.3 Description of included studies

A total of 8 comparative observational studies met inclusion criteria for this review (Bell et al., 2012; Diabetes and Pregnancy Group, France, 2008; Greene et al., 1989; Jensen et al., 2009; Miller et al., 1981; Miodovnik et al., 1985; Suhonen et al., 2000; Tennant et al., 2014). Four of the studies identified did not meet the formal criteria for when HbA1c levels were obtained: specifically they were not obtained in the pre-conception period but in the first trimester (Greene et al., 1989; Miller et al., 1981; Miodovnik et al., 1985; Suhonen et al., 2000). One study used peri-conception HbA1c as a surrogate for pre-conception values (Tennant et al., 2014). None of the studies set specific target values for women to achieve; results were reported based on post hoc HbA1c thresholds or categories.

Six of the studies were retrospective cohorts (Bell et al., 2012; Greene et al., 1989; Jensen et al., 2009; Miller et al., 1981; Suhonen et al., 2000; Tennant et al., 2014), 1 a prospective cohort (Miodovnik et al., 1985) and 1 was cross-sectional (Diabetes and Pregnancy Group, France, 2008). Study locations included the UK (Bell et al., 2012; Tennant et al., 2014), Denmark (Jensen et al., 2009), France (Diabetes and Pregnancy Group, France, 2008), the USA (Greene et al., 1989; Miller et al., 1981; Miodovnik et al., 1985) and Finland (Suhonen et al., 2000). Two studies included women from the same study population but analysed the data with respect to different outcomes (Bell et al., 2012; Tennant et al., 2014). Numbers of participants ranged from 75 to 1677. Women had both type 1 or type 2 diabetes (Bell et al., 2012; Diabetes and Pregnancy Group, France, 2008; Tennant et al., 2014) or type 1 diabetes alone (Greene et al., 1989; Jensen et al., 2009; Miller et al., 1981; Miodovnik et al., 1985; Suhonen et al., 2000). Thresholds for HbA1c analysis were 5.6% (Suhonen et al., 2000), 6.3% (Bell et al., 2012), 6.6% (Tennant et al., 2014), 6.9% (Jensen et al., 2009), 8.0% (Diabetes and Pregnancy Group, France, 2008) and 8.5% (Miller et al., 1981). Two studies measured HbA1 rather than HbA1c and HbA1 thresholds were 9.3% and 12.0% (Greene et al., 1989; Miodovnik et al., 1985). HbA1 values were converted to HbA1c using the Michigan formula. Of all the studies included only 1 report referred to the use of DCCT-aligned HbA1c values[aa] (Bell et al., 2012). Although not specified in the report, the second study of the same population (Tennant et al., 2014) is also likely to have applied DCCT-aligned HbA1c values.

Six of the studies (Bell et al., 2012; Diabetes and Pregnancy Group, France, 2008; Greene et al., 1989; Jensen et al., 2009; Miller et al., 1981; Suhonen et al., 2000) included in this review presented evidence for the effect of HbA1c levels on the risk of congenital malformations. Three studies presented evidence for perinatal mortality (Diabetes and Pregnancy Group, France, 2008; Tennant et al., 2014; Jensen et al., 2009). One additional study reported evidence for the risk of spontaneous abortion (Miodovnik et al., 1985).

3.7.4 Evidence profile

GRADE profiles are presented according to HbA1c thresholds. The reasons for the use of each threshold are given in Table 15.

[aa] HbA1c values are reported in mmol/mol, using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardised HbA1c test. The equivalent values in %, using the Diabetes Control and Complications Trial (DCCT)-aligned HbA1c test, are reported in parentheses

Table 15: HbA1c thresholds for optimal control used in GRADE profiles with associated reasons

HbA1c threshold	Reason for use of threshold	Applied by study or NCC-WCH technical team
5.6% (Suhonen et al., 2000)	5.6% was used as the normal threshold for HbA1c for women with diabetes based on the mean HbA1c in non-diabetic adults using HPLC assays ± the standard deviation (4.93% ± 0.32%).	NCC-WCH
6.3% (Bell et al., 2012)	Derived from regression results of locally weighted scatter plot smoothing (LOWESS).	Study
6.6% (Tennant et al., 2014)	Derived from regression results of locally weighted scatter plot smoothing (LOWESS).	Study
6.9% (Jensen et al., 2009)	Based on the authors' inference that this was the threshold for increased risk in their categorical analysis.	NCC-WCH
8.0% (Diabetes and Pregnancy Group, France, 2008)	Based on an assumption by study authors as actual values were not available for HbA1c less than 8.0%.	Study
8.5% (Miller et al., 1981)	The use of this threshold appears to be arbitrary and may have been based on the finding that approximately half of the women in the study had mean HbA1c values lower than 8.5%; however, this is not explained in the methods.	Study
9.3% (Greene et al., 1989)	9.3% was the mean value in the study population and was used as a reference by study authors. This value is based on HbA1 rather than HbA1c. Using the Michigan formula the corresponding HbA1c value is 8.4%.	NCC-WCH
12.0% (Miodovnik et al., 1985)	12.0% was chosen post hoc based on a statistical association of increased risk. This value is based on HbA1 rather than HbA1c. Using the Michigan formula the corresponding HbA1c value is 10.9%.	Study

The evidence for this is presented in Table 16.

Table 16: GRADE profile for comparison of lower HbA1c values with higher HbA1c values before conception and during the first trimester in women with type 1 diabetes mellitus and type 2 diabetes mellitus

| Number of studies | Number of children and young people | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Congenital malformations											
HbA1c < 5.6% versus ≥ 5.6%											
1 (Suhonen et al., 2000)	1/47	25/616	RR 0.50 (0.07 to 3.61)[a]	20 fewer per 1000 (from 38 fewer to 106 more per 1000)	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	Very serious[2,3]	Very serious[4]	Yes[5]
HbA1c > 6.3% versus ≤ 6.3%											
1 (Bell et al., 2012)	NR	NR	OR 5.22 (3.15 to 8.32)[b]	Not calculable	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	Very serious[6,7]	No serious imprecision	Yes[8]
HbA1c < 6.9% versus ≥ 6.9%											
1 (Jensen et al., 2009)	11/284	34/649	RR 0.74 (0.38 to 1.44)[a]	14 fewer per 1000 (from 32 fewer to 23 more per 1000)	Very low	Retrospective cohort	Serious[9]	No serious inconsistency[1]	Serious[6]	Very serious[10]	Yes[11]
HbA1c ≤ 8.0% versus > 8.0%											
1 (Diabetes and Pregnancy Group, France, 2008)	8/315	10/120	RR 0.30 (0.12 to 0.74)[a]	58 fewer per 1000 (from 22 to 73 fewer per 1000)	Very low	Cross-sectional	No serious bias	No serious inconsistency[1]	Very serious[12,13]	No serious imprecision	Yes[14]
HbA1c ≤ 8.4% versus > 8.4%c											
1 (Greene et al., 1989)	3/99	17/151	RR 0.27 (0.08 to 0.90)[a]	82 fewer per 1000 (from 11 to 104 fewer per 1000)	Very low	Retrospective cohort	Serious[15]	No serious inconsistency[1]	Very serious[3,7,16]	Serious[17]	Yes[18]
HbA1c ≤ 8.5% versus > 8.5%											
1 (Miller et al., 1981)	2/58	13/58	RR 0.15 (0.04 to 0.64)[a]	191 fewer per 1000 (from 81 to 215 fewer per 1000)	Very low	Retrospective review	No serious bias	No serious inconsistency[1]	Serious[19]	No serious imprecision	Yes[20]

| Number of studies | Number of children and young people | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Perinatal mortality											
HbA1c < 6.6% versus ≥ 6.6%											
1 (Tennant et al., 2014)	NR	NR	OR 1.02 (1.00 to 1.04)[d]	NC	Very low	Retrospective cohort	No serious bias	No serious inconsitency[1]	Very serious[21,22]	No serious imprecision	Yes[23]
HbA1c < 6.9% versus ≥ 6.9%											
1 (Jensen et al., 2009)	6/284	25/649	RR 0.55 (0.23 to 1.33)[a]	17 fewer per 1000 (from 30 fewer to 13 more per 1000)	Very low	Retrospective cohort	Serious[9]	No serious inconsistency[1]	Serious[6]	Very serious[10]	Yes[11]
HbA1c ≤ 8.0% versus > 8.0%											
1 (Diabetes and Pregnancy Group, France, 2008)	8/315	11/120	RR 0.28 (0.11 to 0.68)[a]	66 fewer per 1000 (from 29 to 82 fewer per 1000)	Very low	Cross-sectional	No serious bias	No serious inconsistency[1]	Very serious[12,13]	No serious imprecision	Yes[14]
Spontaneous miscarriage											
HbA1c < 10.9% versus ≥ 10.9%e											
1 (Miodovnik et al., 1985)	14/89	12/27	RR 0.35 (0.18 to 0.66)[a]	289 fewer per 1000 (from 151 to 360 fewer per 1000)	Very low	Prospective cohort	No serious bias	No serious inconsistency[1]	Very serious[10,24]	No serious imprecision	Yes[25]

CI confidence interval, NC not calculable, NR not reported, OR odds ratio, RR relative risk

a. Calculated by the NCC-WCH technical team.

b. The OR for an HbA1c threshold of 6.3% was calculated by the NCC-WCH technical team.

c. Based on a reported HbA1 value of 9.3%. This value was converted to HbA1c by the NCC-WCH technical team using a standard conversion formula (HbA1c=0.9HbA1+0.05).

d. Calculated by study authors based on the threshold for increased risk using locally weighted scatter plot smoothing.

e. Based on a reported HbA1 value of 12.0%. This value was converted to HbA1c by the NCC-WCH technical team using a standard conversion formula (HbA1c=0.9HbA1+0.05).

1. Single study analysis.

2. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc.

3. HbA1c measurements were taken at unspecified time points during the first trimester; it is possible that HbA1c is representative of earl pregnancy rather than pre-pregnancy.

4. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25. Power calculations suggested a required sample size of 602 per group for cases (diabetes) and controls (euglycaemic). Data for control subjects were not analysed by the NCC-WCH technical team as these participants do not meet inclusion criteria for this review. The study is therefore likely underpowered to detect differences between women in HbA1c groups used in analyses by the NCC-WCH technical team.

5. The study was carried out in Finland. Participants had type 1 diabetes. Ethnicity was 98% Finnish Caucasian.

6. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc.

7. The use of mean first trimester HbA1c makes the assumption that HbA1c within three months of conception reflects levels around the time of conception; results may be biased towards HbA1c values during pregnancy.

8. The study was carried out in the United Kingdom. Participants had both type 1 and type 2 diabetes. Ethnicity was Caucasian in 97.3% of participants. Other ethnicities are not defined.

9. Only 784 out of 933 (84%) women had complete data for pre-conception HbA1c. First trimester measurements were used as a surrogate in 149 cases.

10. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.

11. The study was carried out in Denmark. Participants had type 1 diabetes. All women were Caucasian.

12. HbA1c was measured in the first trimester but it is not clear when. Authors state HbA1c reflects pre-pregnancy levels but this is not clear. Results may reflect early pregnancy.

13. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc.

14. The study was carried out in France. Participants had both type 1 and type 2 diabetes. Ethnicity was not reported.

15. No explanation was provided for missing data for 31 women. Total sample size was reported as 303; 21 women were formally excluded at the outset and one was additional woman was excluded from analyses however outcome data were only reported for 250 women.

16. The study measured HbA1 rather than HbA1c.

17. Confidence interval for the RR crosses RR=0.75.

18. The study was carried out in the United States of America. Participants had type 1 diabetes. Ethnicity was not reported.

19. HbA1c was measured in the first trimester. The mean gestational age and standard deviation for each group suggested that HbA1c was measured at or before 12 weeks in most women however results may be biased towards HbA1c values during pregnancy.

20. The study was carried out in the United States of America. Participants had type 1 diabetes. Ethnicity was not reported.

21. Peri-conception HbA1c was used as a surrogate for pre-conception HbA1c.

22. This outcome was defined as 'infant death' which comprised both 'neonatal deaths' (deaths, after live birth, within the first 28 days of life) and 'postnatal deaths' (deaths, after live birth, of an infant aged 28 days or more, but less than one year).

23. The study was carried out in the United Kingdom. Participants had both type 1 and type 2 diabetes. Ethnicity was not reported.

24. HbA1 was measured at study entry at approximately 7 to 10 weeks' gestation; results may be biased towards HbA1c values during pregnancy.

25. The study was carried out in the United States of America. Participants had type 1 diabetes. Ethnicity was not reported.

3.7.5 Evidence statements

3.7.5.1 Studies using pre-conception HbA1c measurements

3.7.5.1.1 *HbA1c levels more than 6.3% versus 6.3% or less*

One retrospective cohort study (number of participants not reported) found an increased risk of congenital malformations in women with HbA1c levels above 6.3% compared with HbA1c of 6.3% or less (OR 5.22, 95% CI 3.15 to 8.32). The quality of the evidence for this outcome was very low.

3.7.5.1.2 *HbA1c levels less than 6.9% versus 6.9% or more*

One retrospective cohort study (n=933) found no evidence for an effect of HbA1c levels less than 6.9% on risk of congenital malformations compared with HbA1c of 6.9% or above (RR 0.74, 95% CI 0.38 to 1.44). The quality of the evidence for this outcome was very low.

3.7.5.1.3 *HbA1c levels 8.0% or less versus or more than 8.0%*

One cross-sectional study (n=435) found a reduction in the risk of congenital malformations in women with HbA1c levels of 8.0% or less compared with HbA1c more than 8.0% (RR 0.30, 95% CI 0.12 to 0.74). The quality of evidence for this outcome was very low.

3.7.5.1.4 *HbA1c levels less than 6.9% versus 6.9% or more*

One retrospective cohort study (n=933) found no increase in risk of perinatal mortality in women with HbA1c levels less than 6.9% compared with HbA1c of 6.9% or above (RR 0.55, 95% CI 0.23 to 1.33). The quality of the evidence for this outcome was very low.

3.7.5.1.5 *HbA1c levels 8.0% or less versus more than 8.0%*

One cross-sectional study (n=435) found a decreased risk of perinatal mortality in women with HbA1c levels of 8.0% or less compared with HbA1c more than 8.0% (RR 0.28, 95% CI 0.11 to 0.68). The quality of the evidence for this outcome was very low.

3.7.5.2 Studies using first trimester HbA1c measurements

3.7.5.2.1 *HbA1c levels less than 5.6% versus 5.6% or more*

One retrospective cohort study (n=663) found no difference between groups for the risk of congenital malformations in women with type 1 and type 2 diabetes mellitus who had HbA1c levels less than 5.6% compared with levels of 5.6% or more (RR 0.50, 95% CI 0.07 to 3.61). The quality of the evidence for this outcome was very low.

3.7.5.2.2 *HbA1c levels less than 6.6% versus 6.6% or more*

One retrospective cohort study (number of participants not reported) found an increased risk of perinatal mortality in women with HbA1c levels less than 6.3% compared with HbA1c of 6.6% or more (OR 1.02, 95% CI 1.00 to 1.04). The quality of the evidence for this outcome was very low.

3.7.5.2.3 *HbA1c levels 8.4% or less versus or more than 8.4%*

One retrospective cohort study (n=250) found a reduction in the risk of congenital malformations in women with HbA1c levels of 8.0% or less compared with HbA1c more than 8.0% (RR 0.27, 95% CI 0.08 to 0.90). The quality of evidence for this outcome was very low.

3.7.5.2.4 *HbA1c levels 8.5% or less versus more than 8.5%*

One retrospective review (n=116) found a reduction in the risk of congenital malformations in women with HbA1c levels of 8.5% or less compared with HbA1c more than 8.5% (RR 0.15, 95% CI 0.04 to 0.64). The quality of evidence for this outcome was very low.

3.7.5.2.5 *HbA1c levels less than 10.9% versus 10.9% or more*

One prospective cohort study (n=116) found a decreased risk of spontaneous miscarriage in women with HbA1c levels less than 10.9% compared with HbA1c of 10.9% or more (RR 0.35, 95% CI 0.18 to 0.66). The quality of the evidence for this outcome was very low.

No evidence was identified for maternal hypoglycaemic episodes or acceptability of target values in any of the studies included in this review.

3.7.6 Health economics profile

No published health economic evidence was found addressing target ranges for HbA1c in women with type 1 or type 2 diabetes who are planning pregnancy.

This was not prioritised for health economic analysis. This was because a target of itself does not incur an opportunity cost although the target may affect the interventions and management used to assist the patient in achieving that target.

3.7.7 Evidence to recommendations

3.7.7.1 Relative value placed on the outcomes considered

The guideline development group defined 5 priority outcomes for this review.

Maternal outcomes were:
- hypoglycaemic episodes before pregnancy or in the first trimester
- spontaneous miscarriage
- acceptability of target values, including concordance.

Neonatal outcomes were:
- congenital malformations regardless of gestational age
- mortality.

Mortality was defined as perinatal (stillbirth and death up to 7 days after birth) or neonatal (death up to 28 days after birth).

The guideline development group prioritised congenital malformations at any gestational age as the most important outcome for this review. Maintaining a near normal HbA1c in the pre-conception period is important as organogenesis in the developing fetus takes place during the first trimester. The importance of this outcome was reflected in the evidence that was identified, with 5 of the 6 included studies reporting risks for congenital malformations.

Maternal hypoglycaemic episodes before pregnancy or during the first trimester were also a priority outcome because trying to achieve euglycaemia in the woman may be associated with a greater likelihood of hypoglycaemia.

3.7.7.2 Consideration of clinical benefits and harms

The guideline development group noted that in the literature the absolute risk of congenital abnormalities in background non-diabetic populations is in the order of 2% to 3% but about 10% in women with diabetes. They also noted that the risk of congenital malformations increased with the increase of HbA1c, especially when the value was more than 10.4% (Jensen et al, 2009).

It was noted by the guideline development group that data from the study by Bell et al. (2012) show a threshold effect where the risk of congenital malformations increases in an approximately linear fashion above an HbA1c of 6.3%. Specifically, a 1% increase in HbA1c was associated with a 30% increase in risk. This indicates that even if women do not achieve an HbA1c below 6.3% they could still reduce their risk of having a baby with a congenital malformation. However, the group felt that it was important to align the recommendations with those made in the guideline on type 1 diabetes in adults and therefore recommended 48 mmol/mol (6.5%) as the target threshold. As stated above, the study by Jensen et al. (2009) shows an increase in risk of congenital malformations above HbA1c of 10.4%.

3.7.7.3 Quality of evidence

The quality of the evidence included in this review was very low. This was compounded by the fact that 2 studies necessitated conversion to HbA1c by the NCC-WCH technical team and that DCCT-alignment was not reported for most studies. Different threshold values were examined from the data in the included studies. Significantly fewer congenital malformations and perinatal deaths occurred at HbA1c thresholds below 8%. Only 1 study examined spontaneous miscarriage and significantly fewer occurred below the relatively high HbA1c threshold of 10.4%. No evidence was available regarding maternal hypoglycaemic episodes or acceptability of target values, as the majority of included studies did not set target values for women to achieve.

3.7.7.4 Other considerations

The guideline development group considered that the included studies from the UK, Europe and US examined populations that were relevant to England and Wales.

3.7.8 Key conclusions

There are associative data to suggest that the risk of stillbirth is particularly high for women with an HbA1c above 86 mmol/mol (10%) and women with values above this should be strongly advised to avoid pregnancy. However, women should be advised that the risk of a serious adverse pregnancy outcome increases linearly above an HbA1c of 45 mmol/mol (6.3%).

3.7.9 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.8 Safety of medicines for diabetes before and during pregnancy

The safety of diabetes medications (including oral hypoglycaemic agents and insulin preparations) for use during pregnancy is considered in this section. The effectiveness of insulin preparations and regimens (including continuous subcutaneous insulin infusion (CSII) pumps) is considered in Section 5.4).

3.8.1 Description of the evidence

3.8.1.1 Oral hypoglycaemic agents

Oral hypoglycaemic agents are used to maintain blood glucose control in people with type 2 diabetes. There are four main categories of oral hypoglycaemic agents: sulphonylureas (chlorpropamide, glibenclamide (also known as glyburide), gliclazide, glimepiride, glipizide, gliquidone and tolbutamide), biguanides (metformin), α-glucosidase inhibitors (acarbose) and thiazolidinediones (pioglitazone and rosiglitazone). Two other medications are used to stimulate insulin release (nateglinide and repaglinide). Each works in a different way and is suitable for different clinical situations.

A systematic review and meta-analysis examined the relationship between first-trimester exposure to oral hypoglycaemic agents and subsequent congenital abnormalities and neonatal mortality.[71] The review sought to account for the potential confounding effect of maternal glycaemic control. The meta-analysis included ten studies which reported on 471 women exposed to oral hypoglycaemic agents in the first trimester and 1344 women not exposed. There were three prospective cohort studies, three retrospective cohort studies, three case series and one case– control study. The oral hypoglycaemic agents used in the studies included chlorpropamide (eight studies), tolbutamide (six studies), glibenclamide (four studies), metformin (five studies) and phenformin (three studies). Six studies were rated as of 'poor' quality, two were 'fair' and two were 'good'. Most women in the studies had type 2 diabetes. Women with type 1 diabetes and gestational diabetes were also present in some studies. There was no significant difference in the rate of major malformations between those exposed to oral hypoglycaemic agents and those not exposed (10 studies, OR 1.05, 95% CI 0.65 to 1.70). [EL = 2++]

A further systematic review included seven additional studies that looked at the use of metformin in the first trimester of pregnancy.[72] All the studies were small observational studies, six in women with polycystic ovary syndrome and one in women with type 2 diabetes. There were no reports of birth defects, increased incidence of pre-eclampsia or other adverse maternal or neonatal outcomes. The use of metformin during pregnancy in women with polycystic ovary syndrome is associated with a reduction in miscarriage in early pregnancy, weight loss, a reduction in fasting serum insulin levels and in the incidence of gestational diabetes. [EL = 2+]

Another systematic review evaluated the safety of metformin in pregnancy for women with diabetes and polycystic ovary syndrome.[73] The review reported that metformin use during the first trimester of pregnancy was not associated with an increased risk of major malformations. [EL = 2+]

An RCT compared glibenclamide with insulin for the treatment of gestational diabetes.[74] The study involved 404 women with gestational diabetes. Approximately 83% were Hispanic, 12% were white and 5% were black. Women were randomly assigned between 11 and 33 weeks of gestation to receive either glibenclamide (n = 201) or insulin (n = 203). The mean blood glucose concentrations during treatment were 5.9 ± 0.9 mmol/litre in the glibenclamide group and 5.9 ± 1.0 mmol/litre in the insulin group (P = 0.99). Eight women (4%) in the glibenclamide group required insulin treatment. There were no significant

differences between the glibenclamide and insulin groups in the percentage of babies who were LGA (12% versus 13%), macrosomic (7% versus 4%), had lung complications (8% versus 6%) or neonatal hypoglycaemia (9% versus 6%), were admitted to a NICU (6% versus 7%), or had fetal anomalies (2% and 2%). Cord-serum insulin concentrations were similar in the two groups and glibenclamide was not detected in the cord serum of any baby in the glibenclamide group. [EL = 1++]

An RCT of metformin for the treatment of gestational diabetes (the Metformin in Gestational Diabetes (MIG) trial) is due to report soon. A pilot study randomised 14 women to insulin and 16 to metformin. There were no differences in perinatal outcomes.[75] [EL = 1−]

A retrospective cohort study examined the effects of oral hypoglycaemic agents in 379 singleton pregnancies of women with type 2 diabetes.[76] The women were subdivided into: oral hypoglycaemic agents alone (n = 93 pregnancies); converted from oral hypoglycaemic agents to insulin (n = 249); and insulin alone or converted from diet alone to insulin (n = 37). The oral hypoglycaemic agents assessed were metformin and glibenclamide. Fetal anomaly rates were similar across the three groups, whereas perinatal mortality rates (per 1000 births) were higher in the group that used oral hypoglycaemic agents alone (125, P = 0.003). Conversion from oral hypoglycaemic agents to insulin was protective for perinatal mortality compared with oral hypoglycaemic agents alone (OR 0.220, 95% CI 0.061 to 0.756, P = 0.024). The data suggest that metformin and glibenclamide are not teratogenic. [EL = 2+]

A reference guide to medicines in pregnancy and lactation reported that there were limited data on the use of metformin, acarbose, nateglinide, glimepiride, glipizide and glibenclamide in pregnant women and suggested they present a low risk to the fetus. No data were found on the use of repaglinide or pioglitazone in pregnant women, but it was suggested that they present a moderate risk to the fetus. No comparative studies were found on the use of rosiglitazone in pregnant women, but it was suggested that it presents a risk to the fetus. Evidence suggested that chlorpropamide and tolbutamide present a risk to the fetus if taken by women in the third trimester of pregnancy. Gliclazide and gliquidone were not reviewed.[77] [EL = 3]

The reference guide reported that 14 small observational studies had investigated the use of metformin in pregnant women with diabetes. Metformin has been shown to cross the placenta. The observational studies identified congenital malformations in some babies of women taking metformin, but the rate was not compared with the expected rate of congenital malformations in babies born to women with diabetes who were not taking metformin. The reference guide suggested that use of metformin may decrease fetal and infant morbidity and mortality in developing countries where the proper use of insulin is problematic, but that insulin is still the treatment of choice.[77] [EL = 3]

The reference guide reported that three observational studies had investigated the use of acarbose in pregnant women with diabetes. The observational studies identified congenital malformations in some babies of women taking acarbose, and the rate was not compared with the expected rate of congenital malformations in babies born to women with diabetes who were not taking acarbose. The reference guide noted that high maternal blood glucose is associated with maternal and fetal effects, including congenital abnormalities, and that insulin is the treatment of choice to prevent hyperglycaemia.[77] [EL = 3]

The reference guide stated that one case report had investigated the use of nateglinide in a pregnant woman with diabetes. It is not known whether nateglinide can cross the placenta, and the reference guide suggested that it presents a low risk of developmental toxicity.[77] [EL = 3]

The reference guide reported that no studies had investigated the use of glimepiride in pregnant women. It is not known whether glimepiride can cross the placenta, but the reference guide suggested that it may present a risk of skeletal deformities, growth retardation and intrauterine death.[77] [EL = 3]

The reference guide reported that case reports had investigated the use of glipizide in pregnant women. Glipizide has been shown to cross the placenta. An observational study that looked at the incidence of congenital malformation in women with type 2 diabetes found no association between oral hypoglycaemic agents and organogenesis or congenital malformations.[77] [EL = 3]

The reference guide reported that several observational studies had investigated the use of glibenclamide in pregnant women. Small amounts of glibenclamide may cross the placenta. The observational studies suggested that use of glibenclamide may decrease fetal and infant morbidity and mortality in developing countries where the proper use of insulin is problematic, and the reference guide suggested that it may be an acceptable alternative to insulin for women with gestational diabetes.[77] [EL = 3]

The reference guide reported that no studies had investigated the use of repaglinide in pregnant women. It is not known whether repaglinide can cross the placenta, and the reference guide suggested that it may affect fetal growth.[77] [EL = 3]

The reference guide reported that no studies had investigated the use of pioglitazone in pregnant women. It is not known whether pioglitazone can cross the placenta, but the reference guide suggested that it may result in post-implantation losses, delayed development and reduced fetal weight.[77] [EL = 3]

The reference guide stated that one case report had investigated the use of rosiglitazone in a pregnant woman with diabetes. It is not known whether rosiglitazone can cross the placenta, but the reference guide suggested that it may present a risk of placental toxicity, fetal death and growth retardation.[77] [EL = 3]

The reference guide stated that case reports had investigated the use of chlorpropamide and tolbutamide in pregnant women with diabetes. Chlorpropamide and tolbutamide have been shown to cross the placenta. Out of 74 case reports identified, four babies of women who had taken chlorpropamide experienced prolonged, symptomatic neonatal hypoglycaemia and one baby experienced prolonged neonatal hypoglycaemia and seizures. Several case series looked at the incidence of congenital malformations and found that chlorpropamide did not appear to be related to congenital abnormalities in pregnant women. However, the reference guide suggested that insulin is still the treatment of choice. Ten case reports relating to tolbutamide use identified no increase in the rate of congenital abnormalities over and above that expected in women with diabetes, although another four case reports attributed congenital malformations to tolbutamide. One case of prolonged hypoglycaemia in a baby following maternal treatment with tolbutamide was identified.[77] [EL = 3]

The British National Formulary recommends that metformin, acarbose and repaglinide should be avoided during pregnancy and are normally substituted with insulin.[78] The manufacturers of nateglinide, pioglitazone and rosiglitazone advise pregnant women to avoid them, and insulin is normally substituted in women with diabetes. Sulphonylureas can lead to neonatal hypoglycaemia, and insulin is normally substituted in women with diabetes. If oral hypoglycaemic medicines are used then therapy should be stopped at least 2 days before birth.

There is information on the use of oral hypoglycaemic agents during breastfeeding in Section 8.1.

Insulin

Insulin has been shown to be compatible with pregnancy and is recommended as the drug of choice for pregnant women with diabetes.[77] [EL = 3]

Insulin analogues

Insulin analogues are synthetic insulins created by modifying the chemical structure of insulin to produce either faster acting preprandial insulin or longer acting basal insulin. The insulin analogues currently licensed for use in the UK are the rapid-acting analogues lispro, aspart and glulisine and the long-acting analogues detemir and glargine. No studies were identified in relation to the effectiveness and safety of insulin glulisine or insulin detemir in pregnancy, although some research is in progress.

Insulin aspart

An RCT compared 157 pregnant women with type 1 diabetes treated using insulin aspart with 165 pregnant women with type 1 diabetes treated using human insulin.[79] There were fewer episodes of nocturnal hypoglycaemia (RR 0.48, 95% CI 0.20 to 1.14, P = 0.10) and severe hypoglycaemia (RR 0.72, 95% CI 0.36 to 1.46, P = 0.36) in the aspart group. Prandial increments (mean: breakfast, lunch and dinner) were significantly lower with insulin aspart in the first and third trimester. No differences were observed in 24 hour mean plasma glucose profiles or HbA1c values. Progression of retinopathy and perinatal complications were similar in both groups. [EL = 1++]

A small RCT randomised 27 women with gestational diabetes to either insulin aspart or human insulin.[80] The trial period extended from the diagnosis of gestational diabetes (18–28 weeks) to 6 weeks postpartum. There was no significant difference in mean reduction in HbA1c over the trial period (0.3 ± 0.5% for the insulin aspart group versus 0.1 ± 0.4% for human insulin). The safety profile for both groups was similar. [EL = 1+]

An observational study compared ten pregnant women with type 1 diabetes treated using insulin aspart with ten pregnant women treated using human insulin.[81] Groups did not differ in terms of age, weight, duration of diabetes or gestational age at the time of booking. HbA1c was lower in the insulin aspart group at booking (7.0 ± 1.0% versus 8.6 ± 1.0%, P < 0.05), throughout pregnancy and at birth (5.8 ± 0.8% versus 6.7 ± 0.7%, P < 0.05). FBG values (4.3 ± 1.4 versus 5.4 ± 2.0 mmol/litre, P < 0.01) and pre-lunch blood glucose values (4.5 ± 1.7 versus 5.1 ± 2.3 mmol/litre, P < 0.01) were lower with insulin aspart. There was no significant difference in birthweight between the insulin aspart and human insulin groups (3.4 ± 0.5 kg versus 3.89 ± 0.7 kg, P = 0.13). [EL = 2+]

A pilot study randomised five women with gestational diabetes to receive insulin aspart and five women to receive human insulin.[82] There was no difference between the two groups in mean plasma glucose level, insulin dose or mean birthweight. There were no adverse maternal or fetal outcomes in either group. [EL = 1+]

Insulin lispro

An in vitro perfusion study of the transfer of insulin lispro across the placenta found no transfer at or below a maternal concentration of 200 microU/ml (corresponding to 26 units of insulin).[83] A small placental transfer was observed at maternal concentration of 580 microU/ml (75 units) and 1000 microU/ml (130 units) when maintained for 60 minutes (this duration does not occur in the clinical setting due to the short elimination half-life of insulin lispro). [EL = 3]

A systematic review summarised 42 RCTs that compared rapid-acting insulin analogues (lispro and aspart) with regular insulin in 7933 people (including pregnant women) with type 1 diabetes, type 2 iabetes and gestational diabetes.[84] The review showed no differences between treatments in pregnant women with type 1 diabetes, women with gestational diabetes, or people with type 2 diabetes. One study included in the review assessed pregnant women with type 1 diabetes and found the reduction in HbA1c levels to be similar with rapid-acting insulin analogues and regular insulin. However, biochemical hypoglycaemia was significantly more frequent in women who used insulin analogue compared with those

who used regular insulin (P < 0.05). One study that assessed women with gestational diabetes found the total number of hypoglycaemic events did not differ between the groups. Twenty studies involving women with type 1 diabetes assessed post- treatment HbA1c levels and found weighted mean difference of HbA1c values to be –0.12% (95% CI –0.17% to –0.07%) in favour of rapid-acting insulin analogues compared with regular insulin. One study involving young women with type 1 diabetes did not show any significant reduction in HbA1c levels between rapid-acting insulin analogues compared with regular insulin. [EL = 1++]

An RCT that was included in the systematic review provided additional data not reported by the systematic review.[85] In this study 24 women with gestational diabetes treated using insulin lispro were compared with 24 women treated using regular human insulin and 50 women with normal glucose challenge test (GCT). The 1 hour postprandial blood glucose values were significantly higher in the regular group than in the lispro or control groups. The rate of babies with a cranial : thoracic circumference ratio between the 10th and the 25th percentile was significantly higher in the group treated using regular insulin compared with the lispro and control groups. There were no other differences between the three groups in neonatal outcomes. [EL = 1+]

An open RCT involving 33 women with type 1 diabetes assessed the effectiveness and safety of preprandial administration of insulin lispro and regular rapid-acting insulin.[86] Blood glucose was determined six times daily and HbA1c every 4 weeks. Blood glucose was significantly lower (P < 0.01) after breakfast in the insulin lispro group, while there were no significant differences between the treatment groups in terms of glycaemic control during the rest of the day. Biochemical hypoglycaemia (blood glucose less than 3.0 mmol/litre) was more frequent in the insulin lispro than in the regular insulin group (5.5% versus 3.9%, respectively). HbA1c values declined during the study period and were similar in both groups. Retinopathy progressed in both groups; one woman in the regular insulin group developed proliferative retinopathy. There was no perinatal mortality in either group. The study suggests that it is possible to achieve at least as adequate glycaemic control with lispro as with regular insulin therapy in pregnant women with type 1 diabetes. [EL = 1+] An earlier systematic review[87] was found on the use of insulin lispro in pregnancy. The review included an RCT of 42 women with insulin-requiring gestational diabetes randomly allocated to either insulin lispro or regular insulin. The aim of the study was to investigate whether insulin lispro crosses the placenta. No insulin lispro was detected in umbilical cord blood and there was no difference between the two groups in insulin antibodies. The women receiving insulin lispro had significantly lower glucose excursions after a test meal and experienced fewer episodes of hypoglycaemia before breakfast. They also experienced fewer hyperglycaemic episodes. There was no difference in obstetric or fetal outcomes. [EL = 1+]

The review also included 12 observational studies involving 303 women (294 with type 1 diabetes, nine with type 2 diabetes). There were seven congenital malformations in 170 women (4.1%) with pre-existing type 1 or type 2 diabetes who had been exposed to insulin lispro during embryogenesis. In comparison there were 14 congenital malformations in 133 (10.5%) women treated using regular insulin. Three observational studies reported improved glycaemic control in pregnant women using insulin lispro compared with pregnant women using regular insulin. Two of these studies also reported fewer maternal hypoglycaemic episodes and one study reported greater maternal satisfaction with insulin lispro compared with regular insulin. One study reported the development of proliferative retinopathy in three women without background retinopathy at the beginning of pregnancy. However, other risk factors for progression of retinopathy were present. Nonetheless the development of proliferative retinopathy in people with no retinopathy is rare, although it has been observed in association with rapid and substantial improvement in glycaemic control. There is no theoretical basis for an increased risk of retinopathy with insulin lispro apart from facilitating rapid and/or substantial improvement in glycaemic control.[88] No other cases of progression of retinopathy in association with insulin lispro have been reported. [EL = 2++]

An open RCT involving 33 women with type 1 diabetes assessed the effectiveness and safety of preprandial administration of insulin lispro and regular rapid-acting insulin.86 Blood glucose was determined six times daily and HbA1c every 4 weeks. Blood glucose was significantly lower (P < 0.01) after breakfast in the lispro group, while there were no significant differences between the treatment groups in terms of glycaemic control during the rest of the day. Biochemical hypoglycaemia (blood glucose less than 3.0 mmol/litre) was more frequent in the insulin lispro group than in the regular insulin group (5.5% versus 3.9%, respectively). HbA1c values declined during the study period and were similar in both groups. Retinopathy progressed in both groups; one woman in the regular insulin group developed proliferative retinopathy. There was no perinatal mortality in either group. The study suggests that it is possible to achieve at least as adequate glycaemic control with lispro as with regular insulin therapy in pregnant women with type 1 diabetes. [EL = 1+]

Four case series of women with type 1 diabetes exposed to insulin lispro in pregnancy (n = 696) were published since the systematic review.[89–92] These studies found that insulin lispro improved glycaemic control with no adverse maternal or fetal effects. [EL = 3]

Insulin glargine

An observational study of the use of glargine in 22 centres in the UK reported outcomes from 122 babies in 127 pregnancies.93 One hundred and fifteen women had type 1 diabetes, five had type 2 diabetes and seven had gestational diabetes. HbA1c fell from 8.1 ± 0.2% at booking to 6.7 ± 0.1% during the third trimester. Background retinopathy developed in one woman, progressed in three women and laser photocoagulation was required in seven women. Hypoglycaemia requiring assistance occurred in nine (7%) and 16 (12%) had two or more episodes of hypoglycaemia. There were seven (6%) early miscarriages. All 122 babies were liveborn. There were three congenital malformations (positional talipes, ventricular septal defect and transposition of the great arteries (TGA)), two occurring in women taking glargine before pregnancy giving a congenital malformation rate of 2.5%. [EL = 3]

An observational study compared maternal and perinatal outcomes in 47 women with type 1 diabetes taking glargine before pregnancy to 50 women using long-acting insulin (protaphan).[94] Groups were matched for age, parity, duration of diabetes and diabetic complications. There was no difference in outcomes (gestational age at birth, pregnancy complications, neonatal birthweight, shoulder dystocia or respiratory distress). The decrease in HbA1c between the first and third trimester was greater in the glargine group (P = 0.04) and there was a tendency towards fewer hypoglycaemic episodes (11/47 in glargine group versus 21/50 in protaphan group, P = 0.07). [EL = 2+]

A matched case–control study involving 64 pregnant women with diabetes investigated the association between insulin glargine use during pregnancy and incidence of fetal macrosomia or adverse neonatal outcomes.[95] There was no significant difference between the birthweight or centile birthweight of babies born to the women treated using insulin glargine and those born to the control group treated using intermediate-acting human insulin. Incidence of fetal macrosomia was 37.5% (12/32) in the insulin glargine group and 40.6% (13/32) in the control group. There was no significant difference in neonatal morbidity between the groups. The evidence suggests insulin glargine treatment during pregnancy does not appear to be associated with increased fetal macrosomia or neonatal morbidity. [EL = 2+]

Four case series (26 women with type 1 diabetes, four women with gestational diabetes) and two case reports (both in women with type 1 diabetes) found no adverse maternal or fetal outcomes associated with the use of glargine in pregnancy.[87,96–101] [EL = 3]

3.8.2 Existing guidance

The NSF for diabetes[20] recommends that women with type 2 diabetes who require treatment with oral hypoglycaemic agents to achieve good blood glucose control and who are planning to become pregnant or are already pregnant should be transferred to insulin therapy because of the theoretical risk associated with these medicines crossing the placenta.

3.8.3 Evidence statement

A laboratory study using validated methodology found glibenclamide did not cross the placenta. No high-quality studies have considered the use of oral hypoglycaemic agents in the first 7 weeks of pregnancy, i.e. during the period of organogenesis, although a meta-analysis of observational studies found no increased risk of congenital malformations.

Metformin crosses the placenta; however, a large number of observational studies of its use during pregnancy have found no teratogenic effect.

An RCT has found glibenclamide to be an effective alternative to insulin for the treatment of gestational diabetes.

RCTs and observational studies have shown that insulin aspart is effective for managing diabetes in pregnancy without increasing the risk of hypoglycaemia. A large number of studies have shown no indication that insulin lispro is teratogenic. There have been no clinical trials of glulisine, glargine or detemir in pregnancy.

3.8.4 From evidence to recommendations

Oral hypoglycaemic agents have a number of potential advantages over insulin for the treatment of type 2 diabetes during pregnancy and for the treatment of gestational diabetes. They are more convenient and less expensive than insulin and may improve the long-term prognosis of women with type 2 diabetes and gestational diabetes. The safety record of glibenclamide and metformin is sufficient for well-designed RCTs to be conducted on its use in early pregnancy. These studies are needed before they can be recommended for use in early pregnancy. Until this evidence is available the risks and benefits of metformin during pregnancy, including the risk of hypoglycaemia, should be weighed on an individual basis, promoting the principle of informed choice.

For some women insulin analogues may offer benefits over isophane insulin (also known as NPH insulin) in terms of flexibility and improved glycaemic control. Until sufficiently powered RCTs of insulin lispro in pregnancy have confirmed its safety and effectiveness, the risks and benefits of insulin lispro, including the risk of hypoglycaemia, should be weighed on an individual basis, promoting the principle of informed choice.

The use of other rapid- and long-acting insulin analogues (glulisine, detemir and glargine) during pregnancy should be avoided until more data are available on their safety.

3.8.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.8.6 Research recommendations

There were no research recommendations relating to which medications for diabetes are safe for use during pregnancy and which should be discontinued.

3.9 Safety of medicines for diabetic complications before and during pregnancy

3.9.1 Description of the evidence

3.9.1.1 Angiotensin-converting enzyme inhibitors

In people with diabetes, ACE inhibitors are used to treat hypertension and slow the progression of nephropathy.[102]

Two case series were identified that reported on the use of ACE inhibitors in women with diabetes and nephropathy who were planning a pregnancy and who discontinued treatment on confirmation of pregnancy.

Three cohort studies and two case series were identified that considered the maternal, fetal and neonatal effects of first-trimester exposure to ACE inhibitors.

3.9.1.2 Angiotensin-converting enzyme inhibitors before pregnancy:

In eight women with diabetic nephropathy[103] ACE inhibitors were used for a minimum of 6 months prior to conception. Women attempted conception when proteinuria was less than 500 mg/day and euglycaemia was achieved. At conception ACE inhibitors were discontinued. Before ACE inhibitor treatment proteinuria was 1633 ± 666 mg/day. At conception it was 273 ± 146 mg/ day (P < 0.0001). Proteinuria increased gradually over each trimester to 593 ± 515, 783 ± 813 and 1000 ± 1185 mg/day, respectively (P = 0.2 between trimesters). Three months after birth proteinuria was 619 ± 411 mg/day. In two women (25%), proteinuria exceeded 1000 mg/day during pregnancy. There was no significant change in any other renal function test (creatinine clearance test, serum creatinine, uric acid, potassium). Women remained euglycaemic throughout pregnancy. There were three cases

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dd At the time of publication (February 2015), long-acting insulin analogues did not have UK marketing authorisation for use during pregnancy in women with diabetes. However, the summaries of product characteristics (SPCs) for insulin detemir and insulin glargine state that their use may be considered during pregnancy; see the SPCs of the individual products for details. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

of pre-eclamptic toxaemia (PET) just prior to birth, which resolved immediately following birth. There were two LGA babies without complications. There were no other adverse maternal or neonatal outcomes. [EL = 3]

In a case series of 24 women with diabetic nephropathy and normal to mild renal impairment104 all women received ACE inhibitors for at least 6 months prior to conception and maintained strict glycaemic control from at least 3 months prior to conception. Proteinuria was 1292 ± 656 mg/day before treatment, 202 ± 141 mg/day at conception (P = 0.001), 650 ± 502 mg/day in the first and second trimesters, 1012 ± 1206 mg/day in the third trimester and 590 ± 410 mg/day 6–8 weeks after birth. Mean serum creatinine and uric acid levels increased significantly in the first and third trimesters. Creatinine clearance and potassium remained stable. All women maintained blood glucose levels near to normal throughout pregnancy. There were 11/24 cases (46%) of superimposed pre-eclampsia, 4/24 cases (17%) of preterm birth and 5/24 cases (21%) offetal growth restriction. The rate of caesarean section was 62.5%. There was one intrauterine death at 24 weeks of gestation secondary to early severe fetal growth restriction. One baby was admitted to intensive care because of prematurity. No deterioration was observed in any of the women at 2 year follow-up. Two babies had cerebral palsy due to birth trauma secondary to LGA. [EL = 3]

3.9.1.3 Angiotensin-converting enzyme inhibitors in the first trimester

A cohort study[105] included 29507 babies, 209 of whom had been exposed to ACE inhibitors in the first trimester alone and 202 of whom had been exposed to other antihypertensive medication in the first trimester. Babies of women with diabetes, or who were exposed to ACE inhibitors after the first trimester, or who were exposed to any other potential teratogens, were excluded. Maternal use of prescribed medications was determined from pharmacy files, which included the date when the prescription was filled and the number of days for which the medicine was supplied. Major congenital malformations were identified from medical records. Babies with first- trimester-only exposure to ACE inhibitors had an increased risk of major congenital malformations (RR 2.71, 95% CI 1.72 to 4.27) as compared with babies who had no exposure to antihypertensive medications. In contrast, exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (RR 0.66, 95% CI 0.25 to 1.75). [EL = 2+]

A second cohort study which assessed ACE inhibitor use before pregnancy and in early pregnancy assessed adverse pregnancy outcomes in 18 women and 19 pregnancies.106 No congenital abnormalities or neonatal renal dysfunction were reported. Even in the six pregnancies in which ACE inhibitors were continued beyond 12 weeks of gestation (including one where therapy was continued until 25 weeks of gestation) there were no congenital abnormalities. [EL = 2++]

A third cohort study assessed the effect of prescription of ACE inhibitors at 5–15 weeks of gestation in 21 pregnant women in terms of adverse pregnancy outcomes.[107] There were no stillbirths or congenital malformations among the 21 babies. [EL = 2++]

A report of post-marketing surveillance for ACE inhibitors108 reported outcomes of pregnancy in 66 women who self-enrolled to the registry after first-trimester-only exposure. There were 48 live births and 15 miscarriages (23%). Among the 48 live births there were three cases offetal growth restriction. Another child had a patent ductus arteriosus that required surgical ligation at 18 months. Other known risk factors were present in the three cases of fetal growth restriction (i.e. multiple gestation or hypertension). [EL = 3]

A prospective case series109 reported outcomes for eight women treated using ACE inhibitors in the first trimester. There were no major malformations. There were two cases offetal growth restriction, one of which ended in an intrauterine death. This was attributed to severe disease in the mother rather than drug effect. [EL = 3]

A reference guide to medicines in pregnancy and lactation reported that data from studies involving pregnant women suggest a risk to the fetus if the ACE inhibitors enalapril, lisinopril, moexipril, perindopril, quinapril and trandolapril are used in the second or third trimesters of pregnancy. There was no information about captopril, cilazapril, fosinopril, imidapril or ramipril.[77] [EL = 3]

The British National Formulary recommends that ACE inhibitors should be avoided during pregnancy as they may adversely affect fetal and neonatal blood pressure control and renal function and they may cause skull defects and oligohydramnios.[78]

There is information on the use of ACE inhibitors during breastfeeding in Section 8.1.

3.9.1.4 Angiotensin-II receptor blockers

A reference guide to medicines in pregnancy and lactation reported that data from studies involving pregnant women suggest a risk to the fetus if ARBs are used in the second or third trimesters of pregnancy.[77] [EL = 3]

The British National Formulary recommends that ARBs should be avoided during pregnancy as they may adversely affect fetal and neonatal blood pressure control and renal function; they may also cause skull defects and oligohydramnios.[78]

There is information on the use of ARBs during breastfeeding in Section 8.1.

3.9.1.5 Statins

Statins (HMG CoA reductase inhibitors) are used to reduce elevated levels of cholesterol. Statins currently licensed for use in the UK include atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

A reference guide to medicines in pregnancy and lactation reported that atorvastatin, fluvastatin, pravastatin and simvastatin are contraindicated in pregnancy and lactation.[77] [EL = 3]

The reference guide reported that a small number of case reports and surveillance studies and a case series had investigated the use of atorvastatin, fluvastatin, pravastatin and simvastatin in pregnant women. The case series evaluated 20 cases of malformation in 54 cases of statin exposure reported to the US Food and Drug Administration between 1987 and 2001. The malformations included five major defects of the central nervous system (including two cases of holoprosencephaly) and five unilateral limb deficiencies. There was no review for rosuvastatin. [EL = 3]

The British National Formulary recommends that statins should be avoided during pregnancy as congenital malformations have been reported and decreased synthesis of cholesterol may affect fetal development.[78]

There is information on the use of statins during breastfeeding in Section 8.1.

3.9.1.6 Obesity medicines

A reference guide to medicines in pregnancy and lactation reported that there were no data for the use of orlistat (a lipase inhibitor) or sibutramine (a centrally acting appetite suppressant) in pregnant women, and it suggested that they present a low risk to the fetus. There was no review for rimonabant, another centrally acting appetite suppressant.[77] [EL = 3]

The British National Formulary reports that the manufacturers of orlistat advise that it should be used with caution during pregnancy. The manufacturers of sibutramine and rimonabant recommend that they should be avoided in pregnancy.[78]

There is information on the use of obesity medicines during breastfeeding in Section 8.1.

3.9.2 Evidence statement

Two small case series reported on the use of ACE inhibitors until conception in women with diabetic nephropathy. Renal function did not appear to deteriorate during pregnancy. There was no evidence of teratogenic effect and evidence of moderate-to-good pregnancy outcomes associated with the use of ACE inhibitors.

Two small case series reporting on the use of ACE inhibitors in the first trimester of pregnancy did not detect a teratogenic effect. However a large, well-controlled cohort study that linked pregnancy outcomes to prescription records found that babies with first-trimester-only exposure to ACE inhibitors had an increased risk of major congenital malformations compared with babies who had no exposure to antihypertensive medications.

No clinical evidence was identified in relation to the safety of ARBs or statins in pregnancy. The British National Formulary recommends that ARBs and statins should be avoided during pregnancy.

No clinical evidence was identified in relation to the safety of obesity medicines in pregnancy. The British National Formulary recommends that orlistat should be used with caution in pregnancy and that other medicines for the treatment of obesity should be avoided.

3.9.3 From evidence to recommendations

ACE inhibitors and ARBs (angiotensin-II receptor antagonists) should be avoided throughout pregnancy because of the possible risk of congenital malformations. However, the benefits of continuing with ACE inhibitors until discontinuation of contraception for the purposes of protecting renal function should be considered. For women with microalbuminuria, the risk of progression to macroalbuminuria in the preconception period is thought to be small while the risk of pre-eclampsia is greatly increased.

As cholesterol and products synthesised during pregnancy are important to fetal development and as there is no apparent harm from interrupting cholesterol-lowering therapy during pregnancy.[77] statins should be avoided during pregnancy. [EL = 3]

There were no research recommendations relating to which medications for diabetic complications are safe for use during pregnancy and which should be discontinued.

3.9.4 Recommendations
The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.10 Removing barriers to the uptake of preconception care and when to offer information

Preconception care is aimed at reducing congenital abnormalities by improving maternal glycaemic control before conception and during the first 7 weeks of pregnancy. 'Preconception care', 'preconception counselling' and 'preconception clinic' are often used interchangeably but most definitions include the following components:

- information and education for the woman and her partner
- support in improving glucose control before pregnancy through intensified insulin regimens, dietary advice and glucose monitoring
- preparation for pregnancy, including supplementation with folic acid; medication review; and assessment and treatment (if necessary) of diabetic complications.

3.10.1   Description of the evidence

A CEMACH audit from England, Wales and Northern Ireland and four studies undertaken in the USA were found that looked at the factors influencing uptake of preconception care in women with diabetes.

A CEMACH audit of pregnancy in women with pre-existing diabetes in England, Wales and Northern Ireland (n = 3808) found that only 35% of women received preconception counselling. Of these, 68% received counselling at the adult diabetes clinic, 13% at a preconception clinic and 4% from the GP (the service providing the counselling was not known for 15% of women). Folic acid was taken by 39% of women and 37% were reported as having a measure of long-term glycaemic control in the 6 months prior to pregnancy. Women with type 2 diabetes and women from a minority ethnic group were significantly less likely to have had a measure of long-term glycaemic control (P < 0.001).[2] [EL = 3]

A 2002 audit of units expected to provide maternity care for women with diabetes in England, Wales and Northern Ireland reported that there was no formal arrangement for preconception counselling in 16% of units; in 49% there was advice within the general diabetes clinic only; 17% of units had separate preconception clinics; the remaining units had other arrangements, advice within the general diabetes clinic and by an obstetrician within obstetric services, or advice by an obstetrician within the obstetric services only.[32] [EL = 3]

A population-based study recruited 85/122 (70%) women with diabetes who gave birth at 15 participating hospitals over 12 consecutive months.[112] Nonparticipants included women excluded from the study due to adverse pregnancy outcome. Study methods included: a review of medical records (for HbA1c on entry to preconception care); a self-administered questionnaire (for information on demographics, access to health care, contraceptive behaviour and including the Marital Satisfaction Scale and the Health Locus of Control scale); and interviews (for responses on a range of topics potentially related to pregnancy planning behaviour). A planned pregnancy was defined as a pregnancy that was desired before conception, in which contraception was stopped or avoided for the purposes of becoming pregnant, and in which the woman stated that she attempted to achieve optimal blood glucose control before becoming pregnant. All other pregnancies were defined as unplanned. By this definition 41% (35/85) of pregnancies were planned. The results were as follows. [EL = 2+]

Background characteristics

The average SD above the laboratory mean for glycohaemoglobin at the first antenatal visit was significantly lower in planned than unplanned pregnancies (3.1 versus 5.8, P = 0.004). Women with planned pregnancies had significantly higher income (P < 0.0001), more education (P = 0.05), were more likely to be white (P = 0.007), to have private health insurance (P < 0.001), to have attended for diabetes care in the 6 months before conception (P = 0.003) and were less likely to smoke (P < 0.001).

Contraceptive behaviour and desire for motherhood

Among the 50 women with unplanned pregnancies, 70% (35) used contraception less than half the time. (There were five women who thought that diabetes made it more difficult to

conceive). Seventy percent (35/50) of women with unplanned pregnancies said they were very happy when they found out they were pregnant.

Relationship with partner

Women with planned pregnancies were more satisfied with their relationship with their partner than were women with unplanned pregnancies. Logistic regression found a significant association between Marital Adjustment Scale score and pregnancy planning (OR 3.86, P = 0.0002). In the planned pregnancy group, 80% (28/35) of women believed that their partners were well informed about diabetes and pregnancy issues before the pregnancy. Many couples had attended appointments together and almost all women expressed a feeling of being supported. In contrast 16% (8/50) of women with unplanned pregnancies felt their partners were informed about diabetes and pregnancy before the pregnancy and most 'felt that their partners did not understand the enormity of effort required to achieve good diabetes control'.

Knowledge

Nearly all women with planned pregnancies (33/35, 94%) and 68% (34/50) of women with unplanned pregnancies knew they should be in good diabetes control before pregnancy. However, women with planned pregnancies were more likely to understand the specific association between high blood glucose levels and birth defects (83% versus 30%). Eight women with unplanned pregnancies could not recall hearing any information before pregnancy about diabetes and pregnancy. In women with unplanned pregnancies, 56% (28/50) had a previous pregnancy with diabetes. In the women with planned pregnancies, 49% (17/35) had a previous pregnancy with diabetes.

Personality

Women with unplanned pregnancies were significantly more likely to have an external locus of control (i.e. to attribute their health outcomes to the control of powerful others) than were women with planned pregnancies (OR 2.28, P < 0.004). There was no association between pregnancy planning and internal locus of control (the belief that health outcomes are largely under one's own control) or chance locus of control (the belief that health is due to luck or fate).

Advice from healthcare provider

Among women with planned pregnancies, 75% (26/35) felt they had received reassuring and encouraging advice from their providers before pregnancy. In contrast, 14% (7/50) of women with unplanned pregnancies received reassuring advice. Among women with unplanned pregnancies, 38% (19/50) recalled that pregnancy was discouraged.

Relationship with healthcare provider

A positive relationship with their healthcare provider was described by 75% (25/35) of women with planned pregnancies compared with 28% (14/50) of women with unplanned pregnancies. Women who described a positive relationship 'felt it was important that their doctor understood the difficulty of living with diabetes and did not judge them on their blood glucose control'. [EL = 2+]

A multicentre case–control study113 compared women with pre-existing diabetes making their first preconception visit (n = 57, 53 type 1 diabetes, four type 2 diabetes) with those making their first antenatal visit without having received preconception care (n = 97, 79 type 1 diabetes, 18 type 2 diabetes). In the antenatal group only 24% of pregnancies were planned. After logistic regression the following variables were associated with seeking preconception care: education (OR 4.81, P < 0.01), living with partner (OR 11.25, P < 0.01),

visited a diabetes clinic in the last year (OR 8.25, P < 0.01), encouraged by provider to receive preconception care (OR 3.39, P < 0.02) and adherence to diabetes regimen (OR 3.03, P < 0.03). All women in the study completed a validated questionnaire on knowledge, attitudes, beliefs and behaviours regarding diabetes in pregnancy. Women in the preconception care group were significantly more likely to perceive that preconception care conferred benefits to the woman and child and to report instrumental social support (i.e. social support that involved practical, tangible aid offered by another individual). However these items were not significant when entered into a logistic regression model. [EL = 2+]

A 5 year longitudinal study involved 66 women with type 1 diabetes and 207 women without diabetes.[114] All women with diabetes were at least 1 year post diagnosis. Women were classified as being in one of four stages of the maternal diabetes lifecycle: (1) prevention of unplanned pregnancies; (2) reproductive decision making; (3) commencement of intensive metabolic control; or (4) treatment continuation with pregnancy. The study used annual questionnaires and interviews to assess knowledge, attitudes, personality and social support. In the prevention of unplanned pregnancy stage 82% of women with diabetes and 88% of women without diabetes used contraception. Women with diabetes were more likely to use condoms (P = 0.05). Themes that emerged during interviews included the belief that oral contraceptives were unsafe for women with diabetes and that diabetes made it difficult to conceive. In the 5 years of the study there were 23 pregnancies in women with diabetes, 78% (17) of which were unplanned. In women without diabetes there were 33 pregnancies, 48% (16) of which were unplanned. Consistent use of contraception was significantly associated with higher levels of social support for contraception (P < 0.05) and positive attitudes towards contraception (P < 0.05). There was no significant association with knowledge of contraception, knowledge of diabetes, locus of control or self-esteem. [EL = 2+]

A cross-sectional study surveyed 55 women with pre-existing diabetes attending a preconception clinic.[115] HbA1c levels were determined either before conception or during the first trimester. Values in the normal range (4–6%) were considered 'optimal', values between 6% and 8% were considered 'adequate' and values greater than 8% were considered 'sub-optimal'. All women were given a questionnaire on preconception education and control of glycaemia. Sixty percent (33/55) of women had sub-optimal control while only 11% (6) had values in the normal range. Women with prior poor outcome of pregnancy were significantly more likely to enter pregnancy with poor glycaemic control (P = 0.02). Logistic regression revealed that not being advised to achieve target glucose or HbA1c values (questionnaire response) was associated with entering pregnancy with poor glycaemic control (P = 0.02). Overall 29 women stated that they had planned their pregnancies but only 12 (22%) saw a physician before conception to modify insulin intake or glycaemic control. [EL = 2+]

No comparable studies were found for the UK, although two studies were found in women without diabetes. An interview study using a semi-structured questionnaire included 88 pregnant women and 40 non-pregnant women.[116] Among the pregnant women 45 had a planned pregnancy and 43 had an unplanned pregnancy. Life events, difficulties, quality of relationships, self-esteem and the 'secondary gain' inherent in becoming pregnant were examined. Secondary gain was used to refer to advantage or benefit that may arise from becoming pregnant, for example by alleviating previous problems. Examples of secondary gain included autonomy from parents, solidification of an unstable relationship, an excuse to leave a boring job and/or begin a new and important phase in their lives. Women with unplanned pregnancies were significantly more likely to be rated as having a 'high' chance of secondary gain than women with planned pregnancies (χ^2 = 29.41, P < 0.0001). The study also found that women with planned pregnancies were significantly more likely to have a partnership rated 'high' in overall quality (χ^2 = 7.10, P < 0.05). The authors concluded that women with unplanned pregnancy may in fact fall into a group of 'semi-planned' pregnancy 'who are indifferent or at worst ambivalent about the idea of pregnancy'. [EL = 2+]

An interview study with 47 women without diabetes117 found that, when discussing the circumstances of their pregnancies, women did not use the terms 'planned' or 'unplanned' spontaneously. When asked to apply the terms, women applied the term 'planned' only when four criteria were met. Intending to become pregnant and stopping contraception were not sufficient. Agreeing to the pregnancy with their partner and reaching the right time in terms of lifestyle or life stage were also necessary. The term 'unplanned' covered a wide variety of circumstances. [EL = 2+]

Young women

A case–control study118 examined knowledge, attitudes, intentions and behaviours regarding diabetes and reproductive issues, sexual activity and birth control in young women with diabetes as well in those without diabetes. The study results showed that having diabetes did not appear to significantly decrease the risk-taking behaviour of the young women. [EL = 2−]

A descriptive qualitative study[119] examined whether young women with type 1 diabetes were aware and concerned about pregnancy-related complications and how to prevent them. The study showed that young women with diabetes lacked awareness of pregnancy-related complications associated with diabetes, of the term 'preconception counselling' and its role in preventing such complications, and of the importance for women with diabetes to use a highly effective method of contraception for preventing unplanned pregnancy. [EL = 3]

Current practice

A CEMACH survey of maternity units in England, Wales and Northern Ireland assessed the quality of maternity service provision against standards set out in the NSF for diabetes.32 It found that in 2002 only 17% of maternity units provided a preconception clinic; this proportion had remained largely unchanged from 1994 (16%). [EL = 2+]

Further information about current practice in terms of preconception care and the importance of planning pregnancy is presented in Section 3.2.

3.10.2 From evidence to recommendations

Evidence shows that women with diabetes (including young women) lack awareness of the importance of planning pregnancy and the role and purpose of preconception care. To overcome barriers to preconception care information about the importance of planning pregnancy and achieving good glycaemic control in the periconceptional period should be reinforced at each contact between women with diabetes who are of childbearing age and their healthcare professionals, including the diabetes care team, and the woman's intentions regarding pregnancy in the immediate future or longer term should be discussed.

There were no research recommendations relating to the barriers to uptake of preconception care and the information that should be offered to all women of childbearing age with diabetes and/or women with diabetes who are planning a pregnancy.

3.10.3 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.10.4 Evidence statement

The following barriers to preconception care were identified.

Pregnancy planning

Most pregnancies in women with diabetes are unplanned. The evidence suggests that

pregnancy planning should be considered a continuous rather than a dichotomous variable – only a minority of unplanned pregnancies are due to contraceptive failure. For example, one study found that the majority of women with unplanned pregnancy were not using contraception and said they were very happy when they found out they were pregnant. That some 'unplanned' pregnancies may not have been unexpected or unwanted, reflects 'conflicting or ambivalent emotions' towards motherhood[112] or an underlying desire to bring about change in other areas of life.

Sociocultural factors

Women with unplanned pregnancies are more likely to be from a lower socio-economic group or a minority ethnic group. This reflects complex social and cultural differences in knowledge, attitudes, motivation and support with regard to diabetes self-management and pregnancy planning. Nonetheless, in one study more than half of unplanned pregnancies were in white women with tertiary education.

Knowledge

Common misconceptions are that diabetes decreases fertility and that oral contraceptives have a detrimental effect on diabetes. One study found that 16% of women with an unplanned pregnancy could not recall hearing any information before pregnancy about diabetes and pregnancy. Knowledge of the effects of the benefits of good glycaemic control prior to pregnancy does not guarantee pregnancy planning. One study found nearly half of the women with unplanned pregnancy had a previous pregnancy with diabetes.

Relationship with healthcare professionals

Feeling judged and being discouraged from becoming pregnant is associated with unplanned pregnancy.

Social support

A lack of social support, in particular, an unsupportive partner, is associated with unplanned pregnancy.

Appropriateness and availability of services

Only a minority of maternity units provide a preconception clinic and services currently provided may not be effective in addressing the barriers to uptake of preconception care identified above. In particular, a service that is provided only after women indicate that they are planning to become pregnant will have limited uptake.

Young women

A case–control study and a qualitative study have investigated attitudes to pregnancy in young women with diabetes. Having diabetes did not reduce risk-taking behaviour in young

women and, as for other women with diabetes, they lacked awareness of the importance of planning pregnancy.

3.11 Cost-effectiveness of self-management programmes

The effectiveness of self-management of diabetes in pregnancy was identified by the GDG as a priority for health economic analysis. The GDG approached the analysis by considering the cost-effectiveness of preconception care and advice for women with diabetes. The methods and results from the health economic modelling are summarised here; further details are provided in Appendix N.

A retrospective cohort study[120] examined the effect of an intensive diabetes management programme during pregnancy on women's long-term self-management behaviours and glycaemic control. The study showed that there was a significant improvement in all diabetes self-management behaviours including frequency of self-monitoring of blood glucose, frequency of insulin injections and frequency and complexity of insulin dose adjustment from entry to the programme to birth of the baby. There was also a significant improvement in HbA1c from entry to birth of the baby. [EL = 2−]

An economic model constructed for the purposes of this guideline suggested that some form of preconception care and advice was likely to be cost-effective. Due to data limitations and uncertainty about the effectiveness of different forms of preconception care and advice, the robustness of baseline results were assessed using threshold analyses. These showed that the reduction in major congenital malformations needed for preconception care and advice to be considered cost- effective was much lower than reported in a meta-analysis of cohort studies of preconception care and advice,[121] [EL = 2++] and that cost-effectiveness of preconception care and advice relative to no preconception care and advice was not very sensitive to the costs of preconception care and advice or the 'downstream' costs associated with major congenital malformations.

3.11.1 From evidence to recommendations

NICE recommends that structured education programmes are made available to people with type 1 and type 2 diabetes.[18] The benefits of such programmes, which include DAFNE[69] for type 1 diabetes, Diabetes Education and Self Management for Ongoing and Newly Diagnosed type 2 diabetes (DESMOND) and X-PERT for people with type 2 diabetes, are likely to be even greater for women planning a pregnancy because good glycaemic control improves pregnancy outcomes. The GDG considers, therefore, that it is particularly important that women with diabetes do not forego the benefits of such programmes.

A meta-analysis of preconception care and advice found that it conferred a statistically significant reduction in the rate of major congenital malformations in offspring born to women with diabetes.[62] There is some concern that confounding may explain at least some of the observed effect and that the potential benefits in term of improved glycaemic control may be lessened in settings where structured education programmes are offered more generally to women with diabetes. However, the economic model demonstrated that a much smaller effect size than reported in the meta- analysis would still be considered cost-effective and the GDG considered that preconception care and advice would meet the threshold for cost-effectiveness.

Preconception care and advice can take many different forms and some of this heterogeneity was reflected in the meta-analysis.[121] However, the different methods of delivering preconception care and advice vary enormously in terms of their resource use and ideally the incremental cost- effectiveness ratios (ICERs) of these alternative methods should be compared. However, such an analysis is not really possible using existing data and their inherent limitations. Therefore, the GDG did not recommend a specific form of preconception care and advice.

The GDG has used the phrase 'preconception care and advice' (rather than 'preconception counselling') in the recommendations to emphasise that this is care and advice provided by members of the multidisciplinary diabetes and antenatal care team (see Section 5.11) during the preconception period, rather than services provided by trained counsellors.

3.12 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.12.1 Research recommendations

13. What is the most clinically and cost-effective form of preconception care and advice for women with diabetes? [2008]

Why this is important

Preconception care and advice for women with pre-existing diabetes is recommended because a health economic analysis has demonstrated cost-effectiveness of attendance at a preconception clinic.

Due to limitations in the clinical evidence available to inform the health economic modelling it was not possible to establish the optimal form of preconception care and advice for this group of women.

Future research should seek to establish the clinical and cost-effectiveness of different models of preconception care and advice for women with pre-existing diabetes.

Specifically it should evaluate different forms of content (i.e. what topics are covered), frequency and timing of contact with healthcare professionals (for example, whether one long session is more clinically and cost-effective than a series of shorter sessions), which healthcare professionals should be involved (for example, whether preconception care and advice provided by a multidisciplinary team is more clinically and cost-effective than contact with one healthcare professional), and format (for example, whether group sessions are more clinically and cost-effective than providing care and advice for each woman separately).

The research should also seek to establish whether women with type 1 and type 2 diabetes have different needs in terms of preconception care and advice, and how different models of care and advice compare to structured education programmes already offered to women with type 1 and type 2 diabetes.

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ee The recommendations in NICE technology appraisal guidance 60 relating to type 2 diabetes have been replaced by recommendations in the NICE guideline on type 2 diabetes (update currently under way; publication expected August 2015). The recommendations in TA60 relating to type 1 diabetes will be replaced by new recommendations in the updated NICE guideline on type 1 diabetes (update currently under way; consultation 10 December 2014 to 4 March 2015; publication expected August 2015).

3.13 Retinal assessment in the preconception period

3.13.1 Evidence

The evidence in relation to retinal assessment in the preconception period and the GDG's interpretation of the evidence are presented in Section 5.6.

3.13.2 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

3.13.3 Research recommendations

There were no research recommendations in relation to retinal assessment in the preconception period.

3.14 Renal assessment in the preconception period

3.14.1 Evidence

The evidence in relation to renal assessment in the preconception period and the GDG's interpretation of the evidence are presented in Section 5.7.

3.14.2 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

3.14.3 Research recommendations

There were no research recommendations in relation to renal assessment in the preconception period.

4 Gestational diabetes

4.1 Introduction
This section was updated in 2015

Gestational diabetes is defined classically as glucose intolerance diagnosed in the mother for the first time in pregnancy and resolving following childbirth. The women identified with glucose intolerance in pregnancy as a result of screening comprise 3 sub-groups. The vast majority have exclusively pregnancy-specific glucose intolerance (gestational diabetes). However, some women will be identified in screening with previously undetected type 2 diabetes. Finally, there are a small number of women who present with type 1 diabetes in pregnancy.

Over the years the definition, detection and management of gestational diabetes has been controversial and dominated by opinion. The original guideline on diabetes in pregnancy, published in 2008, redressed that situation to a degree. However, since then the landmark Hyperglycaemia and Pregnancy Outcome (HAPO) study, together with several high quality randomised controlled trials (RCT) of treatment have advanced the field considerably.

Prior to HAPO, the definition of gestational diabetes was based largely upon consensus reviews of glucose tolerance data from the non-pregnant population. This led the World Health Organization (WHO) to define gestational diabetes using the criteria for impaired glucose tolerance (fasting plasma glucose of 7.0–7.8 mmol/litre; 2 hour post 75 g glucose load 7.8–11.1 mmol/litre) and these were the diagnostic criteria for gestational diabetes recommended in the original guideline.

However, it has been recognised that the WHO fasting threshold for the diagnosis of gestational diabetes mellitus (GDM) is too high. The WHO and others recognised a category of impaired fasting glucose (6.1–7.8 mmol/litre) yet did not incorporate this into the definition of gestational diabetes. Consequently there arose the unsatisfactory situation of fasting glucose levels that were regarded as abnormal for women who were not pregnant but which would not be diagnostic for gestational diabetes according to the WHO definition (and the NICE 2008 guideline). HAPO showed, however, that the relationship between maternal glycaemia and pregnancy outcome was linear, with no obvious threshold of plasma glucose for adverse outcome, thus posing the question as to where along this continuum gestational diabetes should be defined.

Since HAPO was published, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed diagnostic criteria based upon the fasting, 1 hour and 2 hour post 75 g oral glucose maternal plasma glucose values associated with a 1.75-fold increased risk for an adverse pregnancy outcome (known as the 'IADPSG criteria'). This definition has since been adopted by WHO but there has been widespread concern about the increased number of women who would be diagnosed with gestational diabetes as a result if these criteria were adopted and the consequent impact on antenatal care provision.

These concerns have been reinforced partly by RCT evidence of a benefit of intensified maternal glycaemic control in women with gestational diabetes, although these studies did not use the latest diagnostic criteria. The data from these studies have, however, provided a basis for addressing questions about screening and diagnosis management of gestational diabetes.

The scope for the revised guideline identified key questions for review in the following areas:
- the best method of screening for gestational diabetes
- the optimum timing of screening for gestational diabetes
- the diagnostic criteria for gestational diabetes determined by clinical and health economic cost effectiveness
- the optimum management of gestational diabetes
- the best test and timing of postnatal assessment of glucose tolerance in women with gestational diabetes.

4.2 Risk factors for gestational diabetes

Gestational diabetes is defined by the World Health Organization (WHO) as 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy'.[31] According to the Pedersen hypothesis,[122] maternal hyperglycaemia results in excess transfer of glucose to the fetus resulting in fetal hyperinsulinaemia. The effects of fetal hyperinsulinaemia include:

- an overgrowth of insulin-sensitive tissues such as adipose tissues, especially around the chest, shoulders and abdomen, which increases the risk of shoulder dystocia, perinatal death, birth trauma and the need for caesarean section
- neonatal metabolic complications such as hypoglycaemia
- a hypoxaemic state in utero which may increase the risk of intrauterine fetal death, fetal polycythaemia, hyperbilirubinaemia and renal vein thrombosis[123]
- an increased long-term risk of obesity and diabetes in the child.

The potential benefits of recognising and treating gestational diabetes include reductions in ill health in the woman and/or the baby during or immediately after pregnancy, as well as the benefits of reducing the risk of progression to type 2 diabetes in the longer term and/or future pregnancies being complicated by pre-existing or gestational diabetes.[124]

The 'gold standard' diagnostic test for gestational diabetes is the 75 g oral glucose tolerance test (OGTT) conducted at 24–28 weeks of gestation. The WHO definition of gestational diabetes encompasses both impaired glucose tolerance (IGT) (fasting blood glucose (FBG) less than 7.0 mmol/L and a 2 hour blood glucose 7.8 mmol/L or more) and diabetes (FBG 7.0 mmol/L or more or 2 hour blood glucose 11.1 mmol/L or more).31

4.2.1 Description of the evidence

A systematic review of screening for gestational diabetes was undertaken for a health technology assessment (HTA)[124] which included one UK study.[125] An additional study was identified that was published after the systematic review was published.[126]

The systematic review included 135 studies, although in only 16 studies were all women given a diagnostic OGTT regardless of screening result.[124] The review found risk factors for gestational diabetes were obesity, advanced maternal age, family history of diabetes, minority ethnic background, increased weight gain in early adulthood and current smoker. [EL = 2++] Ethnic minority groups have an increased risk of developing gestational diabetes.[127]

In the one UK study included in the HTA systematic review,[125] 1.5% (170/11205) of women were diagnosed with gestational diabetes. Women with gestational diabetes were significantly older (32.3 versus 28.3 years, $P < 0.001$), had higher BMI (27.7 kg/m² versus 23.8 kg/m², $P < 0.001$) and were more likely to be from a minority ethnic group (55.4% versus 15.3%, $P < 0.0001$). Rates of gestational diabetes by ethnicity were: white 0.4% (26/6135), black 1.5% (29/1977), south-east Asian 3.5% (20/572) and Indian 4.4% (54/1218). After adjusting for age, BMI and parity, the relative risks (RRs) (with white ethnicity as the reference category) were as follows: black 3.1 (95% CI 1.8 to 5.5), south-east Asian 7.6 (95% CI 4.1 to 14.1) and Indian 11.3 (95% CI 6.8 to 18.8).

The HTA systematic review found that using risk factors alone as a screening test produced low sensitivities (50–69%) and specificities (58–68%; eight studies). One non-randomised, uncontrolled observational study128 that gave all women (n = 1185) a 75 g OGTT found 39.2% (31) of women with gestational diabetes had no risk factors and would have been missed if only selective testing was used. In this study women with no risk factors had a gestational diabetes prevalence of 4.8%. One study129 found that four risk factors (age,

BMI, ethnic group and family history) gave most of the information and that adding other items added little. [EL = 2++]

One study was identified that had been published since the HTA and had given all women a diagnostic OGTT. This prospective population-based study conducted in Sweden offered all pregnant women without diabetes a 75 g OGTT at 28–32 weeks of gestation.[126] Seventy-four percent (3616/4918) of women agreed to the OGTT. Women who did not take the OGTT were more likely to be multiparous and of non-Nordic origin but were less likely to have a family history of diabetes, previous macrosomic baby or previous gestational diabetes. Of the women who had the OGTT, 1.7% (61) had gestational diabetes. The risk factors with the strongest association were previous gestational diabetes (12/61, OR 23.6, 95% CI 11.6 to 48.0) and previous macrosomic baby (9/61, OR 5.59, 95% CI 2.68 to 11.7). Other risk factors were family history of diabetes (13/61, OR 2.74, CI 1.47 to 5.11), non-Nordic origin (13/61, OR 2.19, 95% CI 1.18 to 4.08), weight 90 kg or more (8/61, OR 3.33, 95% CI 1.56 to 7.13), BMI 30 kg/m² or more (11/61, OR 2.65, 95% CI 1.36 to 5.14) and age 25 years or more (55/61, OR 3.37, 95% CI 1.45 to 7.85). [EL = 2+]

A cohort study[130] examined the effects of pre-pregnancy BMI on antenatal, intrapartum, postnatal and neonatal outcomes. The study showed that women who are obese were more likely to develop gestational diabetes (P < 0.001). It was concluded that pre-pregnancy obesity is a risk factor for gestational diabetes. [EL = 2+]

A prospective cohort study[131] examined the incidence and outcomes of pregnancy in women with gestational diabetes in an Iranian population. The study compared women with gestational diabetes to women with normal glucose tolerance. The results showed a statistically significant difference in risk factors between the two groups. Women with gestational diabetes had a significantly higher rate of stillbirth, hydramnios, gestational hypertension, macrosomia and caesarean section. [EL = 2+]

An RCT conducted in the USA[132] compared a risk factor-based screening programme for gestational diabetes with universal screening. Women in the risk factor group were given a 3 hour 100 g OGTT at 32 weeks of gestation if any risk factor was present. Women in the universal screening group were given a 50 g GCT followed by a 3 hour 100 g OGTT if the plasma glucose at 1 hour was 7.8 mmol/Litre or more. The study reported the following PPVs for risk factors: first-degree relative with type 2 diabetes 6.7%, first-degree relative with type 1 diabetes 15%, previous macosomic baby (more than 4500 g) 12.2%, glycosuria in current pregnancy 50%, macrosomia in current pregnancy 40% and polyhydramnios in current pregnancy 40%. The detection rate for gestational diabetes using universal screening was significantly higher than using risk factor screening (2.7% versus 1.45%). [EL = 2+]

A study conducted in Denmark[133] retrospectively investigated the power of pre-screening based on risk factors to identify gestational diabetes and screening to predict adverse clinical outcomes. Pregnant women with at least one risk factor were offered capillary FBG at 20 and 32 weeks of gestation. If the capillary FBG measurements were 4.1 mmol/L or more and less than 6.7 mmol/L, then a 3 hour 75 g OGTT was offered. If capillary FBG values were 6.7 mmol/L or more, the woman was diagnosed as having gestational diabetes. The most frequent pre-screening risk factors were BMI 27 kg/m² or more (present in 65% of women with gestational diabetes) and age 35 years or older (present in 16% of women with gestational diabetes). No single risk factor seemed the best indicator for gestational diabetes. The strongest predictor of developing gestational diabetes was glycosuria (OR 9.04, 95% CI 2.6 to 63.7). [EL = 2−]

A cross-sectional 5 year investigation conducted in the Netherlands[134] examined the clinical utility of antenatal clinical characteristics and measures of glucose tolerance in multi-ethnic women with gestational diabetes for their ability to predict type 2 diabetes within 6 months of birth (early postpartum diabetes). The following risk factors were assessed for all women: age and gestational age at entry into the study, pre-pregnancy BMI, ethnicity, obstetric and clinical history, including the onset of early postpartum diabetes, and pregnancy outcome.

The study showed that apart from family history of diabetes no other risk factor showed an association with the development of early postpartum diabetes. [EL = 2−]

A cohort study[135] of 6214 pregnancies among 6034 women evaluated the sensitivity and cost-effectiveness of various screening schemes for gestational diabetes. Women were tested at 24–28 weeks using 1 hour 50 g GCT without regard to their last meal. Women were also asked for their age and risk factors. Two percent of pregnancies (n = 125) were complicated by gestational diabetes. Gestational diabetes increased with maternal age (P < 0.001). Of women with gestational diabetes, 70 (56%) were younger than 30 years; of these, 58% had one or more risk factors. If a threshold of more than 7.8 mmol/L had been used, 10% of women with gestational diabetes, who had screening values of 7.2–7.8 mmol/L, would have been missed. [EL = 2+]

A cross-sectional survey[136] of 14 613 women without previous gestational diabetes or other known diabetes who reported singleton pregnancy between 1990 and 1994 were used to measure risk factors for gestational diabetes. Gestational diabetes developed in 722 women during the study period. Maternal age over 40 years had a two-fold increased risk of gestational diabetes compared with women aged 25–29 years. Crude RR for gestational diabetes increased 4% (95% CI 2% to 6%) with each year over 25. Gestational diabetes risk increased with weight gain between age 18 and the year the study began, 1989 (RR for weight gain 5–9.9 kg 1.67, 95% CI 1.37 to 2.05 compared with stable weight). Risk for gestational diabetes increased directly with greater weight gain (RR 3.56, 95% CI 2.70 to 4.69) for weight gain of 20 kg or more since age 18 years. Family history of diabetes in a first-degree relative increased the risk of gestational diabetes (RR 1.68, 95% CI 1.39 to 2.04). Women of African-American, Hispanic or Asian ethnicity all had significantly increased age-adjusted RRs for gestational diabetes compared with white women. Higher pre-pregnancy (1989) BMI, higher BMI at age 18 years and weight gain between 18 years and 1989 all significantly increased the risk for gestational diabetes. Current smoking increased the risk of gestational diabetes when compared with never smokers (RR 1.43, 95% CI 1.14 to 1.80). Past smokers had no increased risk. Pre-pregnancy physical activity was not associated with risk for gestational diabetes. [EL = 2+]

Additional information about the prevalence of gestational diabetes was obtained using type 2 diabetes as a marker for gestational diabetes. An atlas showing the worldwide prevalence of type 2 diabetes in 2007 indicated that Middle Eastern countries (Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Egypt, Oman, Qatar, Kuwait and the Lebanon) have high prevalence (more than 10% of women; see www.eatlas.idf.org/webdata/docs/Map%201.1_large.jpg). [EL = 3]

A recent systematic review[137] examined the rates and factors associated with recurrence of gestational diabetes among women with a history of gestational diabetes. A total of 13 studies were included. The review showed the recurrence rate of glucose intolerance during subsequent pregnancies varied markedly across studies. The most consistent predictor of future recurrence appeared to be non-white race/ethnicity, although the racial groups were not always clearly described in the original studies. Recurrence rates varied between 30% and 84% after the index pregnancy. Recurrence rates were higher in the minority ethnic populations (52–69%) compared with lower rates found in non-Hispanic white populations (30–37%). No other risk factors were consistently associated with recurrence of gestational diabetes across studies. Other risk factors, such as maternal age, parity, BMI, OGTT results and insulin use, inconsistently predicted recurrence of gestational diabetes across studies. However, the systematic review included two studies[138,139] that reported the probability of gestational diabetes given insulin-treated gestational diabetes in a previous pregnancy to be 75–77%. [EL = 2++]

An audit conducted in the UK in 2002 assessed whether the introduction of an appointment form for administering an OGTT had improved the understanding of antenatal care staff.[140] The audit showed that 89% of healthcare professionals were aware of the scheduled time for

OGTT administration (26–28 weeks of gestation) in 2002, whereas a similar audit conducted in 2001 showed that only 69% of healthcare professionals knew when to screen. The following risk factors and clinical measurements were listed on the appointment form as indications for OGTT: [EL = 3]

- glycosuria ≥ 1+ on more than one occasion or ≥ 2+ on one occasion
- macrosomia in current pregnancy
- previous large infant (more than 4.5 kg, or above the 95th centile for gestational age)
- previous gestational diabetes
- first-degree relative with diabetes
- previous unexpected perinatal death
- history of polycystic ovary syndrome
- obesity (BMI more than 30 kg/m²) or booking weight more than 100 kg
- polyhydramnios
- Asian ethnic background
- FBG more than 6.0 mmol/L, or random blood glucose more than 7.0 mmol/L

4.2.2 Evidence statement

Evidence shows that risk factors for developing gestational diabetes are: pre-pregnancy obesity, advanced maternal age, previous gestational diabetes, family history of diabetes, minority ethnic background, previous macrosomic baby (4500 g or more for white and black women), increased maternal weight gain in early adulthood, and current smoker. Family origins with a high prevalence of gestational diabetes are South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh), black Carribean and Middle Eastern (specifically women whose country of family origin is Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt).

Recurrence rates for gestational diabetes varied from 30% to 84% after the index pregnancy. The probability of gestational diabetes given insulin-treated gestational diabetes in a previous pregnancy is approximately 75%.

4.2.3 From evidence to recommendations

The following have been shown to be independent risk factors for gestational diabetes and should be recognised as such by healthcare professionals:

- BMI more than 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or more
- previous gestational diabetes
- family history of diabetes (first-degree relative with diabetes)
- family minority ethnic origin with a high prevalence of diabetes.

The consensus view of the combined GDGs for antenatal care and diabetes in pregnancy is that advanced maternal age should not be used as a risk factor for gestational diabetes because this would result in most pregnant women receiving an OGTT (see Section 4.2).

The probability of gestational diabetes for a woman who has had gestational diabetes in a previous pregnancy is 30–84%, and so it is straightforward to demonstrate the cost-effectiveness of offering a diagnostic test for gestational diabetes to women who have had gestational diabetes in a previous pregnancy. Moreover, the probability of a recurrence of gestational diabetes in women with insulin-treated gestational diabetes in a previous pregnancy is approximately 75%. In its discussions, the GDG also noted that there is a strong possibility of developing new-onset type 2 diabetes in women with gestational

diabetes in a previous pregnancy (see Section 8.3). Recommendations relating to recurrence of gestational diabetes and the need for early testing for gestational diabetes in future pregnancies are presented in Section 8.3.

4.2.3.1 Other considerations

The GDG were also aware that several prescribed medicines are associated with an increased risk of the development of diabetes, for example, major tranquillizers (NICE Clinical guideline 45; published February 2007 and due for update December 2014) but review of these agents was not in the SCOPE for the guideline update.

4.2.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

4.3 Screening for gestational diabetes

This section was updated in 2015

4.3.1 Introduction

It is important to identify women who have gestational diabetes for at least 2 reasons. First, there is good evidence that interventions in the pregnancy will improve outcome (see Section 4.5). Second, these women are at greater risk of developing type 2 diabetes in later life. Often type 2 diabetes is insidious in onset and not recognised before irreversible complications have developed. Women who have had gestational diabetes are an at-risk group who might benefit from ongoing surveillance after their pregnancy and early intervention if type 2 develops.

Different screening methods and criteria have been suggested. In the original guideline the guideline development group recommended the use of risk factor screening. However, it was felt that the topic needed to be reviewed again because since that guideline was published new research has been published suggesting different diagnostic criteria for gestational diabetes (see Section 4.4). In addition, the original guideline only recommended screening for gestational diabetes towards the end of the second trimester (except in women who had the diagnosis in a previous pregnancy). But it is recognised that some women who are diagnosed as having gestational diabetes actually have type 2 diabetes which has only been identified during pregnancy. From this it is reasonable to ask the question whether screening for such women in in the first trimester could be of benefit.

4.3.2 Screening for gestational diabetes in the first trimester

4.3.2.1 Review question

What is the effectiveness of the following procedures in detecting glucose intolerance in the first trimester diagnosed using a 75 g oral glucose tolerance test:

- risk factor based screening
- urine test for glycosuria
- random blood glucose test
- 50 g oral glucose challenge test
- fasting blood glucose test
- HbA1c test?

4.3.2.2 Description of included studies

Six cohort studies were identified for inclusion in this review (Agarwal et al., 2007; Bito et al., 2005; Church et al., 2011; Corrado et al., 2012; Kuti et al., 2011; Zhu et al., 2013).

Two were prospective cohort studies (Agarwal et al., 2007; Bito et al., 2005) and 4 were retrospective studies (Church et al., 2011; Corrado et al., 2012; Kuti et al., 2011; Zhu et al., 2013). All women received a diagnostic oral glucose tolerance test (OGTT) in 3 studies (Agarwal et al., 2007; Bito et al., 2005; Kuti et al., 2011). In 2 studies, women with a first trimester fasting plasma glucose of 7.1 or 7.0 mmol/litre or more were excluded from the study and the remaining women all received a diagnostic OGTT (Corrado et al., 2012; Zhu et al., 2013, repectively). In the last study, only women testing positive after screening received a diagnostic OGTT (Church et al., 2011). Three studies used universal screening strategies (Agarwal et al., 2007; Church et al., 2011; Zhu et al., 2013), 2 used a risk factor based selection strategy prior to diagnosis (Bito et al., 2005; Kuti et al., 2011) and in 1 study the premise for selection was not clear, but consecutive white women attending clinic were included (Corrado et al., 2012,).

Three studies examined fasting plasma glucose (FPG) as a screening test in the first trimester compared with a diagnostic 2 hour 75 g OGTT in the second trimester in populations of 708, 744 and 17,186 women (respectively Agarwal et al., 2007; Corrado et al., 2012; Zhu et al., 2013).

Another study examined random blood glucose (RBG) as a screening test in 3 analyses to construct receiver operator curves and establish optimum RBG thresholds (Church et al., 2011). Two analyses used all available RBG screening test results for 17,852 women. These were compared to diagnosis by 2 hour 75 g OGTT alone in 1 analysis and to diagnosis by 2 hour 75 g OGTT or high RBG test results (RBG 11.1mmol/litre or more) in the second. Assumptions were made regarding correct diagnoses in both these analyses because diagnostic OGTTs were not performed for all women. A third analysis was restricted to the 3007 women who also had both screening RBG and diagnostic 2 hour 75 g OGTT results available. The remaining 2 studies did not examine a screening test, but included women with selected risk factors who, as a result, underwent a diagnostic 2 hour 75 g OGTT directly (Bito et al., 2005; Kuti et al., 2011).

Three studies used WHO 1999 criteria for diagnosing gestational diabetes (Agarwal et al., 2007; Bito et al., 2005; Kuti et al., 2011) and 2 studies used ADA 2011 criteria which correspond to IADPSG 2010 diagnostic criteria (Corrado et al., 2012) or IADPSG criteria (Zhu et al., 2013) to diagnose women with gestational diabetes at 24–28 weeks of gestation. The last study used FPG of 7 mmol/litre or above (which is a threshold used in WHO diagnostic criteria to diagnose gestational diabetes and in IADPSG diagnostic criteria to diagnose 'overt diabetes in pregnancy') and 2 hour 75 g OGTT of 11.1 mmol/litre or above (which is not used in either WHO or IADPSG diagnostic criteria to diagnose gestational diabetes or 'overt diabetes in pregnancy', but which is the WHO threshold used to diagnose diabetes outside pregnancy) as diagnostic thresholds to diagnose 'overt diabetes in pregnancy' (Church et al., 2011).

In 2 studies, tests were performed in the first trimester, although no further details are provided (Corrado et al., 2012; Kuti et al., 2011). In another, although the majority of screening and diagnostic tests were performed in the first trimester, testing was performed at up to 18 weeks (Agarwal et al., 2007). In 2 studies, tests were performed at up to 16 weeks of gestation (Bito et al., 2005) and 20 weeks of gestation (Church et al., 2011) and in the remaining study (Zhu et al., 2013) 90% of testing was completed by 18 weeks of gestation.

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4.3.2.3 Evidence profile

The GRADE profiles for this review question are presented in Table 17 to Table 21.

Table 17: GRADE profile for the incidence of gestational diabetes in the first trimester diagnosed using a 75 g OGTT (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more). It also presents the proportion of women who were diagnosed as having gestational diabetes in the first trimester out of the total number of women who were diagnosed as having gestational diabetes in the first and second trimesters combined

Number of studies	Number of potential participants	Number of women who had test	Incidence of gestational diabetes diagnosed in the first trimester in all women tested	Women diagnosed with gestational diabetes in the first trimester as a proportion of all women diagnosed in the first and second trimester	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Screening and/or diagnosis in the first trimester using 75 g OGTT as diagnostic test (WHO 1999)											
1 (Agarwal et al., 2007)	760[a]	708 (93.2%)	79/708 (11.2%)	79/184 (42.9%)	Low	Prospective cohort	Serious[b,c]	NA	No serious indirectness[d]	Serious[e]	Yes[f]
1 (Bito et al., 2005)	163[g]	163 (100%)	8/163 (4.9%)	8/40 (20.0%)	Very low	Prospective cohort	Serious[h]	NA	Serious[i]	Serious[e]	Yes[j]
1 (Kuti et al., 2011)	765[k]	69 (9.0%)	12/69 (17.4%)	12/47 (25.5%)	Very low	Retrospective cohort	Serious[h]	NA	Serious[l]	Serious[e]	Yes[m]

NA not applicable, OGTT oral glucose tolerance test, WHO World Health Organization
a. Universal screening strategy using fasting plasma glucose (FPG) test in the first trimester, 52/760 women did not complete the diagnostic 2 hour 75 g OGTT. Women with a screening FPG ≥ 5.3 mmol/litre underwent a diagnostic 2 hour 75 g OGTT within 2 weeks of screening. Women with a screening FPG < 5.3 mmol/litre underwent a diagnostic 2 hour 75 g OGTT diagnostic test between weeks of gestation 24-28.
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. Screening for gestational diabetes was usually performed in the first trimester (median and mean: gestational week 10) with the diagnostic test being performed 2 weeks later, although some women were screened and diagnosed in the second trimester (range: weeks of gestation 5-18)
e. Total number of events less than 300
f. Country: United Arab Emirates. Ethnicity of population: Arab (92.2%), Indian subcontinent including India, Pakistan, Bangladesh, Sri Lanka (6.2%), other nationalities including Philippines, UK, Indonesia and Nigeria (1.6%)

g. Risk factor based screening strategy with all participants undergoing at least one diagnostic 2 hour 75 g OGTT. Participants did not have previous gestational diabetes nor any history of altered carbohydrate metabolism, but were referred to a specialist outpatient clinic and did have one or more of the following risk factors for gestational diabetes: any family history of type 2 diabetes, a history of a large neonate (≥4000 g), a history of an adverse perinatal outcome (missed abortion, malformation, polyhydramnios, stillbirth or preterm delivery), obesity (pre-pregnant body mass index ≥ 30m^2), age ≥ 35 years and glycosuria. Diagnostic 2 hour 75 g OGTTs were performed at 3 time periods: ≤ gestational week 16, weeks of gestation 24-28 and weeks of gestation 32-34. 8 women diagnosed with gestational diabetes in the first trimester were excluded from the study. Incidence data from OGTTs performed in weeks of gestation 32-34 were not included in this analysis

h. -No screening (index) test was used and diagnosis was made on the basis of a 75 g OGTT (reference standard) in order to exclude women diagnosed with gestational diabetes ≤ gestational week 16 from the study

i. The period when diagnosis was made (≤ gestational week 16) overlaps the first and second trimesters and no further details are given as to when the majority of diagnostic tests were actually performed

j. Country: Hungary. Ethnicity of population: not reported

k. Risk factor based screening strategy with all participants undergoing a diagnostic 2 hour 75 g OGTT. Participants were women at high risk of gestational diabetes (based on a history of fetal macrosomia, maternal obesity, previous intrauterine fetal death, first degree relative with diabetes mellitus, glycosuria or history of gestational diabetes in a previous pregnancy) who were referred to a hospital research unit for a diagnostic 2 hour 75 g OGTT. Women with OGTTs performed between weeks of gestation 4 to 40 were included in the study. Results for 69, 276 and 420 women were available for the first, second and third trimesters respectively. Incidence data from OGTTs performed in the third trimester were not included in this analysis

l. No definition of first trimester or second trimester is reported

m. Country: Nigeria. Ethnicity of population: not reported

Table 18: GRADE profile for the diagnostic test accuracy of fasting plasma glucose test performed in the first trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more)

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Fasting plasma glucose ≥ 3.89 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	99.5 (98.1 to 100)*	0.8 (0.3 to 0.9)*	1.00 (0.98 to 1.01)*	0.71 (0.03 to 6.65)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 4.17 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	98.4 (95.8 to 99.6)*	3.6 (2.7 to 4.0)*	1.02 (0.98 to 1.04)*	0.45 (0.11 to 1.57)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 4.44 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	94.0 (90.0 to 96.7)*	11.6 (10.2 to 12.6)*	1.06 (1.00 to 1.11)*	0.51 (0.26 to 0.98)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Fasting plasma glucose ≥ 4.72 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	79.9 (74.2 to 84.9)*	27.5 (25.5 to 29.2)*	1.10 (1.00 to 1.20)*	0.73 (0.52 to 1.01)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 5.00 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	60.9 (54.4 to 67.1)*	49.4 (47.2 to 51.6)*	1.20 (1.03 to 1.39)*	0.79 (0.64 to 0.97)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 5.28 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwal et al., 2007)	708	39.1 (33.0 to 45.4)*	68.5 (66.4 to 70.7)*	1.24 (0.98 to 1.55)*	0.89 (0.77 to 1.01)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 5.56 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwa l et al., 2007)	708	21.7 (16.9 to 26.9)*	87.6 (85.9 to 89.4)*	1.75 (1.20 to 2.54)*	0.89 (0.82 to 0.97)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 5.83 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwa l et al., 2007)	708	11.4 (7.9 to 15.2)*	94.7 (93.4 to 96.0)*	2.14 (1.20 to 3.79)*	0.94 (0.88 to 0.99)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]
Fasting plasma glucose ≥ 6.11 mmol/litre in the first trimester for detecting gestational diabetes in the first or second trimester												
1 (Agarwa l et al., 2007)	708	8.2 (5.4 to 10.3)*	98.5 (97.5 to 99.2)*	5.34 (2.17 to 13.59)*	0.93 (0.90 to 0.97)*	Moderate	Prospective cohort	Serious[a,b]	NA	No serious indirectness[c]	No serious imprecision	Yes[d]

NA not applicable, OGTT oral glucose tolerance test
* Calculated by the NCC-WCH team from data reported in the paper
a. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
b. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
c. Screening for gestational diabetes was usually performed in the first trimester (median and mean: gestational week 10) with the diagnostic test being performed 2 weeks later, although some women were screened and diagnosed in the second trimester (range: weeks of gestation 5-18)
Country: United Arab Emirates. Ethnicity of population: Arab (92.2%), Indian subcontinent including India, Pakistan, Bangladesh, Sri Lanka (6.2%), other nationalities including Philippines, UK, Indonesia and Nigeria (1.6%)

Table 19: GRADE profile for the diagnostic test accuracy of random blood glucose test performed in the first trimester to detect overt diabetes in pregnancy diagnosed using a 75 g 2 hour OGTT (World Health Organization 1999 diagnostic criteria for diabetes outside pregnancy: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 11.1 mmol/litre or more)

Number of studies	Number of women with test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirect-ness	Impreci-sion	Other considera-tions
Random blood glucose 7.31 – 7.40 mmol/litre in the first trimester for detecting 'overt diabetes in pregnancy' (diagnosed with 75 g OGTT WHO 1999 criteria)												
1 (Church et al., 2011) [a,b]	17,852 [a,b]	78 (NC)	85 (NC)	5.20 (NC)	0.26 (NC)	Very low	Retrospective cohort	Very serious[c,d,e,f]	NA	Serious[g]	Very serious[h]	Yes[i]
Random blood glucose 7.51 – 7.59 mmol/litre in the first trimester for detecting 'overt diabetes in pregnancy' (diagnosed with 75 g OGTT WHO 1999 criteria or RBG ≥ 11.1mmol/litre)												
1 (Church et al., 2011)	17,852 [a,j]	80 (NC)	85 (NC)	6.67 (NC)	0.23 (NC)	Very low	Retrospective cohort	Very serious[c,d,e,f]	NA	Serious[g]	Very serious[h]	Yes[i]
Random blood glucose 8.60 – 8.70 mmol/litre in the first trimester for detecting 'overt diabetes in pregnancy' (diagnosed with 75 g OGTT WHO 1999 criteria)j												
1 (Church et al., 2011)	3007[a,k]	60 (NC)	75 (NC)	2.40 (NC)	0.53 (NC)	Very low	Retrospective cohort	Very serious[c,d,e,f]	NA	Serious[g]	Very serious[h]	Yes[i]

NA not applicable, NC not calculable, OGTT oral glucose tolerance test, RBG random blood glucose, WHO World Health Organization

a. Universal screening program where all women received plasma random blood glucose (RBG) measurement at antenatal booking (n=17,852). Women with a booking RBG test result >7.0 mmol/litre or with a previous history of gestational diabetes were offered a diagnostic 2 hour 75 g OGTT. Women diagnosed as not having gestational diabetes were screened again at 26–28 weeks using a 50 g oral glucose challenge test (GCT). Those with a GCT result > 7.7 mmol/litre were offered a diagnostic 2 hour 75 g OGTT. Women with clinical indications were also offered OGTTs.

b. This model uses all available random blood glucose data (n=17,852). It applies the assumption that women without a positive OGTT did not have 'overt diabetes in pregnancy' (n=17,785). 67 women had 'overt diabetes in pregnancy' (based on OGTT diagnosis) using this assumption.

c. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

d. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

e. Capillary and venous blood samples taken for the OGTT were not analysed separately

f. OGTTs performed at any time during gestation were included

g. The period when screening tests were performed (between 0 and 20 weeks) overlaps the first and second trimesters and no further details are given as to when the majority of diagnostic tests were actually performed

h. The data presented were insufficient to allow calculation of the confidence intervals for point estimates of sensitivity and specificity

i. Country: United Kingdom. Ethnicity of population: Data is presented for 95.9% (17124/17852) of the study population. White British (71.3%), Asian (3.9%), African (0.7%), Caribbean (0.4%), Chinese (1.1%), other white backgrounds (18.5%)

j. This model estimates the maximum diagnostic value of plasma RBG measurement by applying the assumption that those women with no or incomplete OGTT and RBG < 11.1 mmol/litre did not have 'overt diabetes in pregnancy' and by defining an additional 12 women who had RBG ≥ 11.1 mmol/litre, but who did not have a diagnostic OGTT performed, as having a diagnosis of 'overt diabetes in pregnancy'. This may overestimate the di as the authors also state that of 87 women with RBG ≥ 11.1 mmol/litre and who had an OGTT performed, only 30% had 'overt diabetes in pregnancy' diagnosed by OGTT.

k. This model estimates the minimum diagnostic value of plasma RBG measurement using only data from those women who had both plasma RBG measurement and OGTT performed (n=3007). 67 women had 'overt diabetes in pregnancy' (based on OGTT diagnosis)

Table 20: GRADE profile for the incidence of gestational diabetes in the first trimester diagnosed using a 75 g OGTT (International Association of the Diabetes and Pregnancy in Study Groups diagnostic criteria for gestational diabetes: 1 or more plasma venous glucose values, fasting plasma glucose 5.1 mmol/litre or more, 1 hour 10.0 mmol/litre or more, or 2 hour 8.5 mmol/litre or more). It also presents the proportion of women who were diagnosed as having gestational diabetes in the first trimester out of the total number of women who were diagnosed as having gestational diabetes in the first and second trimesters combined

Number of studies	Number of potential participants	Number of women who had test	Incidence of gestational diabetes diagnosed in the first trimester in all women tested	Women diagnosed with gestational diabetes in the first trimester as a proportion of all women diagnosed in the first and second trimester	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Screening and/or diagnosis in the first trimester using 75 g OGTT as diagnostic test (IADPSG)											
1 (Corrado et al., 2012)	775[a]	738 (95.2%)	24/738 (3.25%)	24/88 (27.2%)	Very low	Retrospectivec ohort	Serious[b,c]	NA	Serious[d]	Serious[e]	Yes[f]
1 (Zhu et al., 2013)	17186[g]	17186 (100%)	1959/17186 (11.4%)	779/3002 (25.9%)	Very low	Retrospective cohort	Serious[c,h]	NA	Seriousl	No serious imprecision	Yes[j]

FPG fasting plasma glucose, NA not applicable, IADPSG International Association of the Diabetes and Pregnancy in Study Groups, OGTT oral glucose tolerance test
a. Selective screening strategy as study population was all consecutive white women referred to a hospital department for a 75 g OGTT at weeks of gestation 24-28. Of 775 referred women, exclusions included 12 women with multiple pregnancy, 18 women with no first trimester FPG result, 6 women who had FPG tested after the first trimester, and 1 woman who was diagnosed to have pre-gestational diabetes (first trimester FPG ≥ 7.0 mmol/L) No further details are provided.
b. Selection criteria were unclear
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. No definition of first trimester or second trimester is reported.
e. Total number of events less than 300
f. Country: Italy. Ethnicity of population: white
g. Universal screening strategy used for 1st trimester screening using FPG and diagnostic 2 hour 75 g OGTT at 24-28 weeks gestation.
h. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
i. No definition of first trimester or second trimester is reported The FPG was performed at the first prenatal visit at median 13.4 weeks of gestation (± SD 3.5, range 4-24 weeks of gestation). 90% of FPG tests were performed before 18 weeks
i. Country: China. Ethnicity of population: not reported

Table 21: GRADE profiles for the diagnostic test accuracy of fasting plasma glucose test performed in the first trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT in the second trimester (International Association of the Diabetes and Pregnancy in Study Groups diagnostic criteria for gestational diabetes: 1 or more plasma venous glucose values, fasting plasma glucose 5.1mmol/litre or more, 1 hour 10.0 mmol/litre or more or 2 hour 8.5 mmol/litre or more)

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)		Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other considera-tions
Fasting plasma glucose < 4.1 mmol/litre versus 4.1 to 6.99 mmol/litre in the first trimester for detecting gestational diabetes in the second trimester													
'Unselected' population[a]													
1 (Zhu et al., 2013)	17,186	93.8 (92.9 – 94.6)*	12.4 (12.2– 12.5)*	1.07 (1.06– 1.08)*	0.50 (0.43– 0.58)*		Very low	Retrospective cohort	Serious[b,c]	NA	Serious[d]	No serious imprecision	Yes[e]
Fasting plasma glucose < 4.6 mmol/litre versus 4.6 to 6.99 mmol/litre in the first trimester for detecting gestational diabetes in the second trimester													
'Unselected' population[a]													
1 (Zhu et al., 2013)	17,186	64.8 (63.2– 66.3)*	55.9 (55.6– 56.3)*	1.47 (1.42– 1.52)*	0.63 (0.60– 0.66)*		Very low	Retrospective cohort	Serious[b,c]	NA	Serious[d]	No serious imprecision	Yes[e]
Fasting plasma glucose < 5.1 mmol/litre versus 5.1 to 6.99 mmol/litre in the first trimester for detecting gestational diabetes in the second trimester													
'Unselected' population[a]													
1 (Zhu et al., 2013)	17,186	25.9 (24.7– 27.2)*	91.7 (91.4– 92.0)*	3.12 (2.87– 3.38)*	0.81 (0.79– 0.82)*		Very low	Retrospective cohort	Serious[b,c]	NA	Serious[d]	No serious imprecision	Yes[e]
'Selected' population[f]													
1 (Corrado et al., 2012)	738	27.3 (19.7– 35.0)*	95.5 (94.5– 96.6)*	6.11 (3.59– 10.25)*	0.76 (0.67– 0.85)*		Very low	Retrospective cohort	Serious[c,g]	NA	Serious[h]	Serious imprecision[i]	Yes[j]
Fasting plasma glucose < 5.6 mmol/litre versus 5.6 to 6.99 mmol/litre in the first trimester for detecting gestational diabetes in the second trimester													
'Unselected' population[a]													
1 (Zhu et al., 2013)	17,186	5.4 (4.8– 5.9)*:	99.1 (99.0– 99.2)*	5.93 (4.7– 7.5)*	0.955 (0.95– 0.96)*		Very low	Retrospective cohort	Serious[b,c]	NA	Serious[d]	No serious imprecision	Yes[e]
Fasting plasma glucose < 6.1 mmol/litre versus 6.1 to 6.99 mmol/litre in the first trimester for detecting gestational diabetes in the second trimester													
'Unselected' population[a]													
1 (Zhu et al., 2013)	17,186	1.4 (1.2– 1.6)*	99.9 (99.9– 100)*	16.93 (8.65– 33.83)*	0.987 (0.98– 0.99)*		Very low	Retrospective cohort	Serious[b,c]	NA	Serious[d]	No serious imprecision	Yes[e]

NA not applicable, OGTT oral glucose tolerance test

* Calculated by the NCC-WCH team from data reported in the paper

a. 'unselected': a universal screening strategy was applied comprising screening of the whole population in the first trimester; women with a fasting plasma glucose of ≥ 7.1 mmol/litre were excluded

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. No definition of first trimester or second trimester is reported The FPG was performed at the first prenatal visit at median = 13.4 weeks of gestation (± SD 3.5, range 4-24 weeks of gestation). 90% of FPG tests were performed before 18 weeks

e. Country: China. Ethnicity of population: not reported

f. 'selected': a selective screening strategy was applied comprising screening all consecutive Caucasian women referred to a hospital department for a 75 g OGTT; women with a fasting plasma glucose of ≥ 7.0 mmol/litre were excluded

g. Selection criteria were unclear

h. No definition of first trimester or second trimester is reported.

i. Total number of events is under 300

j. Country: Italy. Ethnicity of population: white

4.3.2.4 Evidence statements

4.3.2.4.1 Incidence of gestational diabetes, WHO criteria

Two prospective cohort studies (n=708; n=163) and 1 retrospective cohort study (n=69) provided very low and low quality evidence that the incidence of gestational diabetes in the first trimester ranged from 4.9% to 17.4% and that the proportion of gestational diabetes diagnosed in the first trimester out of those women diagnosed with gestational diabetes by the end of the second trimester ranged from 20.0% to 42.9%.

4.3.2.4.2 Incidence of gestational diabetes, IADPSG criteria

Two studies (n=775; n=17,186) provided very low quality evidence that the incidence of gestational diabetes in the first trimester ranged from 3.25% to 11.4% and that the proportion of gestational diabetes diagnosed in the first trimester out of those women diagnosed with gestational diabetes by the end of the second trimester ranged from 25.9% to 27.2%.

4.3.2.4.3 Diagnostic test accuracy, WHO criteria

One study (n=708) provided moderate quality evidence that a fasting plasma glucose test is moderately useful for ruling in gestational diabetes at a threshold of 6.11 mmol/litre or more, but not useful for ruling out gestational diabetes at all threshold categories between 3.89 mmol/litre and 6.11 mmol/litre.

One study (n=17,852) provided very low quality evidence from an analysis to maximise estimations of diagnostic accuracy that a random blood glucose test is moderately useful for ruling in and ruling out overt diabetes in pregnancy at a threshold categories of 7.31–7.40 mmol/litre and 7.51–7.59 mmol/litre.

4.3.2.4.4 Diagnostic test accuracy, IADPSG criteria

One study (n=17,186) provided very low quality evidence that a fasting plasma glucose test is moderately useful for ruling in gestational diabetes in the second trimester at a threshold of less than 6.1 mmol/litre compared with 6.1–6.99 mmol/litre but is not useful for ruling in gestational diabetes at thresholds of: less than 4.6 mmol/litre compared with 4.6–6.99 mmol/litre; 5.1 mmol/litre compared with 5.1–6.99 mmol/litre; or less than 5.6 mmol/litre compared with 5.6–6.99 mmol/litre. In the same study, a fasting plasma glucose test was not useful for ruling out gestational diabetes in the second trimester at any threshold investigated.

One study (n=738) provided very low quality evidence that a fasting plasma glucose test was useful for ruling in and not useful for ruling out gestational diabetes in the second trimester at a threshold of less than 5.1 mmol/litre compared with 5.1–6.99 mmol/litre in a selected population.

No evidence was available to assess the diagnostic accuracy of a urine screening test for glycosuria, a 50 g oral glucose challenge screening test or an HbA1c screening test taken in the first trimester compared with a diagnostic 75 g oral glucose tolerance test (and applying the IADPSG or the WHO 1999 criteria or equivalent).

4.3.2.4.5 Maternal and neonatal outcomes

No evidence was available to assess the effect of early screening and diagnosis using a 75 g oral glucose tolerance test (and applying the IADPSG or the WHO 1999 criteria or equivalent) on outcomes for women and their babies.

4.3.2.5 Health economics profile

No published health economic evidence was identified addressing the cost effectiveness of screening for gestational diabetes in the first trimester.

A formal economic analysis of first trimester screening was not undertaken as there is insufficient evidence on which to assess the effectiveness. In the absence of cost effectiveness data, the cost effectiveness of first trimester screening cannot be ascertained.

4.3.2.6 Evidence to recommendations

4.3.2.6.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the incidence of gestational diabetes diagnosed in the first trimester as an outcome because:

- The incidence of abnormal glucose tolerance in early pregnancy is uncertain.
- Particular populations might be at higher risk (warranting earlier screening and diagnosis).
- It might define a higher risk group in whom early treatment may be of benefit.
- Early diagnosis would incur additional costs.

The group prioritised diagnostic accuracy because:

- Performing an OGTT is demanding for the service and is often unpleasant and poorly tolerated by the women. Therefore, a more convenient screening test with good diagnostic accuracy would be useful.
- There are a number of screening tests used and their comparative diagnostic accuracies (against 2 hour 75 g OGTT applying WHO or IADPSG criteria) would be informative.
- The diagnostic accuracies of different screening tests are likely to vary when applied to different populations and when different pre-screening selection strategies are used.

The group wished to determine if a diagnosis of gestational diabetes in the first trimester is of benefit in relation to the predefined outcomes of interest for the mother and her baby. The prioritised maternal outcomes were:

- mode of birth: spontaneous vaginal, operative vaginal, caesarean section (elective/emergency)
- treatment such as diet, oral hypoglycaemic agents and/or insulin
- acceptability/take-up of testing regimen.

Prioritised neonatal outcomes were:

- large for gestational age (however defined in the study, for example using a customised measure based on gestational age and population norms; dichotomous data preferred)
- perinatal and neonatal death up to 28 days ('all mortality' outcome)
- neonatal intensive care unit length of stay (greater than 24 hours)
- shoulder dystocia (no permanent damage, neurological injury (brachial plexus and cerebral palsy).

4.3.2.6.2 *Consideration of clinical benefits and harms*

The guideline development group considered the consequences of a screening test for gestational diabetes in the first trimester of pregnancy.

The advantage of a positive screening test result with a subsequent positive diagnostic test is that it allows for the possibility of therapeutic intervention earlier in the pregnancy than is current normal practice and hence potentially improved outcomes.

The main advantage of a correct negative screening test result is in confirming that glucose regulation in the pregnancy is normal, the reassurance that this gives to the woman and the avoidance of unnecessary interventions.

A consequence of an erroneous positive screening test result is an unnecessary diagnostic test and the inconvenience and anxiety that this would cause.

The group believed that when a woman receives an erroneous negative screening test there is the potential of considerable harm to her or her baby. The consequent lack of effective intervention would increase the potential likelihood of poor outcomes for the woman and her baby, including short- and long-term morbidity.

4.3.2.6.3   Consideration of health benefits and resource uses

Screening for gestational diabetes in the first trimester involves the use of NHS resources and therefore should produce sufficient benefit to justify this cost in order to be recommended. The pathophysiology of gestational diabetes is such that many women who will go on to develop gestational diabetes will not be detected in the first trimester. Therefore, first trimester screening is unlikely to obviate the need to undertake second trimester screening in most women. However, a significant proportion of women who could be identified by a first trimester screening programme may in fact have previously undetected type 2 diabetes and it might be expected that a greater benefit in terms of pregnancy outcomes could be achieved by identifying these women earlier in pregnancy. Against that has to be set the increased inconvenience and anxiety for pregnant women, the majority of whom would not be identified as having gestational diabetes in the first trimester. Furthermore, the effectiveness of any treatment for any gestational diabetes has only recently been demonstrated (Crowther et al., 2005; Landon et al., 2009) and that was based on populations screened in the second trimester. Therefore, it is not possible currently to demonstrate the cost- fectiveness of first trimester screening and so there are insufficient grounds to recommend routine first trimester screening.

4.3.2.6.4   Quality of evidence

The guideline development group prioritised studies that used a 2 hour 75 g OGTT diagnostic test interpreted using IADPSG or WHO 1999 (or equivalent) diagnostic criteria. Although there are a large number of studies investigating screening for gestational diabetes in the first trimester, most were irrelevant according to the review protocol, mainly because either a 100 gm diagnostic oral glucose tolerance test (OGTT) was used or because the diagnostic criteria applied to the OGTT were neither IADPSG nor WHO 1999 (or equivalent).

Only 6 studies were available and evidence quality ranged from very low to moderate. Four of these used WHO criteria. One study stated that testing was performed within the first trimester without providing further details. Although the majority of testing was performed in the first trimester in the remaining 3 studies, testing did extend up until 20 weeks and was beyond the 13^{+6} weeks of gestation timeframe definition used here. Thus the evidence pertains to the first half of pregnancy, rather than being restricted to first trimester only.

Incidence data were available from universal screening of a high risk population in a Middle Eastern study and from risk factor based selective screening of populations in Hungary and Nigeria. The 3 studies demonstrated that first trimester gestational diabetes constitutes a sizable minority of the incidence of all gestational diabetes diagnosed by the end of the second trimester. The study conducted in the United Arab Emirates reported that almost half of all gestational diabetes occurred in the first trimester in this high risk population.

The same study provided moderate quality evidence that a fasting plasma glucose screening test is at best only moderately useful for ruling in gestational diabetes in the first trimester. No evidence was available regarding the accuracy of a random blood glucose test in the first trimester to diagnose gestational diabetes. However, 1 study of universal screening of a

'normal risk' population in the UK provided very low quality evidence that random blood glucose of 7.51–7.59 mmol/litre is moderately useful for ruling in 'overt diabetes' in pregnancy in the first trimester. Hence from the available evidence, women undergoing screening with either fasting plasma glucose or random blood glucose would still need to undergo a diagnostic OGTT.

The guideline development group commented that there was only 1 prospective longitudinal study where all women were tested in the first trimester and, if negative, again in the second trimester. The incidence data from this provides the most relevant population based evidence for the relative incidence of glucose intolerance in the first and second trimesters. However, the overall incidence in different populations varies depending upon a variety of factors such as ethnicity, BMI and age. The guideline development group felt it would be more informative if there were more longitudinal studies from populations in the UK to inform this guidance.

Two studies from low risk populations compared a first trimester fasting plasma glucose to a 75 g OGTT interpreted using IADPSG diagnostic criteria and performed in the second trimester. The incidence of gestational diabetes identified in the first trimester and as a proportion of all gestational diabetes diagnosed was in the same range as studies examining WHO 1999 criteria for diagnosing gestational diabetes. The thresholds at which FPG in the first trimester was a moderately useful tool for diagnosing gestational diabetes ranged from 5.5 to 6.1 mmol/litre in an unselected population in 1 study, and it was demonstrated to be moderately useful at 5.1 mmol/litre in another study with unclear selection criteria.

There were no studies that examined use of urine testing for glycosuria, 50 g oral glucose challenge test or HbA1c test in the first trimester compared with diagnosis using 2 hour 75 g OGTT IADPSG or WHO 1999 (or similar).

No studies were included that investigated the relationship between a diagnosis of gestational diabetes in the first trimester and maternal or neonatal outcomes. The guideline development group noted that several of the RCTs included in Section 4.5 on interventions for gestational diabetes stipulated that the range of recruitment of study participants started within the first trimester (Bertini et al., 2005; Langer et al., 1989; Ijas et al., 2010; Moore et al., 2010) or early in the second trimester (Crowther et al., 2005; Niromanesh et al., 2012). However, the mean gestational ages of women recruited to or receiving treatment in these studies was reflective of the usual treatment window starting at 24 weeks of gestation. In addition, the systematic reviews for the first and second trimester screening questions were checked. However, none of these reviews provided data regarding the prioritised outcomes following diagnosis and treatment in the first trimester. One systematic review (Guedj, 2010) stated that there were no prospective studies demonstrating a decrease in maternal and fetal complications through early diagnosis and treatment of gestational diabetes.

4.3.2.6.5 Other considerations

The guideline development group considered the only available UK data were from a highly selected population and the ethnicity of the study population was not reported. The remaining studies were from populations that were not necessarily comparable to the UK. Furthermore, 2 of these were conducted in countries that have a high background rate of type 2 diabetes.

The 2008 guideline on diabetes in pregnancy recommended that a diagnostic OGTT at 16-18 weeks or early self-monitoring of glucose be offered to women with previous gestational diabetes, with an OGTT at 28 weeks for women who tested normal. Women with any of the other risk factors identified for gestational diabetes should be offered an OGTT at 24–28 weeks. Women without risk factors were not to be screened.

Though the systematic review failed to demonstrate any appropriate studies of glycosuria as a screening test, the guideline development group acknowledged that women with diabetes do have glycosuria more commonly than women without diabetes. Furthermore, they noted that the original 2008 guideline reported both observational data demonstrating a strong

association between glycosuria and diabetes in pregnancy and audit data suggesting that healthcare professionals considered that glycosuria of 1+ or more on more than one occasion or 2+ or more on one occasion was an indication for an OGTT. In summary, although there was no evidence to recommend testing for glycosuria as a population screening test in pregnancy, there was evidence that the presence of glycosuria in pregnancy increased the likelihood of glucose intolerance. Both the original guideline on diabetes in pregnancy and the guideline on antenatal care recommend that screening for gestational diabetes using fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose should not be undertaken. However, the antenatal care guideline does recommend screening for pre-eclampsia with regular measurement of blood pressure and urinalysis for protein. In practice this urinalysis is undertaken using a reagent strip which detects the presence of other substances in the urine, including glucose. The guideline development group therefore felt that it was important to address any opportunistic finding of glycosuria since it would be common occurrence in practice and a minority of these women would have gestational diabetes.

4.3.2.7 Key conclusions

The presented evidence demonstrated that glucose dysregulation occurs in the first trimester and can be detected. However, the only evidence available regarding screening tests examined fasting plasma glucose and a strategy combining the random plasma glucose and the glucose challenge tests. No evidence was available to assess the diagnostic accuracy of a urine screening test for glycosuria, a 50 g oral glucose challenge screening test or an HbA1c screening test.

Fasting plasma glucose (FPG) was moderately useful to rule in gestational diabetes at a threshold of 6.11 mmol/litre or more when compared with a 75 g OGTT interpreted using WHO 1999 criteria, and at thresholds as low as 5.5 mmol/litre when IADPSG criteria were applied in an unselected population. The guideline development group was reluctant to change practice to make a diagnosis of gestational diabetes on the basis of a fasting plasma glucose test alone without consideration of post glucose load testing. Further, the evidence was from a single study in a population with a high risk ethnicity, which defined gestational diabetes using WHO and not IADSPG diagnostic criteria. No other data were available indicating the incidence of gestational diabetes in the first trimester defined using IADPSG diagnostic criteria.

The study combining the random plasma glucose (RPG) and the glucose challenge tests (GCT) to screen for overt diabetes in pregnancy was conducted in a UK population. However, the diagnostic thresholds used in the study are not applicable for diagnosis of gestational diabetes and are not recommended. Overall, the guideline development group considered that the evidence provided by these 2 studies was not strong enough to make a recommendation to use FPG or a combination of RPG/GCT as screening tests in the first trimester to detect gestational diabetes. Therefore the group did not consider that evidence was sufficiently strong to recommend biochemical screening in the first trimester.

There was no evidence from the first trimester review to suggest any amendments to the principle underlying the previous recommendations, namely that:

- Only women with risk factors should be offered a diagnostic test.
- Women who have had gestational diabetes in a previous pregnancy should be offered early self-monitoring of blood glucose or an OGTT at an early point in pregnancy and a further OGTT at 28 weeks if the results are normal.
- Women with any of the other risk factors for gestational diabetes should be offered an OGTT towards the end of the second trimester.

Although evidence of effect in treated or untreated populations of women with previous gestational diabetes and early onset of gestational diabetes in the current pregnancy was not

available, the guideline development group believed that it was plausible that diagnosis would be of benefit given their clinical experience of treating pregnant women with type 2 diabetes. The group saw no reason to change the indication in the 2008 recommendations for women with previous gestational diabetes to be offered an early diagnostic OGTT or early self-monitoring of glucose, but recommended that this should occur as soon as possible after booking and not as late as 16–18 weeks if it were possible to undertake this an earlier point in pregnancy. This is supported by evidence that gestational diabetes can be diagnosed in the first trimester with an OGTT.

The guideline development group did not consider that the evidence was sufficiently strong to recommend screening in the first trimester in England and Wales on the basis of ethnicity or other risk factors. However, in women from populations with a high background risk a substantial minority may have pre-existing diabetes and may benefit from early assessment. The group noted that a proportion of women with these risk factors would also be covered by the recommendation for women with previous gestational diabetes.

The guideline development group considered that there was an urgent need for research in both unselected and high risk populations to determine the true incidence of gestational and type 2 diabetes in the first trimester and whether there are any benefits from earlier treatment on maternal and neonatal outcomes.

4.3.2.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

4.3.3 Screening for gestational diabetes in the second trimester

4.3.3.1 Review question

What is the effectiveness of the following procedures in detecting glucose intolerance in the second trimester diagnosed using a 75 g oral glucose tolerance test (OGTT):

- risk factor based screening
- urine test for glycosuria
- random blood glucose test
- 50 g oral glucose challenge test
- fasting blood glucose test
- HbA1c test?

4.3.3.2 Description of included studies

Eleven cohort studies were identified for inclusion in this review (Agarwal et al., 2006; Agarwal et al., 2005a; Agarwal et al., 2005b; Agarwal et al., 2010; Bito et al., 2005; Black et al., 2010; Catalano et al., 2012; Huynh et al 2011; Kuti et al., 2011; Senanayake et al., 2006; van Leeuwen et al., 2009).

Eight were prospective cohort studies (Agarwal et al., 2006; Agarwal et al., 2005a; Agarwal et al., 2005b; Agarwal et al., 2010; Bito et al., 2005; Catalano et al., 2012; Senanayake et al., 2006; van Leeuwen et al., 2009) and 3 were retrospective studies (Black et al., 2010; Huynh et al., 2011; Kuti et al., 2011). The 4 prospective cohort studies from the United Arab Emirates were from the same research team and the study dates overlapped in some cases (Agarwal et al., 2006; Agarwal et al., 2005a; Agarwal et al., 2005b; Agarwal et al., 2010).

In 10 studies all women received a diagnostic OGTT. However, in 1 study only those women testing positive after screening and a random sample of those testing negative after

screening received a diagnostic OGTT (van Leeuwen et al., 2009). Imputation methods were used to minimise verification bias arising from this less robust methodology. Eight studies used universal screening strategies (Agarwal et al., 2006; Agarwal et al., 2005a; Agarwal et al., 2005b; Agarwal et al., 2010; Black et al., 2010; Catalano et al., 2012; Huynh et al., 2011; van Leeuwen et al., 2009) and 3 used a risk factor based selection strategy prior to screening or diagnosis (Bito et al., 2005; Kuti et al., 2011; Senanayake et al., 2006).

All studies provided data on incidence of the diagnosis of gestational diabetes. Seven used WHO 1999 diagnostic criteria (fasting plasma glucose [FPG] 7.0 mmol/litre or more and/or 2 hour plasma glucose of 7.8 mmol/litre or more) (Agarwal et al., 2006; Agarwal et al., 2005a; Agarwal et al., 2005b; Bito et al., 2005; Kuti et al., 2011; Senanayake et al., 2006; van Leeuwen et al., 2009). Four used International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria (1 or more plasma venous glucose values, FPG 5.1 mmol/litre or more, 1 hour 10.0 mmol/litre or more or 2 hour 8.5 mmol/litre or more) (Agarwal et al., 2010; Black et al., 2010; Catalano et al., 2012; Huynh et al., 2011). Two studies did not use a screening test, but only reported incidence data for women with selected risk factors who, as a result, underwent a diagnostic 2 hour 75 g OGTT directly (Bito et al., 2005; Kuti et al., 2011).

Five studies examined FPG as a screening test compared with a diagnostic 2 hour 75 g OGTT. Of these, three used WHO 1999 diagnostic criteria (Agarwal et al., 2006; Agarwal et al., 2005a; Senanayake et al., 2006) and 2 used IADPSG diagnostic criteria (Agarwal et al., 2010; Huynh et al., 2011). One study examined HbA1c as a screening test (Agarwal et al., 2005b) and one study used a clinical prediction model in combination with a 1 hour 50 g glucose challenge test (van Leeuwen et al., 2009). Both compared these to a diagnostic 2 hour 75 g OGTT using WHO 1999 diagnostic criteria.

Screening tests were predominately performed in the second trimester (14 to 28+6 weeks of gestation) although some women were tested beyond this period in individual studies: see Table 22. One study did not provide a definition of second trimester (Kuti et al., 2011).

Two studies (Black et al., 2010; Catalano et al., 2012) provided data on the relative incidence of maternal and neonatal outcomes when women with a diagnosis of gestational diabetes and who were untreated were compared with those without gestational diabetes. The following outcomes were reported across both studies:

- primary caesarean section (women with no previous caesarean delivery)
- large for gestational age
- birthweight above 90th percentile
- shoulder dystocia/birth injury.

Table 22: Information regarding the timing of the screening/diagnostic test used to detect gestational diabetes mellitus in studies included in this review

Study	Screening schedule	Detail from study regarding the timing of the screening/diagnostic test
Agarwal et al,. 2005a	Universal screening strategy using a diagnostic 75 g OGTT (WHO 1999 criteria) scheduled between 24 and 28 weeks of gestation	Gestational age at screening (weeks) Women without gestational diabetes Mean ± standard deviation (SD) = 24.9±5.3* Median, range = 25, 9–40 Women with gestational diabetes Mean ±SD = 25.2±6.14* Median, range = 25, 7–40 * p=0.45

Study	Screening schedule	Detail from study regarding the timing of the screening/diagnostic test
Agarwal et al,. 2005[b]	Universal screening strategy using a diagnostic 75 g OGTT (WHO 1999 criteria) scheduled between 24 and 28 weeks of gestation	Gestational age at screening (weeks) Women without gestational diabetes Mean ±SD = 26±4.5* Median, range = 25, 16–40 Women with gestational diabetes Mean ±SD = 27±4.85* Median, range = 28, 18–37 *p=0.003
Agarwal et al., 2006	Universal screening strategy using a diagnostic 75 g OGTT (WHO 1999 criteria) scheduled between 24 and 28 weeks of gestation. Occasionally the test was performed earlier for clinical reasons, or later, if the woman presented late for booking	Gestational age (weeks) at OGTT All women Mean ±SD = 25.9±6.3 Median, range = 26, 2–38 weeks
Agarwal et al., 2010	Universal screening strategy using a diagnostic 75 g OGTT (IADPSG criteria) scheduled between 24 and 28 weeks of gestation	Gestational age (weeks) at OGTT All women Mean ±SD = 25.6±6.1
Bito et al., 2005	Universal screening strategy using a diagnostic 75 g OGTT (WHO 1999 criteria) between 24 and 28 weeks of gestation of women who tested negative for gestational diabetes at 16 weeks of gestation	No further details are available
Black et al., 2010	Universal screening strategy using a diagnostic 75 g OGTT (IADPSG criteria) between 24 and 28 weeks of gestation	Gestational age (weeks) at OGTT All women Mean ±SD = 26.7±2.9
Catalano et al., 2012	All women underwent a 75 g OGTT (IADPSG criteria) between 24 and 32 weeks of gestation and as close to 28 weeks as possible	Gestational age (weeks) All women Mean ±SD = 27.8±1.8 N=23,316
Huynh et al., 2011	Universal screening strategy using a diagnostic 75 g OGTT (IADPSG criteria). The timing of testing is not made explicit, but 26 to 28 weeks of gestation is implied.	No further details are available
Kuti et al., 2011	Diagnostic 75 g OGTT (WHO 1999 criteria) in women referred to clinic with at least one risk factor for gestational diabetes	Gestational age at testing ranged from 4 to 40 weeks. 276/765 women (36%) presented in the second trimester. No definition of second trimester is given.
Senanayake et al., 2006	Diagnostic 75 g OGTT (WHO 1999 criteria) in women with at least one risk factor for gestational diabetes. The timing of testing is not explicitly stated.	Gestational age at screening (weeks) All women Mean ±SD = 26.43±5.46 N= 271

Study	Screening schedule	Detail from study regarding the timing of the screening/diagnostic test
van,Leeuwen et al., 2009	Diagnostic 75 g OGTT (WHO 1999 criteria) in women who had screened positive for gestational diabetes (using a 50 g glucose challenge test or a random glucose test) one week previously between 24 and 28 weeks of gestation	No further details are available

IADPSG International Association of the Diabetes and Pregnancy Study Groups, OGTT oral glucose tolerence test, WHO World Health Organization

4.3.3.3 Evidence profile

The GRADE profiles for this review question are presented in Tables 25 to 30.

4.3.3.3.1 Studies using WHO 1999 diagnostic criteria for gestational diabetes

Table 23 presents evidence regarding the incidence of gestational diabetes in the second trimester diagnosed using a 75 g OGTT in unselected and selected populations. Where possible, it also presents the proportion of women diagnosed as having gestational diabetes in the second trimester out of the total number of women diagnosed as having gestational diabetes in the first and second trimesters combined.

Table 24 presents evidence regarding the diagnostic test accuracy of a fasting plasma glucose test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT in selected and unselected populations.

Table 25 presents evidence regarding the diagnostic test accuracy of an HbA1c test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT in an unselected population.

Table 26 presents evidence regarding the diagnostic test accuracy of a 50 g glucose challenge test (GCT) performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT in selected and unselected populations.

Table 27 presents evidence regarding acceptability of the OGTT from studies that used WHO 1999 diagnostic criteria for gestational diabetes.

4.3.3.3.2 Studies using IADPSG criteria

Table 29 presents evidence regarding the diagnostic test accuracy of 50 g GCT performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT in an unselected population.

Table 30 presents evidence regarding the diagnostic test accuracy of an FPG test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour OGTT IADPSG diagnostic criteria for gestational diabetes in an unselected population.

Table 30 presents evidence regarding maternal and neonatal outcomes following diagnosis using 75 g 2 hour OGTT IADPSG diagnostic criteria for gestational diabetes in unselected, untreated populations. Results are also presented for a subgroup analysis of obesity.

Table 23: GRADE profile for the incidence of gestational diabetes in the second trimester diagnosed using a 75 g oral glucose tolerance test (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more) in unselected and selected populations. Where possible, it also presents the proportion of women diagnosed as having gestational diabetes in the second trimester out of the total number of women diagnosed as having gestational diabetes in the first and second trimesters combined

Number of studies	Number of potential participants	Number of women who had test	Incidence of gestational diabetes diagnosed in the second trimester in all women tested	Women diagnosed with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Diagnosis in the second trimester using 75 g OGTT as diagnostic test (WHO 1999) in an unselected study population											
1 (Agarwal et al., 2005a)	1762[a]	1685 (95.6%)	333/1685 (19.8%)	NC	High	Prospective cohort	No serious limitations	NA	No serious indirectness[b]	No serious imprecision	Yes[c]
1 (Agarwal et al., 2006)	4844[d]	4596 (94.9%)	979/4596 (21.3%)*	NC	High	Prospective cohort	No serious limitations	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2005b)	454[g]	442 (97.3%)	84/442 (19%)	NC	Low	Prospective cohort	Serioush	NA	No serious indirectness[h]	Serious[i]	Yes[j]
1 (van Leeuwen et al., 2009)	1301[k]	1266 (97.3%)	47/1266 (3.7%)	NC	Moderate	Prospective cohort	No serious limitations	NA	No serious indirectness[l]	Serious[i]	Yes[m]
Diagnosis in the second trimester using 75 g OGTT as diagnostic test (WHO 1999) in a selected population											
1 (Bito et al., 2005)	163[n]	155 (95.1%)	32/155 (20.64%)*	32/40 (80%)	Moderate	Prospective cohort	No serious limitations	NA	No serious indirectness[o]	Serious[i]	Yes[p]
1 (Kuti et al., 2011)	276[q]	276 (100%)	35/276 (12.6%)*	35/47 (74.5%)*	Very low	Retrospective cohort	Serious[r]	NA	Seriouss	Serious[i]	Yes[t]
1 (Senanayake et al., 2006)	271[u]	271 (100%)	75/271 (27.7%)	NC	Low	Prospective cohort	Serious[r]	NA	No serious indirectnessv	Serious[i]	Yes[w]

NA not applicable, NC not calculable, OGTT oral glucose tolerance test, WHO World Health Organization
* Calculated by NCC-WCH

a. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester. 41/1726 women did not complete the diagnostic OGTT

b. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean ±SD: 25.2±6.14 and 24.9±5.3 for women with and without gestational diabetes respectively) although it was performed when clinically warranted for some women (range, gestational weeks 7-40)

c. Country: United Arab Emirates (UAE). Ethnicity of population: Expatriate and UAE Arab (92.2%), Indian subcontinent including India, Pakistan, Bangladesh, Sri Lanka (6.2%), other nationalities including Philippines, UK, Indonesia and Nigeria (1.6%)

d. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester. 242/4844 women did not complete the diagnostic OGTT

e. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean: 25.9±6.3 gestational weeks, median: 26 weeks, range: 2-38 weeks)

f. Country: UAE. Ethnicity of population: 3473 (75.5%) Arab, 932 (20.3%) South Asian (India, Pakistan, Bangladesh and Sri Lanka), 92 (2%) Other nationalities, 105 (2.3%) unavailable

g. Universal screening strategy using HbA1c screening test and a diagnostic 2 hour 75 g OGTT in the second trimester. 12/454 women did not complete the diagnostic OGTT

h. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean ± SD: 27±4.85 and 26±4.5 for women with and without gestational diabetes respectively (p=0.003), range: 16-40 gestational weeks)

i. Total number of events less than 300

j. Country: UAE. Ethnicity of population: UAE Arab (68.1%), Asian Arab (17.6%), Chami Arab (2.9%), East African Arab (1.1%), Indian subcontinent (1.6%), other nationalities (1.6%), unknown (7%)

k. Universal screening strategy using a risk factor based clinical prediction rule and a random glucose test (RBG) threshold 6.8 mmol/litre and/or 50 g glucose challenge test (GCT) threshold 7.8 mmol/litre in the second trimester to select women requiring a diagnostic 2 hour 75 g OGTT. The OGTT was performed in 322/1266 women. 146 of these women had at least one abnormal RBG or GCT result and 176 women had negative screening results but were randomly asked to undergo an OGTT to estimate the false negative fraction. A multiple imputation procedure was performed to correct for verification bias across the study population.

l. Screening was performed between gestational weeks 24-28 and OGTTs were performed within one week of screening where indicated

m. Country: The Netherlands. Ethnicity of population: white (89.4%), black (2.5%), Asian (0.4%), Other (7.7%)

n. Risk factor based screening strategy with all participants undergoing at least one diagnostic 2 hour 75 g OGTT. Participants did not have previous gestational diabetes nor any history of altered carbohydrate metabolism, but were referred to a specialist outpatient clinic and did have one or more of the following risk factors for gestational diabetes: any family history of type 2 diabetes, a history of a large neonate (≥ 4000 g), a history of an adverse perinatal outcome (missed abortion, malformation, polyhydramnios, stillbirth or preterm delivery), obesity (pre-pregnant body mass index ≥ 30m^2), age ≥ 35 years and glycosuria. 8 women diagnosed with gestational diabetes in the first trimester were excluded from the study. Incidence data from OGTTs performed in gestational weeks 32-34 were not included in this analysis

o. Diagnostic 2 hour 75 g OGTTs were performed at 3 time periods: ≤ gestational week 16, gestational weeks 24-28 and gestational weeks 32-34.

p. Country: Hungary. Ethnicity of population: not reported

q. Risk factor based screening strategy with all participants undergoing a diagnostic 2 hour 7 5g OGTT. Participants were women at high risk of gestational diabetes (based on a history of fetal macrosomia, maternal obesity, previous intrauterine fetal death, first degree relative with diabetes, glycosuria or history of gestational diabetes in a previous pregnancy) who were referred to a hospital research unit for a diagnostic 2 hour 75 g OGTT. Women with OGTTs performed between gestational weeks 4 to 40 were included in the study. Results for 69, 276 and 420 women were available for the first, second and third trimesters respectively.

r. Selection criteria are unclear because no exclusion criteria are presented

s. No definition of first trimester or second trimester is reported

t. Country: Nigeria. Ethnicity of population: not reported

u. Risk factor based screening strategy where women with at least one risk factor for gestational diabetes were referred for OGTT. Risk factors included having a first degree relative with diabetes, maternal BMI > 30kg/m^2 at booking, maternal age > 35 years, previous birth weight > 3.5 kg and previous unexplained stillbirth or fetal anomaly

v. Mean gestational age at screening: 26.43±5.46 gestational weeks

w. Country: Sri Lanka. Ethnicity of population: not reported

Table 24: GRADE profile for diagnostic test accuracy of fasting plasma glucose test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour oral glucose tolerance test (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more) in selected and unselected populations

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other considera-tions
Fasting plasma glucose ≥ 3.9 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	99.7 (98.9 to 100)*	0.3 (0.1 to 0.4)*	1.00 (0.99 to 1.00)*	1.02 (0.04 to 9.50)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Fasting plasma glucose ≥ 4.2 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	97.6 (95.6 to 98.8)*	3.3 (2.8 to 3.6)*	1.01 (0.98 to 1.03)*	0.74 (0.32 to 1.61)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	94.4 (92.9 to 95.7)*	10.4 (10.0 to 10.7)*	1.05 (1.03 to 1.07)*	0.54 (0.40 to 0.71)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Selected population												
1 (Senanayake et al., 2006)	271[i]	97.3 (90.5 to 99.5)*	28.6 (26.0 to 29.4)*	1.36 (1.22 to 1.41)*	0.09 (0.02 to 0.36)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]
Fasting plasma glucose ≥ 4.4 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	93.4 (90.4 to 95.6)*	11.5 (10.8 to 12.1)*	1.06 (1.01 to 1.09)*	0.57 (0.36 to 0.89)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	87.0 (84.9 to 88.9)*	28.8 (28.3 to 29.3)*	1.22 (1.18 to 1.25)*	0.45 (0.38 to 0.54)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Selected population												
1 (Senanayake et al., 2006)	271[i]	92.0 (83.7 to 96.6)*	48.5 (45.3 to 50.2)	1.78 (1.53 to 1.94)*	0.16 (0.07 to 0.36)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other considera-tions
Fasting plasma glucose ≥ 4.7 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	78.1 (73.6 to 82.0)*	32.2 (31.1 to 33.2)*	1.15 (1.07 to 1.23)*	0.68 (0.54 to 0.85)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	71.7 (69.0 to 74.2)*	51.6 (50.8 to 52.3)*	1.48 (1.40 to 1.55)*	0.55 (0.49 to 0.61)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Selected population												
1 (Senanayake et al., 2006)	271[i]	82.7 (73.3 to 89.7)*	66.8 (63.2 to 69.5)*	2.49 (1.99 to 2.94)*	0.26 (0.15 to 0.42)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]
Fasting plasma glucose ≥ 5.0 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	58.3 (53.3 to 63.0)*	63.1 (61.9 to 64.3)*	1.58 (1.34 to 1.76)*	0.66 (0.58 to 0.75)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	55.4 (52.6 to 58.1)*	73.3 (72.6 to 74.1)*	2.08 (1.92 to 2.24)*	0.61 (0.57 to 0.65)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Selected population												
1 (Senanayake et al., 2006)	271[i]	69.3 (59.8 to 77.6)*	83.2 (79.5 to 86.3)*	4.12 (2.91 to 5.66)*	0.36 (0.26 to 0.51)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]
Fasting plasma glucose ≥ 5.3 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	37.5 (33.1 to 42.1)*	83.5 (82.4 to 84.6)*	2.28 (1.88 to 2.74)*	0.75 (0.69 to 0.81)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	40.8 (38.3 to 43.3)*	86.6 (85.9 to 87.3)*	3.04 (2.72 to 3.40)*	0.68 (0.65 to 0.72)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other considera-tions
Selected population												
1 Senanayake et al., 2006	271[i]	45.3 (36.7 to 52.7)*	91.8 (88.5 to 94.6)*	5.55 (3.20 to 9.82)*	0.60 (0.50 to 0.72)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]
Fasting plasma glucose ≥ 5.6 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	24.0 (20.4 to 27.7)*	93.1 (92.2 to 94.0)*	3.49 (2.63 to 4.63)*	0.82 (0.77 to 0.86)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	29.8 (27.7 to 31.8)*	94.3 (93.7 to 94.9)*	5.23 (4.43 to 6.18)*	0.74 (0.72 to 0.77)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Fasting plasma glucose ≥ 5.8 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	17.4 (14.4 to 20.2)*	96.7 (96.0 to 97.4)*	5.35 (3.63 to 7.92)*	0.85 (0.82 to 0.89)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Agarwal et al., 2006)	4602[a]	22.1 (20.5 to 23.6)*	97.4 (97.0 to 97.8)*	8.60 (6.78 to 10.92)*	0.80 (0.78 to 0.82)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[g]	No serious imprecision	Yes[h]
Fasting plasma glucose ≥ 6.1 mmol/litre for detecting gestational diabetes in the second trimester												
Unselected population												
1 (Agarwal et al., 2005a)	1685[a]	9.0 (7.0 to 10.5)*	99.2 (98.7 to 99.5)*	11.07 (5.40 to 23.3)*	0.92 (0.90 to 0.94)*	Moderate	Prospective cohort	Serious[b,c,d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
Fasting plasma glucose ≥ 7.0 mmol/litre for detecting gestational diabetes in the second trimester												
Selected population												
1 (Senanayake et al., 2006)	271[i]	12.0 (7.3 to 13.3)*	99.5 (97.7 to 100)*	23.52 (3.18 to 495.46)*	0.88 (0.87 to 0.95)*	Low	Prospective cohort	Very serious[b,c,d,i]	NA	No serious indirectness[k]	No serious imprecision	Yes[l]

NA not applicable, OGTT oral glucose tolerance test
* Calculated by NCC-WCH
a. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

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d. The index test formed part of the reference standard

e. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean ±SD: 25.2 ± 6.14 and 24.9 ± 5.3 for women with and without gestational diabetes respectively) although it was performed when clinically warranted for some women (range, gestational weeks 7-40)

f. Country: United Arab Emirates (UAE). Ethnicity of population: Expatriate and UAE Arab (92.2%), Indian subcontinent including India, Pakistan, Bangladesh, Sri Lanka (6.2%), other nationalities including Philippines, UK, Indonesia and Nigeria (1.6%)

g. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean: 25.9 ± 6.3 gestational weeks, median: 26 weeks, range: 2-38 weeks)

h. Country: UAE. Ethnicity of population: 3473 (75.5%) Arab, 932 (20.3%) South Asian (India, Pakistan, Bangladesh and Sri Lanka), 92 (2%) Other nationalities, 105 (2.3%) unavailable

i. Risk factor based screening strategy where women with at least one risk factor for gestational diabetes were referred for OGTT. Risk factors included having a first degree relative with diabetes, maternal BMI > 30kg/m^2 at booking, maternal age > 35 years, previous birth weight > 3.5 kg and previous unexplained stillbirth or fetal anomaly

j .Selection criteria are unclear because no exclusion criteria are presented

k. Mean gestational age at screening: 26.43±5.46 gestational weeks

l. Country: Sri Lanka. Ethnicity of population: not reported

Table 25: GRADE profile for diagnostic test accuracy of HbA1c test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour oral glucose tolerance test (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more) in an unselected population

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
HbA1c ≥ 4.5% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	97.6 (94.2 to 99.6)*	1.4 (0.6 to 1.9)*	0.99 (0.95 to 1.02)*	1.70 (0.23 to 9.69)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 5% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	97.6 (94.2 to 99.6)*	4.7 (3.5 to 5.2)*	1.02 (0.96 to 1.05)*	0.50 (0.08 to 2.17)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 5.5% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	82.1 (73.2 to 89.0)*	20.9 (18.9 to 22.6)*	1.04 (0.90 to 1.15)*	0.85 (0.49 to 1.42)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
HbA1c ≥ 6% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	48.8 (38.8 to 58.9)*	55.6 (53.2 to 57.9)*	1.10 (0.83 to 1.40)*	0.92 (0.71 to 1.15)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 6.5% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	21.4 (13.9 to 30.6)*	78.5 (76.7 to 80.6)*	1.00 (0.60 to 1.58)*	1.00 (0.86 to 1.12)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 7% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	10.7 (5.5 to 18.1)*	90.5 (89.3 to 92.2)*	1.13 (0.52 to 2.32)*	0.99 (0.89 to 1.06)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 7.5% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	7.1 (3.1 to 12.9)*	95.8 (94.9 to 97.2)*	1.70 (0.60 to 4.51)*	0.97 (0.90 to 1.02)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]
HbA1c ≥ 8% for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2005b)	442[a]	3.6 (1.0 to 7.0)*	98.6 (98.0 to 99.4)*	2.56 (0.49 to 12.03)*	0.98 (0.94 to 1.01)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[d]	No serious imprecision	Yes[e]

NA not applicable, OGTT oral glucose tolerance test
* Calculated by NCC-WCH
a. Universal screening strategy using HbA1c screening test and a diagnostic 2 hour 75 g OGTT in the second trimester
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. Screening for gestational diabetes was scheduled between gestational weeks 24-28 (mean±SD: 27±4.85 and 26±4.5 for women with and without gestational diabetes respectively (p=0.003), range: 16-40 gestational weeks)
e. Country: United Arab Emirates (UAE). Ethnicity of population: UAE Arab (68.1%), Asian Arab (17.6%), Chami Arab (2.9%), East African Arab (1.1%), Indian subcontinent (1.6%), other nationalities (1.6%), unknown (7%)

Table 26: GRADE profile for diagnostic test accuracy of 50 g glucose challenge test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour oral glucose tolerance test (World Health Organization 1999 diagnostic criteria for gestational diabetes: fasting plasma glucose 7.0 mmol/litre or more and/or 2 hour plasma glucose 7.8 mmol/litre or more) in an unselected population

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limita-tions	Inconsist-ency	Indirectness	Impreci-sion	Other considera-tions
50 g 1 hour GCT at 7.8 mmol/litre threshold in an unselected population												
1 (van Leeuwen et al., 2009)	1266a	68.1 (53.4 to 80.2)*	89.2 (88.6 to 89.6)*	6.28 (4.69 to 7.74)*	0.36 (0.22 to 0.57)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Determination of risk using a clinical prediction rule followed by 50 g 1 hour GCT if indicated: no 50 g 1 hour GCT (low risk n=311) or 50 g 1 hour GCT at 7.8 mmol/litre threshold (intermediate risk) or 50 g 1 hour GCT at 7.1 mmol/litre threshold (high risk)												
1 (van Leeuwen et al., 2009)	1266g	63.8 (49.0 to 76.6)*	87.4 (86.9 to 87.9)*	5.09 (3,74 to 6.35)*	0.41 (0.27 to 0.59)*	Moderate	Prospective cohort	Serious[b,c,d]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]

GCT glucose challenge test, NA not applicable, OGTT oral glucose tolerance test
* Calculated by NCC-WCH
a. Universal screening strategy using a 1 hour 50 g glucose challenge test and a diagnostic 2 hour 75 g OGTT in the second trimester
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. The reference standard was not performed in the whole sample. The OGTT was performed in 322/1266 women. 146 of women had at least one abnormal random blood glucose (RBG) or glucose challenge test (GCT) result and 176 women had negative screening results but were randomly asked to undergo an OGTT to estimate the false negative fraction. A multiple imputation procedure was performed to correct for verification bias across the study population
e. Screening was performed between gestational weeks 24-28 and OGTTs were performed within one week of screening where indicated. The OGTT was performed in 322/1266 women. 146 of women had at least one abnormal RBG or GCT result and 176 women had negative screening results but were randomly asked to undergo an OGTT to estimate the false negative fraction. A multiple imputation procedure was performed to correct for verification bias across the study population
f. Country: The Netherlands. Ethnicity of population: white (89.4%), alack (2.5%), asian (0.4%), other (7.7%)
g. Risk factor based clinical prediction rule (using age, BMI and ethnicity. Low risk = Clinical risk score 0 or 1, Intermediate risk = Clinical risk score 2 or 3, High risk = Clinical risk score higher than 3) and 1 hour 50 g GCT as indicated in the second trimester.
Evidence profile for acceptability of the oral glucose tolerance test (OGTT)

Table 27: GRADE profile for acceptability of the oral glucose tolerance test

Number of studies	Proportion of potential participants who did not complete an OGTT	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Acceptability of OGTT								
1 (Agarwal et al., 2005a)	12/454 (2.6%)[a]	High	Prospective cohort	No serious limitations	NA	No serious indirectness	NA	Yes[b]
1 (Agarwal et al., 2005b)	41/1726 (2.4%)[c]	High	Prospective cohort	No serious limitations	NA	No serious indirectness	NA	Yes[d]
1 (Agarwal et al., 2006)	242/4844 (5.0%)[e]	High	Prospective cohort	No serious limitations	NA	No serious indirectness	NA	Yes[f]

NA not applicable, OGTT oral glucose tolerance test
a. 12 women did not complete the OGTT due to vomiting
b. Country: United Arab Emirates (UAE). Ethnicity of population: Expatriate and UAE Arab (92.2%), Indian subcontinent including India, Pakistan, Bangladesh, Sri Lanka (6.2%), other nationalities including Philippines, UK, Indonesia and Nigeria (1.6%)
c. 41 women did not complete the OGTT due to vomiting, refusal to undergo test, eating food during the test or due to other reasons
d. Country: UAE. Ethnicity of population: UAE Arab (68.1%), Asian Arab (17.6%), Chami Arab (2.9%), East African Arab (1.1%), Indian subcontinent (1.6%), other nationalities (1.6%), unknown (7%)
e. 242 women did not undergo the OGTT due to refusal to undergo the test (65), vomiting (110), eating food during the test or other reasons (67)
f. Country: UAE. Ethnicity of population: 3473 (75.5%) Arab, 932 (20.3%) South Asian (India, Pakistan, Bangladesh and Sri Lanka), 92 (2%) Other nationalities, 105 (2.3%) unavailable
g. Risk factor based clinical prediction rule (using age, BMI and ethnicity. Low risk = Clinical risk score 0 or 1, Intermediate risk = Clinical risk score 2 or 3, High risk = Clinical risk score higher than 3) and 1 hour 50 g GCT as indicated in the second trimester.
Country: The Netherlands. Ethnicity of population: White (89.4%), Black (2.5%), Asian (0.4%), Other (7.7%)

Table 28: GRADE profile for the incidence of gestational diabetes in the second trimester diagnosed using a 75 g oral glucose tolerance test (International Association of the Diabetes and Pregnancy in Study Groups diagnostic criteria for gestational diabetes: one or more plasma venous glucose values, fasting plasma glucose 5.1 mmol/litre or more, 1 hour 10.0 mmol/litre or more or 2 hour 8.5 mmol/litre or more) in unselected populations. It also presents the proportion of women who were diagnosed as having gestational diabetes who were untreated

Number of studies	Number of potential participants	Number of women who had test	Incidence of gestational diabetes diagnosed in the second trimester in all women tested	Women diagnosed with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Diagnosis in the second trimester using 75 g OGTT as diagnostic test (IADPSG) in an unselected population											
1 (Agarwal et al., 2010)	10283[a]	10283 (100%)	3875/10283 (37.70%)	NC	High	Prospective cohort	No serious limitations	NA	No serious indirectness[b]	No serious imprecision	Yes[c]
1 (Huynh et al, 2011)	8486[d]	5473 (64.50%)	1022/5473 (19%)	NC	Moderate	Retrospective cohort	No serious limitations	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
1 (Black et al., 2010)	9199[g]	9199 (100%)	2179/9199 (23.70%)	NC	Moderate	Retrospective cohort	No serious limitations	NA	No serious indirectness[h]	No serious imprecision	Yes[i]
Diagnosis in the second trimester using 75 g OGTT as diagnostic test (IADPSG) in an untreated population											
1 (Catalano et al., 2012)	53295[j]	25,505 (47.8%)[j]	3746/23267* (16.1%)[j]	NC	High	Prospective cohort	No serious limitations	NA	No serious indirectness[k]	No serious imprecision	Yes[l]
1 (Black et al., 2010)	9199[m]	9199 (100%)	1691/8711 (19.40%)	NC	Moderate	Retrospective cohort	No serious limitations	NA	No serious indirectness[h]	No serious imprecision	Yes[i]

NA not applicable, NC not calculable, OGTT oral glucose tolerance test, WHO World Health Organization

a. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester

b. Screening for gestational diabetes was scheduled between gestational weeks 24-28 – no further details provided

c. Country: United Arab Emirates. Ethnicity: 8233 (80.1%) were of Arab ethnicity and 1592 (15.5%) were of South Asian ethnicity

d. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester. 8486 women were included in the study of whom 5473 had diagnostic 2 hour 75 g OGTT results available

e. Screening for gestational diabetes was recommended between gestational weeks 26-28 – no further details provided

f. Country: Australia. Ethnicity: not presented

g. Universal testing with 2 hour 75 g OGTT in the second trimester. Incidence of gestational diabetes pertains to the whole study population (treated and untreated women)

h. Screening for gestational diabetes was performed between gestational weeks 24-28 (mean ± SD: 26.7 ± 2.9)

i. Country: USA. Ethnicity: Non-Hispanic white 626 (7.2%), Hispanic 6484 (74.4%), Black 880 (10.1%), Asian 641 (6.4%), Other 80 (0.9%)

j. 53,295 women from 15 international centres were eligible to participate. 28,562 (53.6%) agreed to participate and 25,505 women completed the OGTT. 746 (2.9%) were excluded because of glucose unblinding, 1,412 (5.5%) were excluded primarily because they had undergone glucose testing or delivery outside the context of the HAPO Study, and 31 (0.1%) were excluded owing to missing key data or improbable results. Data from 23,316 women were available for analysis although only results of only 23,267 women untreated for gestational diabetes contributed to incidence results.
k. Universal diagnostic testing with 2 hour 75 g OGTT was performed between gestational weeks 24 and 32, but as close to gestational week 28 as possible
l. Countries: USA, Australia, UK and Israel Ethnicity: White, non-Hispanic 11,265 (48.3%), Black, non-Hispanic 2,696 (11.6%), Hispanic 1,984 (8.5%), Asian 6,757 (29.0%), Other 614 (2.6%)
m. Universal testing with 2 hour 75 g OGTT in the second trimester. Incidence of gestational diabetes pertains to the untreated women only within the study population

Table 29: GRADE profile for the diagnostic test accuracy of fasting plasma glucose test performed in the second trimester to detect gestational diabetes diagnosed using a 75 g 2 hour oral glucose tolerance test (International Association of the Diabetes and Pregnancy in Study Groups diagnostic criteria for gestational diabetes: one or more plasma venous glucose values, fasting plasma glucose 5.1 mmol/litre or more, 1 hour 10.0 mmol/litre or more, or 2 hour 8.5 mmol/litre or more) in an unselected population

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Fasting plasma glucose ≥ 4.2 mmol/litre for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2010)	10,283[a]	98.3 (97.9 to 98.7)*	11.5 (11.3 to 11.8)*	1.11 (1.10 to 1.12)*	0.15 (0.11 to 0.19)*	Low	Prospective cohort	Very serious[b,c,d,e]	NA	No serious indirectness[f]	No serious imprecision	Yes[g]
Fasting plasma glucose ≥ 4.4 mmol/litre for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2010)	10,283[a]	95.4 (94.7 to 96.0)*	32.0 (31.6 to 32.4)*	1.40 (1.38 to 1.42)*	0.14 (0.12 to 0.17)*	Low	Prospective cohort	Very serious[b,c,d,e]	NA	No serious indirectness[f]	No serious imprecision	Yes[g]
Fasting plasma glucose ≥ 4.7 mmol/litre for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2010)	10,283[a]	88.9 (88.0 to 89.8)*	60.1 (59.6 to 60.7)*	2.23 (2.18 to 2.28)*	0.19 (0.17 to 0.20)*	Low	Prospective cohort	Very serious[b,c,d,e]	NA	No serious indirectness[f]	No serious imprecision	Yes[g]
Fasting plasma glucose ≥ 5.0 mmol/litre for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2010)	10,283[a]	80.5 (79.6 to 81.3)*	90.9 (90.4 to 91.4)*	8.86 (8.28 to 9.49)*	0.22 (0.20 to 0.23)*	Low	Prospective cohort	Very serious[b,c,d,e]	NA	No serious indirectness[f]	No serious imprecision	Yes[g]

Number of studies	Number of women with OGTT	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirectness	Impreci-sion	Other considera-tions
Fasting plasma glucose ≥ 5.1 mmol/litre for detecting gestational diabetes in the second trimester												
1 (Agarwal et al., 2010)	10,283[a]	76.8 (75.4 to 78.1)*	99.99 (99.94 to 100)*	> 1000 (872 to > 1000)*	0.232 (0.232 to 0.234)*	Low	Prospective cohort	Very serious[b,c,d,e]	NA	No serious indirectness[f]	No serious imprecision	Yes[g]
1 (Huynh et al., 2011)	5473[h]	51.17 (48.11 to 54.23)*	99.99 (99.29 to 100)*	> 1000 (404 to > 1000)*	0.488 (0.488 to 0.494)*	Low	Retrospective cohort	Serious[b,c,d]	NA	No serious indirectness[i]	No serious imprecision	Yes[j]

NA not applicable, OGTT oral glucose tolerance test, WHO World Health Organization

* Calculated by the NCC-WCH technical team

a. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. The index test formed part of the reference standard

e. Selection criteria are unclear as no exclusion criteria are presented

f. Screening for gestational diabetes was scheduled between gestational weeks 24-28 – no further details provided

g. Country: United Arab Emirates. Ethnicity: 8233 (80.1%) were of Arab ethnicity and 1592 (15.5%) were of South Asian ethnicity

h. Universal screening strategy using FPG test results performed as part of a diagnostic 2 hour 75 g OGTT in the second trimester. 8486 women were included in the study of whom 5473 had diagnostic 2 hour 75 g OGTT results available

i. Screening for gestational diabetes was recommended between gestational weeks 26-28 – no further details provided

Country: Australia. Ethnicity: not presented

Table 30: GRADE profile for maternal and neonatal outcomes following diagnosis using 75 g 2 hour oral glucose tolerance test (International Association of the Diabetes and Pregnancy in Study Groups diagnostic criteria for gestational diabetes: one or more plasma venous glucose values fasting plasma glucose 5.1 mmol/litre or more, 1 hour 10.0 mmol/litre or more, or 2 hour 8.5 mmol/litre or more) in unselected untreated populations. Results are also presented for a subgroup analysis of obesity

Number of studies	Number of babies/women		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Gestational diabetes	No gestational diabetes	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Primary caesarean section: entire untreated unselected study population											
1 (Black et al., 2010)	336/1691 (19.9%)	1112/7020 (15.8%)	RR 1.25 (1.12 to 1.40)*	40 more per 1000 (from 19 more to 63 more)	Moderate	Retrospective cohort	No serious limitations[a]	No serious inconsistency	No serious indirectness[b]	No serious imprecision	Yes[c]
1 (Catalano et al., 2012)	779/3191 (24.4%)	2952/17541 (16.8%)	RR 1.45 (1.35 to 1.55)*	76 more per 1000 (from 59 more to 93 more)	High	Prospective cohort	No serious limitations[d]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
Primary caesarean section: subgroup of untreated women who were obese[g]											
1 (Catalano et al., 2012)	215/749 28.7%)	430/1868 (23%)	RR 1.25 (1.08 to 1.43)*	58 more per 1000 (from 18 more to 99 more)	Moderate	Prospective cohort	No serious limitations[d]	NA	No serious indirectness[e]	Serious[h]	Yes[f]
Primary caesarean section: subgroup of untreated women who were not obese[g]											
1 (Catalano et al., 2012)	564/2442 (23.1%)	2522/15673 (16.1%)	RR 1.44 (1.32 to 1.56)*	71 more per 1000 (from 51 more to 90 more)	High	Prospective cohort	No serious limitations[d]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Large for gestational age: entire untreated unselected study population											
1 (Black et al., 2010)	264/1691 (15.6%)	528/7020 (7.5%)	RR 2.08 (1.81 to 2.38)*	81 more per 1000 (from 61 more to 104 more)	Moderate	Retrospective cohort	No serious limitations[i]	NA	No serious indirectness[b]	No serious imprecision	Yes[c]
Birthweight > 90th percentile: entire untreated unselected study population											
1 (Catalano et al., 2012)	604/3726 (16.2%)	1617/19491 (8.3%)	RR 1.95 (1.79 to 2.13)*	79 more per 1000 (from 66 more to 94 more)	High	Prospective cohort	No serious limitations[j]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]

Number of studies	Number of babies/women		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Gestational diabetes	No gestational diabetes	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Birthweight > 90th percentile: subgroup of untreated women who were obese[g]											
1 (Catalano al., 2012)	203/935 (21.7%)	278/2247 (12.4%)	RR 1.75 (1.49 to 2.07)*	93 more per 1000 (from 61 more to 132 more)	High	Prospective cohort	No serious limitations[j]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Birthweight > 90th percentile: subgroup of untreated women who were not obese[g]											
1 (Catalano et al., 2012)	401/2791 (14.4%)	1339/17244 (7.8%)	RR 1.85 (1.67 to 2.05)*	66 more per 1000 (from 52 more to 82 more)	High	Prospective cohort	No serious limitations[j]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Shoulder dystocia/birth injury: entire untreated unselected study population											
1 (Black et al., 2010)	96/1691 (5.7%)	268/7020 (3.8%)	RR 1.49 (1.19 to 1.87)*	19 more per 1000 (from 7 more to 33 more)	Moderate	Retrospective cohort	No serious limitations[k]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[c]
1 (Catalano et al., 2012)	67/3728 (1.8%)	244/19499 (1.3%)	RR 1.44 (1.1 to 1.88)*	6 more per 1000 (from 1 more to 11 more)	High	Prospective cohort	No serious limitations[l]	No serious inconsistency	No serious indirectness[e]	No serious imprecision	Yes[f]
Shoulder dystocia/birth injury: subgroup of untreated women who were obese											
1 (Catalano et al., 2012)	26/936 (2.8%)	32/2252 (1.4%)	1.95 (1.17 to 3.26)*	13 more per 1000 (from 2 more to 32 more)	High	Prospective cohort	No serious limitations[l]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]
Shoulder dystocia/birth injury: subgroup of untreated women who were not obese[g]											
1 (Catalano et al., 2012)	41/2792 (1.5%)	212/17247 (1.2%)	RR 1.19 (0.86 to 1.67)*	2 more per 1000 (from 2 fewer to 8 more)	High	Prospective cohort	No serious limitations[l]	NA	No serious indirectness[e]	No serious imprecision	Yes[f]

NA not applicable, OGTT oral glucose tolerance test, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

a. Primary caesarean section confirmed from infant birth certificate

b. Diagnostic testing for gestational diabetes was performed between gestational weeks 24-28 (mean ± SD: 26.7±2.9)

c. Country: USA. Ethnicity: Non-Hispanic white 626 (7.2%), Hispanic 6484 (74.4%), Black 880 (10.1%), Asian 641 (6.4%), Other 80 (0.9%)

d. Primary caesarean section confirmed from infant birth certificate and defined as the need for the first caesarean delivery at the discretion of the subject's primary obstetrical care provider. Total caesarean deliveries was not used as an outcome because of the various policies regarding delivery at various HAPO Study sites

e. Diagnostic testing was performed between gestational weeks 24 and 32, but as close to gestational week 28 as possible

f. Countries: USA, Australia, UK and Israel. Ethnicity: White, non-Hispanic 11,265 (48.3%), Black, non-Hispanic 2696 (11.6%), Hispanic 1984 (8.5%), Asian 6757 (29.0%), Other 614 (2.6%)

g. Obesity was defined at 28 weeks as a BMI ≥ 33.0 kg/m^2, overweight at 28 weeks as a BMI of 28.5–32.9, and normal weight or underweight as a BMI ≤ 28.4. These cut points (from regression analyses) are equivalent to the WHO categories of (nonpregnant) class 1 obesity, BMI ≥ 30.0 kg/m^2, overweight 25.0–29.9, and normal or underweight < 25.0, respectively

h. The confidence intervals for the relative and absolute effect point estimates are wide

i. Large for gestational age was defined as infants in whom sex-specific, race-specific and gestational age-specific birth weight > 90th percentile

j. Birthweight > 90th percentile was defined as birth weight greater than the 90th percentile for the baby's sex, gestational age, ethnicity, field centre, and maternal parity with gestational ages of 30–44 weeks included

k. Shoulder dystocia/birth injury was defined as presence of ICD-9 codes 653.4, 653.5, 660.4, 767.0–767.9 or 959.0–959.9 at delivery

l. When either shoulder dystocia or birth injury was suspected, additional data were abstracted and were reviewed by two members of an outcome review committee (blinded to the mother's glycaemic status) to confirm whether either was present

4.3.3.4 Evidence statements

4.3.3.4.1 *Incidence of gestational diabetes, WHO 1999 diagnostic criteria*

Four studies (n=1762; n=4844; n=454; n=1301) provided low to high quality evidence that the incidence of gestational diabetes diagnosed in the second trimester using a 75 g oral glucose tolerance test (OGTT) according to the WHO 1999 diagnostic criteria in all women tested within an unselected population ranged from 3.7% to 21.3%. The proportion of women who were diagnosed with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester was not calculable.

Three studies (n=163; n=276; n=271) provided very low to moderate quality evidence that the incidence of gestational diabetes diagnosed in the second trimester using a 75 g OGTT according to the WHO 1999 diagnostic criteria in all women tested within a selected population ranged from 12.6% to 27.7%. The proportion of women who were diagnosed with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester ranged from 74.5% to 80%.

4.3.3.4.2 *Incidence of gestational diabetes using IADPSG criteria*

Three studies (n=10,283; n=8486; n=9199) provided high and moderate quality evidence for the incidence of gestational diabetes diagnosed in the second trimester in all women tested, which ranged from 19% to 37.7%. The proportion of women with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester was not calculable.

Two studies (n=53,295; n=9199) provided high and moderate quality evidence for the incidence of gestational diabetes diagnosed in the second trimester using 75 g OGTT ranged from 16.1% to 19.4%. The proportion of women with gestational diabetes in the second trimester as a proportion of all women diagnosed in the first and second trimester was not calculable.

4.3.3.4.3 *Diagnostic test accuracy using WHO criteria*

Fasting plasma glucose

One study (n=1685) provided moderate quality evidence for the accuracy of the fasting plasma glucose (FPG) test performed in the second trimester and found the test was useful for ruling out but not useful for ruling in (specificity 0.3, 95% CI 0.1% to 0.4%) gestational diabetes at a threshold of less than 3.9 mmol/litre using WHO 1999 diagnostic criteria in an unselected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out but not useful for ruling in gestational diabetes at a threshold of greater than 4.2 mmol/litre using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out but not useful for ruling in gestational diabetes at a threshold of greater than 4.2 mmol/litre using WHO 1999 diagnostic criteria in a selected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out but not useful for ruling gestational diabetes at a threshold of greater than 4.4 mmol/litre using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out but not useful for ruling in gestational diabetes at a threshold of greater than 4.4 mmol/litre using WHO 1999 diagnostic criteria in a selected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out or ruling in gestational diabetes at a threshold of of 4.7 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out or ruling in gestational diabetes at a threshold of 4.7 mmol/litre and above using WHO 1999 diagnostic criteria in a selected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out or ruling in gestational diabetes at a threshold of 5.0 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out or moderately useful for ruling in gestational diabetes at a threshold of 5.0 mmol/litre and above using WHO 1999 diagnostic criteria in a selected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was moderately useful for ruling in gestational diabetes at a threshold of 5.3 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 5.3 mmol/litre and above using WHO 1999 diagnostic criteria in a selected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 5.6 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

Two studies (n=1685; n=4602) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 5.8 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

One study (n=1685) provided moderate quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 6.1 mmol/litre and above using WHO 1999 diagnostic criteria in an unselected population.

One study (n=271) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 7.0 mmol/litre and above using WHO 1999 diagnostic criteria in an selected population.

No evidence was available to assess the diagnostic accuracy of a urine screening test for glycosuria or a random blood glucose test compared to a diagnostic 75 g oral glucose tolerance test with application of WHO 1999 diagnostic criteria or equivalent.

4.3.3.4.4 *Diagnostic test accuracy using IADPSG criteria*

One study (n=10,283) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out and ruling in gestational diabetes at a threshold of 4.2 mmol/litre and above using IADPSG diagnostic criteria in an unselected population.

One study (n=10,283) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was useful for ruling out and ruling in gestational diabetes at a threshold of 4.4 mmol/litre and above using IADPSG diagnostic criteria in an unselected population.

One study (n=10,283) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was moderately useful for ruling out but not useful for ruling in gestational diabetes at a threshold of 4.7 mmol/litre and above using IADPSG diagnostic criteria in an unselected population.

One study (n=10,283) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was moderately useful for ruling out and ruling in gestational diabetes at a threshold of 5.0 mmol/litre and above using IADPSG diagnostic criteria in an unselected population.

Two studies (n=10,283; n=5473) provided low quality evidence for the accuracy of the FPG test performed in the second trimester and found the test was not useful for ruling out but was useful for ruling in gestational diabetes at a threshold of 5.1 mmol/litre and above using IADPSG diagnostic criteria in an unselected population.

HbA1c

One study (n=442) provided moderate quality evidence that an HbA1c screening test was not useful for ruling in or ruling out gestational diabetes in an unselected population at any threshold between 4.5% and 8% in the second trimester.

50 g 1 hour GCT

One study (n=1266) provided moderate quality evidence for the accuracy of 50 g 1 hour GCT at 7.8 mmol/litre threshold for detecting gestational diabetes in the second trimester and found the test was not useful for ruling out but was moderately useful for ruling in the diagnosis in an unselected population.

One study (n=1266) provided moderate quality evidence for the accuracy of a determination of risk using a clinical prediction rule followed by a 50 g 1 hour GCT if indicated at 7.1 mmol/litre threshold (high risk) for detecting gestational diabetes in the second trimester and found the test was not useful for ruling out but was moderately useful for ruling in the diagnosis in an unselected population.

4.3.3.4.5 *Acceptability of oral glucose tolerance test*

Three studies (n=454; n=1726; n=4844) provided evidence regarding the acceptability of the OGTT. Between 2.4% and 5.0% of women in the studies carried out in the United Arab Emirates did not complete the OGTT during universal testing. The evidence was of high quality.

No evidence was available regarding length of stay in neonatal intensive care unit or neonatal mortality.

4.3.3.4.6 ***Neonatal outcomes following diagnosis using 75 g 2 hour oral glucose test and the IADPSG diagnostic criteria***

Two studies (n=8711; n=20,732) found an increased risk of primary caesarean section in women with gestational diabetes compared with women without gestational diabetes taken from an entire untreated and unselected population (respectively: RR 1.25, 95% CI 1.12 to 1.40; RR 1.45, 95% CI 1.35 to 1.55). The quality of the evidence for this outcome was moderate and high quality.

One study (n=2617) found an increased risk of primary caesarean section in a subgroup of women who were obese and had gestational diabetes compared with women who were obese without gestational diabetes (RR 1.25, 95% CI 1.08 to 1.43). The quality of the evidence for this outcome was moderate quality.

One study (n=18,095) found an increased risk of primary caesarean section in a subgroup of women who were not obese and had gestational diabetes compared with women who were not obese without gestational diabetes (RR 1.44, 95% CI 1.32 to 1.56). The quality of the evidence for this outcome was high quality.

One study (n=8711) found an increased risk of large for gestational age babies in women with gestational diabetes compared with women without gestational diabetes taken from an entire untreated and unselected population (RR 2.08, 95% CI 1.81 to 2.38). The quality of the evidence for this outcome was moderate.

One study (n=23,217) found an increased risk of greater than 90th percentile birth weight neonates in women with gestational diabetes compared with women without gestational diabetes taken from an entire untreated and unselected population (RR 1.95, 95% CI 1.79 to 2.13). The quality of the evidence for this outcome was high.

One study (n=23,217) found an increased risk of greater than 90th percentile birth weight neonates in a subgroup of women with gestational diabetes who were obese compared with women without gestational diabetes who were obese (RR 1.75, 95% CI 1.49 to 2.07). The quality of the evidence for this outcome was high.

One study (n=20,035) found an increased risk of greater than 90th percentile birth weight neonates in a subgroup of women with gestational diabetes who were not obese compared with women without gestational diabetes who were not obese (RR 1.85, 95% CI 1.67 to 2.05). The quality of the evidence for this outcome was high.

Two studies (n=8711; n=23,227) found an increased risk of shoulder dystocia in the neonates of a subgroup of women with gestational diabetes compared with women without gestational diabetes taken from an entire untreated and unselected population (respectively: RR 1.49, 95% CI 1.19 to 1.87; RR 1.44, 95% CI 1.1 to 1.88). The quality of the evidence for this outcome was moderate and high.

One study (n=3188) found an increased risk of shoulder dystocia in the neonates of a subgroup of women with gestational diabetes who were obese compared with women without gestational diabetes who were obese (RR 1.95, 95% CI 1.17 to 3.26). The quality of the evidence for this outcome was high.

One study (n=20,039) found no difference in risk of shoulder dystocia in the neonates of a subgroup of women with gestational diabetes who were not obese compared with women without gestational diabetes who were not obese taken from an entire untreated and unselected population (RR 1.19, 95% CI 0.86 to 1.67). The quality of the evidence for this outcome was moderate and high.

4.3.3.5 Health economics profile

Three studies were identified which considered the cost effectiveness of screening for gestational diabetes. These studies are described in more detail in Section 9.1.1. It was not thought that these studies could be used as the sole basis for recommendations as the decision problem and/or context was different to that required and therefore additional modelling was undertaken to support the guideline.

Screening for gestational diabetes using risk factors and biochemical testing was prioritised for health economic analysis. The results of this analysis are summarised here but more details are available in Chapter 9.

It was possible to use the model developed for assessing the cost effectiveness of diagnostic criteria to compare the cost effectiveness of universal screening versus NICE risk factor based screening. Using data from 4 centres in the HAPO dataset it was possible to identify the subset of that population that would have been selected for an OGTT using NICE risk factor screening. The incremental cost effectiveness of universal screening over risk factor based screening is given by the cost effectiveness of diagnosis and treatment in that subset of the population who would not be identified by risk factors. Therefore, we were able to identify the subset of the HAPO (4 centres) population who would not be selected for testing based on the presence of risk factors. The model was run for both subsets. In the risk factor selected population there were diagnostic criteria with incremental cost effectiveness ratios (ICERs) in the £20,000 to £30,000 per quality adjusted life year (QALY) range. However, in the subset without risk factors the lowest ICER was £47,000 per QALY and therefore our modelling does not support a change to universal testing.

The HAPO (4 centres) dataset, with more than 6,000 UK and Australian patients, was also used to inform a comparison of NICE risk factor screening compared to the 50 g glucose challenge test (GCT). Using NICE risk factors would identify between 74% and 78% of cases of gestational diabetes using WHO 1999 and IADPSG criteria respectively. This compared similarly or favourably with published estimates for the sensitivity of the 50 g GCT. Therefore, equivalence in detection was assumed and a simple cost analysis of 2 screening alternatives was undertaken. The results of this analysis showed that, in the HAPO (4 centres) population of just over 6,000 patients, the screening and diagnosis costs of the 50 g GCT were approximately £50,000 more than for a NICE risk factor strategy. In this analysis it was assumed that a 50 g GCT was £6 cheaper than an OGTT. A threshold analysis suggested that this differential would have to increase to £14 before there was cost neutrality of the 2 alternatives. Again, this analysis did not suggest that the 50 g GCT should be preferred to NICE risk factor screening on grounds of cost effectiveness.

Finally, an informal analysis was also undertaken to compare fasting plasma glucose (FPG) levels with NICE risk factor based screening. This showed that the FPG would have very low detection rates if set to match the fasting blood glucose used as the diagnostic criteria for the fasting value in an OGTT. Sensitivity could be improved by selecting a lower fasting screening threshold but this would negate most of the advantage an FPG had in terms of false positives and unnecessary testing. The analysis suggested that the cost of an FPG would have to be unfeasibly low in order for it to be preferred to NICE risk factor screening.

In summary, these analyses found no evidence of cost effectiveness that would support a change in guidance offered by NICE on screening for gestational diabetes.

4.3.3.6 Evidence to recommendations

4.3.3.6.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the incidence of gestational diabetes diagnosed in the second trimester as an outcome because this can vary in different populations and

also according to which pre-screening selection strategies, screening tests and diagnostic criteria are applied.

The group prioritised diagnostic accuracy of screening tests because performing an OGTT is demanding for the service and can be unpleasant and poorly tolerated by women. Therefore, identifying an effective screening test or screening strategy with good subsequent diagnostic accuracy would be useful. A number of pre-screening selection strategies and screening tests are used and clarity regarding their comparative diagnostic accuracies would be informative.

The group prioritised outcomes in determining whether screening prior to diagnosis of gestational diabetes is of benefit to the mother and her baby. Prioritised maternal outcomes were:

- mode of birth: spontaneous vaginal, operative vaginal, caesarean section (elective/emergency)
- treatment such as diet, oral hypoglycaemic agents and/or insulin
- acceptability/take-up of testing regimen.

Prioritised neonatal outcomes were:

- large for gestational age (however defined in the study, for example using a customised measure based on gestational age and population norms; dichotomous data preferred)
- perinatal and neonatal death up to 28 days ('all mortality' outcome)
- neonatal intensive care unit length of stay (greater than 24 hours)
- shoulder dystocia (no permanent damage, neurological injury (brachial plexus and cerebral palsy).

4.3.3.6.2 *Consideration of clinical benefits and harms*

The guideline development group considered the consequences of a screening test for gestational diabetes in the second trimester of pregnancy.

The advantage of a correct positive screening test result is the potential to have a subsequent definitive diagnostic test and appropriate care in pregnancy.

The main advantage of a correct negative screening test result is in confirming that glucose regulation in the pregnancy is normal, the reassurance that this gives to the woman and the avoidance of unnecessary interventions.

A consequence of an erroneous positive screening test result would be an unnecessary diagnostic test and the inconvenience and anxiety that this would cause.

The group believed that when a woman receives an erroneous negative screening test there is the potential of considerable harm to her or her baby. The consequent lack of effective intervention would theoretically increase the potential likelihood of poor outcomes for the woman and her baby, including short- and long-term morbidity.

4.3.3.6.3 *Consideration of health benefits and resource uses*

Alternative screening strategies carry different costs but also have different detection rates. Universal screening achieves the highest detection rates but also results in more women having an unnecessary test, which is inconvenient and mildly unpleasant. Therefore, higher cost strategies with higher detection must demonstrate that the additional detection rates are worth the additional cost. It should be borne in mind that the additional cases identified by universal screening will have milder disease on average compared with those identified by risk factor screening.

4.3.3.6.4   *Quality of evidence*

The guideline development group prioritised studies that used a 2 hour 75 g OGTT diagnostic test interpreted using IADPSG or WHO 1999 (or equivalent) diagnostic criteria following screening. Although there are a large number of studies investigating screening for gestational diabetes, most were irrelevant according to the review protocol, mainly because either a 100 g diagnostic OGTT was used or because the diagnostic criteria applied to the OGTT were neither IADPSG nor WHO 1999 (or equivalent).

Eleven studies were available and evidence quality ranged from very low to high. All studies reported incidence data following screening and diagnosis.

When WHO diagnostic criteria were applied, 3 studies from the United Arab Emirates showed a similar high incidence of gestational diabetes in an unselected population which contrasted with a lower incidence in a Dutch study. This is consistent with Middle Eastern ethnicity being a risk factor for gestational diabetes. Three studies conducted in selected populations were of lower quality. Participants in all 3 studies had been referred for OGTT testing and had been selected on the basis of clinical risk factors (including family history of diabetes, a history of a large neonate, previous stillbirth or fetal anomaly, maternal obesity, maternal age above 35 years, history of gestational diabetes in a previous pregnancy and glycosuria). Ethnicity was not considered as a risk factor in any of the studies conducted in Hungary (Bito et al., 2005), Nigeria (Kuti et al., 2011) and Sri Lanka (Senanayake et al., 2006). The range of incidence rates was higher in these selected populations than in the unselected population. The guideline development group believed these countries to have a higher incidence of gestational diabetes since the rates of type 2 diabetes are higher in these countries. However, it was noted that none are currently included in commonly used lists of ethnicity risk factors.

When IADPSG criteria were applied to an unselected population, the evidence from 1 study from the UAE was that incidence of gestational diabetes in a high risk population was nearly double compared with when WHO 1999 were used. These findings were reproduced in lower risk populations from Australia and the USA.

Analysis of HAPO data across the 15 individual study centres revealed that 16.1% of women would have gestational diabetes as defined by IADPSG, but it is not clear how representative the HAPO participants were of the individual centre background population. Further analysis of the HAPO data reported an average incidence using IADPSG diagnostic criteria of 17.8%, with a range of from 9.3% to 25.5% across all study centres and that the mean incidence in the 2 UK HAPO study centres was 24.3%.These studies all applied IADPSG criteria without modification using FPG and 1 hour and 2 hour post load plasma values.

4.3.3.6.5   *Other considerations*

The guideline development group considered that the majority of the evidence identified would have application within the UK, although this would be dependent upon the ethnic mix of the local population.

Though the systematic review failed to demonstrate any appropriate studies of glycosuria as a screening test, the group acknowledged that women with diabetes do have glycosuria more commonly than women without diabetes. Furthermore, they noted that the guideline development group for the original 2008 guideline found both observational data demonstrating a strong association between glycosuria and diabetes in pregnancy and audit data suggesting that healthcare professionals considered that glycosuria of 1+ or more on more than 1 occasion or 2+ or more on 1 occasion was an indication for an OGTT. In summary, although there was no evidence to recommend testing for glycosuria as a population screening test in pregnancy, there was evidence that the presence of glycosuria in pregnancy increased the likelihood of glucose intolerance. Both the original guideline on diabetes in pregnancy and the guideline on antenatal care recommend that screening for

gestational diabetes using fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose should not be undertaken. However, the antenatal care guideline does recommend screening for pre-eclampsia with regular measurement of blood pressure and urinalysis for protein. In practice this urinalysis is undertaken using a reagent strip which detects the presence of other chemicals in the urine, including glucose. The guideline development group therefore felt that it was important to address the opportunistic finding of glycosuria since it would be common occurrence in practice and a minority of these women would have gestational diabetes. Thus the group felt that there should be a recommendation addressing the approach to glycosuria in pregnancy in the context of screening for gestational diabetes.

The guideline development group reflected on the recommendation made in the previous guideline regarding the information needs of women considering screening. They considered that most women with gestational diabetes require treatment in addition to diet and exercise and increased this estimate to 70% as they believed that the previous estimate was too low and that the increased estimate was a fairer reflection of their combined experience. Following discussion, the group made an amendment to the recommendations regarding the complications from which women might be at greater risk with undiagnosed gestational diabetes. The group considered that describing the risk as a 'small increased risk of serious birth complications such as shoulder dystocia' reflected the evidence from RCTs of intervention.

4.3.3.7 Key conclusions

The guideline development group believed that the clinical evidence generally supported the use of screening in a selected population to target OGTT diagnostic testing. This would minimise the associated costs and harms of exposing all women to unnecessary screening and diagnostic testing.

There was evidence that diagnostic testing was not acceptable or tolerated by all women. The group noted that a much greater percentage of women in the Netherlands study did not complete an OGTT compared with women in the 3 studies from the United Arab Emirates. Based on their clinical experience, the group believed that the data from the Netherlands would be more transferable to women in England and Wales.

The guideline development group noted that although a review was not performed to examine each risk factor outlined in the 2008 guideline, there was sufficient evidence to support many of them as they were used in the studies as the method to identify their subgroups for diagnostic testing. Similarly, no evidence was found to contradict the other risk factors.

With regard to the screening test to be used, the group noted there was some supportive evidence for the use of an FPG screening test in populations at high risk due to ethnicity. The evidence from the UAE studies (that used WHO 1999 diagnostic criteria) supports the use of a universal testing strategy using FPG in populations with a high ethnicity risk to rule in gestational diabetes with a threshold of 6.1 mmol/litre. However, FPG was only very useful to rule out gestational diabetes at a threshold of 4.2 mmol/litre in a Sri Lankan study of a selected population. FPG testing was not as useful a screening test when IADPSG diagnostic criteria were applied in an unselected population.

There were limited data to support the usefulness of a 50 g GCT as a screening test in both unselected and selected populations when WHO 1999 diagnostic criteria were applied and no evidence for either an RPG or urine analysis. However, there was evidence that HbA1c testing was not a useful test and this was not considered further in the health economic analysis.

With regard to outcomes, women diagnosed with gestational diabetes using IADPSG criteria were more likely to have babies that were large for gestational age and to have a primary

caesarean section than those without gestational diabetes. Shoulder dystocia and birth injury rates were also higher in babies of women with gestational diabetes but maternal obesity was an important modifier in 1 study. Therefore, the guideline development group saw no reason according to the available clinical evidence to discontinue or amend the recommendation to screen women late in the second trimester on the basis of risk factors to detect gestational diabetes. The only exception to this was that women with a history of gestational diabetes in a previous pregnancy should be screened as early as possible in the next pregnancy to rule out underlying type 2 diabetes or a recurrence of gestational diabetes.

4.3.3.8 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.4 Diagnostic criteria for gestational diabetes
This section was updated in 2015

4.4.1 Review question

Which criteria should be used to diagnose gestational diabetes using the 75 g oral glucose tolerance test (OGTT):

- World Health Organization (WHO) 1999 or
- International Association of Diabetes and Pregnancy Study Groups (IADPSG)?

4.4.2 Introduction

The 2008 guideline recommended that women with risk factors for gestational diabetes should be offered testing for gestational diabetes using the WHO 1999 diagnostic criteria for interpreting a 75 g 2 hour OGTT. More specifically, the guideline recommended that:

- Women who have had gestational diabetes in a previous pregnancy should be offered early self-monitoring of blood glucose or an OGTT at 16–18 weeks, and a further OGTT at 28 weeks if the results are normal.
- Women with any other risk factors for gestational diabetes should be offered an OGTT at 24–28 weeks.

Since the publication of the 2008 guideline, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study has indicated that there is a continuum of risk of adverse pregnancy outcomes associated with rising maternal glucose values (HAPO Study Cooperative Research Group 2008). Moreover, the IADPSG has proposed new diagnostic criteria for gestational diabetes based on glucose values associated with a 1.75-fold increased risk of macrosomia, fetal hyperinsulinaemia and adiposity from the HAPO study (IADPSG Consensus Panel 2010).

The IADPSG criteria provide thresholds for diagnosis of gestational diabetes in the first and second trimesters. Diagnosis of gestational diabetes in the first trimester is made on the basis of a fasting plasma glucose (FPG) value of 5.1 mmol/litre or more but below 7.0 mmol/litre. Women who have a first trimester FPG value of less than 5.1mmol/litre are tested in the second trimester with a 2 hour 75 g OGTT. One or more values higher than the following thresholds in the second trimester are diagnostic of gestational diabetes:

- FPG value of 5.1 mmol/litre or more
- a 1 hour plasma glucose value of 10.0 mmol/litre or more
- a 2 hour plasma glucose value of 8.5 mmol/litre or more.

These diagnostic criteria can be applied within universal or targeted screening strategies, for example using risk factors to identify women to be offered a diagnostic test.

The main potential benefit of the IADPSG criteria is to identify more women who are at higher risk of an adverse pregnancy outcome and who might benefit from therapeutic interventions to improve pregnancy outcomes.

4.4.3 Methods

This review investigates whether using IADPSG criteria rather than the existing recommendation to use WHO 1999 criteria would improve both of the following for women who are diagnosed with gestational diabetes, specifically in the context of whether diagnosis based on the IADPSG criteria would lead to improved outcomes for pregnant women and their babies:

- clinical diagnostic effectiveness
- cost effectiveness of diagnosis

The review was performed in 3 parts and included studies in which:

- Data from a specified population have been analysed to estimate incidence of gestational diabetes using both the WHO and IADPSG criteria. This would provide information regarding any increase in the number of women who would require therapeutic interventions following a diagnosis of gestational diabetes.
- Diagnostic test accuracy of the IADPSG criteria has been evaluated using the WHO 1999 criteria as the reference standard. This would provide information regarding the proportion of women who would be diagnosed regardless of the criteria used and regarding those who would or would not be diagnosed if the IADPSG criteria were implemented
- Incidence of maternal and neonatal clinical outcomes has been compared in untreated pregnant women diagnosed using the 2 sets of criteria. This would provide information regarding the relative incidence and spread of outcomes in women diagnosed using the different criteria, and their babies.

The guideline development group was aware that there were likely to be few studies published given the relatively recent publication of the IADPSG criteria in 2010. However, they were also aware that relevant unpublished data might be available to inform a health economic model to further examine any increase in the number of women who would be diagnosed with gestational diabetes using the IADPSG criteria rather than the WHO criteria. This model might also provide information to suggest alternative diagnostic thresholds to either WHO 1999 or IADPSG 2010.

4.4.4 Description of included studies

Five studies were identified for inclusion for this review question (Dahanayaka et al., 2012; Jenum et al., 2012; Kun et al., 2011; Nallaperumal et al., 2013; Wendland et al., 2012).

Two of these studies were population based: 1 was a prospective cohort study (Jenum et al., 2012) and the other was based on a local screening programme (Kun et al., 2011). One study was cross-sectional in design, but it also used data collected retrospectively (Dahanayaka et al., 2012). The fourth study was a retrospective cohort of women for whom there was a high index of suspicion and who underwent screening for gestational diabetes at 4 diabetes centres. The final study was a systematic review of prospective and retrospective cohort studies that included women with gestational diabetes who did not receive any treatment (Wendland et al., 2012).

Three studies compared the application of WHO and IADPSG criteria as part of universal screening strategies (Jenum et al., 2012; Kun et al., 2011; Wendland et al., 2012) and 1 study compared their application as part of risk factor based and universal screening strategies (Dahanayaka et al., 2012). The last study did not specify selection criteria but noted that their population was a selected group and that the prevalence of gestational diabetes at the diabetes centres they attended would be higher than in the community

(Nallaperumal et al., 2013). Three studies specified that pregnant women with pre-existing gestational diabetes were excluded (Jenum et al., 2012; Kun et al., 2011; Wendland et al., 2012) and the other 2 studies did not specify any exclusion criteria (Dahanayaka et al., 2012; Nallaperumal et al., 2013).

The WHO definition of gestational diabetes was interpreted as FPG of 7.0 mmol/litre or more or 2 hour plasma glucose of 7.8 mmol/litre or more in all 5 studies. Three studies used FPG of 5.1 mmol/litre or more or 1 hour plasma glucose of 10 mmol/litre or more or 2 hour plasma glucose of 8.5 mmol/litre or more as the IADPSG definition of gestational diabetes (Dahanayaka et al., 2012; Nallaperumal et al., 2013; Wendland et al., 2012). The other studies used a modified IADPSG definition of gestational diabetes in which 1 hour plasma glucose values were not measured (Jenum et al., 2012; Kun et al., 2011). The definition used in both these studies was FPG of 5.1mmol/litre or more or 2 hour plasma glucose of 8.5 mmol/litre or more. One study presented results comparing FPG of 5.1 mmol/litre or more in the first trimester (part of the IADPSG diagnosis of gestational diabetes) with WHO criteria in the second trimester (Dahanayaka et al., 2012).

Four studies provided evidence regarding incidence of gestational diabetes and regarding the comparative diagnostic test accuracy of the WHO and IADPSG criteria (Dahanayaka et al., 2012; Jenum et al., 2012; Kun et al., 2011; Nallaperumal et al., 2013). One study (the systematic review) provided evidence regarding maternal and neonatal clinical outcomes from 2 prospective cohort studies (Wendland et al., 2012). The authors of the systematic review had direct access to a database from 1 of the cohort studies (the Brazilian Study of Gestational Diabetes) but it was unclear how they obtained the results they reported from the other cohort study (HAPO).

4.4.5 Evidence profile

The GRADE profiles for this review question are presented in Tables 31 to 33.

Table 31: GRADE profile for the incidence of diagnosis of gestational diabetes using WHO and IADPSG criteria.

Number of studies	Number of potential participants	Number of women who had test	Incidence of gestational diabetes using WHO criteria	Incidence of gestational diabetes using IADPSG criteria	Quality	Design	Limitations	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Universal screening with 75 g oral glucose tolerance tests											
1 (Dahanayaka et al., 2012)	NR[a]	405 (10%)	29/405 (7.2%)	36/405 (8.9%)	Low	Cross-sectional	Serious[b,c]	NA	No serious indirectness	Serious[d]	Yes[e]
1 (Jenum et al., 2012)	823	759 (92.2%)	99/759 (13.0%)	239/759 (31.5%)	Low	Prospective cohort	Serious[b,c]	NA	Serious[f]	No serious imprecision	Yes[g]
1 (Kun et al., 2011)	2260	1835 (81.2%)	159/1835 (8.7%)	304/1835 (16.6%)	Low	Population based	Serious[b,c]	NA	Serious[f]	No serious imprecision	Yes[h]
Screening in a selected population											
Nallaperuamal et al., 2013)	1351	1351	699/1351 women (51.7%)	699/1351 women (51.7%)	Very low	Retrospective cohort	Serious[b,c]	NA	No serious indirectness	No serious imprecision	Yes[i]

IADPSG International Association of Diabetes and Pregnancy Study Groups, NA not applicable, NR not reported, WHO World Health Organization

a. Annual births not reported, but would be approximately 4000 because recruitment was performed to cover 10% of annual births (n=400)

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. Total number of events less than 300

e. Country: Sri Lanka. Ethnicity of population: not reported

f. Incidence of gestational diabetes estimated using modified IADPSG criteria (fasting plasma glucose and 2 hour plasma glucose values only, no 1 hour plasma glucose values reported)

g. Country: Norway. Ethnicity of population: 59% of women were of an ethnic minority, the largest groups being South Asians (25%) and Middle Easterners (15%)

h. Country: Hungary. Ethnicity of population: not reported, although the study authors reported that most of the Hungarian population is white

Country: Sri Lanka. Ethnicity of population: not reported, although the study authors make reference to the study being performed in an Asian Indian population

Table 32: GRADE profile for the diagnostic test accuracy of 2 hour 75 g OGTT in the second trimester interpreted using IADPSG thresholds (FPG 5.1 mmol/litre or more, 1 hour PG 10.0 mmol/litre or more or 2 hour PG 8.5 mmol/litre for detecting gestational diabetes in the second trimester) compared with reference standard WHO 1999 criteria thresholds (FPG 7.0 mmol/litre or more or 2 hour PG 7.8 mmol/litre or more)

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency		Indirectness	Imprecision	Other considerations
Fasting plasma glucose ≥ 5.1 mmol/litre or 1 hour plasma glucose ≥ 10 mmol/litre or 2 hour plasma glucose ≥ 8.5 mmol/litre for detecting gestational diabetes in the second trimester													
1 (Dahanayaka et al., 2012)	405	60.8 (59.5 to 68.8)[a]	6.2 (0.32 to 36.9)[a]	0.65 (0.6 to 1.21)[a]	6.27 (0.72 to 3400786)[a]	Moderate	Cross-sectional	Serious[b, c]	NA		No serious indirectness	No serious imprecision	Yes[d]
1 (Jenum et al., 2012)	759	71.7 (62.4 to 79.7)	74.5 (73.2 to 75.7)	2.82 (2.32 to 3.28)	0.38 (0.27 to 0.51)	Low	Prospective cohort	Serious[b, c]	NA		Serious[e]	No serious imprecision	Yes[f]
1 (Kun et al., 2011)	1835	65.4 (58.1 to 72.1)	88.1 (87.4 to 88.7)	5.48 (4.6 to 6.38)	0.39 (0.31 to 0.48)	Low	Population based	Serious[b, c]	NA		Serious[e]	No serious imprecision	Yes[g]
Selected population													
1 (Nallaperumal et al., 2013)	1351	80 (77.7 to 82.0)*	78.5 (76.1 to 80.8)*	3.72 (3.26 to 4.26)*	0.26 (0.22 to 0.29)*	Very low	Retrospective cohort	Serious[b, c]	NA		No serious indirectness	No serious imprecision	Yes[j]
Fasting plasma glucose ≥ 5.1 mmol/litre for detecting gestational diabetes in the first trimester													
1 (Dahanayaka et al., 2012)	16	12.5 (0.63 to 60.2)	82.1 (78.6 to 94.7)	0.7 (0.0 to 10.61)	1.07 (0.46 to 1.27)	Very low	Cross-sectional (retrospective data)	Serious[b, c]	NA		No serious indirectness	Serious[h]	Yes[d,i]

FPG fasting plasma glucose, IADPSG International Association of Diabetes and Pregnancy Study Groups, NA not applicable, PG plasma glucose, WHO World Health Organization

a. Calculated by the NCC-WCH technical team from data reported in the article

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. Country: Sri Lanka. Ethnicity of population: not reported

e. Incidence of gestational diabetes estimated using modified IADPSG criteria (fasting plasma glucose and 2 hour plasma glucose values only, no 1 hour plasma glucose values reported

f. Country: Norway. Ethnicity of population: 59% of women were of an ethnic minority, the largest groups being South Asians (25%) and Middle Easterners (15%)

g. Country: Hungary. Ethnicity of population: not reported, although the study authors reported that most of the Hungarian population is white

h. Confidence interval for sensitivity was wider than 40 percentage points

i. Although the study was cross-sectional in design, retrospective methods were used to obtain the data and thus the initial quality rating in GRADE is moderate

j. Country: Sri Lanka. Ethnicity of population: not reported, although the study authors make reference to the study being performed in an Asian Indian population

Table 33: GRADE profile of the incidence of clinical outcomes in untreated pregnant women with gestational diabetes diagnosed using the WHO compared with IADPSG criteria and their babies

Number of studies	Number of women who had test	Incidence in women with gestational diabetes diagnosed using WHO criteria and their babies	Incidence in women with gestational diabetes diagnosed using IADPSG criteria and their babies	Quality	Design	Limita-tions	Inconsist-ency	Indirectness	Imprecision	Other considera-tions
Caesarean section										
1 (Wendland et al., 2012 [EBDG 2001])	4345	151/321 (47.0%)	309/801 (38.6%)	Moderate	Systematic review (prospective cohort study data)	Serious[a]	NA	No serious indirectness	No serious imprecision	Yes[b]
1 (Wendland et al., 2012 [HAPO 2008])	20732	564/2314 (24.4%)	813/3338 (24.4%)	Low	Systematic review (prospective cohort study data)	Very serious[a,c]	NA	No serious indirectness	No serious imprecision	Yes[d]
Large for gestational age (birthweight ≥ 90th centile)										
1 (Wendland et al., 2012 [EBDG 2001])	Varies[e]	45/294 (15.3%)	87/772 (11.3%)	Very low	Systematic review (prospective cohort study data)	Very serious[a,f]	NA	No serious indirectness	Serious[g]	Yes[b]
1 (Wendland et al., 2012 [HAPO 2008])	Varies[h]	361/2642 (13.7%)	605/3738 (16.2%)	Low	Systematic review (prospective cohort study data)	Very serious[a,c,f]	NA	No serious indirectness	No serious imprecision	Yes[d]
Perinatal mortality										
1 (Wendland et al., 2012 [EBDG 2001])	4431	12/330 (3.6%)	27/812 (3.3%)	Low	Systematic review (prospective cohort study data)	Serious[a]	NA	No serious indirectness	Serious[g]	Yes[b]

EBDG Brazilian Study of Gestational Diabetes, HAPO Hyperglycemia and Adverse Pregnancy Outcomes study, IADPSG International Association of Diabetes and Pregnancy Study Groups, NA not applicable, WHO World Health Organization
a. The data presented in the systematic review did not allow calculation of the statistical significance of the results
b. Country: Brazil. Ethnicity of population: white 44.9%, mixed 41.4%, black 13.6%, other 0.4%
c. Unclear where the data presented in the systematic review for the HAPO 2008 study were sourced
d. Country: multinational. Ethnicity of population: white 48.3%, black 11.6%, Hispanic 8.5%, Asian 29.0%, other 2.6%
e. Total number of untreated women tested using WHO criteria 3,924, total number of untreated women tested using IADPSG criteria 3,974
f. Unclear why the number of women tested for gestational diabetes using each criteria is different
g. Total number of events less than 300
h. Total number of untreated women tested using WHO criteria 23,027, total number of untreated women tested using IADPSG criteria 23,217

4.4.6 Evidence statements

4.4.6.1 Incidence of gestational diabetes

Three studies (n=405; n=1582; n=4095) reported the incidence of gestational diabetes according to the WHO and IADPSG diagnostic criteria. In 3 studies, the incidence of gestational diabetes defined according to the WHO criteria ranged from 7.2% to 13% and according to the IADPSG criteria ranged from 8.9% to 31.5%. A greater proportion of women were diagnosed with gestational diabetes when IADPSG criteria were applied compared with when WHO criteria were applied, ranging from 1.7% more to 18.5% more. The evidence for these findings was of low quality.

In 1 study of women with a high index of risk for gestational diabetes (n=1351), the incidence of gestational diabetes was much higher than in the other 3 studies (51.7%) and was the same value irrespective of whether IADPSG or WHO criteria were applied. The quality of this evidence was very low.

4.4.6.2 Diagnostic test accuracy

Four studies (n=405; n=759; n=1835; n=1351) evaluated the diagnostic test accuracy of a 2 hour 75 g OGTT in the second trimester applying the IADPSG criteria compared with applying the WHO 1999 criteria.

Two studies (n=759; n=1835) indicated that, at best, a positive or negative diagnosis of gestational diabetes using IADPSG criteria was a moderately useful test for ruling in or ruling out gestational diabetes as defined by the WHO 1999 criteria. The evidence for these findings was of low quality.

One study (n=405) did not find IADPSG criteria to be a useful test for ruling in or ruling out gestational diabetes as defined by the WHO 1999 criteria. The evidence for this finding was of moderate quality.

One study (n=1351) indicated that in a selected population using IADPSG criteria a 2 hour 75 g OGTT in the second trimester was not useful for ruling in gestational diabetes as defined by the WHO 1999 criteria, but was moderately useful for ruling it out. The evidence for this finding was of very low quality.

One study (n=16) evaluated the diagnostic test accuracy of an FPG test in the first trimester applying IADPSG threshold criteria compared with 75 g 2 hour OGTT in the second trimester using WHO 1999 criteria. A positive or negative diagnosis of gestational diabetes using IADPSG criteria was not useful for ruling out but was moderately useful for ruling in gestational diabetes as defined by the WHO 1999 criteria. The evidence for this finding was of very low quality.

4.4.6.3 Incidence of clinical outcomes

Two studies (n=4345; n=20,732) reported the incidence of clinical outcomes in untreated pregnant women according to the WHO and IADPSG diagnostic criteria. The incidence of caesarean section in women with gestational diabetes defined according to the WHO criteria ranged from 24.4% to 47.0% and 24.4% to 38.6% according to the IADPSG criteria. The evidence for these findings was moderate.

Two studies (population size not reported) reported the incidence of birth weight that was large for gestational age at or above the 90th percentile in women with gestational diabetes. When defined according to the WHO criteria it ranged from 13.7% to 15.3% whereas according to the IADPSG criteria it was 11.3% to 16.2%. The evidence for these findings was very low and low.

One study (n=4431) reported the incidence of perinatal mortality in women with gestational diabetes defined according to the WHO criteria as 3.6% whereas according to the IADPSG criteria it was 3.3%. The evidence for these findings was low.

4.4.7 Health economics profile

A literature review identified 5 studies which considered the cost effectiveness of the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria for gestational diabetes. These studies are discussed in more detail in Section 9.1.3. It was not possible to make recommendations based on these papers as they did not include all the comparators relevant to the NHS context.

This question was prioritised for health economic analysis.

A de novo model using individual patient data was developed to assess the cost effectiveness of various alternative diagnostic thresholds for gestational diabetes. This include the WHO 1999 criteria which was used in the previous NICE guideline on diabetes in pregnancy and also the new IADPSG criteria and some variants of it that were discussed in the guideline development group. This analysis is discussed in more detail in Chapter 9 but is summarised here.

The cost effectiveness of 13 diagnostic thresholds and no treatment were compared in 2 datasets – HAPO (4 centres in the UK and Australia) and Norwich. Logistic regression was used to predict a baseline risk of a number of maternal and neonatal outcomes in each woman. Then for each threshold it was determined whether a woman would be identified as having gestational diabetes. If a woman was identified as having gestational diabetes then her baseline risk would be adjusted according to the treatment effect size reported in intervention studies. In this way it was possible to calculate a cost and QALY for each woman. These were then aggregated across all the women in the dataset, which in turn facilitated a comparison of the incremental costs and QALYs for different diagnostic criteria.

In the base case analysis, no treatment was the cost-effective option in the Norwich dataset with WHO 1999 criteria having the lowest incremental cost effectiveness ratio (ICER) (£35,000 per QALY). A number of base case analyses were run on the HAPO (4 centres) dataset but the most relevant for guideline development group decision-making, given their screening recommendations, was the analysis undertaken on a subset of that dataset having NICE risk factors. This suggested that WHO 1999 criteria was cost effective if a £30,000 per QALY willingness to pay threshold was used.

Sensitivity analysis suggested that WHO 1999 diagnostic criteria could be considered cost effective at £30,000 per QALY in the Norwich dataset if a higher cost of pre-eclampsia was assumed.

In the HAPO (4 centres) dataset using the subset with NICE risk factors, sensitivity analysis showed that a fasting threshold of 5.6 mmol/litre and 2 hour threshold of 7.8 mmol/litre could be considered cost effective at £30,000 per QALY if the opportunity cost of nursing time was lower than in the base case. Furthermore, sensitivity analysis also suggested that a threshold of 5.5 mmol/litre fasting blood glucose and 2 hour 7.8 mmol/litre was cost effective at £30,000 per QALY if a higher pre-eclampsia cost was used.

4.4.8 Evidence to recommendations

4.4.8.1 Relative value placed on the outcomes considered

Priority clinical outcomes selected for this review question were:
- mode of birth
- preterm birth (birth before 37^{+0} weeks' gestation)

- need for treatment for gestational diabetes
- large for gestational age
- neonatal intensive care unit length of stay greater than 24 hours
- shoulder dystocia
- raised neonatal blood concentrations of insulin or C-peptide
- perinatal or neonatal mortality.

The guideline development group prioritised estimation of gestational diabetes incidence according to the 2 sets of diagnostic criteria (WHO 1999 and IADPSG criteria). Both sets of criteria provide thresholds for diagnosing gestational diabetes in the second trimester. The group believed that more women might be diagnosed with gestational diabetes when IADPSG criteria are applied by comparison with WHO 1999. The IADPSG criteria also allow an earlier diagnosis of gestational diabetes to be made in the first trimester (if FPG value is 5.1 mmol/litre or more but less than 7.0 mmol/litre). In addition, IADPSG criteria allow the diagnosis of 'overt diabetes in pregnancy'. The thresholds for this diagnosis are either an FPG of 7 mmol/litre or more or an HbA1c of 48 mmol/litre or more (6.5%). If a random plasma glucose of 11.1 mmol/litre or more is the initial measure, a tentative diagnosis of overt diabetes in pregnancy should be confirmed by an FPG or HbA1c using the above thresholds. Therefore, the guideline development group acknowledged that changing the criteria used to diagnose gestational diabetes might imply increased treatment costs relative to those indicated in the 2008 guideline.

The guideline development group decided to assess the degree of agreement between IADPSG and WHO 1999 criteria using diagnostic test accuracy measures (likelihood ratios for positive and negative results).

The group selected clinical outcomes, recognising that pregnancy and birth are life-changing events and the care that a woman receives during pregnancy has the potential to affect the woman and baby physically and emotionally in both the short and longer term. The outcomes chosen were considered to be clinically meaningful for the woman and baby, could be reliably assessed in clinical research studies and were expected to be commonly reported in the evidence available for inclusion.

The prioritised maternal outcomes were:
- mode of birth (spontaneous vaginal, operative vaginal, caesarean section (planned or unplanned)
- preterm birth (birth before 37^{+0} weeks' gestation)
- need for treatment for gestational diabetes, such as diet, oral hypoglycaemic agents or insulin.

The prioritised neonatal outcomes were:
- large for gestational age (however defined in the study, for example using a customised measure based on gestational age and population norms)
- neonatal intensive care unit length of stay greater than 24 hours
- shoulder dystocia
- neonatal hyperinsulinaemia or hyper C-peptide-aemia (raised neonatal blood concentrations of insulin or C-peptide)
- mortality[ff].

[ff] The definition of mortality includes perinatal mortality (stillbirth and death up to 7 days after birth) and neonatal mortality (death up to 28 days after birth).

4.4.8.2 Consideration of clinical benefits and harms

The guideline development group considered the consequences of a diagnosis of gestational diabetes to the woman and her baby, including the potential clinical benefits and harms associated with being correctly and incorrectly diagnosed as having gestational diabetes.

The advantages of a correct positive diagnosis of gestational diabetes are that appropriate, timely management to stabilise plasma glucose can start and the potential harms of glucose dysregulation in pregnancy are minimised. The successful management of diabetes in pregnancy also may reduce incidence of type 2 diabetes in the baby. The group also noted that a diagnosis of gestational diabetes can initiate a care pathway for women that may result in increased interventions and reduction in choice of care for the women.

The main advantage of a correct negative diagnosis is in confirming that the pregnancy is normal with regard to glucose regulation and the reassurance that this gives to the woman, as well as the avoidance of unnecessary interventions.

A consequence of an erroneous positive diagnosis may be unnecessary intervention to gain tighter control of glucose regulation. The group recognised that the clinical benefit of achieving tighter glucose control might not be outweighed by the harms caused by unnecessary intervention (for example unnecessary anxiety, additional clinical appointments or exposure to medication).

The group believed that when a woman receives an erroneous negative diagnosis there are no appreciable benefits, but there is the potential of considerable harm to her or her baby. The consequent lack of effective intervention would increase the likelihood of poor outcomes for the woman and her baby, including short- and long-term morbidity.

4.4.8.3 Consideration of health benefits and resource uses

The IADPSG criteria would lead to a substantial increase in the number of women in England and Wales being identified with gestational diabetes. Although IADPSG generally led to increased benefit when compared with WHO 1999, the guideline development group agreed with the model that this would be achieved only at an unacceptably high incremental cost.

WHO 1999 criteria, which were used in previous NICE guidance, came out as one of the most cost-effective criteria, but the group did not feel able to continue to recommend this as an appropriate threshold for gestational diabetes. In particular, they considered that the fasting threshold of 7 mmol/litre was too high and noted that this was the view expressed by many authors. They noted that the intervention studies used a lower fasting threshold for inclusion and therefore these studies made a case for intervention at these lower levels. They were also concerned that the model results were driven by a regression analysis that downplayed the role of fasting blood glucose levels in the outcomes included in the model. They were of the view that a relationship between fasting blood glucose had been well established with biochemical markers of disease. As a result, they decided that a fasting blood glucose of 5.6 mmol/litre and a 2 hour blood glucose of 7.8 mmol/litre was reasonable, especially as these criteria had some cost effective evidence to support it.

4.4.8.4 Quality of evidence

To minimise bias the guideline development group limited this review to the highest quality data from studies that compared plasma glucose values from a single population of women. Hence only 4 studies were included in the review. None of the studies identified for inclusion examined diagnosis using a risk factor based screening strategy and the included studies involved women who had not received treatment for gestational diabetes.

Three studies provided low quality evidence of an increase in the number of women diagnosed with gestational diabetes when IADPSG criteria are applied in the second

trimester compared with when the WHO 1999 criteria are applied. One study performed in a selected population provided very low quality evidence that the same number of women were diagnosed irrespective of whether WHO or IADPSG criteria were used. There was no evidence available regarding IADPSG diagnosis and incidence of gestational diabetes or overt diabetes in the first trimester.

Four studies provided low to moderate quality evidence that second trimester application of the IADPSG diagnostic criteria is, at best, moderately useful for ruling in or ruling out gestational diabetes as defined by the WHO 1999 criteria. However, the positive and negative likelihood ratios did not show a consistent effect size. A further study compared IADPSG first trimester diagnostic thresholds for gestational diabetes and overt diabetes in pregnancy with second trimester diagnosis using the WHO 1999 criteria. The evidence was, however, of very low quality and did not demonstrate the IADPSG first trimester test to be useful compared with WHO 1999. The group considered that the WHO diagnostic criteria were a reference standard rather than a gold standard in the review of diagnostic accuracy. They acknowledged that other diagnostic criteria can be applied but this review was limited to WHO (1999) because these were the criteria recommended by the NICE 2008 diabetes in pregnancy clinical guideline.

Very low to moderate quality evidence was identified for inclusion from 2 cohort studies within a systematic review for 3 of the 7 prioritised clinical outcomes (incidence of caesarean section, large for gestational age and perinatal mortality). Although there was some evidence to indicate that the incidence of caesarean section and perinatal mortality was lower when diagnosis has been based on the IADPSG, the evidence of incidence of large for gestational age was inconsistent and the statistical significance of the results could not be calculated. Moreover, the guideline development group noted that there was a lack of clarity regarding the data sourced for the systematic review, especially from the HAPO 2008 study. Overall, the group noted that the available evidence did not clearly demonstrate differences in the incidence of specific maternal or neonatal outcomes (rates of caesarean section, large for gestational age and perinatal mortality) when the different diagnostic criteria were used, and that no evidence was identified for other prioritised outcomes (need for treatment for gestational diabetes, preterm birth, neonatal intensive care unit length of stay greater than 24 hours, shoulder dystocia or raised neonatal blood concentrations of insulin or C-peptide).

4.4.8.5   Other considerations

The 4 studies that reported diagnostic test accuracy were from Hungary, Norway India and Sri Lanka. The highest incidence of gestational diabetes in an unselected population was reported in the Norwegian study where 59% of women were from an ethnic minority that might be expected to have a higher incidence of gestational diabetes. The Hungarian study was conducted in a largely white population and the incidence of gestational diabetes was higher in this study than that reported in the Sri Lankan population. Although this may seem counterintuitive (because according to the 2008 diabetes in pregnancy guideline, women of South Asian origin are at high risk of gestational diabetes and the incidence of gestational diabetes in Sri Lanka might be expected to be higher than that in Hungary), the studies give insufficient information about the baseline characteristics of the 2 study populations to allow accurate interpretation. Two cohort studies from a systematic review were included; 1 was from Brazil and the other was a multinational study which measured repeated clinical outcomes. The multinational cohort study included a study centre in the UK.

The guideline development group also noted that the WHO criteria are not consistent for pregnancy and non pregnancy with regard to fasting glucose values. Thus, a fasting value of more than 6.1 mmol/litre is 'normal' for pregnancy but 'impaired' for non-pregnancy.

There is widespread disregard for the fasting glucose threshold of 7 mmol/litre of more for gestational diabetes. A recent survey has shown that many centres use values derived from the ACHOIS study (Australian Carbohydrate Intolerance Study in Pregnant Women) and other studies of 5.4–5.5 mmol/litre, reasoning that they represent an evidence base for intervention.

The guideline development group agreed that referral to the joint diabetes and antenatal clinic should be prompt, occurring within 1 week of the diagnosis of gestational diabetes being made. This reflected current practice, established on the basis that treatment benefit is maximised by early intervention to make best use of the remaining treatment window during the pregnancy.

Finally, the group was aware that the current trend is for women with low risk pregnancies to only see midwives for antenatal care. However, the NICE antenatal care guideline recommends that such women should be cared for by midwives and GPs and that for complicated pregnancies obstetricians and specialist teams should be involved. The guideline development group felt that the involvement of the GP in the care of women with diabetes was important. If a midwife was the only point of contact in primary care, GPs may have no knowledge of their patient having a pregnancy where gestational diabetes has been diagnosed. This is important, not only because hospitals may ask women's GPs to prescribe medications or testing kits, but also in consideration of women's holistic care and their need for postnatal screening. However, the guideline development group recognised this practice was covered in the NICE guideline on patient experience in adult NHS services which recommends that healthcare professionals:

Ensure clear and timely exchange of patient information:

- between healthcare professionals (particularly at the point of any transitions in care)
- between healthcare and social care professionals (with the patient's consent).

4.4.9 Key conclusions

The guideline development group noted that the quality of the evidence that was identified for inclusion was very low to moderate at best. A trend of increased incidence of the diagnosis of gestational diabetes was observed across studies when IADPSG criteria were applied, though the degree of higher incidence was not consistent.

The WHO 1999 criteria are the current reference standard for diagnosing gestational diabetes, but these criteria were derived from practice in non-pregnant adults. By contrast, the IADPSG criteria were derived from a study of pregnant women and the group believed that this physiological difference in the study populations would make the IADPSG criteria more appropriate for diagnosing gestational diabetes. The group noted that although the HAPO study (2008) demonstrated a continuum of risk associated with increasing plasma glucose concentration, it was an observational study and did not investigate the benefit of treatment following diagnosis.

Moreover, it is not clear whether there is any additional benefit of treatment in the first trimester following diagnosis of gestational diabetes or overt diabetes in pregnancy, rather than treatment in the second trimester.

The guideline development group noted that the outcome data had been gathered from women who had not received treatment for gestational diabetes. The appropriate treatment would be expected to reduce incidence of mortality and large for gestational age in babies, but the effect on caesarean section rates might be less clear, if determined, for example, by pathways of care that are unrelated to the presence of gestational diabetes.

The evidence demonstrated that the use of the IADPSG criteria results in more women being diagnosed with gestational diabetes compared with using the WHO 1999 criteria. The guideline development group speculated that these additional women might have a milder condition and would be less likely to benefit from treatment, given the lower fasting thresholds of the IADPSG criteria and the lack of consistently higher incidence in adverse outcomes when these criteria were applied. The group noted that the model, although inevitably subject to a number of limitations, did not provide any evidence in support of IADPSG being cost-effective diagnostic criteria. After considering the health economic evidence, the group recommended a fasting blood glucose of 5.6 mmol/litre and a 2 hour blood glucose of 7.8 mmol/litre, but recognised the limitations in the model.

The guideline development group was aware that these diagnostic criteria are different from recently recommended WHO diagnostic thresholds for gestational diabetes (WHO, 2013) which are the same as the IADPSG recommended thresholds. The group also recognises that it would be desirable to have internationally agreed diagnostic thresholds. However, the group noted that the strength of the WHO recommendation was weak and that the WHO guideline suggested that these thresholds could be rapidly revised in the event of newly published evidence on cost effectiveness: "It is likely that a substantial body of new data will emerge in the near future, providing currently scarce health and economic evaluation of the recommended criteria applied to various populations and with different approaches (universal screening, screening only women at high risk, diagnostic testing only). The guideline will be updated in 3-5 years, or earlier if new evidence becomes available which could substantially impact the recommendations."

4.4.10 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5 Interventions in women with gestational diabetes

This section was updated in 2015

4.5.1 Information for women with gestational diabetes

Women with gestational diabetes should be informed that they are at increased risk of having a macrosomic baby, trauma during birth to themselves and the baby, neonatal hypoglycaemia, perinatal death, induction of labour and caesarean section. They should also be informed about the role of diet, body weight and exercise, the importance of maternal glycaemic control during labour and birth and early feeding of the baby in order to reduce the risk of neonatal hypoglycaemia, and the risk of the baby developing obesity and/or diabetes in later life.

4.5.2 Review question

What is the effectiveness of the following interventions (alone or in combination) in women with gestational diabetes:

- non-pharmacological interventions (diet and/or exercise)
- pharmacological interventions (metformin, glibenclamide and insulin)?

4.5.3 Introduction

The purpose of this review is to determine the effectiveness of interventions for gestational diabetes mellitus, alone or in combination. The search included randomised controlled trials (RCTs) and systematic reviews of RCTs. The same search criteria were used to identify results for each of the interventions addressed by this review. Interventions included:

- diet strategy/advice (including strategies to increase intake of vitamins, minerals and micronutrients), with or without insulin use
- exercise regimen with or without diet strategy/advice
- metformin – a biguanide which lowers hepatic glucose output and improves insulin sensitivity: this has a low risk of hypoglycaemia and does not cause weight gain
- glibenclamide – a sulfonylurea which works by stimulating insulin release from the pancreas: this can cause hypoglycaemia and is associated with weight gain.

The following combinations of intervention were identified by the guideline development group as being potentially important for reducing maternal and fetal adverse outcomes in women with gestational diabetes mellitus:

- diet
  - diet strategy/advice versus standard care or no diet strategy/advice
  - insulin plus diet strategy/advice versus diet strategy/advice
  - exercise regimen plus diet strategy/advice versus exercise regimen
  - comparison of 2 different diets (diet A versus diet B)
- exercise
  - exercise regimen versus standard care or no exercise regimen
  - exercise regimen plus diet strategy/advice versus diet strategy/advice
  - intense exercise regimen versus exercise regimen
  - comparison of 2 different exercise regimens (A versus B)
- pharmacological interventions
  - metformin versus Insulin
  - glibenclamide versus metformin

4.5.4   Description of included studies

4.5.4.1   Diet

Sixteen trials met the inclusion criteria for this review (Asemi et al., 2013; Bevier et al., 1999; Bonomo et al., 2005; Coustan et al., 1978; Crowther et al., 2005; Cypryk et al., 2007; Garner et al., 1997; Grant et al., 2011; Landon et al., 2009; Langer et al., 1989; Louie et al., 2011; Moreno-Castilla et al., 2013; Moses et al., 2009; Persson et al., 1985; Rae et al., 2000; Thompson et al., 1990). One trial was partially randomised (Coustan et al., 1978).

Five trials compared dietary strategy/advice versus standard care (Bevier et al., 1999; Crowther et al., 2005; Garner et al., 1997; Landon et al., 2009; Langer et al., 1989). The populations of 4 of the studies comprised women with 'mild' gestational diabetes (abnormal glucose tolerance or impaired glucose tolerance) (Bevier et al., 1999; Crowther et al., 2005; Landon et al., 2009; Langer et al., 1989). Women were borderline overweight (Bevier et al., 1999; Garner et al., 1997), overweight (Crowther et al., 2005) or obese (Landon et al., 2009; Langer et al., 1989). Of the guideline development group's priority outcomes, data were available for the need for additional treatment, large for gestational age births, shoulder dystocia, mode of delivery, hyperinsulinaemia, admission to neonatal care and mortality. Data for neonatal hypoglycaemia were also extracted as 1 trial of low quality reported hyperinsulinaemia (Landon et al., 2009). In addition, 2 composite outcomes (Crowther et al., 2005; Landon et al., 2009) were included owing to their use in the health economic analysis for this review. These outcomes were assessed in women with impaired glucose tolerance (Crowther et al., 2005) and gestational diabetes (Landon et al., 2009). No data were available for the acceptability of the intervention.

Three trials compared diet plus insulin versus diet alone (Coustan et al., 1978; Persson et al., 1985; Thompson et al., 1990). Women were of normal weight or borderline overweight (Coustan et al., 1978 Persson et al., 1985) or overweight (Thompson et al., 1990). Data were available for large for gestational age births, shoulder dystocia, mode of delivery, mortality, hypoglycaemia and the need for additional treatment. Hyperinsulinaemia, acceptability of treatment and length of stay in a neonatal intensive care unit (NICU) were not reported.

Nine trials compared two different diets (Asemi et al., 2013; Bonomo et al., 2005; Coustan et al., 1978; Cypryk et al., 2007; Grant et al., 2011; Louie et al., 2011; Moses et al., 2009; Moreno-Castilla et al., 2013; Rae et al., 2000). Women were normal weight (Asemi et al., 2013, Bonomo et al., 2005; Coustan et al., 1978; Louie et al., 2011), overweight (Grant et al., 2011; Moreno-Castilla et al., 2013) or obese (Moses et al., 2009; Rae et al., 2000). One study did not report either weight or body mass index (BMI) (Cypryk et al., 2007). Sufficient data were available to report the need for additional treatment, large for gestational age

births, shoulder dystocia, hypoglycaemia, mode of delivery and admission to NICU, which was used as a proxy for NICU length of stay. Data for hyperinsulinaemia, mortality or acceptability of treatment were not available.

No studies were identified which reported RCT data comparing the effect of an exercise regimen plus diet strategy/advice with an exercise regimen alone.

The summary of key details of the studies of diet is shown in Table 34.

Table 34: Diagnostic criteria used for gestational diabetes mellitus by studies of diet included in this review

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Degree of glucose intolerance	Treatment initiation	Intervention
Asemi et al., 2013	GCT: 7.8 mmol/litre (140 mg/dl) 1 hour. OGTT (not reported): <5.3 mmol/litre (95 mg/dl) fasting, <10.1 mmol/litre (182 mg/dl) 1 hour, <8.7 mmol/litre (157 mg/dl) 2 hours, <7.8 mmol/litre (140 mg/dl) 3 hours	Not reported	Gestational diabetes	The intervention was performed for 4 weeks	Diet A versus diet B
Bevier et al., 1999	Not reported	Fasting plasma glucose <90 mg/dl (5.0 mmol/litre) or one hour postprandial values <120 mg/dl (6.7 mmol/litre)	Abnormal glucose tolerance[a]	Initiation not reported. The intervention was continued until delivery	Diet strategy/ advice versus standard care/no diet
Bonomo et al., 2005	GCT: >7.8 mmol/litre (140 mg/dl) 1 hour OGTT (100 g): <5.3 mmol/litre (95 mg/dl) fasting, <10.1 mmol/litre (182 mg/dl) 1 hour, <8.7 mmol/litre (157 mg/dl) 2 hours, <7.8 mmol/litre (140 mg/dl) 3	Fasting plasma glucose <5.0 mmol/litre or two hour postprandial values <6.7 mmol/litre	Abnormal glucose tolerance [a]	Between 30 and 34 weeks of gestation until delivery	Diet A versus diet B

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Degree of glucose intolerance	Treatment initiation	Intervention
	hours				
Coustan et al., 1978	GCT: Not used OGTT (modified for serum glucose) (100 g): >95 mg/dl (5.3 mmol/litre) fsting, >180 mg/dl (10.0 mmol/litre) 1 hour, >160 mg/dl (8.9 mmol/litre) 2 hours, >135 mg/dl (7.5 mmol/litre) 3 hours	Not reported	Gestational diabetes	Initiation not reported however in most women this was not before 30 weeks of gestation. The intervention was continued until delivery	Insulin plus diet strategy/ advice versus diet strategy/ advice alone and diet A versus diet B
Crowther et al., 2005	GCT: ≥7.8 mmol/litre (140 mg/dl) 1 hour. OGTT (75 g): <7.8 mmol/litre (140 mg/dl) fasting, between 7.8 and 11.0 mmol/litre (198 mg/dl) 2 hours	Fasting plasma glucose >5.5 mmol/litre or postprandial glucose >7.0 mmol/litre at ≤ 35 weeks' gestation, postprandial glucose ≥ 8.0 mmol/litre >35 weeks' gestation or one capillary blood glucose value ≥9.0 mmol/litre	Impaired glucose tolerance[b]	Between 16 and 30 weeks of gestation until delivery	Diet strategy/ advice versus standard care/no diet
Cypryk et al., 2007	WHO criteria (year not reported and not referenced)	Fasting plasma glucose ≤90 mg/dl (5.0 mmol/litre) or two hour postprandial values ≤120 mg/dl (6.7 mmol/litre)	Presumed gestational diabetes	Initiation not reported. The intervention was continued until delivery	Diet A versus diet B
Garner et al., 1997	GCT: >8.0 mmol/litre (145 mg/dl) 1 hour. OGTT (75 g): >7.5 mmol/litre (135 mg/dl) (2nd trimester) and >9.6 mmol/litre (173 mg/dl) (3rd	Fasting plasma glucose >4.4 mmol/litre or one hour postprandial glucose >7.8 mmol/litre	Gestational diabetes	Between 24 and 32 weeks of gestation until delivery	Diet strategy/ advice versus standard care/no diet

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Degree of glucose intolerance	Treatment initiation	Intervention
		trimester)			
Grant et al., 2011	Not reported	Fasting plasma glucose between 3.8 and 5.2 mmol/litre or two hour postprandial glucose between 5.0 and 6.6 mmol/litre	Gestational diabetes and impaired glucose tolerance	After 34 weeks of gestation	Diet A versus diet B
Landon et al., 2009	GCT: between 7.5 mmol/litre (135 mg/dl) and 11.1 mmol/litre (200 mg/dl) at 1 hour. OGTT (100g): <5.3 mmol/litre (95 mg/dl) fasting, >10.0 mmol/litre (180 mg/dl) 1 hour, >8.6 mmol/litre (155 mg/dl) 2 hours, >7.8 mmol/litre (140 mg/dl) 3 hours	Fasting plasma glucose values >5.3 mmol/litre or two hour postprandial glucose values >6.7 mmol/litre between clinic visits	Mild gestational diabetes[c]	Between 24 weeks of gestation and 0 days and 30 weeks and 6 days until delivery	Diet strategy/ advice versus standard care/no diet
Langer et al., 1989	GCT (50g): ≥7.2 mmol/litre (130 mg/dl) at 1 hour OGTT (load not reported): Not reported	Blood glucose <5.3mmol/litre (95 mg/dl). Likely to refer to fasting values but this is not reported in the study methods.	Mild gestational diabetes[d]	Between 24 and 28 weeks of gestation	Diet strategy/ advice versus standard care/no diet
Louie et al., 2011	GCT: Not used OGTT (75 g): ≥5.5 mmol/litre (100 mg/dl) fasting, ≥10.0 mmol/litre (180 mg/dl) 1 hour, ≥8.0 mmol/litre (145 mg/dl) 2 hours	Mean fasting plasma glucose >5.2 mmol/litre or mean one hour postprandial glucose >7.5 mmol/litre during the preceding week	Gestational diabetes	Between 20 and 32 weeks of gestation until delivery	Diet A versus diet B

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Degree of glucose intolerance	Treatment initiation	Intervention
Moreno-Castilla et al., 2013	GCT (50 g): 1 hour ≥7.8 mmol/litre OGTT (100g): Not reported	Fasting and preprandial ≥5.3mmol/litre or 1 hour postprandial ≥7.8mmol/litre at least twice in one week	Gestational diabetes	Before or equal to 35 weeks of gestation until delivery	Diet A versus diet B
Moses et al., 2009	GCT: Not used OGTT (75 g): ≥5.5 mmol/litre (100 mg/dl) fasting, ≥8.0 mmol/litre (145 mg/dl) 1 hour	Fasting plasma glucose ≥5.5 mmol/litre or one hour postprandial glucose ≥8.0 mmol/litre more than once in a week	Gestational diabetes	Between 28 and 32 weeks of gestation until delivery	Diet A versus diet B
Persson et al., 1985	GCT: Not used OGTT (50 g): area under the curve of ≥2 standard deviations above normal (not defined)	Fasting glucose exceeded 7.0 mmol/litre or one hour postprandial values >9.0 mmol/litre at least three times in one week	Gestational diabetes	Initiation not reported. The intervention was continued until delivery	Insulin plus diet strategy/ advice versus diet strategy/ advice alone
Thompson et al., 1990	GCT: fasting ≥105 mg/dl (5.8 mmol/litre) or 1 hour ≥ 140 mg/dl OGTT (100g): >105 mg/dl (5.8 mmol/litre) fasting, >190 mg/dl (10.6 mmol/litre) 1 hour, >165 mg/dl (9.2 mmol/litre) 2 hours, >145 mg/dl (8.0 mmol/litre) 3 hours	Fasting glucose >5.8 mmol/litre on one occasion or two hour postprandial glucose >6.7 mmol/litre on two occasions	Gestational diabetes	At or before 28 weeks of gestation until delivery	Insulin plus diet strategy/ advice versus diet strategy/ advice alone

GCT glucose challenge test, OGTT oral glucose tolerance test

a. Abnormal glucose tolerance was diagnosed based on a positive GCT screening result but negative OGTT test result.

b. Impaired glucose tolerance was diagnosed based on the presence of risk factors or a positive 50 g GCT and an OGTT response that was between normal and diabetic thresholds. Severe cases were removed from the study population at the outset.

c. Study authors describe the population as having mild gestational diabetes; severe cases were removed from the study population. Subsequent diagnosis of gestational diabetes was made based on two or more abnormal postprandial values and a fasting OGTT value < 5.3 mmol/litre.

Study authors describe women included in the study as only having one abnormal OGTT value.

4.5.4.2 Exercise

Three studies were identified which addressed the effect of exercise-based interventions (Avery et al., 1997; Brankston et al., 2004; de Barros et al., 2010). All studies were RCTs. Trials were small, with numbers of participants ranging from 29 to 64 women. Locations included Brazil (de Barros et al., 2010), the USA (Avery et al., 1997) and Canada (Brankston et al., 2004).

Two trials compared the effect of exercise with no exercise in women with gestational diabetes mellitus (Avery et al., 1997; de Barros et al., 2010). Women in 1 trial were obese with a mean BMI of 32.2 kg/m^2 in the intervention group and 30.0 kg/m^2 in the control group at study entry (Avery et al., 1997). Intervention participants were instructed to perform 8 circuit-based activities using a resistance band. Women performed fifteen 15 repetitions of each exercise 3 days a week and progressed from 2 circuits initially to 3 circuits after 3 weeks. Controls did not undertake an exercise programme and continued dietary therapy. Details of the dietary therapy in intervention subjects were not reported. Participants self-monitored blood glucose 3 days a week. The mean gestational age at diagnosis was 28.7 and 26.3 weeks for the intervention and control groups respectively. The second trial did not report baseline characteristics of the study population (de Barros et al., 2010). Intervention participants undertook 30 minutes of exercise 3 to 4 times per week until delivery. Two exercise sessions a week were monitored by study staff. Controls maintained their usual physical activity level alongside dietary therapy. Women self-monitored their blood glucose before each exercise session. Glycaemia was also measured weekly by the clinic. Data were available for treatment failure, reported as the need for insulin, mode of delivery (caesarean section) and macrosomia as a proxy for large for gestational age as no data were available for this outcome. Hyperinsulinaemia, acceptability of treatment, NICU length of stay, shoulder dystocia and perinatal mortality were not reported.

One trial compared diet plus exercise with diet alone in women with gestational diabetes mellitus (Brankston et al., 2004). Women were overweight with a mean BMI of 25.9 kg/m^2 in the intervention group and 28.0 kg/m^2 in the control group. Intervention participants received a standard diabetic diet (40% carbohydrate, 40% protein, 20% fat) comprising 24 to 30 kcal/kg/day of ideal pre-pregnancy body weight plus a progressive physical activity program of circuit-type exercise until delivery. Controls received instruction in the standard diabetic diet alone. The mean gestational age at first visit was 29.6 and 29.0 weeks for the diet plus exercise and diet alone groups respectively. All participants self-monitored blood glucose daily. The only outcome reported by this study was treatment failure, reported as the need for insulin. No data were available for the other 7 of the guideline development group's priority outcomes.

No studies were identified which reported RCT data comparing either an intense exercise regimen versus 'normal' exercise regimen or exercise regimen A versus exercise regimen B.

A summary of the key details of the studies of exercise is shown in Table 35.

Table 35: Diagnostic criteria used for gestational diabetes mellitus by studies of exercise included in this review

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Degree of glucose intolerance	Treatment initiation	Intervention
Avery et al., 1997	GCT: not reported OGTT (100 g): >5.0 mmol/litre fasting, >9.2 mmol/litre 1 hour, >8.1 mmol/litre 2 hours, >6.9 mmol/litre 3 hours	Not reported	Gestational diabetes	Before 34 weeks of gestation until delivery	Exercise regimen versus standard care or no exercise regimen.
Brankston et al., 2004	GCT: ≥10.3 mmol/litre (185 mg/dl) 1 hour OGTT (75 g): ≥5.3 mmol/litre (95 mg/dl) fasting, ≥10.6 mmol/litre (191 mg/dl) 1 hour, ≥8.9 mmol/litre (160 mg/dl) 2 hours	Fasting blood glucose ≥5.3 mmol/litre, one hour postprandial ≥7.8 mmol/litre or two hour postprandial ≥6.7 mmol/litre consistently at any time during diet therapy.	Gestational diabetes	Between 26 and 32 weeks of gestation until delivery	Exercise regimen plus diet strategy/advice versus diet strategy/advice.
de Barros et al., 2010	Not reported	Not reported	Unclear	Not reported	Exercise regimen versus standard care or no exercise regimen.

GCT glucose challenge test, OGTT oral glucose tolerance test

Pharmacological interventions

4.5.4.3

Fifteen randomised controlled trials met the inclusion criteria for this review (Bertini et al., 2005; Hague et al., 2003; Ijas et al., 2010; Lain et al., 2009; Langer et al., 2000; Mesdaghinia et al., 2013; Moore et al., 2007; Moore et al., 2010; Mukhopadhyay et al., 2012; Niromanesh et al., 2012; Ogunyemi et al., 2007; Rowan et al., 2008; Silva et al., 2012; Spaulonci et al., 2013; Tertti et al., 2013).

Trial locations included Finland (Ijas et al., 2010; Tertti et al., 2013), Australia (Hague et al., 2003; Rowan et al., 2008), the USA (Lain et al., 2009; Langer et al., 2000; Moore et al., 2007; Moore et al.,2010; Ogunyemi et al., 2007), Brazil (Bertini et al., 2005; Silva et al., 2012; Spaulonci et al., 2013), India (Mukhopadhyay et al., 2013) and Iran (Mesdaghinia et al., 2013; Niromanesh et al., 2012). The number of participants ranged from 30 to 404 women.

All included women had gestational diabetes. An oral glucose tolerance test (OGTT) was used to diagnose women with gestational diabetes, although different glucose loads and diagnostic criteria were used in the trials and women could be diagnosed as early as 11 weeks of gestation in some studies.

4.5.4.3.1 *Metformin versus insulin*

Eight trials compared metformin with insulin (Hague et al., 2003; Ijas et al., 2010; Mesdaghinia et al., 2013; Moore et al., 2007; Niromanesh et al., 2012; Rowan et al., 2008; Spaulonci et al., 2013; Tertti et al., 2013).

Two trials did not provide treatment details with regard to the doses of metformin and insulin that were used, nor were further details given with regard to any concurrent dietary or exercise interventions or monitoring techniques used (Hague et al., 2003; Spaulonci et al., 2013). Women in the remaining 6 trials received dietary advice/instruction and glucose levels were monitored (Ijas et al., 2010; Mesdaghinia et al., 2013; Moore et al., 2007; Niromanesh et al., 2012; Rowan et al., 2008; Tertti et al., 2013). Women in 3 trials also received lifestyle counselling/exercise advice (Ijas et al., 2010; Niromanesh et al., 2012; Rowan et al., 2008).

The initial dose of metformin was 500 mg/day (Mesdaghinia et al., 2013; Moore et al., 2007; Niromanesh et al., 2012; Rowan et al., 2008; Tertti et al., 2013) or 750 mg/day (Ijas et al., 2010) increasing to a maximum dose of 2000 mg/day (Moore et al., 2007; Tertti et al., 2013), 2250 mg/day (Ijas et al., 2009) or 2500 mg/day (Mesdaghinia et al., 2013; Niromanesh et al., 2012; Rowan et al., 2008). In the 7 trials that described treatments, treatment failure with metformin occurred when normoglycaemia or targets were not reached on a maximum dose (Niromanesh et al., 2012; Tertti et al., 2013), or were not reached on a maximum dose over a 1 to 2 week period (Ijas et al., 2010). One trial did not report criteria for starting insulin therapy when treatment with metformin failed but did report the use of supplementary insulin (Spaulonci et al., 2013). In 4 trials (Ijas et al., 2010; Niromanesh et al., 2012; Rowan et al., 2008; Tertti et al., 2013) when failure of treatment with metformin occurred, supplementary insulin was added as required. In 1 study (Moore et al., 2007) metformin was stopped and insulin started. In 1 trial women who failed treatment with metformin were excluded from the study and from analyses and were replaced with women who did not fail treatment (Mesdaghinia et al., 2013).

Insulin treatment consisted of long-acting and rapid-acting insulin in 1 trial (Ijas et al., 2010), split doses of regular insulin and NPH insulin in 3 trials (Mesdaghinia et al., 2013; Moore et al., 2007; Niromanesh et al., 2012) and NPH insulin and/or rapid acting insulin lispro or aspart in 1 trial (Tertti et al., 2013). One trial (Rowan et al., 2008) stated that insulin was prescribed according to usual practice.

Maternal outcomes reported were mode of birth, treatment failure (need for additional treatment with insulin) and acceptability of treatment. Outcomes related to mode of birth were spontaneous vaginal birth, induction of labour, operative vaginal, vacuum extraction and caesarean section. Acceptability of treatment was assessed using a questionnaire in 1 trial (Rowan et al., 2008). Reported neonatal outcomes were large for gestational age, NICU admission and length of stay, shoulder dystocia, neonatal hypoglycaemia fetal death and perinatal mortality. One composite outcome (Rowan et al., 2008) was included owing to its use in the health economic analysis for this review.

4.5.4.3.2 *Glibenclamide versus insulin*

Five trials compared glibenclamide with insulin (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000; Mukhopadhyay et al., 2012; Ogunyemi et al., 2007).

One trial (Langer et al., 2000) prescribed a diet for normal weight and obese women and confirmed all women performed self-monitoring of blood glucose. One trial prescribed a diet with caloric intake calculated according to pre-gestational BMI and asked women to self-monitor 7 times a day; women included in the trial were those who had failed dietary treatment (Mukhopadhyay et al., 2012). However, 3 trials (Bertini et al., 2005; Lain et al., 2009; Ogunyemi et al., 2007) did not provide details of any concurrent dietary or exercise interventions, although 1 of these (Ogunyemi et al., 2007) was conducted in a population of women in whom diet therapy had failed. One trial reported that blood glucose was tested in

the clinic weekly. The 2 remaining trials (Lain et al., 2009; Ogunyemi et al., 2007) did not detail the monitoring techniques used.

One trial did not provide treatment details with regard to the doses of metformin and insulin that were used (Ogunyemi et al., 2007). The initial dose of glibenclamide in the remaining 4 trials was 2.5 mg/day (Lain et al., 2009; Langer et al., 2000; Mukhopadhyay et al., 2012) or 5 mg/day (Bertini et al., 2005), increasing weekly to a maximum dose of 20 mg/day (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000; Mukhopadhyay et al., 2012). In all 4 trials, glibenclamide treatment failure occurred when glucose control was not achieved despite taking the maximum dose. Oral medication was stopped and insulin therapy started. Two trials stipulated that glucose control was assessed over a 2 week period for a decision of treatment failure to be made (Langer et al., 2000; Mukhopadhyay et al., 2012).

Insulin doses started at 0.7 U/kg (Bertini et al., 2005; Langer et al., 2000; Mukhopadhyay et al., 2012) or 0.8 U/kg (Langer et al., 2000) administered in multiple daily injections.

Maternal outcomes reported were caesarean section, treatment failure (need for additional treatment with insulin) and acceptability of treatment. Acceptability of treatment was assessed using reporting of maternal hypoglycaemic episodes. Reported neonatal outcomes were large for gestational age, NICU admission, shoulder dystocia, neonatal hypoglycaemia, intrauterine and neonatal mortality.

4.5.4.3.3 *Glibenclamide versus metformin*

Two trials compared metformin with glibenclamide (Moore et al., 2010; Silva et al., 2012).

In both trials all women were given instructions for a diet prescribed according to normal or obese weight and performed self-monitoring of blood glucose. In addition, in 1 trial the importance of exercise in controlling blood glucose was stressed and 30 minutes of walking per day was recommended (Moore et al., 2010).

In both trials, the initial dose of glibenclamide was 2.5 mg 2 times a day which, following a weekly review, was increased as necessary to a maximum dose of 20 mg/day.

In both trials, the initial dose of metformin was 500 mg/day in divided doses and was increased as necessary following a weekly review until glucose control was achieved or until a maximum dose was reached of 2000 mg/day (Moore et al., 2010) or 2500 mg/day (Silva et al., 2012).

Treatment failures were defined in 1 trial (Moore et al., 2010) as occurring when 2 or more glucose values in the same meal exceeded target glucose values by 10 mg/dl (0.56 mmol/litre) or more for 2 consecutive weeks while the maximum dose was taken. In this trial, oral medication was stopped and insulin therapy started. In the second trial (Silva et al., 2012), insulin therapy was started at 0.7 IU/kg/day regular insulin preprandially and neutral protamine hagedorn (NPH) insulin at bedtime when glycaemic goals were not met. Of the guideline development group's priority outcomes, maternal data were available for caesarean section and treatment failure (need for additional treatment with insulin). Acceptability of treatment was assessed using reporting of maternal hypoglycaemic episodes.

Reported neonatal outcomes were large for gestational age, NICU admission, shoulder dystocia, neonatal hypoglycaemia, stillbirth and neonatal mortality.

A summary of the details of the studies of pharmacological interventions is shown in Table 36.

Table 36: Details regarding diagnosis, blood glucose target values and treatment duration used in studies included in this review

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Treatment initiation	Intervention
Bertini et al., 2005	2 hour OGTT (75 g), WHO criteria: ≥110 mg/dl (≥6.1 mmol/litre) fasting, ≥140 g/dl (≥7.8 mmol/litre) 2 hours	Fasting plasma glucose 90 mg/dl (5.0 mmol/litre) and postprandial values <100 mg/dl (<5.6 mmol/litre)	Between 11 and 33 weeks of gestation	Glibenclamide versus insulin
Hague et al., 2003	ADIPS criteria no further details reported	Not reported	Not reported	Metformin versus insulin
Ijas et al., 2010	2 hour OGTT (75 g): >5.3 mmol/litre fasting, >11 mmol/litre 1 hour, >9.6 mmol/litre 2 hours (1 or more abnormal values required for diagnosis of gestational diabetes)	Fasting plasma glucose <5.3 mmol/litre and postprandial values <6.7 mmol/litre	Between 12 and 34 weeks of gestation	Metformin versus insulin
Lain et al., 2009	1 hour OGTT (50 g) as a screening test and 3 hour OGTT (100 g) when screen value >135 mg/dl (7.5 mmol/litre) Diagnosis of gestational diabetes when there were 2 abnormal values, a raised fasting value with 3 hour OGTT (100 g) or 1 hour OGTT (50 g) >200 mg/dl (11.1 mmol/litre)	Not reported	Not reported	Glibenclamide versus insulin
Langer et al., 2000	1 hour OGTT (50 g) as a screening test and 3 hour OGTT (100 g) Carpenter Coustan 1982 criteria when screen value >130 mg/dl (7.2 mmol/litre) Diagnosis of gestational diabetes 95-140 mg/dl (5.2-7.8 mmol/litre) fasting value or also enrolled if at testing <95 mg/dl (5.3 mmol/litre) fasting value, but following dietary advice, postprandial value >120 mg/dl (>6.7 mmol/litre)	Fasting plasma glucose 60-90 mg/dl (3.4-5.0 mmol/litre), preprandial value 80-95 mg/dl (3.4-5.0 mmol/litre and postprandial values <120 mg/dl (<6.7 mmol/litre)	Between 11 and 33 weeks of gestation	Glibenclamide versus insulin
Niromanesh et al., 2012	1 hour GCT (50 g) >130 mg/dl (7.2 mmol/litre) and 3 hour OGTT (100 g) according to Carpenter and Coustan 1982 criteria	Fasting glucose <95 mg/dl (5.3 mmol/litre), postprandial (no time given) <120 mg/dl (6.7 mmol/litre)	Between 20 and 34 weeks of gestation	Metformin versus insulin

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Treatment initiation	Intervention
Mesdaghinia et al., 2013	1 hour GCT (50 g) followed by OGTT (100 g) fasting >95 mg/dl (5.0 mmol/litre), 1 hour >180 mg/dl (10.0 mmol/litre), 2 hour >155 mg/dl (8.6 mmol/litre) or 3 hour >140 mg/dl (7.8 mmol/litre)	Not reported	Between 24 and 34 weeks of gestation	Metformin versus insulin
Moore et al., 2007	3 hour OGTT (not reported), ADA criteria: >105 mg/dl (5.8 mmol/litre) fasting, 190 mg/dl (10.5 mmol/litre) 1 hour, 165 mg/dl (9.2 mmol/litre) 2 hour, 145 mg/dl (8.0 mmol/litre) 3 hour (2 abnormal values required for diagnosis of gestational diabetes)	Fasting plasma glucose 60-90 mg/dl (3.4-5.0 mmol/litre) and 2 hour postprandial values <120 mg/dl (<6.7 mmol/litre)	Between 24 and 30 weeks of gestation	Metformin versus insulin
Moore et al., 2010	1 hour OGTT (50 g) as a screening test and 3 hour OGTT (100 g) Carpenter Coustan 1998 criteria when screen value >130 mg/dl (7.2 mmol/litre). Diagnosis of gestational diabetes when there were 2 abnormal values or also enrolled if normal at testing, but following dietary advice, >105 mg/dl (5.8 mmol/litre) fasting value or postprandial value >120 mg/dl (>6.7 mmol/litre)	Not reported	Between 11 and 33 weeks of gestation	Glibenclamide versus metformin
Mukhopadhyay et al., 2012	2 hour OGTT (75 g) >140 mg/dl (7.8 mmol/litre) according to the WHO criteria (1998).	Fasting glucose <90 mg/dl (5.0 mmol/litre) and postprandial peaks <120 mg/dl (6.7 mmol/litre).	Between 20 and 28 weeks of gestation	Glibenclamide versus insulin
Ogunyemi et al., 2007	Not reported. Participants were women with gestational diabetes refractory to dietary management	Not reported	Not reported	Glibenclamide versus insulin
Rowan et al., 2008	ADIPS criteria no further details reported. On monitoring, following lifestyle advice, women	Fasting plasma glucose <5.5 mmol/litre and 2 hour postprandial values <7 mmol/litre	Between 20 and 33 weeks of gestation	Metformin versus insulin

Study	Diagnostic criteria used	Target values for blood glucose or the use of additional treatment	Treatment initiation	Intervention
	also had more than one fasting plasma glucose value >5.4 mmol/litre and more than one 2 hour postprandial value >6.7 mmol/litre			
Silva et al.,2012	ADA 2009 criteria no further details reported	Fasting plasma glucose <90 mg/dl (<5.0 mmol/litre), and postprandial values <120 mg/dl (<6.7 mmol/litre)	Not reported	Glibenclamide versus metformin
Spaulonci et al., 2013	Not reported	Unsatisfactory glycaemic control was defined as >30% of capillary glucose results above the reference values. These values were not reported.	Not reported	Metformin versus insulin
Tertti et al., 2013	Before December 2008: Fasting value ≥4.8 mmol/litre, 1 hour ≥10.0 mmol/litre, 2 hour ≥8.7 mmol/litre. After 2008: Fasting value ≥5.3 mmol/litre, 1 hour ≥10.0 mmol/litre, 2 hour ≥8.6 mmol/litre.	Fasting glucose <5.5 mmol/litre and 1 hour postprandial <7.8 mmol/litre.	Between 22 and 34 weeks of gestation	Metformin versus insulin

ADA American Diabetes Association, ADIPS Australasian Diabetes in Pregnancy Society, OGTT oral glucose tolerance test, WHO World health organization

4.5.5 Evidence profile

4.5.5.1 Diet

Diagnostic criteria for gestational diabetes varied across studies as did the types of interventions used. Meta-analysis was carried out where it was deemed to be appropriate; however, for the majority of outcomes study designs were not sufficiently similar. One trial (Coustan et al., 1978) was included for both the comparison of diet plus insulin versus diet alone and for diet A versus diet B due to the use of 3 groups of participants, each receiving different interventions. The use of additional treatments was reported in 1 trial (Thompson et al., 1990); this was defined as treatment failure.

The GRADE profiles for this intervention are shown in Tables 37 to 39.

Table 37: GRADE profile for comparison of dietary strategy/advice with standard care

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet strategy or advice)	Comparator (no diet strategy or advice)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Maternal outcomes											
Caesarean[1]											
3 (Bevier et al., 1999; Crowther et al., 2005; Garner et al., 1997; Landon et al., 2009)	315/1166	358/1177	RR 0.89 (0.77 to 1.02)[a,b]	33 fewer per 1000 (from 70 fewer to 6 more per 1000)	Very low	Randomised controlled trial	Very serious[2,3,4]	Serious[5]	No serious indirectness	Serious[6,7,8]	Yes[9,10,11,12,13]
1 (Bonomo et al., 2005)	44/150	42/150	RR 1.05 (0.73 to 1.50)[a]	14 more per 1000 (from 76 fewer to 140 more per 1000)	Very low	Randomised controlled trial	Very serious[14,15,16]	No serious inconsistency[17]	No serious indirectness	Very serious[18]	Yes[19,20]
Vaginal delivery											
1 (Garner et al., 1997)	118/149	121/150	RR 0.98 (0.87 to 1.10)[c]	16 fewer per 1000 (from 105 fewer to 81 more per 1000)	Low	Randomised controlled trial	Serious[4]	No serious inconsistency[17]	No serious indirectness	Serious[6]	Yes[12,21]
Spontaneous vaginal delivery											
1 (Bevier et al., 1999)	22/35	30/48	RR 1.01 (0.72 to 1.41)	6 more per 1000 (from 175 fewer to 256 more per 1000)	Very low	Randomised controlled trial	Very serious[22,23]	No serious inconsistency[17]	No serious indirectness	Very serious[18]	Yes[10,24]
Induction of labour[1]											
3 (Bevier et al., 1999; Crowther et al., 2005; Landon et al., 2009)	325/1017	272/1027	RR 1.20 (0.87 to 1.65)[a,d]	53 more per 1000 (from 34 fewer to 172 more per 1000)	Very low	Randomised controlled trial	Serious[25]	Serious[26]	No serious indirectness	Serious[8,27]	Yes[10,11,13,28]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet strategy or advice)	Comparator (no diet strategy or advice)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Treatment failure[29,30,31]											
1 (Garner et al., 1997)	36/149	NR	NC	NC	Moderate	Randomised controlled trial	Serious[4]	No serious inconsistency[17]	No serious indirectness	NA	Yes[12,21]
1 (Crowther et al., 2005)	100/490	17/510	RR 6.12 (3.72 to 10.08)[c]	171 more per 1000 (from 91 to 303 more per 1000)	High	Randomised controlled trial	No serious bias	No serious inconsistency[17]	No serious indirectness	No serious imprecision	Yes[11,32]
1 (Landon et al., 2009)	37/476	2/455	RR 17.68 (4.29 to 72.93)[c]	73 more per 1000 (from 14 to 316 more per 1000)	Moderate	Randomised controlled trial	Serious[33]	No serious inconsistency[17]	No serious indirectness	No serious imprecision	Yes[13,34]
Neonatal outcomes											
Large for gestational age[1]											
4 (Bevier et al., 1999; Crowther et al., 2005; Landon et al., 2009; Langer et al., 1989)	107/1081	208/1089	RR 0.49 (0.34 to 0.71)[a,e]	94 fewer per 1000 (from 55 fewer to 126 fewer per 1000)	Very low	Randomised controlled trial	Serious[35]	Serious[36]	No serious indirectness	Serious[6,8]	Yes[10,11,13,28,37,38]
1 (Bonomo et al., 2005)	9/150	21/150	RR 0.43 (0.20 to 0.91)[a]	80 fewer per 1000 (from 13 to 112 fewer per 1000)	Very low	Randomised controlled trial	Very serious[14,15,16]	No serious inconsistency[17]	No serious indirectness	Serious[6]	Yes[19,20]
Shoulder dystocia[1,39]											
3 (Bevier et al., 1999; Crowther et al., 2005; Landon et al., 2009)	15/1017	36/1027	RR 0.42 (0.23 to 0.77)[a,f]	20 fewer per 1000 (from 8 fewer to 27 fewer per 1000)	Very low	Randomised controlled trial	Serious[25]	Very serious[26,40]	No serious indirectness	Serious[6,8]	Yes[10,11,13,28]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet strategy or advice)	Comparator (no diet strategy or advice)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Serious perinatal complications[41]											
1 (Crowther et al., 2005)	7/506g	23/524g	RR 0.32 (0.14 to 0.73)[h]	30 fewer per 1000 (from 12 fewer to 38 fewer per 1000)	Moderate	Randomised controlled trial	No serious bias	No serious inconsistency[17]	Serious[42]	No serious imprecision	Yes[11,32]
Admission to neonatal care											
1 (Crowther et al., 2005)	357/506g	321/524g	RR 1.15 (1.05 to 1.26)[h]	92 more per 1000 (from 31 more to 159 more per 1000)	Low	Randomised controlled trial	Serious[43]	No serious inconsistency[17]	Serious[44]	Serious[27]	Yes[11,32]
1 (Bonomo et al., 2005)	5/150	7/150	RR 0.71 (0.23 to 2.19)[a]	14 fewer per 1000 (from 36 fewer to 56 more per 1000)	Very low	Randomised controlled trial	Very serious[14,15,16]	No serious inconsistency[17]	Serious[44]	Very serious[18]	Yes[19,20]
NICU stay > 24 hours											
1 (Langer et al., 1989)	4/63	7/63	RR 0.57 (0.17 to 1.87)[a]	48 fewer per 1000 (from 92 fewer to 97 more per 1000)	Very low	Randomised controlled trial	Serious[45]	No serious inconsistency[17]	Serious[46]	Very serious[18]	Yes[37,38]
Composite perinatal outcome[47]											
1 (Landon et al., 2009)	149/460	163/440	RR 0.87 (0.72 to 1.07)	48 fewer per 1000 (from 104 fewer to 26 more per 1000)	Very low	Randomised controlled trial	Very serious[33,48]	No serious inconsistency[17]	Serious[49]	Serious[6]	Yes[13,34]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet strategy or advice)	Comparator (no diet strategy or advice)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hyperinsulinaemia											
1 (Landon et al., 2009)	75/423	92/403	RR 0.78 (0.57 to 1.05)	50 fewer per 1000 (from 98 fewer to 11 more per 1000)	Low	Randomised controlled trial	Serious[50]	No serious inconsistency[17]	No serious indirectness	Serious[6]	Yes[13,34]
Hypoglycaemia (not defined)											
1 (Garner et al., 1997)	21/149	13/150	RR 1.63 (0.85 to 3.11)[c]	55 more per 1000 (from 13 fewer to 183 more per 1000)	Low	Randomised controlled trial	Very serious[4,51]	No serious inconsistency[17]	Serious[52]	Very serious[7,27]	Yes[12,21]
1 (Crowther et al., 2005)	35/506g	27/524[g]	RR 1.34 (0.82 to 2.18)[a]	18 more per 1000 (from 9 fewer to 61 more per 1000)	Low	Randomised controlled trial	Serious[51]	No serious inconsistency[17]	Serious[52]	Serious[27]	Yes[11,32]
Hypoglycaemia (< 1.7mmol/l)[53]											
1 (Bonomo et al., 2005)	5/150	6/150	RR 0.83 (0.26 to 2.66)[a]	7 fewer per 1000 (from 30 fewer to 66 more per 1000)	Very low	Randomised controlled trial	Very serious[14,15,16]	No serious inconsistency[17]	Serious[52]	Very serious[18]	Yes[19,20]
Hypoglycaemia (< 1.9mmol/l)											
1 (Langer et al., 1989)	1/63	8/63	RR 0.13 (0.02 to 1.01)[a]	110 fewer per 1000 (from 124 fewer to 1 more per 1000)	Very low	Randomised controlled trial	Very serious[45]	No serious inconsistency[17]	Serious[46,52]	Serious[6]	Yes[37,38]
Perinatal mortality											
1 (Garner et al., 1997)	0/149	0/150	NC	NC	Moderate	Randomised controlled trial	Serious[4]	No serious inconsistency[17]	No serious indirectness	NA	Yes[12,21]
1 (Landon et al., 2009)	0/485	0/473	NC	NC	Low	Randomised controlled trial	Serious[33]	No serious inconsistency[17]	No serious indirectness	NA	Yes[13,34]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet strategy or advice)	Comparator (no diet strategy or advice)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Crowther et al., 2005)	0/506g	5/524g	RR: 0.09 (0.005 to 1.62)[c]	9 fewer per 1000 (from 9 fewer to 6 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[17]	No serious indirectness	Very serious[18]	Yes[11,32]

CI confidence interval, NA not applicable, NC not calculable, NR not reported, RR relative risk

a. Data combined using Mantel-Haenszel random effects meta-analysis of study relative risks.

b. RR=1.08 (95% CI 0.68 to 1.71) for Garner et al., RR=0.57 (95% CI 0.22 to 1.47) for Bevier et al., RR=0.96 (95% CI 0.80 to 1.15) for Crowther et al., RR=0.79 (95% CI 0.65 to 0.97) for Landon et al., heterogeneity I2=13% overall.

c. Calculated by the NCC-WCH technical team.

d. RR=17.69 (95% CI 1.03 to 304.09) for Bevier et al., RR=1.30 (95% CI 1.09 to 1.56) for Crowther et al., RR=1.02 (95% CI 0.82 to 1.26) for Landon et al., heterogeneity I2 = 70%. The high I2 value is due to there being no events in one study leading to a very wide CI around the RR; it was therefore judged to be acceptable not to split the meta-analysis into individual studies.

e. RR=0.11 (95% CI 0.02 to 0.84) for Bevier et al., RR=0.61 (95% CI 0.47 to 0.81) for Crowther et al., RR=0.49 (95% CI 0.33 to 0.73) for Landon et al., heterogeneity I2 = 40%.

f. RR=0.69 (95% CI 0.06 to 7.27) for Bevier et al., RR=0.45 (95% CI 0.19 to 1.09) for Crowther et al., RR=0.37 (95% CI 0.16 to 0.88) for Landon et al., heterogeneity I2 = 0%.

g. Denominator represents the total number of births, not women.

h. Unadjusted values are reported.

1. Different definitions of gestational diabetes and diagnostic criteria were used by each study.

2. All four studies did not completely specify whether allocation was concealed; three studies did not describe randomisation methods (Crowther et al., Garner et al. and Bevier et al.) and one study used minimisation to allocate participants (Landon et al.).

3. Data for Bevier et al. were combined for repeat and primary caesareans; data were missing for four controls for mode of birth.

4. It was not possible to determine how similar groups were at baseline for Garner et al. as not all relevant confounders were reported (ethnicity and parity were omitted).

5. Bevier et al. and Garner et al. applied a kcal limit for dietary intake in the intervention group in addition to counselling; the remaining two studies specified the use of counselling/advice only.

6. Confidence interval for the RR crosses RR=0.75.

7. Small sample size for Garner et al. meant that the study was very underpowered and unable to detect significant differences for operative deliveries.

8. 97% confidence intervals were used by Landon et al. due to adjustment of p-values to allow for changes in the type 1 error caused by the use of multiple testing. Meta-analyses were therefore performed which both included and excluded this study. It was deemed appropriate to present the results which include this study because 97% CIs are more conservative/wider than 95% CIs and, due to the large effect size, should therefore not have adversely affected the overall conclusions of the analysis.

9. The studies were carried out in Australia, the United Kingdom, Canada and the United States of America. Ethnicity was primarily Hispanic, followed by white, Asian, other and African-American.

One study did not report ethnicity.

10. Interventjons for Bevier et al.: dietary counselling, instruction in self-monitoring of blood glucose and 30kcal/kg/day or 24kcal/kg/day if body weight was > 120% of ideal body weight.

11. Interventions for Crowther et al.: individualised dietary advice, instruction in self-monitoring of blood glucose (four times daily until within the recommended range for two weeks) and insulin if required.

12. Interventions for Garner et al.: standard obstetric care and strict glycaemic control which included counselling, 35kcal/kg/day dietary intake and instruction in self-monitoring of blood glucose.

13. Interventions for Landon et al.: dietary counselling and therapy, instruction in self-monitoring of blood glucose and insulin where appropriate.

14. Allocation was not concealed from investigators, clinicians or participants.

15. Groups were unbalanced with respect to attrition; 6 in the diet group left care versus none in the standard care group.
16. Performance bias is likely as participants in the diet group received more care than those in the standard care group.
17. Single study analysis.
18. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.
19. The study was carried out in Italy. All participants were Caucasian.
20. The intervention group received dietary advice to consume 24 to 30kcal/kg/day based on pre-pregnancy weight (50 to 50% carbohydrates, 25 to 30% protein, 20 to 25% fat). The control group received no special care, diet or pharmacological intervention.
21. The study was carried out in Canada. Ethnicity was not reported.
22. Attrition/missing data as only 83/103 participants were included in final analyses; the distribution between groups was not reported.
23. The method of randomisation was not described.
24. The study was carried out in the United States of America. Ethnicity was 4% white, 94% Hispanic and 2% African-American in the intervention group and 6% white and 94% Hispanic in controls.
25. All three studies did not completely specify whether allocation was concealed; two studies did not describe randomisation methods (Crowther et al. and Bevier et al.) and one study used minimisation to allocate participants (Landon et al.).
26. Bevier et al. applied a kcal limit for dietary intake in the intervention group in addition to counselling; the remaining two studies specified the use of counselling/advice only.
27. Confidence interval for the RR crosses RR=1.25.
28. The studies were carried out in Australia, the United Kingdom, Canada and the United States of America. Ethnicity was primarily Hispanic, followed by white, Asian, other and African-American.
29. Garner et al. defined treatment failure as a requirement for insulin based on fasting plasma glucose > 4.4mmol/l or one hour postprandial glucose >7.8mmol/l.
30. Crowther et al. defined treatment failure as a requirement for insulin based on fasting plasma glucose > 5.5mmol/l or postprandial glucose > 7.0mmol/l at ≤ 35 weeks' gestation, postprandial glucose ≥ 8.0mmol/l > 35 weeks' gestation or one capillary blood glucose value ≥ 9.0mmol/l during two weeks of self-monitoring of blood glucose.
31. Landon et al. defined treatment failure as a requirement for insulin if the majority of fasting plasma glucose values > 5.3mmol/l or two hour postprandial glucose values > 6.7mmol/l between clinic visits.
32. The study was carried out in Australia and the United Kingdom. Ethnicity was 73% white, 19% Asian and 9% other in the intervention group and 78% white, 14% Asian and 8% other in controls.
33. Minimisation was used as the randomisation technique which is not a truly random method of allocation.
34. The study was carried out in the United States of America. Ethnicity was 11.5% black, 25.4% white, 4.5% Asian, 57.9% Hispanic and 0.6% other in the intervention group and 11.4% black, 25.2% white, 5.9% Asian, 56.0% Hispanic and 1.5% other in controls.
35. All four studies did not completely specify whether allocation was concealed; three studies did not describe randomisation methods (Crowther et al., Bevier et al. and Langer et al.) and one study used minimisation to allocate participants (Landon et al.).
36. Bevier et al. and Langer et al. applied a kcal limit for dietary intake in the intervention group in addition to counselling; the remaining two studies specified the use of counselling/advice only.
37. Women in the intervention group received dietary advice to consume 25kcal/kg if pre-pregnancy BMI ≥ 27 or 30kcal/kg if pre-pregnancy BMI < 27. Women in the control group were advised to continue with their normal eating habits.
38. The study was carried out in the United States of America. Ethnicity was 30% black, 33% Hispanic and 36% white in the intervention group and 33% black, 33% Hispanic and 33% white in the control group.
39. Shoulder dystocia was assessed using a standardised checklist at birth (Crowther et al.), defined clinically (Landon et al.) or not defined (Bevier et al.).
40. Definitions were not given or not consistent across studies.
41. Serious perinatal complications comprised stillbirth, neonatal death, shoulder dystocia, bone fracture and nerve palsy.
42. Two of the composite outcome variables were not relevant to the GDG's priority outcomes specified in the protocol for this review (bone fracture and nerve palsy).
43. The term "neonatal nursery" was not defined.
44. No duration of admission was specified.
45. Randomisation methods were not described.
46. The ethnicity of women in the study is not comparable to the population in the United Kingdom therefore generalisability is poor.
47. The composite perinatal outcome comprised hypoglycaemia, hyperbilirubinaemia, elevated cord-blood C-peptide level, stillbirth or neonatal death and birth trauma.

48. There were substantial missing data for this outcome (25/485 intervention, 33/473 control overall; additional data were missing for individual components of this outcome).
49. Three of the composite outcome variables are not relevant to the GDG's priority outcomes specified in the protocol for this review (hypoglycaemia, hyperbilirubinaemia and birth trauma).
50. Data were missing for this outcome (62 intervention subjects, 70 control subjects).
51. Hypoglycaemia was not defined.
52. Hypoglycaemia is included as an outcome as a proxy for hyperinsulinaemia.
53. Hypoglycaemia was defined as any two blood glucose values < 1.7 mmol/litre.

Table 38: GRADE profile for comparison of diet plus insulin with diet alone

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (diet + insulin)	Comparator (diet alone)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Maternal outcomes											
Caesarean delivery											
1 (Coustan et al., 1978)	5/27	4/11	RR 0.51 (0.07 to 3.71)[a]	178 fewer per 1000 (from 338 fewer to 985 more per 1000)	Very low[b]	Partially randomised trial	Very serious[1,2,3]	No serious inconsistency[4]	No serious indirectness	Very serious[5]	Yes[6,7]
1 (Thompson et al., 1990)	14/45	16/50	RR 0.97 (0.54 to 1.76)[a]	10 fewer per 1000 (from 147 fewer to 243 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[4]	No serious indirectness	Very serious[5]	Yes[8,9]
Treatment failure[10,11]											
1 (Persson et al., 1985)	NR	15/105	NC	NC	Low	Randomised controlled trial	No serious bias	No serious inconsistency[4]	No serious indirectness	NA	Yes[12,13]
1 (Thompson et al., 1990)	9/45	16/50	RR 0.63 (0.04 to 9.90)[a]	118 fewer per 1000 (from 307 fewer to 1000 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[4]	No serious indirectness	Very serious[5]	Yes[8,9]

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (diet + insulin)	Comparator (diet alone)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Neonatal outcomes											
Large for gestational age (> 90th percentile)											
1 (Persson et al., 1985)	11/97	14/105	RR 0.85 (0.41 to 1.78)[a]	20 fewer per 1000 (from 79 fewer to 104 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[4]	No serious indirectness	Very serious[5]	Yes[12,13]
Hypoglycaemia (plasma glucose < 30 mg/dl)											
1 (Thompson et al., 1990)	2/34	5/34	RR 0.40 (0.08 to 1.92)[a]	88 fewer per 1000 (from 135 fewer to 135 more per 1000)	Very low	Randomised controlled trial	No serious bias	No serious inconsistency[4]	Serious[14]	Very serious+	Yes[8,9]
Hypoglycaemia (not defined)											
1 (Persson et al., 1985)	20/97	13/105	RR 1.67 (0.88 to 3.17)[a]	83 more per 1000 (from 15 fewer to 269 more per 1000)	Very low	Randomised controlled trial	Serious[15]	No serious inconsistency[4]	Serious[14]	Serious[5]	Yes[12,13]
Shoulder dystocia											
1 (Coustan et al., 1978)	0/27	0/11	NC	NC	Very low[b]	Partially randomised trial	Very serious[1,2,3,16]	No serious inconsistency[4]	No serious indirectness	NA	Yes[6,7]
1 (Thompson et al., 1990)	0/34	0/34	NC	NC	Moderate	Randomised controlled trial	No serious bias	No serious inconsistency[4]	Serious[17]	NA	Yes[8,9]
Perinatal mortality											
1 (Coustan et al., 1978)	0/27	0/11	NC	NC	Very low[b]	Partially randomised trial	Very serious[1,2,3]	No serious inconsistency[4]	No serious indirectness	NA	Yes[6,7]
1 (Thompson et al., 1990)	0/34	0/34	NC	NC	High	Randomised controlled trial	No serious bias	No serious inconsistency[4]	No serious indirectness	NA	Yes[8,9]

CI confidence interval, NA not applicable, NC not calculable, RR relative risk
a. Calculated by the NCC-WCH technical team.
b. Starting point of moderate quality due to incomplete randomisation.
1. The first 20 participants that entered the study were allocated based on their gestational age at diagnosis of gestational diabetes rather than randomly.

2. The baseline comparability of patient characteristics is unclear: age is not reported and neither are p-values.

3. Follow-up was not the same for all participants; this was not accounted for in analyses.

4. Single study analysis.

5. Confidence interval for the relative risk crosses the line of no effect and RR=0.75 and RR=1.25.

6. The study was carried out in the United States of America. Ethnicity was not reported.

7. Interventions for Coustan et al.: The control group received instruction in a diet of 30-35kcal/kg ideal weight/day comprising 500 kcal protein with the rest of the intake split equally between fat and carbohydrates. The intervention group received the same diet as controls plus 20 units NPH insulin and 10 units regular insulin 30 minutes before breakfast.

8. The study was carried out in the United States of America. Ethnicity was not reported.

9. Interventions for Thompson et al.: The control group received instruction in a diet of 35 kcal/kg ideal body weight/day comprising 50% kcal as carbohydrate, 30% as fat and 20% as protein. The intervention group received the above diet plus 20 units of NPH insulin and 10 units of regular insulin 30 minutes before breakfast.

10. Thompson et al. defined treatment failure as requiring insulin in the diet alone group or an increase in insulin dosage in the diet plus insulin group. Thresholds for insulin therapy were fasting glucose > 5.8 mmol/litre on one occasion or two hour postprandial glucose > 6.7 mmol/litre on two occasions.

11. Persson et al. defined treatment failure in the diet alone group as the requirement of insulin when fasting glucose exceeded 7.0 mmol/litre or one hour postprandial values > 9.0 mmol/litre at least three times in one week.

12. The study was carried out in Sweden. Ethnicity was not reported.

13. Interventions for Persson et al.: The control group received instruction in a diet comprising 50% calories from carbohydrates, 20% from protein, 30% from fat. The intervention group received the same diet as controls plus an initial dose of 8 to 12IU/day of intermediate or fast-acting insulin.

14. Hypoglycaemia is included as an outcome as a proxy for hyperinsulinaemia.

Table 39: GRADE profile for comparison of two different diets

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Maternal outcomes											
Caesarean delivery											
1 (Cypryk et al., 2007)	7/15	5/15	RR 1.40 (0.57 to 3.43)[a]	133 more per 1000 (from 143 fewer to 810 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Serious[3]	Very serious[4]	Yes[5,6]
1 (Coustan et al., 1978)	4/11	9/34	RR 1.37 (0.52 to 3.58)[a]	98 more per 1000 (from 127 fewer to 683 more per 1000)	Very low	Randomised controlled trial	Very serious[7,8,9]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[10,11]
1 (Rae et al., 2000)	26/65	19/56	RR 1.18 (0.74 to 1.89)[a]	61 more per 1000 (from 88 fewer to 302 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[12,13]
1 (Moreno-Castilla et al., 2013)	25/74	20/75	RR 1.27 (0.78 to 2.08)[a]	72 more per 1000 (from 59 fewer to 288 more per 1000)	Low	Randomised controlled trial	Serious[14]	No serious inconsistency[2]	No serious indirectness	Serious[15]	Yes[16,17]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Asemi et al., 2014)	12/26 (46.2%)	21/26 (80.8%)	RR 1.18 (0.74 to 1,89)	61 fewer per 1000 (from 88 fewer to 302 more per 1000)	Very low	Randomised controlled trial	Serious[28]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[18,19]
Emergency caesarean delivery											
1 (Louie et al., 2011)	9/44	5/44	RR 1.80 (0.64 to 1.85)[a]	91 more per 1000 (from 41 fewer to 97 more per 1000)	Very low	Randomised controlled trial	Serious[18]	No serious inconsistency[2]	Serious[19]	Very serious[4]	Yes[20,21]
Vaginal delivery											
1 (Cypryk et al., 2007)	7/15	9/15	RR 0.77 (0.39 to 1.52)[a]	138 fewer per 1000 (from 366 fewer to 312 more per 1000)	Very low	Randomised controlled trial	Very serious[1,22]	No serious inconsistency[2]	Serious[3]	Very serious[4]	Yes[5,6]
Spontaneous vaginal delivery											
1 (Rae et al., 2000)	31/65	30/56	RR 0.89 (0.63 to 1.27)[a]	59 fewer per 1000 (from 198 fewer to 145 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[12,13]
Induction of labour											
1 (Rae et al., 2000)	29/63	23/51	RR 1.02 (0.18 to 5.76)[a]	9 more per 1000 (from 370 fewer to 1000 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[12,13]
Treatment failure [23,24,25,26,27]											
1 (Moses et al., 2009)	9/31	19/32	RR 0.49 (0.26 to 0.91)[a]	303 fewer per 1000 (from 53 to 439 fewer per 1000)	Very low	Randomised controlled trial	Very serious[28]	No serious inconsistency[2]	No serious indirectness	Serious[29]	Yes[30,31]
1 (Rae et al., 2000)	11/63	9/54	RR 1.05 (0.47 to 2.34)[a]	8 more per 1000 (from 88 fewer to 223 more per 1000)	Low	Randomised controlled trial	No serious bias	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[12,13]
1 (Louie et al., 2011)	25/47	29/45	RR 0.83 (0.59 to 1.17)[a]	110 fewer per 1000 (from 264 fewer to 100 more per 1000)	Low	Randomised controlled trial	Serious[18]	No serious inconsistency[2]	No serious indirectness	Serious[29]	Yes[20,21]

| Number of studies | Number of women | | Effect | | | | Quality assessment | | | | |
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Moreno-Castilla et al., 2013)	41/75	41/75	RR 1.00 (0.75 to 1.34)[a]	0 fewer per 1000 (from 137 fewer to 186 more per 1000)	Low	Randomised controlled trial	Serious[14]	No serious inconsistency[2]	No serious indirectness	Serious[15]	Yes[16,17]
1 (Grant et al., 2011)	13/18	12/20	RR 1.20 (0.75 to 1.93)[a]	120 more per 1000 (from 150 fewer to 558 more per 1000)	Low	Pilot study	Serious[35,36]	No serious inconsistency[2]	No serious indirectness	Serious[15]	Yes[37,38]
Neonatal outcomes											
Large for gestational age (> 90th percentile)											
1 (Moses et al., 2009)	3/31	3/29	RR 1.03 (0.22 to 4.72)[a]	3 more per 1000 (from 81 fewer to 385 more per 1000)	Very low	Randomised controlled trial	Very serious[28,32]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[30,31]
1 (Louie et al., 2011)	6/47	2/43	RR 2.87 (0.97 to 8.46)[a]	87 more per 1000 (from 1 fewer to 347 more per 1000)	Very low	Randomised controlled trial	Serious[18]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[20,21]
1 (Moreno-Castilla et al., 2013)	3/74	6/75	RR 0.51 (0.13 to 1.96)[a]	39 fewer per 1000 (from 70 fewer to 77 more per 1000)	Very low	Randomised controlled trial	Serious[14]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[16,17]
1 (Grant et al., 2011)	2/18	3/20	RR 0.74 (0.13 to 4.18)[a]	39 fewer per 1000 (from 130 fewer to 477 more per 1000)	Very low	Pilot study	Serious[35,36]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[37,38]
Shoulder dystocia											
1 (Rae et al., 2000)	0/63	0/54	NC	NC	Moderate	Randomised controlled trial	Serious[33]	No serious inconsistency[2]	No serious indirectness	NA	Yes[12,13]
1 (Coustan et al., 1978)	0/11	1/34	RR 0.97 (0.04 to 22.25)[a]	1 fewer per 1000 (from 28 fewer to 625 more per 1000)	Very low	Randomised controlled trial	Very serious[7,8,9,33]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	Yes[20,21]
Hypoglycaemia (< 30mg/100ml; <1.7 mmol/litre)											
1 (Coustan et al., 1978)	0/11	2/34	RR 0.58 (0.03 to 11.25)[a]	25 fewer per 1000 (from 57 fewer to 603 more per 1000)	Very low	Randomised controlled trial	Very serious[7,8,9]	No serious inconsistency[2]	Serious[34]	Very serious[4]	Yes[10,11]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				Other considerations
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Hypoglycaemia (< 40mg/100ml; <2.2 mmol/litre)											
1 (Moreno-Castilla et al., 2013)	9/74	10/75	RR 0.91 (0.39 to 2.11)[a]	12 fewer per 1000 (from 81 fewer to 148 more per 1000)	Very low	Randomised controlled trial	Serious[14]	No serious inconsistency[2]	Serious[34]	Very serious[4]	Yes[16,17]

CI confidence interval, NA not applicable, NC not calculable, RR relative risk
a. Calculated by the NCC-WCH technical team.
1. No baseline characteristics were provided for each group and confounders were not adjusted for in analyses: it is unclear whether confounding may have affected the effect estimate.
2. Single study analysis.
3. Not clear whether an OGTT was performed to diagnose women with gestational diabetes: three-day diaries were reviewed to obtain 24 hour average estimates of glycaemia before diets were prescribed.
4. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.
5. The study was carried out in Poland. All women were Caucasian.
6. The intervention group received 45% of daily intake as carbohydrates, 25% protein and 30% fat. The control group received 60% of daily intake as carbohydrates, 25% protein and 15% fat.
7. The first 20 participants that entered the study were allocated based on their gestational age at diagnosis of gestational diabetes rather than randomly.
8. The baseline comparability of patient characteristics is unclear: age is not reported and neither are p-values.
9. Follow-up was not the same for all participants; this was not accounted for in analyses.
10. The study was carried out in the United States of America. Ethnicity was not reported.
11. The intervention was a diet of 30 to 35kcal/kg/day comprising 500kcal protein with the rest split equally between carbohydrate and fat. Control subjects received dietary counselling as per a standard prenatal care protocol aimed at 15 to 20lb weight gain.
12. The study was carried out in Australia. Ethnicity was not reported.
13. The intervention was a moderately energy-restricted diet comprising 1590 to 1776kcal per day. The control group received instruction in an unrestricted diet of between 2010 and 2220kcal per day.
14. Allocation was not concealed from clinicians responsible for providing care.
15. Confidence interval for the RR crosses RR=1.25.
16. The study was carried out in Spain. Ethnicity was Caucasian in 92.0% of the control group and 98.7% of the intervention group. No other ethnicities were reported.
17. The intervention was a low carbohydrate diet comprising 40% carbohydrates, 40% fat and 20% protein. The control group received a diet comprising 55% carbohydrates, 25% fat and 20% protein. No changes to the carbohydrate content of each diet were allowed unless insulin therapy was initiated.
18. The study was carried out in Iran. Ethnicity was not reported
19. The control group received a diet base on 45-55% carbohydrates, 15-20% protein and 25-30% total fat. Th intervention group received the DASH diet which was similar to the control diet, but was rich in fruits, vegetables, whole grains and low-fat dairy products and low in saturated fats, cholesterol, refined grains and sweets
20 The study was carried out in Australia. Ethnicity was 59.6% Asian and 31.9% Caucasian in the intervention group and 55.6% Asian and 40% Caucasian in the control group
21 The intervention group received a diet based on 40 to 45% carbohydrate, 15 to 25% protein and 25 to 30% fat and a target GI of < 50 was imposed. The control group received a diet based on 40 to 45% carbohydrate, 15 to 25% protein and 25 to 30% fat and a target GI of < 60 was imposed
22. Possible attrition bias as 7 participants withdrew but the distribution between groups was not reported.
23. Does not include all Caesarean deliveries reported in the study.
24. The study was carried out in Australia. Ethnicity was 59.6% Asian, 31.9% Caucasian and 8.5% other in the low GI group, 55.6% Asian, 40.0% Caucasian and 4.4% other in the control group.

25. Both diets comprised 40 to 45% carbohydrate, 15 to 25% protein and 25 to 30% fat. Target GI levels were < 50 for the intervention group and < 60 for the control group.

26. Reported as "physiological delivery" but this was not defined.

23. Moses et al. defined treatment failure as a requirement for insulin based on fasting plasma glucose ≥ 5.5 mmol/litre or one hour postprandial glucose ≥ 8.0 mmol/litre more than once in a week.

24. Rae et al. defined treatment failure as a requirement for insulin based on fasting plasma glucose > 5.5 mmol/litre or two hour postprandial glucose > 7.0 mmol/litre on two or more occasions within 72 hours.

25. Louie et al. defined treatment failure as a requirement for insulin based on mean fasting plasma glucose > 5.2 mmol/litre or mean one hour postprandial glucose > 7.5 mmol/litre during the preceding week.

26. Moreno-Castilla et al. defined treatment failure as at least two values exceeding fasting and preprandial blood glucose ≤ 5.3 mmol/litre and one hour postprandial glucose ≤ 7.8 mmol/litre within one week.

27. Grant et al. defined treatment failure as not meeting self-monitoring targets within two to three weeks of treatment starting. Targets were defined according to the Canadian Diabetes Association of fasting glucose between 3.8 and 5.2 mmol/litre and 2 hour postprandial between 5.0 and 6.6 mmol/litre.

28. Unclear whether participants and investigators were blinded to allocation.

29. Confidence interval for the RR crosses RR=0.75.

30. The study was carried out in Australia. All women except one were white.

31. Both groups received 175 g carbohydrate as part of their prescribed diets. The intervention group were advised to consume low GI foods including grain breads and unprocessed cereals with a high fibre content. Intervention participants were told to avoid white bread, processed cereals and potatoes. The control group were advised to follow a high fibre, low sugar diet comprising whole wheat bread and high fibre, high-to-moderate GI breakfast cereals.

32. 19/32 (59%) of women in the control arm (high GI diet) required insulin therefore were switched to the low GI during the trial. This will have diluted the effect estimate towards the null.

33. Shoulder dystocia was not defined.

34. Hypoglycaemia is included as an outcome as a proxy for hyperinsulinaemia.

35. The method of randomisation was not described and it was unclear whether investigators were blinded to allocation.

36. Women in the study had either gestational diabetes or impaired glucose tolerance. Diagnostic criteria were not reported for either condition.

37. The study was carried out in Canada. Women had either gestational diabetes or impaired glucose tolerance. Ethnicity was 25% South East Asian, 21% Indian, 21% white, 11% East Asian, 9% Caribbean, 6% mixed and 6% Hispanic.

38. The intervention group were advised in a low glycaemic index diet where starchy foods were chosen from a list of low GI foods. The control group were advised in a diet where starchy foods were chosen from a list of intermediate and high GI foods.

4.5.5.2 Exercise

Diagnostic criteria for gestational diabetes varied across studies as did the types of interventions used. These are described in Table 35.

The GRADE profiles for this intervention are shown in Tables 40 and 41.

Table 40: GRADE profile for comparison of exercise with no exercise in women with gestational diabetes mellitus

Number of studies	Number of women		Effect				Quality assessment				
	Intervention (exercise)	Comparator (no exercise)	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Requirement for insulin											
1 (de Barros et al., 2010)	7/32	18/32	RR 0.38 (0.18 to 0.78)[a]	180 fewer per 1000 (from 124 to 461 fewer per 1000)	Very low	Randomised controlled trial	Very serious[1,2,3]	No serious inconsistency[4]	No serious indirectness	Serious[5]	Yes[6,7,8]
1 (Avery et al., 1997)	4/15	2/14	RR 1.86 (0.40 to 8.62)[a]	123 more per 1000 (from 86 fewer to 1000 more per 1000)	Very low	Randomised controlled trial	Serious[9,10]	No serious inconsistency[4]	No serious indirectness	Very serious[11]	Yes[12,13,14]
Caesarean delivery											
1 (Avery et al., 1997)	3/15	3/14	RR 0.93 (0.22 to 3.87)[a]	15 fewer per 1000 (from 167 fewer to 615 more per 1000)	Very low	Randomised controlled trial	Serious[9]	No serious inconsistency[4]	No serious indirectness	Very serious[11]	Yes[12,13,14]
Macrosomia (> 4000g)											
1 (Avery et al., 1997)	3/15	3/14	RR 0.93 (0.22 to 3.87)[a]	15 fewer per 1000 (from 167 fewer to 615 more per 1000)	Very low	Randomised controlled trial	Serious[9]	No serious inconsistency[4]	No serious indirectness	Very serious[11]	Yes[12,13,14]
Neonatal hypoglycaemia (< 45mg/dl)											
1 (Avery et al., 1997)	0/15	0/14	Not calculable	Not calculable	Low	Randomised controlled trial	Serious[9]	No serious inconsistency[4]	No serious indirectness	NA	Yes[12,13,14]

CI confidence interval, NA not applicable, RR relative risk,
a. Calculated by the NCC-WCH technical team.
1. Possible selection bias as no baseline characteristics were reported.
2. Blinding was not clear and randomisation methods were not described.
3. Criteria for starting insulin therapy were not reported.
4. Single study analysis.
5. Confidence interval for the RR crosses RR=0.75.
6. The study was carried out in Brazil. Ethnicity was not reported.

7. Intervention participants were instructed to perform eight circuit-based activities using a resistance band. Women performed 15 reps of each exercise three days per week .nd progressed from 2 circuits initially to 3 circuits after 3 weeks. Controls did not undertake an exercise programme.

8. No concurrent diet was reported. Women self-monitored their blood glucose before each exercise session. Glycaemia was also measured weekly by the clinic.

9. Participants were not blinded to allocation; blinding of study investigators and clinicians is not clear.

10. Blood glucose thresholds for initiation of insulin therapy were not reported.

11. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.

12. The study was carried out in the United States of America. All women in the intervention group were Caucasian. Two women in the control group were Japanese, the remainder were Caucasian.

13. Intervention participants undertook 30 minutes of exercise three to four times per week until delivery. Two exercise sessions per week were monitored by study staff. Controls maintained their usual physical activity level alongside dietary therapy.

14. Dietary therapy was provided for controls but not reported in the intervention group. Participants self-monitored blood glucose three days per week.

Table 41: GRADE profile for comparison of diet and exercise with diet alone in women with gestational diabetes mellitus

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (diet + exercise)	Comparator (diet alone)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Requirement for insulin[1]											
1 (Brankston et al., 2004)	7/16	9/16	RR 0.78 (0.39 to 1.58)[a]	124 fewer per 1000 (from 343 fewer to 326 more per 1000)	Very low	Randomised controlled trial	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	Yes[4,5,6]

CI confidence interval, RR relative risk

a. Calculated by the NCC-WCH technical team.

1. Insulin therapy was initiated if: fasting blood glucose ≥ 5.3mmol/litre, one hour postprandial ≥ 7.8 mmol/litre or two hour postprandial ≥ 6.7 mmol/litre consistently at any time during diet therapy.

2. Attrition is 16% overall but the split between groups is not reported; attrition bias is possible.

3. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.

4. The study was carried out in Canada. Ethnicity was not reported.

5. Intervention participants received a standard diabetic diet (40% carbohydrate, 40% protein, 20% fat) comprising 24 to 30kcal/kg/day of ideal pre-pregnancy body weight plus a progressive physical activity program of circuit-type exercise. Controls received instruction in the standard diabetic diet only.

6. All participants self-monitored blood glucose daily.

4.5.5.3 Pharmacological interventions

The GRADE profiles for this review question are presented in Tables 42 to 44.

Table 42: GRADE profile for comparison of metformin and insulin in women with gestational diabetes

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Mode of birth											
Spontaneous vaginal birth											
1 (Hague et al., 2003)	5/16 (31.3%)	11/14 (78.6%)	RR 0.4 (0.18 to 0.86)[a]	471 fewer per 1000 (from 110 fewer to 644 fewer)	Low	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Yes[3,4]
1 (Ijas et al., 2010)	24/47 (51.1%)	26/50 (52%)	RR 0.98 (0.67 to 1.45)[a]	10 fewer per 1000 (from 172 fewer to 234 more)	Low	RCT	No serious bias[5]	No serious inconsistency	No serious indirectness	Very serious imprecision[6]	Yes[7,8]
Induction of labour											
3 (Hague et al., 2003; Ijas et al., 2010; Tertti et al., 2013)	69/172 (40.1%)	103/171 (60.2%)	RR 0.67 (0.54 to 0.83)[a]	199 fewer per 1000 (from 102 fewer to 277 fewer)	Low	RCT	Serious[1,5,9]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Yes[3,4,7,8,10,11]
1 (Rowan et al., 2008)	196/363 (54%)	208/370 (56.2%)	RR 0.96 (0.84 to 1.09)[a]	22 fewer per 1000 (from 90 fewer to 51 more)	Moderate	RCT	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[13,14]
Vacuum extraction											
1 (Ijas et al., 2010)	7/47 (14.9%)	4/50 (8%)	RR 1.86 (0.58 to 5.95)[a]	69 more per 1000 (from 34 fewer to 396 more)	Low	RCT	No serious bias[5]	No serious inconsistency	No serious indirectness	Very serious imprecision[6]	Yes[7,8]
Caesarean section											
7 (Hague et al., 2003; Ijas et al. 2010; Moore et al., 2007; Niromanesh et al., 2012; Rowan et al., 2008; Spaulonci et al., 2013; Tertti et al., 2013)	248/693 (35.8%)	250/698 (35.8%)	RR 1.00 (0.87 to 1.15)[a]	0 fewer per 1000 (from 47 fewer to 54 more per 1000)	Moderate	RCT	Serious[1,5,9,12,15,16,17]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[3,4,7,8,10,11,13,14,18,19,20,21,22,23]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Elective Caesarean section											
1 (Hague et al., 2003)	8/16 (50%)	2/14 (14.3%)	RR 3.5 (0.89 to 13.82)[a]	357 more per 1000 (from 16 fewer to 1000 more)	Low	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[24]	Yes[3,4]
1 (Rowan et al., 2008)	55/363 (15.2%)	63/370 (17%)	RR 0.89 (0.64 to 1.24)[a]	19 fewer per 1000 (from 61 fewer to 41 more)	Low	RCT	Serious[12]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Yes[13,14]
Emergency caesarean section											
1 (Niromanesh et al., 2012)	25/80 31.3%	16/80 20.0%	RR 1.6 (0.9 to 2.7)	120 more per 1000 (from 20 fewer to 340 more per 1000)	Low	RCT	Serious[16]	No serious inconsistency	No serious indirectness	Serious[24]	Yes[18,19]
Assisted vaginal delivery											
1 (Tertti et al., 2013)	9/109 8.3%	8/107 7.5%	RR 1.10 (0.44 to 2.74)[a]	7 more per 1000 (from 42 fewer to 130 more per 1000)	Very low	RCT	Serious[9]	No serious inconsistency	Serious[25]	Very serious[6]	Yes[10,11]
Need for additional insulin											
5 (Ijas et al., 2010; Moore et al., 2007; Niromanesh et al., 2012; Spaulonci et al., 2013; Rowan et al., 2008)	206/568 (36.3%)	NC	NC	NC	Moderate	RCT	Serious[5,12,15,16,17]	No serious inconsistency	No serious indirectness	NC[26]	Yes[7,8,13,14,18,19,20,21,22,23]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Acceptability											
How often did you forget to take your medication?											
1(Rowan et al., 2008)	Never/rarely: 231/333 (69.4%) 1–3 times/wk: 81/333 (24.3%) 4–6 times/wk: 12/333 (3.6%) >6 times/wk: 9/333 (2.7%)	Never/rarely: 267/331 (80.7%) 1–3 times/wk: 52/331 (15.7%) 4–6 times/wk: 2/331 (0.6%) >6 times/wk: 10/331 (3.0%)	p<0.001	NC	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	NA	Yes[10,11]
Which medicine would you choose in another pregnancy?											
1(Rowan et al., 2008)	Metformin tablets: 256/334 (76.6%) Insulin injections: 42/334 (12.6%) Not sure: 36/334 (10.8%)	Metformin tablets: 127/331 (38.4%) Insulin injections: 90/331 (27.2%) Not sure: 114/331 (34.4%)	p<0.001	NC	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	NA	Yes[10,11]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				Other considerations
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
1(Rowan et al., 2008)	Start with metformin and add insulin if needed: 270/334 (80.8%) Go straight to insulin injections: 36/334 (10.8%) Not sure: 28/334 (8.4%)	Start with metformin and add insulin if needed: 179/331 (54.1%) Go straight to insulin injections: 94/331 (28.4%) Not sure: 58/331(17.5%)	p<0.001	NC	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	NA	Yes[10,11]
Which part of your diabetes treatment was the easiest?											
1(Rowan et al., 2008)	Doing finger-prick tests: 74/334 (22.2%) Being careful with diet: 63/334 (18.9%) Taking medication: 197/334 (59.0%)	Doing finger-prick tests: 119/331 (36.0%) Being careful with diet: 95/331 (28.7%) Taking medication: 117/331 (35.3%)	p<0.001	NC	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	NA	Yes[10,11]

	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1(Rowan et al., 2008)	Doing finger-prick tests: 123/334 (36.8%) Being careful with diet: 176/334 (52.7%) Taking medication: 35/334 (10.5%)	Doing finger-prick tests: 91/331 (27.5%) Being careful with diet: 150/331 (45.3%) Taking medication: 90/331 (27.2%)	p=0.001	NC	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	NA	Yes[10,11]
Large for gestational age											
5 (Ijas et al., 2010; Mesdaghinia et al., 2013; Niromanesh et al., 2012; Rowan et al., 2008; Tertti et al., 2013)	120/699 (17.2%)	143/707 (20.2%)	RR 0.85 (0.68 to 1.05)[a]	30 fewer per 1000 (from 65 fewer to 10 more)	Very low	RCT	Serious[5,9,12,16,27]	Serious[28]	No serious indirectness	Serious[2]	Yes[7,8,10,11,13,14,18,19,29,30]
1 (Spaulonci et al., 2013)	0/46 (0.0%)	3/46 (6.5%)	RR 0.14 (0.007 to 2.64)[a]	56 fewer per 1000 (from 65 fewer to 107 more per 1000)	Very low	RCT	Serious[17]	No serious inconsistency	Serious[31]	Very serious[6]	Yes[20,21]
>24 hours NICU stay											
1 (Rowan et al., 2008)	46/363 (12.7%)	45/370 (12.2%)	RR 1.04 (0.71 to 1.53)[a]	5 more per 1000 (from 35 fewer to 64 more)	Very low	RCT	Serious[12]	No serious inconsistency	No serious indirectness	Very serious[6]	Yes[13,14]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Admission to NICU											
5 (Ijas et al., 2010; Niromanesh et al., 2012; Mesdaghinia et al., 2013; Moore et al., 2007; Tertti et al., 2013)	62/368 (16.8%)	89/368 (24.2%)	RR 0.69 (0.52 to 0.92)[a]	75 fewer per 1000 (from 19 fewer to 116 fewer)	Very low	RCT	Serious[5,9,15,16,25]	No serious inconsistency	No serious indirectness	Very serious[6]	Yes[7,8,10,11,18,19,22,23.29,30]
Composite neonatal outcomeb											
1 (Rowan et al., 2008)	116/363 (32%)	119/370 (32.2%)	RR 0.99 (0.8 to 1.23)[a]	3 fewer per 1000 (from 64 fewer to 74 more)	Moderate	RCT	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[13,14]
Shoulder dystocia											
4 (Niromanesh et al., 2012; Mesdaghinia et al., 2013; Moore et al., 2007; Rowan et al., 2008)	11/575 (1.9%)	15/581 (2.6%)	RR 0.76 (0.36 to 1.59)[a]	6 fewer per 1000 (from 17 fewer to 15 more)	Very low	RCT	Serious[12,15,16,27]	No serious inconsistency	No serious indirectness	Very serious[6]	Yes[13,14,18,19,22,23,29,30]
Neonatal hypoglycaemia											
6 (Ijas et al., 2010; Mesdaghinia et al., 2013; Moore et al., 2007; Niromanesh et al., 2012; Spaulonci et al., 2013; Tertti et al., 2013)	38/414 (9.2%)	54/414 (13.0%)	RR 0.71 (0.48 to 1.04)[a]	38 fewer per 1000 (from 68 fewer to 5 more per 1000)	Very low	RCT	Serious[5,9,15,16,17,27]	Serious[32]	No serious indirectness	Serious[2]	Yes[7,8,10,11,18,19,20,21,22,23,29,30]
Supplemental feeding											
1 (Rowan et al., 2008)	129/363 (35.5%)	145/370 (39.2%)	RR 0.91 (0.75 to 1.09)[a]	35 fewer per 1000 (from 98 fewer to 35 more)	Moderate	RCT	Serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[10,11]
Intravenous dextrose											
2 (Hague et al., 2003; Rowan et al., 2008)	29/379 (7.7%)	23/384 (6%)	RR 1.27 (0.75 to 2.15)[a]	16 more per 1000 (from 15 fewer to 69 more)	Low	RCT	Serious[1,9]	No serious inconsistency	No serious indirectness	Serious[24]	Yes[3,4,10,11]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Metformin	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Fetal death											
1 (Rowan et al., 2008)	0/363 (0%)	1/370 (0.27%)	RR 0.34 (0.01 to 8.31)[a]	2 fewer per 1000 (from 3 fewer to 20 more)	Very low	RCT	Serious[9]	No serious inconsistency	No serious indirectness	Very serious[6]	Yes[10,11]
Perinatal Mortality											
1 (Ijas et al., 2010)	0/47 (0%)	0/50 (0%)	NC	NC	Low	RCT	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[6]	Yes[7,8]

CI confidence interval, NA not applicable, NC not calculable, NR not reported, P probability, RCT randomised controlled trial, RR relative risk

a. Calculated by the NCC-WCH technical team from data reported in the article

b. The components of the composite neonatal outcome were hypoglycemia, respiratory distress, phototherapy, birth trauma, Apgar scores below 7, and preterm delivery. Infants could have one or more of the components

c. No definitions were given in either RCT for shoulder dystocia

1. Hague et al., 2003: It is unclear if an appropriate randomisation method or adequate allocation concealment was used. It is unclear whether the treatment groups received the same care (apart from the intervention). Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

2. Confidence interval for the relative risk crosses RR=0.75

3. Hague et al., 2003: Metformin and insulin were the treatments compared but no further details of these treatments were given. No details of any concurrent dietary interventions or monitoring techniques were presented

4. Hague et al., 2003: Ethnicity data is not presented

5. Ijas et al., 2010; Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors

6. Confidence interval for the relative risk crosses RR=0.75 and RR=1.25

7. Ijas et al., 2010: Metformin was started at 750mg once/day in the first week, 750mg twice/day in the second week and 750mg three times/day from the third week onwards. Medication was discontinued if significant side effects (eg diarrhoea) occurred. Supplemental insulin was added if normoglycaemia was not achieved in the 1-2 weeks using the maximum dose. Insulin treatment consisted of long acting insulin to normalise fasting glucose concentrations and rapid acting insulin to normalise postprandial glucose concentrations. Women continued to measure daily profiles of capillary glucose concentrations twice a week and reported values to the diabetes nurse.

8. Ijas et al., 2010: Ethnicity data is not presented

9. Tertti et al., 2013: Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

10. Tertti et al., 2013: All women attended the hospital for dietary counselling and were taught to measure overnight fasting and 1 hour postprandial glucose at least four times daily. Metformin was initiated at a dose of 500mg once daily for the first two days, increased to twice daily for the first week. The dose was increased to a maximum of 1g twice daily if required. Target values were < 5.5mmol/litre after an overnight fast and < 7.8mmol/litre 1 hour postprandial. Insulin was added if these targets were not met with metformin alone. Insulin treatment comprised NPH insulin and/or rapid acting insulin lispro or aspart.

11. Tertti et al., 2013: The study was carried out in Finland. Ethnicity data were not reported.

12. Rowan et al., 2008: It is unclear if adequate allocation concealment was used. There were no outcome data available for 10 women in the metformin group and 8 in the insulin group. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors. Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently.

13. Rowan et al., 2008: All women received lifestyle advice about diet and exercise prior to randomisation. All sites aimed for ADIPS 1998 recommendations for capillary glucose levels (fasting <5.5 mmol/litre; 2-hour postprandial <7.0 mmol/litre), several sites aimed for lower target levels. The initial dose of metformin was 500 mg once or twice daily with food and was typically increased over 1 to 2 weeks, to meet glycemic targets up to a maximum daily dose of 2500 mg. If the targets were not achieved with metformin alone, insulin was added. Metformin was stopped if maternal contraindications (such as liver or renal impairment or sepsis) or fetal growth restriction developed. Insulin was prescribed according to usual practice.

14. Rowan et al., 2008: Ethnicity data - Metformin group (n=363): European or white 175 (48.2%), Polynesian 73 (20.1%), Indian 38 (10.5%), Chinese or Southeast Asian 49 (13.5%), Other or mixed 28 (7.7%). Insulin group (n=370): European or white 168 (45.4%), Polynesian 83 (22.4%), Indian 55 (14.9%), Chinese or Southeast Asian 37 (10.0%), Other or mixed 27 (7.3%)

15. Moore et al., 2007: Groups were generally comparable at baseline except that women in the metformin group were significantly heavier than those in the insulin group. Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

16. Niromanesh et al., 2012: Participants were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

17. Spaulonci et al., 2013: No baseline characteristics were reported therefore comparability of the groups at baseline is unclear. Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

18. Niromanesh et al., 2012: All women were given counselling on diet and physical activity. Daily caloric intake was based on BMI. Carbohydrate intake was restricted to 45% of calories with remainder as protein (20%) and fat (35%). An exercise program of 30 minutes per day was recommended. Metformin was given as an initial dose of 500mg twice daily and increased by 500 to 1000mg up to a maximum dose of 2500mg divided dose with each meal and continued until delivery. Insulin was added if glucose control was not achieved with maximal metformin doses. Women in the insulin group were treated with NPH insulin at an initial dose of 0.2units/kg. If fasting glucose was high insulin was given before bedtime. If postprandial glucose was high, regular short-acting insulin was given before meals based on postprandial glucose levels (1 unit for every 10mg/dl glucose). If both fasting and postprandial values were high insulin was started at a dose of 0.7units/kg (two thirds NPH insulin before breakfast and bedtime, one third regular insulin as two or three preprandial injections).

19. Niromanesh et al., 2012: The study was carried out in Iran. Ethnicity data were not reported.

20. Spaulonci et al., 2013: Treatment information about dosages of metformin and insulin was not reported. Women who failed treatment with metformin were given supplemental insulin.

21. Spaulonci et al., 2013: The study was carried out in Brazil. Ethnicity data were not reported.

22. Moore et al., 2007: All women received dietary instruction by a registered dietician and also from a nurse educator. The diet was designed to provide 30kcal/kg body weight or 25kcal/kg body weight in women who were obese. The calories were split by source: 40% carbohydrates, 20% protein, 30 to 40% fat. The patient received 10% at breakfast, 20-30% for both lunch and dinner and 30% for snacks. All women were trained to use a portable glucose meter at home and tested their blood glucose x3/day: in the morning (fasting value) and 2 hours after each meal. The initial dose of metformin was 500mg/day and was increased as necessary to attain glucose control (maximum dose 1000mg x2/day. Women taking the maximum dose of metformin with 2 values that exceeded the goals for a measurement period for 2 consecutive weeks were considered metformin failures and were started on insulin. Insulin was started at a dosage of 0.7 units of insulin/kg actual body weight, and injected twice daily to maintain euglycaemia (fasting 60-90mg/dl; 2 hour postprandial <120mg/dl). The total daily dose was split; two thirds by subcutaneous injection in the morning and one third injected before the evening meal. A combination of regular insulin and NPH insulin was used.

23. Moore et al., 2007: Ethnicity data - Metformin group (n=32): African American 20 women, Native American 11 women and Caucasian 1 woman. Insulin group (n=32): African American 11 women, Native American 17 women and Caucasian 3 women.

24. Confidence interval for the relative risk crosses RR=1.25

25. Tertti et al., 2013: Assisted vaginal delivery was not defined and is used as a proxy for operative vaginal delivery.

26. Confidence interval cannot be calculated.

27. Mesdaghinia et al., 2013: In the metformin group 22 out of 100 women randomised received supplemental insulin. These women were excluded and replaced by women who had not failed treatment. Participants were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not used for all outcomes.

28. Definitions of LGA varied across studies however meta-analysis was deemed appropriate due to a low level of heterogeneity (I2=32%) and the power gained by pooling data from multiple studies.

29. Mesdaghinia et al., 2013: Women were initially taught lifestyle modification and fasting and 2 hour postprandial blood glucose was measured for one week. If women obtained fasting values > 95mg/dl or 2 hour values > 120mg/dl pharmacological treatment was initiated. Women in the metformin group received an initial dose of 500mg per day. If necessary this dose was adjusted up to a maximum of 2500g per day. Women in the insulin group received an initial dose of 0.5IU/kg/day (two thirds in the morning, one third in the afternoon). Two thirds of the insulin dose was NPH and one third regular insulin. One IU of insulin was added to the dose per 10mg/dl increase in blood glucose above target values.

30. Mesdaghinia et al., 2013: The study was carried out in Iran. Ethnicity was not reported.

31. Spaulonci et al., 2013: Macrosomia is a proxy for large for gestational age.

32. Definitions of neonatal hypoglycaemia varied across studies however meta-analysis was deemed appropriate due to a low level of heterogeneity (I2=0%) and the power gained by pooling data from multiple studies.

Table 43: GRADE profile for comparison of glibenclamide and insulin in women with gestational diabetes

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Glibenclamide	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mode of birth											
Caesarean section											
2 (Bertini et al., 2005; Ogunyemi et al., 2007)	30/67 (44.8%)	37/72 (51.4%)	RR 0.87 (0.61 to 1.23)[a]	67 fewer per 1000 (from 200 fewer to 118 more)	Very low	RCT	Very serious risk of bias[1,2]	No serious inconsistency	No serious indirectness	Serious[3]	Yes[4,5,6,7]
Need for additional insulin											
4 (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000;Ogunyemi et al., 2007)	19/322 (5.9%)	NC	NC	NC	Low	RCT	Very serious risk of bias[1,2,8,9]	No serious inconsistency	No serious indirectness	NC	Yes[4,5,6,7,10,11,12,13]
Maternal hypoglycaemia											
1 (Ogunyemi et al., 2007)	18/48 (37.5%)	15/49 (30.6%)	RR 1.23 (0.7 to 2.14)[a]	70 more per 1000 (from 92 fewer to 349 more)	Very low	RCT	Very serious risk of bias[2]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[6,7]
Large for gestational age											
3 (Bertini et al., 2005; Lain et al., 2009; Mukhopadhyay et al., 2012)	22/95 (23.2%)	6/95 (6.3%)	RR 3.62 (1.54 to 8.49)[a]	165 more per 1000 (from 34 more to 473 more)	Low	RCT	Very serious risk of bias[1,8,15]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[4,5,10,11,16,17]
1 (Langer et al., 2000)	24/201 (11.9%)	26/203 (12.8%)	RR 0.93 (0.55 to 1.57)[a]	9 fewer per 1000 (from 58 fewer to 73 more)	Low	RCT	No serious risk of bias[9]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[12,13]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Glibenclamide	Insulin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Admission to NICU											
3 (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000)	17/274 (6.2%)	14/280 (5%)	RR 1.22 (0.63 to 2.37)[a]	11 more per 1000 (from 19 fewer to 68 more)	Very low	RCT	Very serious risk of bias[1,8,9]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[4,5,10,11,12,13]
Shoulder dystocia											
1 (Lain et al., 2009)	1/49 (2%)	2/50 (4%)	RR 0.51 (0.05 to 5.45)[a]	20 fewer per 1000 (from 38 fewer to 178 more)	Very low	RCT	Very serious risk of bias[8]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[10,11]
Neonatal hypoglycaemia											
5 (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000; Ogunyemi et al., 2007; Mukhopadhyay et al., 2012)	46/347 (13.3%)	22/355 (6.2%)	RR 2.13 (1.32 to 3.43)[a]	70 more per 1000 (from 20 more to 151 more)	Low	RCT	Very serious risk of bias[1,2,8,9,15]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[4,5,6,7,10,11,12,13,16,17]
IV glucose therapy											
1 (Langer et al., 2000)	28/201 (13.9%)	22/203 (10.8%)	RR 1.29 (0.76 to 2.17) a	31 more per 1000 (from 26 fewer to 127 more)	Moderate	RCT	No serious risk of bias[9]	No serious inconsistency	No serious indirectness	Serious[18]	Yes[12,13]
Intrauterine death											
1 (Lain et al., 2009)	1/40 (2.5%)	0/50 (0%)	RR 3.73 (0.16 to 89.21)[a]	-	Very low	RCT	Very serious risk of bias8	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[10,11,19]
Stillbirth											
1 (Langer et al., 2000)	1/201 (0.5%)	1/203 (0.49%)	RR 1.01 (0.06 to 16.04)[a]	0 more per 1000 (from 5 fewer to 74 more)	Low	RCT	No serious risk of bias[9]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[12,13]
Neonatal death											
3 (Bertini et al., 2005; Lain et al., 2009; Langer et al., 2000)	1/274 (0.36%)	1/280 (0.36%)	RR 1.01 (0.06 to 16.04)[a]	0 more per 1000 (from 3 fewer to 54 more)	Very low	RCT	Very serious risk of bias[1,8,9]	No serious inconsistency	No serious indirectness	Very serious[14]	Yes[4,5,10,11,12,13]

NC not calculable, NR not reported, P probability, RCT randomised controlled trial, RR relative risk
a. Calculated by the NCC-WCH technical team from data reported in the article

1. Bertini et al., 2005: Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. One woman from an unknown group did not complete treatment. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors

2. Ogunyemi et al., 2007: At baseline the treatment groups were similar at baseline for maternal age, parity, BMI, history of previous gestational diabetes and previous neonatal macrosomia. Results of blood glucose tests were significantly higher in the insulin group compared to the glibenclamide group and the gestational age at the time of recruitment was on average 4 weeks earlier. It is unclear whether the groups received the same care apart from the intervention. Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions were not reported. For some outcomes, there were no data available for up to 4 participants in the insulin group and 5 in the glibenclamide group. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

3. Confidence interval for the relative risk crosses RR=0.75

4. Bertini et al., 2005: All women had three days of diet and physical activity and then their fasting and postprandial glucose levels were measured. No details of diet or exercise are given. Blood glucose was reviewed in clinic weekly. Women were tested in the fasting state and 2 hours after breakfast. If either test was abnormal, testing was performed after lunch and dinner to establish glucose profile and adjust doses as necessary. Glibenclamide group: An initial dose of 5mg in the morning was increased every week as necessary to a maximum dose of 20mg/day. Insulin group: Women were admitted to hospital for 24 hrs to learn how to use insulin and to receive guidance. Insulin was started at a dosage of 0.7 units of insulin/kg actual body weight, increasing by 0.1 IU/kg in each trimester. Rapid action and slow acting insulins were used in equal doses before main meals and at bedtime respectively. Treatment failure was defined taking the maximum dose without achieving glucose control. Oral medication was stopped in treatment failure and insulin therapy started.

5. Bertini et al., 2005: Ethnicity: no details are provided

6. Ogunyemi et al., 2007: No diet or monitoring details are presented. No details of dose for glibenclamide or insulin are presented

7. Ogunyemi et al., 2007: Ethnicity: 80% of participants were Hispanic and 15% were African American.

8. Lain et al., 2009: It is unclear whether an appropriate randomisation method or adequate allocation concealment was used. Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Depending on outcome, up to 13 participants were lost from the insulin group and up to 8 in the glibenclamide group. Precise outcome definition is available for two outcomes - large for gestational age and treatment failure. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

9. Langer et al., 2000: Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently. Precise outcome definitions are available for three outcomes - treatment failure, large for gestational age and neonatal hypoglycaemia. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

10. Lain et al., 2009: No details of diet, exercise or monitoring techniques are presented. Glibenclamide group: doses started at 2.5mg/day and were increased by 2.5-5mg weekly. Doses were taken once or twice daily. If a maximum dose of 20mg/day glibenclamide did not achieve goals, then women were transitioned to insulin. Insulin group: Insulin doses started at 0.8U/kg administered in multiple daily injections and were increased up to twice weekly as necessary. Women receiving glibenclamide were transitioned to insulin if the maximum dose of 20mg/day did not achieve targets.

11. Lain et al., 2009: Ethnicity: no details are provided

12. Langer et al., 2000: All women received dietary instruction for 3 meals and 4 snacks daily. Adherence was evaluated and reinforced at weekly clinic visits. The diet was designed to provide 30kcal/kg body weight for women of normal weight. Women who were obese (BMI>30) received a diet designed to deliver 25kcal/kg body weight. The calories were split by source with 40% from carbohydrates. All women were trained to use a portable glucose meter at home and tested their blood glucose x7/day: in the morning (fasting value), before and 2 hours after lunch and dinner, at bedtime. Targets were fasting 60-90mg/dl; preprandial 80-95 mg/dl; 2 hour postprandial <120mg/dl. Blood glucose was measured for comparison at weekly clinic. Glibenclamide group: An initial dose of 2.5mg in the morning was increased in the first week by 2.5mg and by 5mg weekly thereafter if necessary to a maximum dose of 20mg/day. Blood glucose was reviewed in clinic weekly. Insulin group: Insulin was started at a dosage of 0.7 units of insulin/kg actual body weight given subcutaneously, injected three times daily and increased as necessary to maintain targets. Treatment failure was defined taking the maximum dose without achieving glucose targets over a two week period. Oral medication was stopped in treatment failure and insulin therapy started.

13. Langer et al., 2000: Ethnicity: no details are provided

14. Confidence interval for the relative risk crosses RR=0.75 and RR=1.25

15. Mukhopadhyay et al., 2012: Participants and care givers were not kept 'blind' to allocation as this was not possible as the treatments were administered differently.

16. Mukhopadhyay et al., 2012: The initial dose of glibenclamide was 2.5mg/day orally in the morning. Doses were increased when necessary by 2.5mg per week up to a maximum of 20mg/week. Doses > 7.5mg were given as divided doses. If glycaemic control was not maintained for two weeks on the maximal dose then treatment was switched to insulin. Insulin treatment was initiated at 0.7units/kg/day, subcutaneously three times daily and increased weekly as necessary.

17. *Mukhopadhyay et al., 2012: Ethnicity: no details are provided*
18. *Confidence interval for the relative risk crosses RR=1.25*
19. *The intrauterine death was associated with trisomy 21*

Table 44: GRADE profile for comparison of metformin and glibenclamide in women with gestational diabetes

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Glibencla mide	Metformin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecisi on	Other considerati ons
Mode of birth											
Non-elective Caesarean delivery											
1(Moore et al., 2010)	2/74 (2.7%)	11/75 (14.7%)	RR 0.18 (0.04 to 0.8)[a]	120 fewer per 1000 (from 29 fewer to 141 fewer)	Moderate	RCT	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[2]	Yes[3,4]
Need for additional insulin											
1(Moore et al., 2010)	12/74 (16.2%)	26/75 (34.7%)	RR 0.47 (0.26 to 0.86)[a]	184 fewer per 1000 (from 49 fewer to 257 fewer)	Moderate	RCT	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[2]	Yes[3,4]
1(Silva et al., 2012)	28/96 (29.2%)	22/104 (21.2%)	RR 1.38 (0.85 to 2.24)[a]	80 more per 1000 (from 32 fewer to 262 more)	Moderate	RCT	No serious risk of bias[6]	No serious inconsistency	No serious indirectness	Serious[7]	Yes[8,9]
Maternal hypoglycaemia											
1(Moore et al., 2010)	1/74 (1.4%)	2/75 (2.7%)	RR 0.51 (0.05 to 5.47)[a]	13 fewer per 1000 (from 25 fewer to 119 more)	Low	RCT	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[3,4]
Neonatal hypoglycaemia											
1(Moore et al., 2010)	0/74 (0%)	1/75 (1.3%)	RR 0.34 (0.01 to 8.16)[a]	9 fewer per 1000 (from 13 fewer to 95 more)	Low	RCT	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[3,4]
1(Silva et al., 2012)	13/96 (13.5%)	11/104 (10.6%)	RR 1.28 (0.6 to 2.72)[a]	30 more per 1000 (from 42 fewer to 182 more)	Low	RCT	No serious risk of bias[6]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[8,9]
Shoulder dystocia											
1(Moore et al., 2010)	1/74 (1.4%)	0/75 (0%)	RR 3.04 (0.13 to 73.44)[a]	NC	Very low	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[3,4]
Admission to NICU											
2 (Moore et al., 2010; Silva et al., 2012)	8/167 (4.8%)	13/179 (7.3%)	RR 0.66 (0.28 to 1.55)[a]	25 fewer per 1000 (from 52 fewer to 40 more)	Very low	RCT	Serious[1,6]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[3,4,8,9]

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Glibenclamide	Metformin	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Large for gestational age											
1(Silva et al., 2012)	19/96 (19.8%)	9/104 (8.7%)	RR 2.29 (1.09 to 4.81)[a]	112 more per 1000 (from 8 more to 330 more)	Low	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	Yes[8,9]
Death											
1(Silva et al., 2012)	1/96 (1%)	1/104 (0.96%)	RR 1.08 (0.07 to 17.08)[a]	1 more per 1000 (from 9 fewer to 155 more)	Very low	RCT	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[10]	Yes[8,9]

NC not calculable, NICU neonatal intensive care unit, NR not reported, RCT randomised controlled trial, P probability, RR relative risk

* Calculated by the NCC-WCH technical team from data reported in the article

1. Moore et al., 2010: Participants and care givers were not kept 'blind' to allocation. Precise outcome definitions were not used for all outcomes (shoulder dystocia and NICU admission). 6 women in the glibenclamide group and 8 women in the metformin group did not complete treatment. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

2. Confidence interval for the relative risk crosses RR=0.75

3. Moore et al., 2010: All women were given instructions for a diet designed to provide 30kcals/kg at normal body weight and 25kcals/kg at obese body weight with 40% calories from carbohydrates, 20% from protein and 30-40% from fats.10% of calories were consumed at breakfast, 20-30% at lunch and dinner and 30% as snacks. The importance of exercise in controlling blood glucose was stressed and 30 minutes of walking per day was recommended to all women. All women were taught how to use memory based glucometers. Women performed testing in the fasting state and 2 hours post prandially. Glibenclamide group: An initial dose of glibenclamide 2.5mg twice per day was increased as necessary to a maximum dose of 20mg/day (10mg twice/day). Blood glucose was reviewed weekly. Metformin group: An initial dose of 500mg/day taken in divided doses was increased as necessary to a maximum dose of 2grams/day. Blood glucose was reviewed weekly.Treatment failures were defined as women taking the maximum dose with two or more glucose values in the same meal exceeding target glucose values by 10mg/dl or more for 2 consecutive weeks. Oral medication was stopped in treatment failures and insulin therapy started.

4. Moore et al., 2010 : Glibenclamide group : Hispanic 66, Native American 3,White 5 and African American 0. Metformin group : Hispanic 66, Native American 2, White 6 and African American 1

5. Confidence interval for the relative risk crosses RR=0.75

6. Silva et al., 2012: Participants and care givers were not kept 'blind' to allocation. Women in the glibenclamide group on average were heavier and had had fewer babies previously. Precise outcome definitions were not used for all outcomes (NICU admission or death). 6 women in the glibenclamide group and 8 women in the metformin group did not complete treatment. It is unclear whether the investigators were kept 'blind' to allocation and to other important confounding and prognostic factors.

7. Confidence interval for the relative risk crosses RR=1.25

8. Silva et al., 2012: All women were given instructions for a diet designed to provide 35kcals/kg at normal body weight and 25kcals/kg at obese body weight, with 35-45% calories from carbohydrates and consisting of 3 full meals and four light meals. No details are given regarding any exercise regimen women were to follow. All women performed home glucose self-monitoring of fasting and postprandial capillary glucose testing to adjust dosage of medication. Glibenclamide group: An initial dose of 2.5mg before breakfast and dinner was increased as necessary by 2.5 - 5mg weekly until glucose control was acheived or until a maximum dose of 20mg/day was reached. Metformin group: An initial dose of 500mg before breakfast and dinner was increased as necessary by 500-1000 mg weekly until glucose control was acheived or until a maximum dose a maximum dose of 2500 mg/day was reached. Insulin therapy was started at 0.7 IU/kg/day regular insulin preprandial and neutral protamine hagedorn (NHP) insulin at bedtime when glycaemic goals were not met.

9. Silva et al., 2012: Ethnicity data was not provided

10. Confidence interval for the relative risk crosses RR=0.75 and RR=1.25

4.5.6 Evidence statements

4.5.6.1 Diet

4.5.6.1.1 *Dietary strategy/advice versus standard care or no dietary strategy/advice*

Maternal outcomes

Two trials (n=1000; n=931) found increased risk of treatment failure (RR 6.12, 95% CI 3.72 to 10.08 and RR 17.68, 95% CI 4.29 to 72.93) in women who received dietary strategy/advice compared with women who did not receive dietary strategy/advice. The quality of the evidence for this outcome was high and moderate. One further trial (n=149 in intervention arm) reported treatment failure in women who received dietary strategy/advice but did not report this outcome in controls, so comparative analyses were not possible. The quality of the evidence for this outcome was moderate.

No difference was found between groups that received diet strategy and advice compared with those who did not receive dietary advice for mode of delivery. Three trials (n=2343) reporting rates of caesarean deliveries were combined in a meta-analysis which found no difference in the risk of caesarean in those participants who received dietary advice compared with those who didn't receive dietary advice (RR 0.89, 95% CI 0.77 to 1.02); the evidence was of very low quality. The fourth trial (n=300) also found no difference in the risk of caesarean associated with dietary advice (RR 1.05, 95% CI 0.73 to 1.50) and the evidence was of very low quality. One trial (n=83) reported no difference in risk of spontaneous vaginal delivery (RR 1.01, 95% CI 0.72 to 1.41) and the evidence was of low quality. One trial (n= 299) reported no difference in the risk of vaginal delivery (RR 0.98, 95% CI 0.87 to 1.10) and the evidence was of low quality. Three trials combined in a meta-analysis (n=2044) reported no difference in the risk of induction of labour (RR 1.20, 95% CI 0.87 to 1.65); the evidence was of very low quality.

Neonatal outcomes

A meta-analysis of data from 4 trials (n=2170) found a reduced risk of large for gestational age births (RR 0.49, 95% CI 0.34 to 0.71) and the evidence was of very low quality. An additional study (n=300) also found a reduced risk of large for gestational age (RR 0.43, 95% CI 0.20 to 0.9) and the evidence was of very low quality.

In terms of shoulder dystocia, 3 trials (n=2044) which were meta-analysed, found reduced risk of shoulder dystocia in babies of women with impaired glucose tolerance or abnormal glucose tolerance who received dietary strategy/advice compared with babies of women who received no dietary strategy/advice (RR 0.42, 95% CI 0.23 to 0.77). The evidence was of very low quality.

A reduced risk of serious perinatal complications (stillbirth, neonatal death, shoulder dystocia, bone fracture and nerve palsy) was found in 1 trial (n=1030) including babies of women with impaired glucose tolerance who received dietary strategy/advice compared with babies of women who received no dietary strategy/advice (RR 0.32, 95% CI 0.14 to 0.73). The evidence was of moderate quality.

One trial (n=1030) found an increased risk of admission to neonatal care in babies of women with impaired glucose tolerance who received dietary strategy/advice compared with babies of women who received no dietary strategy/advice (RR 1.15, 95% CI 1.05 to 1.26). The evidence was of low quality. Another trial (n=300) found no difference in admission rate (RR 0.57, 95% CI 0.23 to 2.19) and the evidence was of very low quality.

One trial (n=11) found no difference in NICU stay for greater than 24 hours between babies of women with impaired glucose tolerance who received dietary strategy/advice and babies of women who received no dietary strategy/advice (RR 0.57, 95% CI 0.17 to 1.87) and the evidence was of very low quality.

One trial (n=900) found no difference in risk of composite neonatal outcomes which included: neonatal hypoglycaemia, neonatal hyperbilirubinaemia, elevated cord-blood C-peptide level, stillbirth or neonatal death and birth trauma, between babies of women with impaired glucose tolerance who received dietary strategy/advice and babies of women who received no dietary strategy/advice (RR 0.87, 95% CI 0.72 to 1.07). The evidence was of very low quality.

One study (n=826) found no difference in hyperinsulinaemia between babies of women with impaired glucose tolerance who received dietary strategy/advice and babies of women who received no dietary strategy/advice (RR 0.78, 95% CI 0.57 to 1.05). The evidence for this outcome was of low quality.

In terms of hypoglycaemia (undefined by specific glucose level), 2 trials (n=299; n=1030) showed found no difference between babies of women with impaired glucose tolerance who received dietary strategy/advice and babies of women who received no dietary strategy/advice (RR 1.63, 95% CI 0.85 to 3.11 and RR 1.34, 95% CI 0.82 to 2.18 respectively). No difference between groups in a trial (n=300) was found for hypoglycaemia defined as below 1.7 mmol/litre blood glucose (RR 0.83, 95% CI 0.26 to 2.66) and the evidence was considered to be of very low quality. No difference was found between groups in 1 trial (n=126) for hypoglycaemia defined as below 1.9 mmol/litre blood glucose (RR 0.13, 95% CI 0.02 to 1.01); the evidence was of very low quality.

One trial (n=299) found no difference in the rates of perinatal mortality associated with women who received dietary strategy/advice compared with women who did not receive dietary strategy/advice (RR 0.09, 95% CI 0.005 to 1.62) and this evidence was of low quality. Two further trials (n=958; n=1030) reported perinatal mortality as an outcome; however, there were no events observed in either treatment group. The quality of the evidence for these outcomes were moderate and low.

4.5.6.1.2 *Insulin plus dietary strategy/advice versus dietary strategy/advice alone*

Maternal outcomes

Two trials (n=38; n=95) found no difference in caesarean rates between those assigned to the diet and insulin group compared with those who received dietary advice alone (RR 0.51, 95% CI 0.07 to 3.71 and RR 0.97, 95% CI 0.54 to 1.76). The quality of the evidence for this outcome was very low and low, respectively.

One trial (n=95) found no difference in the rate of treatment failure (in women who required insulin treatment or additional insulin) between treatment groups (RR 0.63, 95% CI 0.04 to 9.90) and the quality of the evidence for this outcome was low. One further trial (n=105) reported treatment failure in women who received dietary strategy/advice plus insulin but did not report the event rate for this outcome in the control group. The quality of the evidence was low.

Neonatal outcomes

One trial (n=202) found no difference in rates of large for gestational age births between treatment groups (RR 0.85, 95% CI 0.41 to 1.78). The quality of the evidence for this outcome was low.

One trial (n =68) found no difference in the risk of neonatal hypoglycaemia (defined as plasma glucose less than 30 mg/dl) in babies of women who received insulin plus dietary strategy/advice compared with babies of women who received dietary strategy/advice alone

(RR 0.40, 95% CI 0.08 to 1.92) and this evidence was of very low quality. Additionally, 1 trial (n=202) found no difference between groups in the risk of neonatal hypoglycaemia (plasma glucose level not defined) (RR 1.67, 95% CI 0.88 to 3.17) and the evidence was of very low quality.

Two trials (n=38; n=68) reported the rate of shoulder dystocia; however, no events were observed in either treatment group. The quality of evidence for these outcomes was very low and moderate. These 2 trials also assessed the rate of perinatal mortality, but no events were observed in either treatment group.

4.5.6.1.3 Comparison of 2 diets

Maternal outcomes

One trial (n=63) found a reduced risk of treatment failure in women who were advised to consume low glycaemic index carbohydrates compared with women who were advised to consume a high-fibre, low-sugar diet comprising high-to-moderate glycaemic index foods (RR 0.49, 95% CI 0.26 to 0.91). The quality of the evidence for this outcome was very low.

Four trials (n=397) found no difference in the risk of treatment failure. One trial (n=117) was in women who were advised to consume a moderately energy-restricted diet of 1590 to 1776 kcal per day compared with an unrestricted diabetic diet of 2010 to 2220 kcal per day (RR 1.05, 95% CI 0.47 to 2.34). The second trial (n=92) compared women with a low glycaemic index diet with women with a conventional healthy diet (RR 0.83, 95% CI 0.59 to 1.17). The third trial (n=150) compared women taking a low carbohydrate diet with women consuming a normal carbohydrate diet (RR 1.00, 95% CI 0.75 to 1.34). The fourth trial (n=38) was in women with low GI starch diet compared with women with high GI starch content (RR 1.20, 95% CI 0.75 to 1.93). The quality of the evidence for these outcomes was of low quality.

No difference was observed for the rates of different modes of delivery. Modes of delivery included caesarean, which included a total of 5 trials. Evidence from 2 trials (n=30; n=45) was very low quality (RR 1.40, 95% CI 0.57 to 3.43 and RR 1.37, 95% CI 0.52 to 3.58 respectively), from a further 2 trials (n=121; n=149) was of low quality (RR 1.18, 95% CI 0.74 to 1.89 and RR 1.27, 95% CI 0.78 to 2.08 respectively) and from the fifth trial (n=52) was very low quality (RR 1.18, 95% CI 0.74 to 1.89).

One trial (n=88) produced very low quality evidence finding no difference in emergency caesarean (RR 1.80, 95% CI 0.64 to 1.85). One trial (n=30) with very low quality evidence found no difference in vaginal delivery (RR 0.77, 95% CI 0.39 to 1.52). Another trial (n=121) gave low quality evidence finding no difference in spontaneous vaginal delivery (RR 0.89, 95% CI; 0.63 to 1.27) and 1 trial (n=114) produced low quality evidence showing no difference in induction to labour (RR 1.02, 955 CI 0.18 to 5.76).

Neonatal outcomes

One trial (n=300) found a reduced risk of large for gestational age births in babies of women with abnormal glucose tolerance gestational diabetes who received dietary advice to consume 24 to 30 kcal/kg/day compared with babies of women who received no special care, diet or pharmacological intervention (RR 0.43, 95% CI 0.20 to 0.91). The quality of the evidence for this outcome was very low.

Four trials (n=6, n=8, n=9, n=5) found no difference in the risk of large for gestational age births in babies of women. This included 2 trials (n=6; n= 9), both of very low quality evidence, in women who received a low carbohydrate diet compared with women with a normal carbohydrate diet (RR 1.03, 95% CI 0.22 to 4.72 and RR 0.51, 95% CI 0.13 to 1.96 respectively) and 2 trials (n=8; n=5), both of very low quality evidence, in women who received a low glycaemic index diet compared with a normal glycaemic diet (RR 2.87, 95% CI 0.97 to 8.46 and RR 0.74, 95% CI 0.13 to 4.18 respectively).

One trial (n=45) found no difference in the risk of shoulder dystocia in babies of women who were instructed in a calorie-restricted diet compared with babies of women who were not calorie-restricted (RR 0.97, 95% CI 0.04 to 22.25). The quality of the evidence for this outcome was very low. Another trial (n=117) reported shoulder dystocia, yet no events occurred during the study. The quality of the evidence for this outcome was moderate.

In terms of hypoglycaemia, 2 trials found no difference in rates of neonatal hypoglycaemia in babies of women with abnormal glucose tolerance or gestational diabetes. Of these, 1 trial (n=45), classified hypoglycaemia as less than 1.7 mmol/litre blood glucose (RR 0.58, 95% CI 0.03 to 11.25) and the evidence was considered very low quality. Another trial (n=149) classified hypoglycaemia as less than 2.2 mmol/litre blood glucose, (RR 0.91, 95% CI 0.39 to 2.11) and was of very low quality.

4.5.6.2 Exercise

4.5.6.2.1 Exercise versus no exercise

Maternal outcomes

One trial (n=64) found a reduction in the risk of needing additional treatment comprising insulin therapy in women who exercised compared with women who did not exercise (RR 0.38, 95% CI 0.18 to 0.78). The quality of the evidence for this outcome was very low. One further trial (n=29) did not find a difference in the requirement for insulin between groups (RR 1.86, 95% CI 0.40 to 8.62). The quality of the evidence for this outcome was very low.

One trial (n=29) found no difference in rates of caesarean delivery in babies of women who exercised compared with babies of women who did not exercise (RR 0.93, 95% CI 0.22 to 3.87). The quality of the evidence for this outcome was very low.

Neonatal outcomes

One trial (n=29) found no difference in rates of macrosomia in babies of women who exercised compared with babies of women who did not exercise (RR 0.93, 95% CI 0.22 to 3.87). The quality of the evidence for this outcome was very low.

One trial (n=29) reported neonatal hypoglycaemia as an outcome, but no events were observed in either treatment group. The quality of the evidence for this outcome was low.

4.5.6.2.2 Diet and exercise versus diet alone

Maternal outcomes

One trial (n=32) found no difference in the need for additional treatment comprising insulin therapy in women who received dietary advice and exercise compared with women who received dietary advice alone (RR 0.78, 95% CI 0.39 to 1.58). The quality of the evidence for this outcome was very low.

Neonatal outcomes

No studies reported neonatal outcomes for this comparison.

4.5.6.3 Pharmacological interventions

4.5.6.3.1 *Metformin versus insulin*

Maternal outcomes

Seven outcomes pertaining to mode of birth were reported in 7 RCTs that compared metformin with insulin treatment in women with gestational diabetes. Heterogeneity prevented full meta-analysis of data for spontaneous vaginal birth (2 trials), induction of labour (4 trials) and elective caesarean section (2 trials) and only 1 trial presented data on vacuum extraction, emergency caesarean section and assisted vaginal delivery.

Data were conflicting in 2 trials that reported spontaneous vaginal birth. One small trial (n=30) found fewer spontaneous vaginal births among women who received metformin compared to those who received insulin (RR 0.4, 95% CI 0.18 to 0.86) and the evidence was of low quality, while another trial (n=97) provided low quality evidence which found no difference (RR 0.98, 95% CI 0.67 to 1.45). A meta-analysis of data from 3 trials (n=343) found that the risk of requiring induction of labour among women who received metformin compared with insulin treatment was lower (RR 0.67, 95% CI 0.54 to 0.83) and the evidence was of low quality. One further trial (n=733) found no difference in labour induction rates between treatment groups (RR 0.96, 95% CI 0.84 to 1.09) and the evidence was considered of moderate quality.

One trial (n=97) provided low quality evidence of no difference between treatment groups in the number of births requiring vacuum extraction (RR 1.86, 95% CI 0.58 to 5.95). A meta-analysis of data from 7 trials (n=1391) found no difference in the risk of caesarean section among women who received metformin compared with those receiving insulin (RR 1.00, 95% CI 0.87 to 1.15) and the evidence was of moderate quality. Two trials (n=30; n =733) reported no difference in rates of elective caesarean section (RR 3.5, 95% CI 0.89 to 13.82 and RR 0.89, 95% CI 0.64 to 1.24, respectively) and the evidence was of low quality. One trial (n=41) provided low quality evidence which demonstrated no difference in the risk of emergency caesarean section between groups (RR 1.6, 95% CI 0.9 to 2.7). One further trial (n=216) found no difference in the risk of assisted vaginal delivery (RR 1.10, 95% CI 0.44 to 2.74) and the evidence was of very low quality. In terms of need for additional insulin, 36% of women who received metformin in 5 trials (206 out of 568 participants) had a treatment failure requiring insulin. The evidence for this finding was of moderate quality.

One trial (n=664) assessed the acceptability of metformin compared with insulin. More women forgot to take metformin compared with insulin (p<0.001) during the course of the study. However, more women would choose metformin over insulin in a subsequent pregnancy (p<0.001). If given the choice in a subsequent pregnancy, more women would start with metformin and add insulin if needed (p<0.001). In terms of assessing the easiest part of the diabetes treatment, more women in the insulin group said that doing the finger-prick test was easiest. Less women in the metformin group (n=63 versus n=95) said that being careful with diet was the easiest aspect. More women in the metformin group (n=197 versus n=117) said that taking the medication was the easiest.

Neonatal outcomes

A meta-analysis of 5 trials (n=736) found a reduction in the risk of admission to NICU in babies of women with gestational diabetes who received metformin compared with babies of women who received insulin (RR 0.69, 95% CI 0.52 to 0.92). The quality of the evidence for this outcome was very low. An additional trial (n=733) found no difference between groups for a NICU stay of more than 24 hours for babies of women with gestational diabetes who received metformin compared with babies of women who received insulin (RR 1.04, 95% CI 0.71 to 1.53).

There were no differences in any other neonatal outcomes when metformin was compared with insulin treatment. Outcomes examined included large for gestational age, which included a meta-analysis of data from 5 trials (n=1406) that found no difference between treatment groups (RR 0.85, 95% CI 0.68 to 1.05) and was of very low quality. One trial (n=92) assessed macrosomia as a proxy for large for gestational age and the very low quality evidence found no difference between groups (RR 0.14, 95% CI 0.007 to 2.64). One trial (n=733) assessed a composite neonatal morbidity outcome (RR 0.99, 95% CI 0.8 to 1.23) and found moderate quality evidence of no difference between groups. Data from 4 trials (n=1156) were combined in a meta-analysis for shoulder dystocia (RR 0.76, 95% CI 0.36 to 1.59) which found low quality evidence of no difference between groups. Six trials (n=828) combined in a meta-analysis examined neonatal hypoglycaemia and found very low quality evidence of no difference between groups (RR 0.71, 95% CI 0.48 to 1.04). One trial (n=733) found no difference between groups using supplemental feeding (RR 0.91, 95% CI 0.75 to 1.09); evidence was moderate quality. Two trials (n=7636) that meta-analysed data for intravenous dextrose found low quality evidence of no difference between groups (RR 1.27, 95% CI 0.75 to 2.15) while 1 trial (n=733) reported no difference between groups for fetal death (RR 0.34, 95% CI 0.01 to 8.31); evidence was very low quality. There were no cases of perinatal mortality in 1 trial (n=97) which was considered of very low methodological quality.

4.5.6.3.2 *Glibenclamide versus insulin*

Maternal outcomes

A meta-analysis of 2 trials (n=139) found no difference in risk of caesarean section for women with gestational diabetes who received glibenclamide compared with those who received insulin (RR 0.87, 95% CI 0.61 to 1.23). The evidence for this outcome was of very low quality.

In 4 trials, 5.9% (19 out of 322) of women who received glibenclamide experienced a treatment failure that required insulin. The evidence for this finding was of low quality.

One trial (n=33) reported no difference in the number of women with gestational diabetes experiencing hypoglycaemia when treated with glibenclamide compared with insulin treatment (RR 1.23, 95% CI 0.7 to 2.14). The quality of evidence for this finding was very low.

Neonatal outcomes

A meta-analysis of 3 trials (n=190) found that women with gestational diabetes who had been treated glibenclamide had a greater risk of giving birth to babies that were large for gestational age compared with women who had received treatment with insulin (RR 3.62, 95% CI 1.54 to 8.49). The evidence for this outcome was of low quality. A fourth trial (n=404) found no difference between groups in the risk of giving birth to babies that were large for gestational age (RR 0.93, 95% CI 0.55 to 1.57). The evidence for this outcome was of low quality.

A meta-analysis of 5 trials (n=702) found higher risk of neonatal hypoglycaemia in the babies of women who received glibenclamide compared with those who received insulin (RR 2.13, 95% CI 1.32 to 3.43). The evidence for this outcome was of low quality.

There were no differences in any other reported neonatal outcomes when glibenclamide was compared with insulin treatment in women with gestational diabetes. Data from 3 trials (n=554) were combined in a meta-analysis (RR 1.22, 95% CI 0.63 to 2.37) and provided low quality evidence for NICU admission; 1 trial (n=99) provided very low quality evidence for the outcome of outcome of shoulder dystocia (RR 0.51, 95% CI 0.05 - 5.45) and 1 trial (n=404) for intravenous glucose therapy (RR 1.29, 95% CI 0.76 to 2.17) which was of moderate quality. One trial (n=90) reported very low quality evidence finding no difference in the risk of

intrauterine death between groups (RR 3.73, 95% CI 0.16 to 89.21). One trial (n=404) reported on risk of stillbirth (RR 1.01, 95% CI 0.06 to 16.04) which was of low quality evidence. Three trials reporting data for neonatal death (n=554) were combined in a meta-analysis (RR 1.01, 95% CI 0.06 to 16.04) giving very low quality evidence.

4.5.6.3.3 *Glibenclamide versus metformin*

Maternal outcomes

One trial (n=149) reported a lower risk of non-elective caesarean section in women with gestational diabetes who received glibenclamide compared with those who received metformin (RR 0.18, 95% CI 0.04 to 0.8). The evidence for this outcome was of moderate quality.

Two trials presented conflicting findings with regard to treatment failure. One trial (n=149) found lower risk of treatment failure requiring insulin in women who received glibenclamide compared with those who received metformin (n=0.47, 95% CI 0.26 to 0.86), while the other trial (n=200) found no difference between treatment groups (RR 1.38, 95% CI 0.85 to 2.24). The evidence for both of these outcomes were of moderate quality.

One trial (n=149) reported no difference in the risk of maternal hypoglycaemia between women with gestational diabetes who received treatement with glibenclamide compared with those who received metformin (RR 0.51, 95% CI 0.05 to 5.47). The evidence for this outcome was of low quality.

Neonatal outcomes

One trial (n=200) provided low quality evidence that demonstrated an increased risk of delivering a baby that was large for gestational age associated with glibenclamide compared with metformin (RR 2.29, 95% CI 1.09 to 4.81). There were no differences between groups for any other neonatal outcomes when treatment with glibenclamide was compared with treatment with metformin in women with gestational diabetes. Outcomes reported were neonatal hypoglycaemia, which included 1 trial (n=149) which was of low quality (RR 0.34, 95% CI 0.01 to 8.16) and another trial (n =200) which was also of low quality (RR 1.28, 95% CI 0.6 to 2.72). One trial (n=149) provided very low quality evidence for shoulder dystocia (RR 3.04, 95% CI 0.13 to 73.44). Data from 2 trials (n=346) assessing NICU admission was combined in a meta-analysis and assessed as being of very low quality (RR 0.66, 95% CI; 0.28 to 1.55). One trial (n=200) reported very low quality evidence which found no difference between groups for the risk of neonatal death (RR 1.08, 95% CI 0.07 to 17.08).

4.5.7 Health economics profile

A review identified 9 studies which considered the cost effectiveness of interventions for gestational diabetes. Different studies evaluated a different decision problem, such as no treatment for gestational diabetes versus treatment or prevention programmes. None of the studies compared the incremental cost effectiveness of different treatment strategies for gestational diabetes in a way which could be used by the guideline development group to make recommendations for UK practice. These studies are discussed in more detail in Section 9.1.2.

Treatment alternatives for women diagnosed with gestational diabetes and who did not achieve ideal blood glucose control with a trial of diet and exercise was identified as a priority for health economic analysis. However, a formal economic analysis was not undertaken as the group considered there were more important priorities and a model was thought unlikely to influence recommendations.

The cost effectiveness of metformin, insulin and glibenclamide was assessed in the previous guideline as part of a model that considered screening, diagnosis and treatment. Although that analysis suggested that metformin would be likely to be the most cost effective, that guideline did not recommend one type of hypoglycaemic therapy over another because its

guideline development group thought that the evidence on relative effectiveness would be established by the MiG trial (Rowan et al., 2008) which had not published at that time. Metformin was considerably cheaper than the alternatives, but choice of treatment had little impact on the cost effectiveness of screening as hypoglycaemic therapy represented a relatively small component of the overall treatment and management cost.

The MiG trial was published shortly after the original guideline was published and insulin treatment failed to demonstrate any benefit over treatment with metformin. Furthermore, metformin was shown to be far more acceptable to women. Metformin is also cheaper, with a daily drug cost of £0.12 based on 1.5 g daily[gg] compared with a daily drug and needle cost of £1.02 a day for insulin (see Chapter 9). However, the cost saving is not quite as great as might be suggested by these figures because the MiG trial (Rowan et al., 2008) also showed that a significant proportion of the women on metformin would subsequently require supplemental insulin.

It should be noted that in the economic modelling undertaken for this guideline, the guideline development group suggested that a diagnosis of gestational diabetes results in greater management and monitoring resource use than was assumed in the modelling in the 2008 guideline. Therefore, hypoglycaemic therapy represents an even smaller proportion of treatment costs.

Since publication of the previous guideline, current practice has changed and metformin is the normal first line hypoglycaemic therapy. This change seems to be consistent with the clinical evidence and for the reasons outlined above is also likely to be cost effective. Intervention studies also suggest that this change reflects the preferences of most pregnant women.

4.5.8 Evidence to recommendations

4.5.8.1 Relative value placed on the outcomes considered

Shoulder dystocia was the primary outcome of interest to the guideline development group. This was motivated by the rare but often permanent complication of neurological injury to the brachial plexus and associated cerebral palsy from the asphyxial injury resulting from the delay in delivery. Shoulder dystocia was also recognised to be an outcome useful to health economic analysis as an associated QALY could be derived. Large for gestational age and NICU admission for more than 24 hours were of secondary importance, although the group acknowledged their overlap with shoulder dystocia.

However, it was noted that there were limitations in prioritising shoulder dystocia. For example, the diagnosis of shoulder dystocia is somewhat subjective and is greatly influenced by the experience and confidence of the midwife or obstetrician. What one healthcare professional may define as shoulder dystocia another may not, though this is more likely to be in association with the milder form of the complication. There is a relationship between the antenatal diagnosis of a fetus as large for gestational age and a higher incidence of shoulder dystocia (see below). It is speculative whether some of this relationship is self-fulfilling, with clinicians expecting the large fetus to develop shoulder dystocia.

It was acknowledged that shoulder dystocia is strongly related to birth weight (see CEMACH 2002/03). Furthermore, birth weight was a stronger risk factor for shoulder dystocia in women with pre-existing diabetes than in the background non-diabetic antenatal population.

Large for gestational age was considered to be the most robust and frequently reported outcome for gestational diabetes.

The pattern of fetal growth seen in women with gestational diabetes is similar to women with pre-existing diabetes (Lim et al., 2009). There is increasing evidence that this pattern of

[gg] http://www.ppa.org.uk/edt/July_2014/mindex.htm

abnormal fetal growth is associated with an adverse metabolic profile in later life, with an increased risk of childhood obesity and early onset type 2 diabetes

The guideline development group also recognised that shoulder dystocia, mode of birth and local protocols would have an impact on the care of the neonate. If shoulder dystocia had occurred during birth, the infant would be more likely to be closely monitored in NICU. This was regarded as an important clinical and economic outcome.

Treatment failure (the need for insulin treatment or escalation of treatment from diet to oral agents to insulin) was thought to be a measure of the effectiveness of treatment. It was of particular relevance in the comparison of metformin with glibenclamide.

Although mode of birth outcomes were not strongly prioritised because of potential bias (for example some units might electively undertake a caesarean section for an estimated fetal weight of 4.5 kg whereas others may set the threshold at 4.0 kg), they were recognised as important in the health economic evaluation.

Neonatal hyperinsulinaemia (and potential for resultant nenoatal hypoglycaemia) reflects intrauterine exposure to maternal hyperglycaemia. Although this is recognised as being very important, the guideline development group considered these data rarely available. Neonatal hypoglycaemia was considered a relatively poor surrogate and likely to be greatly affected by local protocols. For example, some units routinely give infants of diabetic women early extra feeds with the intention of avoiding neonatal hypoglycaemia while others undertake frequent capillary blood glucose testing in the newborn and treat promptly in those cases where hypoglycaemia occurs.The group recognised the importance of the acceptability and take-up of treatment (including hypoglycaemic episodes where insulin is used) but believed there would be a paucity of data available for all the interventions examined.

4.5.8.2 Consideration of clinical benefits and harms

Shoulder dystocia, particularly where neurological injury results, was considered to be a disastrous event. Ultrasound scanning of the fetus (see Section 5.8) was acknowledged to be an intervention that could decrease the risk of high birth weight (for example by elective delivery at 38 weeks) and shoulder dystocia (for example by an elective caesarean section) in cases where a large fetus was identified.

The impact of an elective caesarean section on the woman and her family in the index and subsequent pregnancies was also considered.

The guideline development group noted that oral hypoglycaemic agents were likely to be more acceptable than insulin in terms of administration. The group noted the potential benefit of glibenclamide in not crossing the placenta, but was aware of specific side-effects (such as weight gain, maternal and neonatal hypoglycaemia) associated with glibenclamide and noted that longer term follow-up studies were available for metformin but not glibenclamide.

4.5.8.3 Consideration of health benefits and resource use

Advice on diet and exercise is part of current practice and is not contingent on the recommendation to offer a trial of diet and exercise as the first line treatment for women with a diagnosis of gestational diabetes. The intervention is low cost and although there may be issues with compliance, diet and exercise leading to tighter blood glucose control would be likely to result in significant benefits for maternal and neonatal outcomes, with some savings from a reduction in adverse outcomes.

Pharmacological treatment represents a relatively small component resulting from a diagnosis of gestational diabetes. Metformin is cheap, is more convenient for women as it only requires them to take a pill rather than administer daily insulin injections, can avoid the need for insulin instruction, reduces the risk of hypoglycaemia and is the first line drug of

choice in type 2 diabetes. However, some of the resource benefits can be obviated if metformin does not sufficiently reduce plasma glucose levels, in which case insulin may be required as a second line pharmacological therapy or be given as a supplement to metformin. The evidence does not suggest that insulin produces greater health benefits than metformin as a first line pharmacological treatment.

4.5.8.4 Quality of evidence

Treatment failure for both diet and exercise was not defined by 2 studies. In all other studies treatment failure definitions were based on failure to achieve euglycaemia. Target values differed across studies, ranging from 4.4–5.5 mmol/litre for fasting values, 7.0–9.0 mmol/litre for 1 hour postprandial and 6.0–7.0 mmol/litres 2 hours postprandial. The most common values were: fasting 5.3 mmol/litre; 1 hour postprandial 7.8 mmol/litre; and 2 hour postprandial 6.7 mmol/litre. In addition, insulin was usually only added if these targets were not achieved within 1 to 2 weeks. The definitions of treatment failure and criteria for starting insulin therapy therefore broadly align with blood glucose targets during pregnancy recommended in this guideline.

4.5.8.5 Diet

There were significant improvements in the top 3 outcomes when diet was compared to no diet.

Three RCTs were in women who had mild gestational diabetes and who were above normal weight. The guideline development group noted that in the Landon (2009) study women had mild gestational diabetes and women with more severe gestational diabetes were excluded as it was unethical to limit their treatment to diet. The group noted that there was a package of care given including diet rather than diet alone.

There was a statistically significant reduction in shoulder dystocia on its own or as a component of the composite perinatal outcome in women following a diet.

The incidence of large for gestational age was also significantly reduced with diet. No information about duration of admission to NICU was provided (the protocol stipulated 24 hours or more). Many more of the women in the intervention arm received insulin which increases the risk of neonatal hypoglycaemia (or is more likely to result in greater vigilance for neonatal hypoglycaemia and hence admission). This is, therefore, a plausible clinical reason for why there were no significant differences in neonatal hyperinsulinaemia and hypoglycaemia.

However, significantly more women required insulin ('treatment failure') in the diet group compared to the standard care group.

There were no significant differences for mode of birth outcomes (although a meta-analysis of 4 RCTs showed a reduction in caesarean section rates, this was not statistically significant) or other neonatal outcomes.

Although more women receiving diet required additional insulin than those receiving no diet, when diet plus insulin was compared to diet alone, there were no significant differences between treatment groups. The guideline development group noted that the studies were inadequately powered and the target ranges were different in different studies.

The group was surprised that the addition of insulin did not have a bigger impact on outcomes but also noted that the type of treatment regimen used in older papers may not be clinically relevant today (Persson et al., 1985; Thompson et al., 1990). The group believed that the fasting thresholds described in one of these older papers were too high to be clinically relevant (Persson et al., 1985) but that the other study used more relevant thresholds (Thompson et al., 1990).

There was some evidence that a low GI diet reduced the need for additional insulin compared to a medium GI diet, but as expected there were no differences between other dietary interventions for this outcome.

The guideline development group noted that across the comparisons for dietary interventions, very few trials had detailed whether women had had a previous caesarean section or whether there were other factors that contributed to the management decision to undertake a caesarean section

4.5.8.6 Exercise

The guideline development group noted that there was no available evidence for 2 comparisons stipulated in the protocol, that 3 studies were very small RCTs that provided limited evidence for the remaining 2 comparisons, that the top 3 outcomes were not reported in the studies and that in 1 comparison only 1 outcome was reported.

One RCT reported a reduced need for insulin in the group who received exercise compared with those who did not.

Despite the poor quality of the evidence, the guideline development group believed that the observation that post prandial exercise improved post prandial blood glucose values was a plausible finding.

The guideline development group reasoned that given that the evidence suggested that exercise in pregnant women with type 1 and type 2 diabetes reduced blood glucose values with the anticipation of improved outcomes, it would also be reduced in gestational diabetes with the same effect. The group also noted that intensive exercise might be too much for some women.

4.5.8.7 Pharmacological

The guideline development group noted in Table 36 that there was a great variation in diagnostic criteria, target values, treatment initiation and interventions in included studies. Overall the group thought that doses used in studies reflected current practice in UK, although metformin is not available in 750 mg tablets.

Treatment failure was not defined by 2 studies. In all other studies treatment failure definitions were based on failure to achieve euglycaemia. Target values differed across studies but ranged from 3.4–5.5 mmol/litre fasting, 7.8 mmol/litre only for 1 hour postprandial and 5.6–7.0 mmol/litre 2 hours postprandial. The most common fasting value was 5.0 mmol/litre and the most common 2 hour postprandial was 6.7 mmol/litre. In addition insulin was usually only added if these targets were not achieved within 1 to 2 weeks. The definitions of treatment failure and criteria for starting insulin therapy therefore broadly align with blood glucose targets during pregnancy recommended in this guideline.

4.5.8.7.1 *Metformin versus insulin*

There were no significant differences in the top 3 outcomes between treatment groups when metformin was compared with insulin. Nor were there any significant differences in other neonatal outcomes (a composite perinatal outcome, hypoglycaemia and mortality outcomes). The guideline development group thought that the rate for 'need for additional insulin' in the metformin group was high (41%). Four papers may have included women with type 2 diabetes, since some received treatment from 11 weeks and this could explain the transfer to insulin rate of 44%.

There were conflicting results for mode of birth outcomes with a contrast of small RCTs identifying significant differences whereas larger single studies reported no difference in treatment effect for rates of spontaneous birth, induction of labour and caesarean section. This heterogeneity in findings could be due, in part, to the smaller studies having some selection bias.

Finally results of a survey in 1 RCT demonstrated that metformin was more acceptable than insulin in terms of choice of future treatment and ease of medication administration.

In the light of this evidence, the guideline development group concluded that metformin was a reasonable therapeutic option to insulin, provided it resulted in good blood glucose control.

4.5.8.7.2 Glibenclamide versus insulin

There were no significant differences in shoulder dystocia rates or admission to NICU (for a stay of not more than 24 hours) when glibenclamide was compared with insulin. There were conflicting results for large for gestational age, with a contrast of small RCTs identifying a significant reduction in this outcome in the insulin group whereas a single larger RCT reported no difference in treatment effect between groups. The guideline development group commented that the lack of detail about associated management was disappointing.

The guideline development group noted that there was a low (5.9%) treatment failure rate in women receiving glibenclamide. The group considered that this finding was driven by the Langer et al. (2000) study which had only a 4% incidence of treatment failure requiring insulin in a large study population. The other studies have a much higher incidence of a need for additional insulin. The population in the Langer et al. (2000) trial is of mainly Hispanic origin and it is possible that these women may respond better to sulfonylurea therapy. The group commented that the findings of the Langer et al. (2000) study have not been reproduced in UK clinical practice.

There were significantly fewer babies with neonatal hypoglycaemia in the group that received insulin. The result of this meta-analysis is being driven by the Bertini and Lain studies. The definition of neonatal hypoglycaemia was not given in 2 trials and was defined as less than 40 mg/dl (2.2 mmol/litre) in the other 2 trials. Data from the HAPO study have indicated that there is not a direct relationship with maternal blood glucose values for this outcome. Furthermore, the timing of evaluation of hypoglycaemia was not been reported in any study. There would be some overlap with NICU admission as babies with severe hypoglycaemia are admitted to NICU and this may be the more relevant outcome. However, there was no significant difference in NICU admission rates for this comparison. Mode of birth and mortality outcomes were not significantly different between the treatment groups.

4.5.8.7.3 Glibenclamide versus metformin

There were no significant differences for any of the 3 top outcomes when glibenclamide was compared with metformin. Non-elective caesarean section rates were significantly higher in the metformin treatment group in 1 RCT; however, the guideline development group considered the reported rates to be atypically low for women with gestational diabetes. There were conflicting results from 2 trials for treatment failure, with 1 RCT finding a reduced need for addtitional insulin in the glibenclamide group but an opposite, though not significant, effect (favouring metformin) in the other RCT.

4.5.8.8 Other considerations

The guideline development group noted that in 5 of the studies in the pharmacological review (Bertini et al., 2005; Ijas et al., 2010; Hague et al., 2003; Langer et al., 2000; Moore et al., 2010) some women were recruited in the first trimester, meaning that some of the women may have had previously undiagnosed type 2 diabetes.

Although oral hypoglycaemic agents have been shown to be a reasonable alternative to insulin in the management of gestational diabetes, the guideline development group felt that there may be levels of hyperglycaemia that would make insulin a preferable starting option. The group considered a fasting glucose of 7 mmol/litre as a reasonable threshold as this was the WHO fasting level for the diagnosis of diabetes (WHO 2008).

The incidence of 'treatment failure' of diet and exercise in the studies varied widely. However, the guideline development group felt that the proportion of women with gestational

diabetes who would need oral hypoglycaemic agents or insulin in practice was much higher than the figure of 'between 10% and 20%' used in the original guideline. The clinical members of the group felt that the majority of women with gestational diabetes would not meet glycaemic targets with lifestyle changes alone and required pharmacological treatment. The group felt that at least 1 week should be allowed to establish whether good glucose control can be achieved with diet and exercise in a woman with newly diagnosed gestational diabetes. They felt that after that time a decision should be made whether to start metformin or insulin. However, they felt that that decision should not be delayed by more than 2 weeks to avoid prolonged hyperglycaemia and the attendant risks.

The guideline development group was of the general view that the initial treatment offered to women with gestational diabetes should be lifestyle change (diet and exercise). However, they recognised that in some women the level of glucose intolerance might be so severe that these measures would be unlikely to achieve glycaemic targets on their own. For these women, the early addition of insulin, with or without metformin, would be needed to achieve timely blood glucose control, and in the absence of any evidence a threshold of a fasting level of 7.0 mmol/litre was chosen, as this is the diagnostic value for type 2 diabetes.

Finally, the guideline development group discussed the issue of speed of referral for specialist advice and treatment once the diagnosis of gestational diabetes has been made. There was unanimous agreement that referral to the specialist diabetes pregnancy service should be prompt and within 1 week.

4.5.9 Key conclusions

The guideline development group had methodological concerns about the studies identified for the reviews.

For an intervention to have an effect there needs to be a reasonable therapeutic window and not all studies had incorporated this into their design. Many of the included studies were small.

Results from studies which examined the effect of exercise should be interpreted with caution as control subjects may have undertaken exercise outside the study if they thought that this may help the outcome of their pregnancy.

In addition compliance is a particular issue in behavioural interventions such as dietary and exercise advice: low compliance in the intervention group would attenuate any observed effect. Some studies monitored compliance using food diaries or by implementing supervised exercise sessions and these studies may have had higher compliance.

The guideline development group agreed that it was a good practical approach for a checklist of information to be given to women who have just been diagnosed with gestational diabetes covering:
- why gestational diabetes occurs
- the likelihood of a normal outcome
- complications and their incidence
- treatment lessens risk of complications.

4.5.9.1 Diet

Overall the guideline development group believed that important outcomes were improved when diet was prescribed (compared with none). The additional routine use of insulin with diet from diagnosis did not appear to further improve outcomes. The group noted that the use of insulin at time of diagnosis would not be routine practice and some women could manage their blood glucose using diet alone.

There was limited evidence of a reduced need for treatment when a low GI diet was offered and the guideline development group believed that modifying the existing recommendations to reflect this would be appropriate.

(See also related NICE clinical guidelines on antenatal care, weight management before during and after pregnancy [for women who are obese and pregnant but do not have diabetes], type 1 diabetes in children, young people and adults [due for publication August 2015], and type 2 diabetes 1 [due for publication August 2015].)

4.5.9.2 Exercise

The guideline development group believed that all women would benefit from exercise and they changed the recommendation for exercise to include all women at diagnosis and not only those with a BMI of more than 27 kg/m^2.

4.5.9.3 Pharmacological

The oral route of drug administration was more acceptable to women than alternatives. There were significant findings for acceptability of metformin over insulin in 1 large study but conflicting results for mode of birth outcomes, no difference for the top 3 outcomes and a 41% treatment failure rate.

However, the guideline development group felt there were longer follow-up studies with metformin and that it is effective in many women.

Glibenclamide is rarely used in the UK because of concerns regarding maternal hypoglycaemia. It might be used as an alternative to insulin in women who decline injections (rather than as an alternative to metformin) or as an option in women who are intolerant of metformin.

4.5.9.4 Overall

The guideline development group believed that diet and exercise should be given to women with a fasting plasma glucose (FPG) at diagnosis of less than 7 mmol/litre.

Women who do not achieve targets should be offered metformin and/or insulin.

Overall, given the comparability of clinical effectiveness of metformin compared with insulin, and its greater acceptability and ease of administration, the guideline development group felt that metformin should be offered first or insulin if metformin were contraindicated or unacceptable.

Glibenclamide should be considered in the 10–15% of women who are intolerant of metformin.

The group believed that, given the result of the MIG trial (Rowan et al., 2008), insulin with or without metformin should be considered in women who have an FPG of more than 7 mmol/litre without recourse to a trial of diet and exercise first.

Definitions of treatment failure and treatment with insulin used in the included studies broadly align with blood glucose targets during pregnancy recommended in this guideline. In particular the targets align with those in the ACHOIS study (Crowther et al., 2005), Landon et al. (2009) and the MIG trial (Rowan et al., 2008).

4.5.10 Recommendations

4.5.10.1 Risk assessment, testing and diagnosis

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.10.1.1   Risk assessment

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.10.1.2   Glycosuria detected by routine antenatal testing
The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.10.1.3   Testing

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.10.1.4   Diagnosis

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.10.2 Interventions

The current recommendations can be found at www.nice.org.uk/guidance/ng3

4.5.11   Research recommendations

14. What is the incidence in both unselected and high risk populations of previously undetected type 2 diabetes and gestational diabetes in the first trimester of pregnancy and the relationship to adverse pregnancy outcomes?

Why this is important

No accurate data exists for the prevalence of undiagnosed type 2 diabetes in early pregnancy and it will vary considerably dependent on risk factors such as maternal ethnic group, age and obesity. Undiagnosed type 2 diabetes exposes the mother to the risk of a nu ber of complications in pregnancy including the development of ketoacidosis as pregnancy

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the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

ii   Although metformin is commonly used in UK clinical practice in the management of diabetes in pregnancy and lactation, and there is strong evidence for its effectiveness and safety (presented in the full version of the guideline), at the time of publication (February 2015) metformin did not have a UK marketing authorisation for this indication. The summary of product characteristics advises that when a patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

jj   Although metformin is commonly used in UK clinical practice in the management of diabetes in pregnancy and lactation, and there is strong evidence for its effectiveness and safety (presented in the full version of the guideline), at the time of publication (February 2015) metformin did not have a UK marketing authorisation for this indication. The summary of product characteristics advises that when a patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

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ll   At the time of publication (February 2015) glibenclamide was contraindicated for use up to gestational week 11 and did not have UK marketing authorisation for use during the second and third trimesters of pregnancy in women with gestational diabetes. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

progresses with a significant risk of fetal death. Fetal hyperinsulinaemia is likely to be present before 20 weeks of pregnancy with undiagnosed type 2 diabetes, prior to standard screening for gestational diabetes. If present, there is a significant risk of irreversible excessive fetal growth occurring, which may have long term effects on the offspring. There is a need for observational population studies in early pregnancy in both high and low risk women to determine the prevalence of undiagnosed type 2 diabetes. Such women would require active intervention. However, such studies would also determine the true prevalence of gestational diabetes and it would be appropriate to perform intervention studies to determine whether early intervention rather than traditional intervention at the end of the second trimester improves maternal, fetal and neonatal outcomes.

15. When should testing for gestational diabetes take place – in the first or second trimester?

Why this is important

Conventionally, testing for gestational diabetes takes place in the second trimester. Intervention has been shown to improve outcomes for women diagnosed with gestational diabetes. However, maternal age and obesity are increasing, and some women (especially those from populations with a high incidence of type 2 diabetes) enter pregnancy with undiagnosed type 2 diabetes, but may not be tested for diabetes until the second trimester. This exposes the woman and the fetus to risks resulting from early and prolonged maternal hyperglycaemia. It is presumed that this is associated with increased morbidity. UK population studies are needed to establish the incidence of glucose intolerance in women in the first trimester. Well-designed randomised controlled trials are needed to establish if testing, diagnosis and intervention in the first rather than the second trimester improves maternal, fetal and neonatal outcomes, including fetal hyperinsulinaemia.

16. What is the optimum dietary and exercise strategy for the initial management of women diagnoses with gestational diabetes?

Why this is important

Diet and exercise are known to affect glycaemic control, and this guideline recommends that women diagnosed with gestational diabetes are treated initially with diet and exercise. However, there are a great variety of diets and methods of giving dietary advice, but there is little evidence to support one above another. Similarly, there is limited evidence regarding the nature, quantity, duration, and necessary support for exercise programmes that is both effective and acceptable to women. Randomised control trials are needed to establish what is the optimum strategy for offering women 'diet and exercise'.

17. What is the positive predictive value of one or more positive urine tests for glucose in the first trimester for a diagnosis of gestational diabetes?

Why this is important

The renal threshold for glucose reabsorption from the glomerular filtrate is known to be reduced in pregnancy. For this reason its utility for diagnosing gestational diabetes has been discredited. However, the reduction in glycaemic thresholds for the diagnosis of gestational diabetes prompts a re-evaluation of this test, particularly as it is routinely performed at every ante-natal visit. Historical data suggest that two consecutive positive tests for glycosuria might have a high specificity for a diagnosis of gestational diabetes and more recent data suggest that glycosuria predicts an abnormal OGTT in a significant number of women. Moreover the increasing incidence of type 2 diabetes in younger adults would imply that pregnant women might present with previously undiagnosed diabetes at pregnancy booking. Early diagnosis would enable timely treatment and potentially reduce the chance of a serious adverse pregnancy outcome.

18. Do women with gestational diabetes achieving good glucose control with diet, exercise and metformin need to have blood glucose tested as frequently as women taking insulin?

Why this is important

Good glycaemic control during pregnancy in women with gestational diabetes lessens the risk of a poor pregnancy outcome including giving birth to a macrosomic infant. Home/self glucose monitoring is an integral part of assessing glycaemic control as well as identifying episodes of hypoglycaemia and providing the necessary information to allow for safe inulin dose adjustment. Women with gestational diabetes treated with diet and exercise with or without the addition of metformin are not at risk of hypoglycaemia. It is currently unknown whether women with gestational diabetes achieving good glucose control not treated with insulin need to perform blood glucose monitoring at the same frequency as those women treated with insulin. A randomised trial would be undertaken in women with GDM to compare women having an intense blood glucose monitoring regime (testing 7 times daily) with a less intense regimen (testing 4 times daily).

5 Antenatal care

This section was updated in 2015
Note that glibenclamide was removed from recommendations in the 2020 guideline update. See the current recommendations at www.nice.org.uk/guidance/NG3

5.1 Monitoring blood glucose and ketones during pregnancy

5.1.1 Blood glucose monitoring

5.1.1.1 Review question

What is the effectiveness of blood glucose monitoring in predicting adverse outcomes in women with type 1, type 2 or gestational diabetes during pregnancy?

5.1.1.2 Introduction

The aim of this review was to evaluate the effectiveness of monitoring blood glucose in pregnant women with type 1, type 2 or gestational diabetes.

In the previous guideline on diabetes in pregnancy, 2 recommendations were made to inform how self monitoring of intermittent capillary blood glucose should be performed. During pregnancy, women with diabetes were to be advised to test fasting blood glucose levels and blood glucose levels 1 hour after every meal and women with insulin-treated diabetes were to be advised to additionally test blood glucose levels before going to bed at night.

The review question in this update does not examine the evidence available for the performance of self monitoring, but specifically focuses on the frequency of monitoring blood glucose and timing relative to meals.

5.1.1.3 Description of included studies

Nine studies were included in the current review (Bancroft et al., 2000; Espersen et al., 1985; Goldberg et al., 1986; Hawkins et al., 2009; Langer et al., 1994; Manderson et al., 2003; de Veciana et al., 1995; Weisz et al., 2005) that examined 5 comparisons of self monitoring strategies.

Four studies were randomised controlled trials (RCTs) (Bancroft et al., 2000; Manderson et al., 2003; de Veciana et al., 1995; Varner et al., 1983), 3 were prospective cohort studies (Espersen et al., 1985 [had historical controls]; Weisz et al., 2005; Langer et al., 1994), 1 study was a retrospective cohort (Hawkins et al., 2009) and 1 was a retrospective case-control study (Goldberg et al., 1986).

The studies were conducted in the UK (Bancroft et al., 2000; Manderson et al., 2003), Denmark (Espersen et al.), the USA (Goldberg et al., 1986; Hawkins et al., 2009; de Veciana et al., 1995; Langer et al., 1994; Varner et al., 1983) and Israel (Weisz et al., 2005). The number of women in the studies ranged from 28 (Varner et al., 1983) to 2,461 (Langer et al., 1994).

Six studies reported on women with gestational diabetes (Goldberg et al., 1986; Bancroft et al., 2000; Hawkins et al., 2009; Langer et al., 1994; de Veciana et al., 1995; Weisz et al., 2005), 2 studies reported on women with type 1 diabetes (Manderson et al., 2003; Varner et al., 1983) and 1 study reported on women with insulin dependent diabetes mellitus (Espersen et al., 1985).

Two studies compared monitoring with no monitoring (Bancroft et al., 2000; Espersen et al., 1985), 3 studies compared daily self monitoring with weekly monitoring in clinic (Goldberg et al., 1986; Hawkins et al., 2009; Varner et al., 1983), 2 studies compared preprandial with

postprandial monitoring (Manderson et al., 2003; de Veciana et al., 1995), 1 prospective cohort study compared 1 hour postprandial to 2 hours postprandial capillary blood glucose

monitoring (Weisz et al., 2005) and the final study compared monitoring 4 times a day (conventional strategy involving fasting and 2 hour post prandial sampling after each meal) to monitoring 7 times a day (intensified strategy involving a fasting sample and sampling before breakfast, preprandial, 2 hour post prandial and at bedtime) (Langer et al., 1994).

Table 45: Description of the methods used for monitoring of blood glucose in each study and other interventions as detailed

Study (type)	Study population	Monitoring strategy		Comparative monitoring strategy	
		Frequency and timing of monitoring	Other monitoring performed and interventions received	Frequency and timing of monitoring	Other monitoring performed and interventions
Monitoring versus no monitoring					
Bancroft et al., 2000 (RCT)	68 women with fasting blood glucose <7.0 mmol/litre and 2 hour blood glucose 7.8-11.0 mmol/litre Gestation at entry ranged from 15 to 38 weeks	Monitored by capillary glucose sampling one or two hours after meals performed five times per week.	Dietary advice regarding restriction of carbohydrates to 185 g/day and a diet sheet listing calorific values of common foods provided. HbA1c tested monthly (results were not made known) Insulin was introduced if five or more self measurements were greater than 7.0 mmol/litre in one week.	No capillary glucose self monitoring	Received same dietary advice, information and HbA1c testing as the "self monitoring group". Although HbA1c results were not made known, women could be withdrawn from the study if there was clinical concern
Espersen et al., 1985 (Prospective cohort with historical controls)	121 women with insulin dependent diabetes mellitus (White's classification B, C, D and FR[a]) Gestation at entry ranged from 8 to 15 weeks	Tuition on self monitoring of blood glucose provided and blood glucose tested at least twice weekly at 5 prespecified times throughout the day (7am, 10am, 1pm, 4pm and 8pm). Results recorded and discussed with the woman in outpatients clinic	Blood glucose and urine testing performed in out patients clinic at one or two week intervals according to diabetological and obstetrical status Insulin was introduced based on the woman's self evaluation of her condition and adjusted according to self monitoring and in clinic testing results	No capillary glucose self monitoring performed (historical control group)	Received same testing in clinic as "self monitoring group" No details provided regarding insulin use

Study (type)	Study population	Monitoring strategy		Comparative monitoring strategy	
		Frequency and timing of monitoring	Other monitoring performed and interventions received	Frequency and timing of monitoring	Other monitoring performed and interventions
Daily versus weekly monitoring					
Goldberg et al.,1986 (Retrospective case control study)	116 women with gestational diabetes Gestation at entry under 36 weeks	Performed fasting and 1 hour post prandial capillary blood testing every day	Referral to the prenatal diabetes clinic and started on diabetic diet. 1 hour post prandial capillary blood testing performed weekly in clinic Insulin started if fasting value >5.28 mmol/litre (95 mg/dl) or postprandial value >6.67 mmol/litre (120 mg/dl) and adjusted as necessary	No capillary blood testing performed	Referral to the prenatal diabetes clinic and started on diabetic diet. 2 hour post prandial capillary blood testing performed weekly in clinic Insulin started if postprandial value >6.67 mmol/litre (120 mg/dl) and adjusted as necessary
Hawkins et al., 2009 (retrospective cohort study)	990 women had gestational diabetes Gestation at entry ranged from approx 21 to 32 weeks	Performed self monitoring of capillary blood glucose four times daily (preprandially, including a morning fasting value and before bedtime)	Received dietary counselling with instructions regarding daily caloric intake (35 kcals/kg) and food types to avoid Serum blood glucose tested weekly in clinic. Women with persistent fasting value >5.83 mmol/litre (105 mg/dl) required insulin and were excluded from the study	No self monitoring of capillary blood	Received same dietary counselling and serum blood glucose testing as the "self monitoring group". Women with persistent fasting value >5.83 mmol/litre (105 mg/dl) required insulin and were excluded from the study
Varner et al., 1983 (randomised controlled trial)	30 women with type 1 diabetes Gestation at entry was less than 20 weeks	Performed self-monitoring of blood glucose after fasting and two hours postprandially in the morning, afternoon and evening.	All women were admitted after the first clinic visit for metabolic control. Glucose targets were fasting of 3.89 to 6.11 mmol/litre (70 to 110 mg/dl) and two-hour postprandial of 4.44 to 7.22 mmol/litre (80 to 130 mg/dl).	Performed serum glucose measurements after fasting, 2 hours after breakfast and 2 hours after lunch on 1 day each week.	Received the same standard care including diet and admission to the clinic for metabolic control and baseline tests.

Study (type)	Study population	Monitoring strategy		Comparative monitoring strategy	
		Frequency and timing of monitoring	Other monitoring performed and interventions received	Frequency and timing of monitoring	Other monitoring performed and interventions
			Women received a 3 meal/3 snack American Diabetes Association diet based on 35 kcal/kg ideal body weight.		
Preprandial versus postprandial monitoring					
Mande rson et al., 2003 (RCT)	61 women with type 1 diabetes Gestation at entry was 16 weeks	Daily preprandial capillary blood glucose monitoring (before breakfast and before meals)	Received bolus insulin four times daily and were seen in clinic fortnightly or more frequently if clinically indicated HbA1c tested at 16, 20, 28, 32, 36 and 38 weeks of gestation (results were not made known)	Daily postprandial capillary blood glucose monitoring (before breakfast and 1 hour after starting each meal)	Received same insulin regime, clinic attendance schedule and HbA1c testing as "preprandial group"
de Vecian a et al., 1995 (RCT)	66 women with insulin requiring gestational diabetes Gestation at entry under 30 weeks	Daily preprandial (fasting – before breakfast, preprandial and at bedtime)	Women were evaluated in clinic on a weekly basis and started on a diabetic diet HbA1c was measured at the start of the study and in the month before delivery	Daily postprandial (fasting, and 1 hour after each meal) capillary blood glucose monitoring	Received same diet, weekly evaluation in clinic and HbA1c testing as "preprandial group"
1 hour postprandial versus 2 hours postprandial monitoring					
Weisz et al., 2005 (prosp ective cohort study)	112 women with gestational diabetes Gestation at entry not reported	1 hour postprandial capillary blood glucose monitoring	Received counselling and instructions from a dietician and were placed on the ADA diet. Women were "routinely seen in clinic" Women requiring insulin were excluded	2 hours postprandial capillary blood glucose monitoring	Received same diet, and routine evaluation in clinic as "1 hour group" Women requiring insulin were excluded
4 daily measurements versus 7 daily measurements					
Langer et al., 1994 (prosp ective cohort	2461 women with gestational diabetes Gestation at entry ranged	Monitoring 4 times a day (conventional strategy involving fasting, and 2	Assigned to diet on basis of OGTT and mean blood glucose values since diagnosis. If targets not met	Monitoring 7 times a day (intensified strategy involving fasting – before	Received same as "4 daily measurement group"

Study (type)	Study population	Monitoring strategy		Comparative monitoring strategy	
		Frequency and timing of monitoring	Other monitoring performed and interventions received	Frequency and timing of monitoring	Other monitoring performed and interventions
study)	from 8 to 38 weeks	hour post prandial sampling after each meal)	with diet, then insulin was started Assessed weekly for fasting and 2 hour postprandial venous plasma glucose in clinic	breakfast, preprandial, 2 hour post prandial and bedtime sampling)	

OGTT oral glucose tolerance test, RCT randomised controlled trial,
a. White's classification of diabetes: B (diabetes onset at age 20 or older and duration of less than 10 years), C (diabetes onset at age 10-19 or duration of 10–19 years), D (diabetes onset before age 10 or duration greater than 20 years) and FR (diabetes with retinopathy and nephropathy)

5.1.1.4 Evidence profile

The GRADE profiles for this review question are presented in Tables 46 to 50.

Table 46: GRADE profile for monitoring of blood glucose versus no monitoring of blood glucose

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				Other considerations
	Monitoring	No monitoring	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Mode of birth											
Vaginal birth											
1 (Bancroft, 2000)	22/32 (69%)	25/36 (69%)	RR 1.0 (0.7 to 1.4)[a]	7 fewer per 1000 (from 194 fewer to 250 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
Caesarean section											
1 (Bancroft, 2000)	10/32 (31%)	11/36 (31%)	RR 1.0 (0.5 to 2.1)[a]	6 more per 1000 (from 153 fewer to 330 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
HbA1c (%)											
At 28 weeks											
1 (Bancroft, 2000)	8 women (mean 4.9 SD 0.7)	8 women (mean 5.5 SD 1.1)	NC	MD 0.6 lower (1.5 lower to 0.3 higher)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[e]
At 32 weeks											
1 (Bancroft, 2000)	20 women (mean 5.2 SD 0.8)	19 women (mean 5 SD 1.3)	NC	MD 0.2 higher (0.5 lower to 0.9 higher)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[e]
At 36 weeks											
1 (Bancroft, 2000)	31 women (mean 5.3 SD 0.8)	32 women (mean 5.6 SD 1.3)	NC	MD 0.3 lower (0.8 lower to 0.2 higher)[a]	Moderate	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[e]
At 38 weeks											
1 (Bancroft, 2000)	24 women (mean 5.3 SD 0.9)	27 women (mean 5.5 SD 0.9)	NC	MD 0.2 lower (0.7 lower to 0.3 higher)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[e]
At term											
1 (Bancroft, 2000)	10 women (mean 5.1 SD 0.8)	10 women (mean 5.5 SD 0.9)	NC	MD 0.4 lower (1.2 lower to 0.4 higher)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[e]
Large for gestational age											
> 90th percentile											
1 (Bancroft, 2000)	8/32 (25%)	7/36 (19%)	RR 1.3 (0.5 to 3.2)[a]	56 more per 1000 (from 91 fewer to 418 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				Other consider ations
	Monitoring	No monitoring	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
1 (Espersen, 1985)	12/61 (20%)	19/62 (31%)	RR 0.6 (0.3 to 1.2)[a]	110 fewer per 1000 (from 202 fewer to 64 more)[a]	Very low	Prospect ive cohort	Serious limitations[g]	No serious inconsistency[c]	Serious indirectness[h]	Serious imprecision[d]	Yes[i]
Shoulder dystocia											
1 (Bancroft, 2000)	0/32 (0%)	1/36 (3%)	RR 0.4 (0.0 to 8.9)[a]	18 fewer per 1000 (from 27 fewer to 218 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
Neonatal hypoglycaemia											
1 (Bancroft, 2000)	2/32 (6%)	6/36 (17%)	RR 0.4 (0.1 to 1.7)[a]	103 fewer per 1000 (from 153 fewer to 122 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]

MD mean difference, NC not calculable, RCT randomised controlled trial, RR relative risk, SD standard deviation

a. Calculated by the NCC-WCH technical team from data reported in the article

b. Participants were not blinded to treatment allocation. It is not clear whether the groups were comparable at baseline. It is not clear whether investigators were blinded to the invention exposure.

c. Single study analysis

d. Confidence interval for the RR crosses the line of no effect (RR=1) and RR=0.75 and/or RR=1.25

e. The study was undertaken in the UK. Women with gestational diabetes (fasting blood glucose <7.0 mmol/litre and 2 hour blood glucose 7.8-11.0 mmol/litre) were included. 69% of the women were Caucasian and 31% were Asian. Both groups were given dietary advice regarding restriction of carbohydrates to 185g/day and a diet sheet listing calorific values of common foods were provided to both groups. HbA1c was tested monthly in both groups although the results were not made known. The self monitoring group performed capillary glucose sampling one or two hours after meals five times per week. The control group did not perform capillary glucose self monitoring.

f..The confidence interval for the mean difference crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the two groups)

g. No attempts were made to balance the comparison groups for potential confounders. Investigators were not blinded to participants' exposure to the intervention or to important confounding and prognostic factors. Participants were not blinded to treatment allocation. It is not clear whether groups were comparable at baseline. It is not clear whether the clinicians administering care were kept blind to treatment allocation. Controls were historical.

h. This study used outdated self monitoring methods and a schedule of monitoring that was insufficiently intensive to be adequately reflective of current practice.

i. The study was undertaken in Denmark. Women with insulin dependent diabetes mellitus were included. Ethnicity of the included women was not reported. For both groups, blood glucose and urine testing was performed in out patient clinic at one or two week intervals according to the woman's diabetological and obstetrical status. The monitoring group received tuition on self monitoring of blood glucose and tested their blood glucose at least twice weekly at 5 prespecified times throughout the day (7am, 10am, 1pm, 4pm and 8pm). The control group did not perform capillary glucose self monitoring.

Table 47: GRADE profile for daily monitoring versus weekly testing of blood glucose

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				
	Daily monitoring	Weekly testing	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mode of birth											
Vaginal birth (including vaginal birth with forceps)											
1 (Hawkins, 2009)	199/315 (63%)	453/675 (67%)	RR 0.94 (0.85 to 1.04)[a]	40 fewer per 1000 (from 101 fewer to 27 more)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
1 (Varner, 1983)	7/14 (50%)	5/14 (36%)	RR 1.40 (0.56 to 3.50)[a]	143 more per 1000 (from 157 fewer to 893 more)[a]	Very low	Randomised controlled trial	Serious limitations[e]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[g]
Vaginal birth (not including vaginal birth with forceps)											
1 (Goldberg, 1986)	27/58 (47%)	37/58 (64%)	OR 0.49 (0.24 to 1.04)[a]	175 fewer per 1000 (from 341 fewer to 9 more)[a]	Very low	Retrospective case control	Serious limitations[h]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[i]	Yes[j]
Vaginal birth with forceps											
1 (Goldberg, 1986)	12/58 (21%)	5/58 (9%)	OR 2.77 (0.9 to 8.4)[a]	121 more per 1000 (from 7 fewer to 357 more)[a]	Very low	Retrospective case control	Serious limitations[h]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[k]	Yes[j]
1 (Hawkins, 2009)	7/315 (2%)	25/675 (4%)	RR 0.6 (0.3 to 1.4)[a]	15 fewer per 1000 (from 27 fewer to 14 more)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[d]
Caesarean section											
1 (Goldberg, 1986)	18/58 (31%)	14/58 (24%)	OR 1.41 (0.6 to 3.2)[a]	68 more per 1000 (from 77 fewer to 264 more)[a]	Very low	Retrospective case control	Serious limitations[h]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[g]
1 (Hawkins, 2009)	116/315 (37%)	222/675 (33%)	RR 1.12 (0.9 to 1.3)[a]	39 more per 1000 (from 23 fewer to 112 more)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[k]	Yes[d]

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				
	Daily monitoring	Weekly testing	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 Varner, 1983	7/14 (50%)	9/14 (64%)	RR 0.78 (0.39 to 1.54)[a]	141 fewer per 1000 (from 392 fewer to 347 more)[a]	Very low	Randomised controlled trial	Serious limitations[e]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[g]
Large for gestational age											
≥90th percentile											
1 (Hawkins, 2009)	73/315 (23%)	232/675 (34%)	RR 0.7 (0.5 to 0.9)a	113 fewer per 1000 (from 52 fewer to 158 fewer)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
Not defined											
1 (Goldberg, 1986)	7/58 (12%)	24/58 (41%)	OR 0.19 (0.08 to 0.5)[a]	296 fewer per 1000 (from 153 fewer to 360 fewer)[a]	Very low	Retrospective case control	Serious limitations[e]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[g]
Shoulder dystocia											
1 (Hawkins, 2009)	5/315 (2%)	13/675 (2%)	RR 0.8 (0.3 to 2.3)[a]	3 fewer per 1000 (from 13 fewer to 25 more)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[d]
Neonatal hypoglycaemia											
1 (Hawkins, 2009)	23/315 (7%)	30/675 (4%)	RR 1.6 (1.0 to 2.8)[a]	28 more per 1000 (from 1 fewer to 79 more)[a]	Very low	Retrospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[k]	Yes[d]
1 (Varner, 1983)	4/14 (29%)	7/14 (50%)	RR 0.57 (0.20 to 1.59)[a]	215 fewer per 1000 (from 400 fewer to 295 more)[a]	Very low	Randomised controlled trial	Serious limitations[e]	No serious inconsistency[c]	No serious indirectness	Very serious imprecision[f]	Yes[g]

OR odds ratio, RR relative risk
a. Calculated by the NCC-WCH technical team from data reported in the article
b. The groups were not comparable at baseline. Participants were not kept blind to their treatment allocation. Individuals administering care were not kept blind to treatment exposure. Investigators were not kept blind to treatment exposure or other confounding and prognostic factors. It is not clear whether the participants received the same care (apart from the intervention studied).
c. Single study analysis

d. The study was undertaken in the USA. Included women had gestational diabetes. 81% of women were Hispanic, 10% of women were African American, 5% of women were white, and 4% of women were classified as 'other' ethnicity. Both groups received dietary counselling with instructions regarding daily caloric intake (35kcals/kg) and food types to avoid. Serum blood glucose tested weekly in clinic in both groups. In addition, the daily monitoring group performed self-monitoring of capillary blood glucose four times daily (preprandially, including a morning fasting value and before bedtime)

e. It was unclear whether groups were comparable at baseline due to the very limited reporting of baseline characteristics.

f. Confidence interval for the OR/RR crosses the line of no effect and OR/RR=0.75 and OR/RR=1.25.

g. The study was undertaken in the USA. Women had type 1 diabetes. Ethnicity was not reported. Women in both groups were admitted at the first clinic visit for metabolic control and baseline evaluation. Women in the daily monitoring group self-monitored blood glucose after fasting and two hours postprandially in the morning, afternoon and evening. Women in the weekly monitoring group had serum glucose measured after fasting, two hours after breakfast and two hours after lunch on one day each week.

h. The participation rate for each group was not reported. The participants and non-participants were not compared to establish similarities and differences. Measures were not taken to prevent knowledge of primary exposure from influencing case ascertainment.

i. Confidence interval for the OR/RR crosses OR/RR=0.75.

j. The study was undertaken in the USA. Women in the study had gestational diabetes. 62% of women were Hispanic, and 34% were black. The ethnicity of the remaining women was not reported. Women in both groups were referred to the prenatal diabetes clinic and started on a diabetic diet. In the daily monitoring group a 1 hour post prandial capillary blood test was performed weekly in clinic and the women performed fasting and 1 hour post prandial capillary blood self-testing every day. In the weekly monitoring group, 2 hour post prandial capillary blood testing was performed weekly in clinic, but women did not perform capillary blood self-testing.

k. Confidence interval for the OR/RR crosses OR/RR=1.25.

Table 48: GRADE profile for preprandial monitoring versus postprandial monitoring of blood glucose

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				Other consider ations
	Preprandial monitoring	Postprandial monitoring	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consider ations
Mode of birth											
Caesarean section											
1 (Manderson, 2003)	21/31 (68%)	14/30 (47%)	RR 1.45 (0.9 to 2.3)[a]	210 more per 1000 (from 37 fewer to 597 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
1 (de Veciana, 1995)	13/33 (39%)	8/33 (24%)	RR 1.63 (0.8 to 3.4)[a]	153 more per 1000 (from 53 fewer to 579 more)[a]	Low	RCT	Serious limitations[f]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[g]
HbA1c (%)											
Final HbA1c value											
1 (Manderson, 2003)	31 women (mean 6.3 SD 0.7)	30 women (mean 6.0 SD 0.8)	NC	MD 0.3 higher (0.1 lower to 0.7 higher)[a]	Moderate	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[e]
Change in HbA1c from booking											
1 (Manderson, 2003)	31 women (mean -1.3 SD 1)	30 women (mean -1.4 SD 1.3)	NC	MD 0.1 higher (0.5 lower to 0.7 higher)[a]	Moderate	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[e]

| Number of studies | Number of women/babies | | Effect | | Quality | Design | Quality assessment | | | | Other consider ations |
	Preprandial monitoring	Postprandial monitoring	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Large for gestational age											
>90th percentile											
1 (Manderson, 2003)	18/31 (58%)	15/30 (50%)	RR 1.2 (0.7 to 1.9)[a]	80 more per 1000 (from 135 fewer to 425 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
Not defined											
1 (de Veciana, 1995)	14/33 (42%)	4/33 (12%)	RR 3.5 (1.3 to 9.5)[a]	303 more per 1000 (from 35 more to 1000 more)[a]	Moderate	RCT	Serious limitations[f]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[g]
Shoulder dystocia											
1 (de Veciana, 1995)	6/33 (18%)	1/33 (3%)	RR 6.0 (0.8 to 47.1)[a]	152 more per 1000 (from 7 fewer to 1000 more)[a]	Low	RCT	Serious limitations[f]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[g]
Neonatal hypoglycaemia											
1 (Manderson, 2003)	9/31 (29%)	8/30 (27%)	RR 1.1 (0.5 to 2.5)[a]	24 more per 1000 (from 139 fewer to 387 more)[a]	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
1 (de Veciana, 1995)	7/33 (21%)	1/33 (3%)	RR 7.0 (0.9 to 53.8)[a]	182 more per 1000 (from 3 fewer to 1000 more)[a]	Low	RCT	Serious limitations[f]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[g]
Neonatal/fetal mortality											
Stillbirth											
1 (Manderson, 2003)	1/32 (3%)	0/30 (0%)	RR 2.8 (0.1 to 66.6)[a]	NC	Low	RCT	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
1 (de Veciana, 1995)	1/33 (3%)	0/33 (0%)	RR 3 (0.1 to 71.1)[a]	NC	Low	RCT	Serious limitations[f]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[g]

MD mean difference, NC not calculable, RCT randomised controlled trial, RR relative risk, SD standard deviation
a. Calculated by the NCC-WCH technical team from data reported in the article
b. The groups were not comparable at baseline. Participants and clinicians were not blinded to treatment allocation. It is not clear whether an appropriate method of randomisation was used. 13 women were excluded from the analysis, but it is not clear which group they were in, so it is not possible to determine whether the groups were comparable for treatment completion or whether the groups were comparable with respect to the availability of outcome data. It is not clear whether investigators were blinded to participants' exposure to the intervention or to other important confounding factors.
c. Single study analysis

d. Confidence interval for the RR crosses the line of no effect and RR=0.75 and/or RR=1.25

e. The study was undertaken in the UK. It included women with type 1 diabetes. All women were white. The daily preprandial capillary blood glucose monitoring group tested before breakfast and before meals whilst the daily postprandial capillary blood glucose monitoring group tested before breakfast and 1 hour after starting each meal.

f. Participants were not blinded to treatment allocation. It is not clear whether allocation was adequately concealed. It is not clear whether clinicians giving care were blinded. It is not clear whether investigators were blinded to exposure to the intervention or to other confounding factors.

g. The study was undertaken in the USA and included women with gestational diabetes. 85% of women were Hispanic, 11% of women were white, and 5% of women were black or Asian (adds up to more than 100% due to rounding errors). Women in both groups were evaluated in clinic on a weekly basis, started a diabetic diet and had HbA1c measured at the start of the study and in the month before delivery. The daily preprandial monitoring group tested capillary blood fasting – before breakfast, preprandially and at bedtime. The daily postprandial monitoring group tested capillary blood fasting, and one hour after each meal.

Table 49: GRADE profile for 1 hour postprandial monitoring versus 2 hour postprandial monitoring of blood glucose

| Number of studies | Number of women/babies | | Effect | | Quality | Design | Quality assessment | | | | |
	1 hour postprandial	2 hours postprandial	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mode of birth											
Caesarean section											
1 (Weisz, 2005)	15/66 (23%)	14/46 (30%)	RR 0.8 (0.4 to 1.4)[a]	76 fewer per 1000 (from 183 fewer to 119 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]
Large for gestational age											
Not defined											
1 (Weisz, 2005)	5/66 (8%)	7/46 (15%)	RR 0.5 (0.2 to 1.5)[a]	76 fewer per 1000 (from 126 fewer to 72 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[d]	Yes[e]

CI confidence interval, RR relative risk

a. Calculated by the NCC-WCH technical team from data reported in the article

b. The groups were not comparable at baseline. Participants and clinicians were not blinded to treatment allocation. 6 women were lost to follow up, but it is not clear which group they were in, therefore it is not possible to determine whether the groups were comparable for treatment completion or the availability of outcome data. It is not clear whether attempts were made to balance the comparison groups for potential confounders. It is not clear whether investigators were kept blind to participants' exposure or to other confounding factors.

c. Single study analysis

d. Confidence interval for the RR crosses the line of no effect and RR=0.75 and/or RR=1.25

e. Study was undertaken in Israel. Included women had gestational diabetes. Ethnicity of the participants was not reported. All women received counselling and instructions from a dietician, were placed on the ADA diet and were "routinely seen in clinic". One group tested postprandial capillary blood glucose monitoring after 1 hour and the other group tested after 2 hours

Table 50: GRADE profile for 4 daily measurements versus 7 daily measurements of blood glucose

| Number of studies | Number of women/babies | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	4 daily measurements	7 daily measurements	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Mode of birth											
Caesarean section											
1 (Langer, 1994)	283/1316 (22%)	172/1145 (15%)	RR 1.4 (1.2 to 1.7)[a]	65 more per 1000 (from 32 more to 105 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
Large for gestational age											
≥90th percentile											
1 (Langer, 1994)	265/1316 (20%)	150/1145 (13%)	RR 1.5 (1.3 to 1.9)[a]	71 more per 1000 (from 37 more to 111 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
Neonatal intensive care unit length of stay (days)											
1 (Langer, 1994)	1316 babies (mean 4.4 SD 3)	1145 babies (mean 2.8 SD 2)	NC	MD 1.7 higher (1.5 higher to 1.9 higher)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[e]	Yes[d]
Shoulder dystocia											
1 (Langer, 1994)	18/1316 (1%)	5/1145 (<1%)	RR 3.1 (1.2 to 8.4)[a]	9 more per 1000 (from 1 more to 32 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
Neonatal hypoglycaemia											
1 (Langer, 1994)	263/1316 (20%)	44/1145 (4%)	RR 5.2 (3.8 to 7.1)[a]	161 more per 1000 (from 108 more to 234 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	No serious imprecision	Yes[d]
Neonatal/fetal mortality											
Stillbirth rate (per 1000)											
1 (Langer, 1994)	4/1000 (<1%)	1/1000 (<1%)	RR 4 (0.5 to 35.7)[a]	3 more per 1000 (from 1 fewer to 35 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[d]

Number of studies	Number of women/babies		Effect		Quality	Design	Quality assessment				Other considerations
	4 daily measurements	7 daily measurements	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Neonatal death rate (per 1000)											
1 (Langer, 1994)	2/1000 (<1%)	3/1000 (<1%)	RR 0.7 (0.1 to 4.0)[a]	1 fewer per 1000 (from 3 fewer to 9 more)[a]	Very low	Prospective cohort	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness	Serious imprecision[f]	Yes[d]

MD mean difference, NC not calculable, RCT randomised controlled trial, RR relative risk, SD standard deviation

a. Calculated by the NCC-WCH technical team from data reported in the article

b. Participants and clinicians were not blinded to treatment allocation. It is not clear whether attempts were made to balance the comparison groups for potential confounders. 69 women were lost to follow up, but it is not clear which group they were in, and so it is unclear whether the groups were comparable for treatment completion and availability of outcome data. It is unclear whether investigators were kept blind to participants' exposure to interventions or to confounding factors.

c. Single study analysis

d. The study was undertaken in the USA. Included women had gestational diabetes. 80% were Hispanic, 15% were white, 4% of women were black, and 1% were classed as 'other'. Women in both groups were assigned to diet on basis of OGTT at diagnosis and mean blood glucose values since diagnosis and were assessed weekly for fasting and 2 hour postprandial venous plasma glucose in clinic. The group that monitored 4 times a day followed a conventional strategy involving fasting, and 2 hour post prandial sampling after each meal. The group that monitored 7 times a day followed an intensified strategy involving fasting – before breakfast, preprandial, 2 hour post prandial and bedtime sampling.

e The confidence interval for the mean difference crosses the line of no effect (MD=0) and the minimally important difference (50% of the combined standard deviation of the two groups)f Confidence interval for the RR crosses the line of no effect and RR=0.75 and/or RR=1.25

5.1.1.5 Evidence statements

5.1.1.5.1 *Monitoring versus no monitoring*

One study (n=68) found no difference in the number of vaginal births (relative risk [RR] 1.0, 95% confidence interval [CI] 0.7 to 1.4) or caesarean sections (RR 1.0, 95% CI 0.5 to 2.1) when comparing women with type 1, type 2 or gestational diabetes who had their blood glucose monitored with those who did not. There was also no difference between groups whose HbA1c values were measured at 28 weeks (MD −0.6, 95% CI −1.5 to 0.3), 32 weeks (MD 0.2, 95% CI 0.5 to 0.9), 36 weeks (MD −0.3, 95% CI −0.8 to 0.2)), 38 weeks (MD −0.2 95% CI −0.7 to 0.3) or at term (MD −0.4, 95% CI −1.2 to 0.4). The evidence for this outcome was of moderate quality.

One study (n=68) found no difference in the number of neonates born large for gestational age (RR 1.3, 95% CI 0.5 to 3.2), the incidence of shoulder dystocia (RR 0.4, 95% CI 0.0 to 8.9) or the incidence of neonatal hypoglycaemia (RR 0.4, 95% CI 0.1 to 1.7) when comparing women who had their blood glucose monitored with those who did not. The quality of this evidence was low.

One study (n=123) found no difference in the risk of large for gestational age neonates born to women with type 1, type 2 or gestational diabetes between groups associated with monitoring compared with no monitoring of blood glucose. The quality of this evidence was very low.

5.1.1.5.2 *Monitoring strategies*

Daily monitoring versus weekly monitoring

Two studies (n=990; n=116) found no difference between groups in the number of vaginal births (including births with forceps) associated with women with type 1, type 2 or gestational diabetes who received blood glucose monitoring compared to those who did not (RR 0.94, 95% CI 0.85 to 1.04; RR 1.40, 95% CI 0.56 to 3.50, respectively). The quality of the evidence was very low.

Two studies (n=116; n=990) found no difference between groups in the number of vaginal births with forceps associated with women with type 1, type 2 or gestational diabetes who received blood glucose monitoring compared to those who did not (odds ratio [OR] 2.77, 95% CI 0.9 to 8.4; RR 0.6, 95% CI 0.3 to 1.4, respectively). The quality of the evidence was very low.

One study (n=116) found no difference between groups for vaginal births without forceps (OR 0.49, 95% CI 0.24 to 1.04) when comparing women with type 1, type 2 or gestational diabetes who monitored their blood glucose daily with women who had weekly monitoring of their blood glucose. The quality of the evidence was very low.

Three studies (n=116; n=990; n=28) found no difference between groups for the risk of caesarean sections when comparing women with type 1, type 2 or gestational diabetes (respectively OR 1.41, 95% CI 0.6 to 3.2; RR 1.12 95% CI 0.9 to 1.3; RR 0.78, 95% CI 0.39 to 1.54). The quality of the evidence was very low.

One study (n=990) found a lower risk of neonates large for gestational age (on the 90th centile or above) being born to women with type 1, type 2 or gestational diabetes who monitored their blood glucose daily compared with women who performed weekly monitoring of their blood glucose (RR 0.7, 95% CI 0.5 to 0.9). The quality of the evidence was very low.

One study (n=116) found a reduced risk of neonatal hypoglycaemia (OR 0.19, 95% CI 0.08 to 0.5), while 2 studies (n=990; n=28) found no difference in the risk of neonatal hypoglycaemia (RR 1.6, 95% CI 1.0 to 2.8; RR 0.57, 95% CI 0.20 to 1.59 respectively) when

comparing women with type 1, type 2 or gestational diabetes. The quality of the evidence for this outcomes was very low.

One study (n=990) found no difference in the risk of shoulder dystocia between groups (RR 0.8, 0.3 to 2.3) when comparing women with type 1, type 2 or gestational diabetes. The quality of the evidence for this outcome was very low.

Preprandial versus postprandial monitoring

Two studies (n=61; n=66) found no difference between groups in the risk of caesarean section associated with women with type 1, type 2 or gestational diabetes who received preprandial monitoring compared with those who did not (RR 1.45, 95% CI 0.9 to 2.3; RR 1.63, 95% CI 0.8 to 3.4). The evidence for this outcome was low quality.

One study (n=61) found no difference in the final HbA1c value between groups (MD 0.3, 95% CI −0.1 to 0.7) or in the change in HbA1c value from booking (MD 0.1, 95% CI −0.5 to 0.7) between women with type 1, type 2 or gestational diabetes who received postprandial monitoring compared with preprandial measurements to monitor their blood glucose. The evidence for this outcome was of moderate quality.

One study (n=66) found an increased risk of neonates large for gestational age (greater than 90th centile) associated with the group of women who underwent preprandial compared with postprandial measurements to monitor their blood glucose (RR 1.2, 95% CI 0.7 to 1.9). The quality of evidence for this outcome was low.

One study (n=66) found an increased risk of large for gestational age (greater than 90th percentile) neonates associated with the group of women who underwent preprandial compared with postprandial measurements to monitor their blood glucose (RR 3.5, 95% CI 1.3 to 9.5). The quality of evidence for this outcome was moderate.

One study (n=66) found no increased risk of shoulder dystocia associated with the group of women who underwent preprandial compared with postprandial measurements to monitor their blood glucose (RR 6.0, 95% CI 0.8 to 47.1). The quality of evidence for this outcome was moderate.

Two studies (n=61; n=66) found no difference between groups in the risk of neonatal hypoglycaemia in women with type 1, type 2 or gestational diabetes who underwent preprandial compared with postprandial measurements to monitor their blood glucose (RR 1.1, 95% CI 0.5 to 2.5; RR 7.0, 95% CI 0.9 to 53.8, respectively). The quality of evidence for this outcome was low.

Two studies (n=62; n=66) found no difference between groups in the risk of neonatal hypoglycaemia in women with type 1, type 2 or gestational diabetes who underwent preprandial compared with postprandial measurements to monitor their blood glucose (RR 2.8, 95% CI 0.1 to 66.6; RR 3, 95% CI 0.1 to 71.1, respectively). The quality of evidence for this outcome was low.

One hour postprandial versus 2 hours postprandial monitoring

One study (n=112) found no difference between groups in the risk of caesarean section in women with type 1, type 2 or gestational diabetes who received 1 hour postprandial monitoring compared with 2 hour postprandial measurements to monitor their blood glucose (RR 0.8, 95% CI 0.4 to 1.4). The quality of evidence for this outcome was very low.

One study (n=112) found no difference between groups in the risk of large for gestational age neonates in women with type 1, type 2 or gestational diabetes who received 1 hour postprandial monitoring compared with 2 hour postprandial measurements to monitor their blood glucose (RR 0.5, 95% CI 0.2 to 1.5). The quality of evidence for this outcome was very low.

Four daily (fasting and 3 post prandial measurements) versus 7 daily measurements

One study (n=2461) found an increased risk of caesarean section in women with type 1, type 2 or gestational diabetes associated with 4 daily measurements compared with 7 daily measurement of blood glucose (RR 1.4, 95% CI 1.2 to 1.7). The quality of this evidence was very low.

One study (n=2461) found an increased length of neonatal intensive care unit (NICU) length of stay associated with women with type 1, type 2 or gestational diabetes who had 4 daily measurements compared with 7 daily measurements of blood glucose (MD 1.7, 95% CI 1.5 to 1.9). The quality of this evidence was very low.

One study (n=2461) found an increased risk of large for gestational age (greater than 90th centile) neonates in women with type 1, type 2 or gestational diabetes associated with 4 daily measurements compared with 7 daily measurements of blood glucose (RR 1.5, 95% CI 1.3 to 1.9). The quality of this evidence was very low.

One study (n=2461) found an increased risk of shoulder dystocia in the neonates of women with type 1, type 2 or gestational diabetes who had 4 daily measurements compared with 7 daily measurement of blood glucose (RR 3.1, 95% CI 1.2 to 8.4). The quality of this evidence was very low.

One study (n=2461) found an increased risk of neonatal hypoglycaemia associated with women with type 1, type 2 or gestational diabetes who had 4 daily measurements compared with 7 daily measurements of blood glucose (RR 5.2, 95% CI 3.8 to 7.1). The quality of this evidence was very low.

One study (n=2000) found no difference between groups of women with type 1, type 2 or gestational diabetes who had 4 daily measurements compared with 7 daily measurements of blood glucose for the outcomes of stillbirth (per 1000) (RR 4, 95% CI 0.5 to 35.7) or neonatal death (per 1000) (RR 0.7, 95% CI 0.1 to 4.0). The quality of this evidence was very low.

5.1.1.6 Health economics profile

No health economic evidence was identified that considered blood glucose monitoring in predicting adverse outcomes in women with type 1, type 2 or gestational diabetes during pregnancy.

De novo analysis was not undertaken for this question as it was not considered as high priority as other issues within the guideline.

5.1.1.7 Evidence to recommendations

5.1.1.7.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the following maternal outcomes for this review:
- mode of birth (spontaneous vaginal, operative vaginal, caesarean section [elective or emergency])
- HbA1c % (as a measure of glycaemic control during pregnancy)
- hypoglycaemic episodes during pregnancy (another measure of glycaemic control during pregnancy).

The group also prioritised the following neonatal outcomes:
- large for gestational age (however defined in the study, for example using a customised measure based on gestational age and population norms; dichotomous data preferred)
- neonatal intensive care unit length of stay greater than 24 hours
- shoulder dystocia (as a specific example of birth trauma)

- neonatal hypoglycaemia (however defined)
- mortality.

The guideline development group prioritised mode of birth as an outcome for this review and noted that babies of women with diabetes whose blood glucose levels were tested weekly or less frequently had a higher incidence of instrumental birth.

The gorup argued that maternal hypoglycaemia was an important outcome that was distinct from estimates of glycaemic control measured by HbA1c percentage, but this outcome was not reported in any of the studies.

The group prioritised large for gestational age and noted that babies of women with diabetes who are tested frequently tend to be smaller than babies of women who are tested less frequently.

The group also considered that NICU stay of more than 24 hours was a surrogate measure of significant neonatal problems, such as prolonged neonatal hypoglycaemia or respiratory distress. They noted that this stay was significantly shorter in babies of women who had monitoring 7 times daily compared with those who had less frequent monitoring.

5.1.1.7.2 *Consideration of clinical benefits and harms*

The guideline development group noted that, overall, the evidence supported the view that more frequent testing of blood glucose (and subsequent adjustment of treatment) led to better outcomes.

Intermittent glucose monitoring requires pricking a finger for a capillary blood sample several times during the day and using a meter to measure blood glucose. This is disruptive and requires a significant commitment from the woman. The group believed that self monitoring of blood glucose would be especially helpful to women who are more likely to experience hypoglycaemic episodes (such as those who experience wide variability in their glucose regulation, or who are on insulin or glibenclamide, or who may have hypoglycaemia unawareness). The 2008 guideline on diabetes in pregnancy recommended this as the standard method of glucose monitoring for all women with type 1 and those with type 2 diabetes on insulin therapy.

The guideline development group recognised that frequent self monitoring can also provoke anxiety in that some women who may feel pressure to manipulate their treatment regimen or achieve overly tight regulation.

Thus, the group believed that women's individual perceptions of the greater likelihood of good outcomes would be an important motivation in their commitment to and satisfaction with blood glucose self monitoring. However, the group also noted that if an adverse outcome occurs despite a woman's adherence to the monitoring strategy and subsequent modification of her glycaemic control, this might have a negative impact on her experience of pregnancy and adversely affect her engagement in any future pregnancy.

Finally, the guideline development group was of the view that the frequency of monitoring should reflect the severity of the disease and its treatment and to improve compliance in women with less severe disease. Hence they felt that it would be reasonable to write recommendations for 3 different categories of women with diabetes in pregnancy in decreasing order of severity: women with type 1 diabetes; women with type 2 or gestational diabetes on a multiple insulin dose regimen; and women with type 2 or gestational diabetes who were on diet and exercise therapy only, or taking oral therapy or a single daily dose of intermediate-acting or long-acting insulin.

5.1.1.7.3 Consideration of health benefits and resource uses

The guideline development group noted that self monitoring of blood glucose is part of standard NHS treatment for people with diabetes. Any increase in frequency of testing during pregnancy will incur an additional cost. However, because tight blood glucose control is particularly important for improving pregnancy outcomes, the benefits of additional testing are likely to outweigh testing costs.

5.1.1.7.4 Quality of evidence

The quality of the evidence ranged from moderate to very low.

There is no new evidence regarding women with type 2 diabetes. The majority of the reported evidence regards women with gestational diabetes, with only 1 study reporting on women with type 1 diabetes.

Monitoring versus no-monitoring

Because monitoring and adjusting treatment to target values is central to clinical management in diabetic pregnancies, the guideline development group recognised that the comparison of 'monitoring versus no monitoring' was, arguably, inappropriate in this review. There were no significant differences in any outcomes when self monitoring was compared to no self monitoring and the evidence was moderate to very low in quality. Specifically, the Bancroft (2000) study included women with impaired glucose tolerance with a wide range of gestation up to 38 weeks who may have been studied too late to be able to demonstrate any effect on fetal growth and maternal delivery. Given the small size of the study, the group felt it was underpowered to detect significant differences in outcomes. In addition, the Espersen (1985) study was considered to use outdated self monitoring methods and a schedule of monitoring that was insufficiently intensive to be adequately reflective of current practice.

Daily monitoring versus weekly monitoring

The evidence for the comparison of daily monitoring versus weekly testing was of low and very low quality. The guideline development group considered that the 2 studies examining this comparison did not contain useful data because weekly testing was performed in the clinic setting by a healthcare professional and this was not self monitoring. As such, it is not a practical or cost-effective option for pregnant women with diabetes.

Preprandial versus postprandial testing

There were 2 trials that compared pre- and postprandial testing in women with type1 diabetes and in women with insulin-requiring gestational diabetes respectively, which were moderate to low in quality. The guideline development group noted that in these studies the postprandial groups received more insulin and had smaller babies than the preprandial groups.

The 2008 guideline recommended that fasting and postprandial testing be performed by women with diabetes and those requiring insulin should also test at bedtime. The guideline development group recognised that postprandial testing is important because it correlates with fetal growth in the third trimester. However, they considered that women on basal bolus dosage regimes could not adjust their insulin dosage without knowing their preprandial blood glucose values as well.

The guideline development group was aware that women with type 1 diabetes who are not pregnant are required to test preprandially and at bedtime as part of intensification of glucose control which also involves carbohydrate counting and adjustment of insulin dosage as a result. Further, the group recognised that the carbohydrate/insulin ratio differs for different meals through the day and also changes throughout pregnancy, and that both preprandial and postprandial testing would therefore be needed.

One hour postprandial versus 2 hour postprandial comparison

One study compared 1 hour with 2 hour postprandial testing and provided very low quality evidence of no significant difference in the 2 outcomes examined (caesarean section and large for gestational age). The guideline development group commented on the lack of detail reported in this study regarding the exact timing of testing; notably was it from the beginning or from the end of each meal? The group noted from the review of continuous glucose monitoring that the postprandial peak in glucose is likely to be 60 to 90 minutes after meals, though again it was not clear whether this was from the start or the end of the meal. The group also considered that it may be more convenient and women may be more likely to remember to perform testing if it was performed sooner (at 1 hour) rather than later (2 hours) after the meal finished.

Four measurements per day versus 7 measurements per day

One prospective study compared 4 daily measurements with 7 daily measurements, providing evidence of very low quality. In terms of the outcomes considered in this review, 7 measurements per day conferred more benefit to women and their babies than 4, although it was not entirely clear that the benefit came solely from monitoring alone, given the different management protocols used in the study (different clinics and teams, different interventions in clinics and different monitoring methods). The guideline development group further noted that the paper was not likely to have been peer reviewed, the 2 groups were not truly randomised, as randomisation depended on availability of the memory meters, and the intensive therapy group (who had memory meters) only performed 5 plus or minus 2 home glucose tests each day rather than 7 tests.

The guideline development group had concerns that advising women to test 7 times a day would represent a change in practice for women with gestational diabetes and might prove unpopular.

5.1.1.7.5 *Other considerations*

The guideline development group had some concern that the Latina population in the last study might limit the applicability of the findings to a UK population.

The group also expressed uncertainty regarding whether overall glucose control or peak glucose values influence fetal growth. Although there have been suggestions that postprandial peaks are more important, the HAPO 2008 study suggests that both fasting and postprandial glucose concentrations influence fetal growth.

5.1.1.8 Key conclusions

The guideline development group concluded that for all women with diabetes both pre- and postprandial testing was important during pregnancy and that it should be performed 7 times a day for women with type 1 or insulin-requiring type 2 or gestational diabetes.

Women who achieved glucose regulation using diet or oral therapy or single dose intermediate or long-lasting insulin did not need to test preprandially and testing could be limited to a fasting sample and samples at 1 hour after meals every day.

5.1.1.9 Recommendations
The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

5.1.1.10 Research recommendations

19. Post-meal blood glucose testing in women with diabetes in pregnancy: is the 1 hour test more acceptable than the 2 hour test?

Why this is important

Self-monitoring of blood glucose is an important tool in the management of diabetes in pregnancy. Many studies have shown that post prandial hyperglycaemia is a predictor for fetal macrosomia and may contribute to neonatal hypoglycaemia. Current recommendations state that tests should be performed at either one or two hours post meals. Studies have demonstrated however, that the 1hour post prandial test is more likely to detect abnormal values which may require treatment and helps the person understand the relationship between food and blood glucose levels. Identifying acceptability of blood monitoring regimes using qualitative studies may improve both compliance and accuracy of testing and optimise pregnancy outcomes.

20. What is the optimum frequency of blood glucose testing in pregnancy in women with pre-existing diabetes who are not taking insulin?

The optimum frequency of blood glucose testing in pregnancy in women with pre-exsiting diabetes who are not taking insulin is unknown. While daily fasting blood glucose values in women on insulin are required to optimize the basal insulin dose and avoid nocturnal hypoglycaemia for women not taking insulin a daily fasting glucose is less informative as there is little day-to-day variability. Unlike women taking insulin there is no need to perform a pre-bedtime glucose value to lessen the risk of nocturnal hypoglycaemia. The frequency of blood glucose tests for other times in the day are currently recommended to be the same as for women on insulin. Randomised control trials are required to inform on the optimum frequency of blood glucose testing in pregnancy in women who are not taking insulin

5.1.2 Ketone monitoring

5.1.2.1 Review question

What is the effectiveness of blood ketone monitoring compared with urine ketone monitoring for women with type 1, type 2 or gestational diabetes during pregnancy?

5.1.2.2 Introduction

Ketones are derived from the breakdown of fat and can be used as a source of energy, for example during starvation. Ketones are usually present in very low concentrations in urine and blood in non-diabetic populations. The concentration of ketones in blood is normally less than 0.3 mmol/litre and they are usually undetectable by routine urine tests. Various factors can contribute to a raised concentration of ketones in the blood or urine, including metabolic

disorders (such as uncontrolled diabetes or weight loss), dehydration, low carbohydrate intake and individual variations in the threshold for ketonuria.

In someone with diabetes, increased ketone concentrations might indicate impending or established ketoacidosis (DKA). This serious condition can occur at relatively low blood glucose concentrations in pregnant women and requires urgent medical attention because of an increased risk of harm to the fetus. Although ketoacidosis is more common in women with type 1 diabetes, it has also been described in women with type 2 and gestational diabetes. Because DKA can profoundly compromise the wellbeing of both the woman and her baby (including maternal and fetal death), the 2008 guideline recommended that women with type 1 diabetes who are planning to become pregnant should be offered ketone testing strips and advised to test for ketonuria or ketonaemia if they become hyperglycaemic or unwell. In the absence of any evidence, this recommendation was based on a consensus of the guideline development group's knowledge and the best clinical practice at the time.

The 2008 guideline did not include research recommendations related to ketone monitoring in the preconception period.

5.1.2.3 Description of included studies

No studies were identified that assessed how blood ketones should be monitored during pregnancy.

5.1.2.4 Health economics profile

No health economic evidence was identified that considered blood ketone monitoring compared with urine ketone monitoring for women with type 1, type 2 or gestational diabetes during pregnancy.

This question was not prioritised for health economic evaluation as the guideline development group thought there were more important priorities.

5.1.2.5 Evidence to recommendations

5.1.2.5.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the following maternal outcomes for this review:
- preterm birth (birth before 37^{+0} weeks' gestation; dichotomous or continuous data)
- non-routine hospital contact or assessment for ketosis (ketonaemia or ketonuria, however defined), including phone contact
- hospital admission for diabetic ketoacidosis
- maternal satisfaction.

The group also prioritised these fetal and neonatal outcomes:
- mortality – perinatal and neonatal death
- neonatal intensive care unit (NICU) length of stay greater than 24 hours.

The outcomes chosen were considered to be clinically meaningful for the woman and baby, could be reliably assessed in clinical research studies and were expected to be commonly reported in the evidence available for inclusion.

The guideline development group decided to prioritise non-routine hospital contact or assessment for ketosis as an outcome because pregnant women with diabetes will be tested routinely for ketones.

The group recognised that maternal mortality in association with diabetic ketoacidosis is a possibility, but agreed that it is a rare event in UK clinical settings and so it was not prioritised for this review.

5.1.2.5.2 *Consideration of clinical benefits and harms*

The guideline development group recognised the potential health risk to babies from high concentrations of ketones in blood or urine of pregnant women with diabetes. Although high maternal ketone levels during pregnancy have not been proven conclusively to be dangerous to the fetus, neither have they have been proven to be harmless. The 2008 guideline assumed that there was a benefit in measuring ketones in women who are pregnant if they become hyperglycaemic or unwell. This was consistent with the NICE clinical guideline on type 1 diabetes which recommends monitoring blood or urine for the presence of ketones. The guideline development group for this guideline agreed with the previous guideline that there are potential benefits in the ability to measure blood ketones in women who are pregnant if the woman is unwell or has very high blood glucose values. The group believed the benefits in terms of prompt recognition of DKA and its treatment were greater than the harms of unnecessary testing.

The group recognised that one of the main advantages of using a blood ketone test is that it can provide an accurate, convenient and timely assessment of ketosis. In contrast, urine testing only provides a qualitative measure of any ketosis over the preceding period since the woman last passed urine. (This is discussed at greater length in the section on biochemical issues below). Furthermore, it does not precisely correlate with blood ketone concentration which is more likely to reflect the severity of DKA. Finally, blood ketone levels increase before urine ketone levels, allowing an earlier identification of any metabolic deterioration.

In summary, the guideline development group felt that blood ketone tests give a specific value that more accurately reflects the level of ketosis and its severity, thus leading to more timely recognition of DKA and earlier treatment.

5.1.2.5.3 *Consideration of health benefits and resource uses*

Although the guideline development group noted that blood testing strips are more expensive than those used for urine testing, and notwithstanding that a full health economic analysis was not undertaken, they were of the view that the convenience of undertaking blood testing for ketones (which can be performed at the same time as testing blood glucose levels and with the same device) would result in greater patient compliance than using urine testing strips. In turn this would lead to a more prompt response and treatment following an abnormal result, which should result in a lower overall cost as suggested by a study in young people with type 1 diabetes (Laffel et al., 2006). In this study it was shown that the higher costs of blood ketone testing were offset by reduced treatment costs for DKA as a result of lower rates of hospitalisation.

The guideline development group noted that although blood ketone testing meters are not universally available for all diabetic patients, in general many patients with an increased risk of DKA (such as women with type 1 diabetes and unstable glucose control, and those on insulin pumps) would already have been issued with one.

The group was of the view, because of the serious risk to the fetus of DKA, that all pregnant women with type 1 diabetes should be issued with blood ketone monitoring equipment and receive appropriate training on its use and advice on when to test. Most meters are able to measure both blood glucose and blood ketone concentrations.

However, the guideline development group felt that, although DKA has been reported in pregnant women with type 2 diabetes and gestational diabetes, this was less common than in women with type 1 diabetes. They did not, therefore, feel that it was justified to issue ketone monitoring equipment routinely to women with type 2 diabetes or gestational diabetes, although they recommended that women should be advised to seek prompt medical attention if they became hyperglycaemic or unwell in order to exclude DKA.

The group noted that no new evidence was found to establish the most effective method for monitoring ketones in women with type 1, type 2 and gestational diabetes during pregnancy. In the absence of pregnancy-specific evidence, the group relied in part on consensus opinion and current best clinical practice.

5.1.2.5.4 Other considerations

Practical issues

The guideline development group noted that for many patients with diabetes the convenience of testing blood for both glucose and ketones at the same time from a single capillary sample represented a distinct advantage of blood testing for ketones. Also, many people with diabetes (particularly the young) find urine testing inconvenient and unpleasant, and would rather avoid doing it.

Biochemical factors

Urine ketone testing strips are based on the nitroprusside reaction, which primarily detects aceto-acetate and acetone. The strips are read visually, comparing the colour obtained with a colour-coded chart, so do not require instrumentation for automatic reading. With this method the presence and quantity of ketones is reported subjectively either as 'negative', 'small', 'moderate' or 'large'.

Blood ketone testing strips measure beta-hydroxybutyric acid, which is the predominant ketone body in ketoacidosis. The strip is read by a meter using a chemical process that does not require a colour chart and gives an accurate blood concentration. Moreover, blood beta-hydroxybutyric acid measurements are used to assess the severity of DKA and inform insulin and fluid replacement, and help monitor response to treatment.

The guideline development group also noted that urine strips degrade over time and their accuracy is reduced after 6 months. In addition, urine strips can give a false-negative reading, either because:

- they have been exposed to the air for long periods
- the urine specimen is highly acidic
- the women is using certain prescription medicines (such L-DOPA metabolites)
- there are high levels of phenylketones.

Other guidelines in development

During the development of this guideline, NICE established liaison between the guideline development groups that were concurrently updating several diabetic guidelines, with the aim of aligning recommendations (the other guidelines were on type 1 diabetes in adults, type 2 diabetes in adults, and diabetes in children and young people). As a result, the guideline development group for this guideline was aware that the group working on the guideline for diabetes in children and young people was recommending blood ketone testing rather than urine testing and that the group working on the guideline for type 1 diabetes in adults was recommending it for in-patients.

5.1.2.6 Key conclusions

Due to the lack of new evidence, the guideline development group used their knowledge and understanding of best clinical practice at the time to review the 2008 recommendation. The discussions and conclusions of the guideline development groups working on the guidelines for type 1 diabetes in adults and diabetes in children and young people were also noted and discussed. The group working on this guideline agreed that because blood ketone testing can provide more accurate information about the severity of ketosis, as well as helping monitor the response to therapy, it should be recommended in pregnant women with type 1 diabetes if they become hyperglycaemic or unwell in preference to urine testing. The group also argued that blood testing ketones could be logistically easier than urine in that it could be carried out at the same time as a capillary test was performed for glucose testing.

The group recognised that it is important to inform pregnant women with type 2 diabetes and gestational diabetes to seek urgent medical advice if they become hyperglycaemic or unwell, in order to detect possible DKA and avoid further metabolic deterioration that could lead to

significant maternal and fetal morbidity and even mortality. For the same reason, the group believed that it is essential for healthcare professionals to test routinely for ketonaemia in all pregnant women with diabetes who present with hyperglycaemia or who are otherwise unwell.

5.1.2.7 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

5.1.2.8 Research recommendations

21. What is the value of ketone testing in pregnancy in women with type 2 diabetes or GDM?

Why this is important

Ketoacidosis develops more rapidly with hyperglycaemia in pregnancy and also with lower levels of hyperglycaemia. If it occurs it requires high dependency care and is associated with a significant risk of fetal death. Women with type I diabetes are advised to check for ketones in their blood if they have sustained hyperglycaemia or feel unwell to check whether ketoacidosis is developing. However this advice is traditionally not usually given to women with type 2 diabetes, but reports do show that these women and even occasionally women with gestational diabetes may develop ketoacidosis.

Accordingly there is a need to perform studies on the prevalence of significant ketonaemia and ketonuria in women with type 2 diabetes and gestational diabetes and to randomise women who meet the pre-specified diagnostic criteria to either an intervention or routine management to determine whether this will reduce the risk of diabetic ketoacidosis.

5.2 Target blood glucose values for women with type 1, type 2 or gestational diabetes during pregnancy

5.2.1 Review question

What are the target ranges for blood glucose in women with type 1, type 2 or gestational diabetes during pregnancy?

mm   Level 2 critical care is defined as care for patients requiring detailed observation or intervention, including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care.

5.2.2 Introduction

The purpose of this review was to determine the optimal target values for blood glucose in women with type 1, type 2 or gestational diabetes during pregnancy. The search for this question included randomised controlled trials (RCTs), systematic reviews and comparative observational studies. Non-comparative observational studies were to be included only if no comparative studies were identified. The same search was used to identify studies for this review and the reviews of target values for blood glucose pre-conception, target values for HbA1c pre-conception and during pregnancy, and for blood glucose and HbA1c monitoring during pregnancy.

The guideline development group defined 8 maternal and neonatal priority outcomes.

Maternal outcomes were:
- mode of birth (spontaneous vaginal, operative vaginal or elective or emergency caesarean section)
- pre-eclampsia
- HbA1c levels at any time during pregnancy
- hypoglycaemic episodes at any time during pregnancy.

Neonatal outcomes were:
- large for gestational age
- neonatal intensive care unit (NICU) length of stay greater than 24 hours
- shoulder dystocia
- mortality, whether perinatal (stillbirth and death up to 7 days after birth) or neonatal (death up to 28 days after birth).

The original review question in the 2008 guideline was "What are the target ranges for blood glucose during pregnancy?" Studies that examined glycaemic control using blood glucose or HbA1c measurements were included as evidence in the chapter.

A more specific approach has been taken for this update. Four separate review questions have been stipulated to examine blood glucose or HbA1c measurements prior to conception and during pregnancy.

Sixteen studies were included in the chapter in the original guideline on target values during pregnancy. The majority of these studies examined HbA1c and were considered as part of the current review protocol. Six of the 16 studies were assessed for their relevance to this review. One was included (Landon et al., 1987) and five were excluded (Evers et al., 2002, Langer et al., 1994, Jovanovic et al., 1981, Jovonovic Peterson et al., 1991, Karlsson & Kjellmer 1972).

5.2.3 Description of included studies

Overall, 6 studies were identified for inclusion in this review. Three studies were RCTs (DeMarini et al., 1994; Farrag, 1987; Sacks et al., 2006), 1 a secondary analysis of RCT data (Rowan et al., 2010) and 2 were retrospective cohort studies (Combs et al., 1992; Landon et al., 1987). Locations included the USA (Combs et al., 1992; DeMarini et al., 1994; Landon et al., 1987; Sacks et al., 2006), Australia and New Zealand (Rowan et al., 2010) and Saudia Arabia (Farrag, 1987). The number of participants ranged from 22 to 724. Participants had White class diabetes B to D (Landon et al., 1986), White class diabetes B or C (Farrag, 1987), gestational diabetes (Rowan et al., 2010), White class diabetes B to RF (Combs et al., 1992), White class B to RT (DeMarini et al., 1994) and type 1 diabetes mellitus (Sacks et al., 2006). The ethnicity of participants in the 2 studies where it was reported was primarily white (Rowan et al., 2010; Sacks et al., 2006).
Optimal blood glucose control ranged from 5.3 mmol/litre to 9.7 mmol/litre, depending upon the type of blood glucose measurement taken. Three studies used postprandial blood glucose (Combs et al., 1992; DeMarini et al., 1994; Rowan et al., 2010), 2 studies used mean blood glucose, which included fasting plasma glucose measurements (Landon et al., 1987; Sacks et al., 2006) and 1 study reported fasting blood glucose (Rowan et al., 2010).

One study did not specify the blood glucose measurements to which targets were related (Farrag, 1987) but it was assumed that targets related to fasting blood glucose due to the low values assigned. Two studies did not implement specific blood glucose target values for participants to reach (Landon et al., 1987; Rowan et al., 2010), instead using thresholds applied post hoc for optimal glucose control. When included as an outcome, 2 studies measured HbA1 rather than HbA1c (DeMarini et al., 1994; Landon et al., 1987). Mean HbA1 values were converted to HbA1c using the Michigan formula.

Of the guideline development group's priority outcomes, evidence was available for mode of birth (Landon et al., 1987; Sacks et al., 2006), pre-eclampsia (Rowan et al., 2010), HbA1c during pregnancy (DeMarini et al., 1994; Landon et al., 1987; Rowan et al., 2010; Sacks et al., 2006), maternal hypoglycaemic episodes (Farrag, 1987), perinatal mortality (Farrag, 1987) and large for gestational age (Combs et al., 1992; Landon et al., 1987; Rowan et al., 2010). One study (DeMarini et al., 1994) used the term 'glycosylated haemoglobin' rather than HbA1c and 1 study specified that HbA1 was measured (Landon et al., 1987).

5.2.4 Evidence profile

GRADE profiles are presented according to glucose thresholds. Reasons for the use of each threshold are given in Table 51.

Table 51: Blood glucose thresholds for optimal control used in GRADE profiles with associated reasons

Blood glucose threshold (Timing of measurement)	Reason for use of threshold	Applied by study or NCC-WCH technical team?
5.3 mmol/litre (Rowan et al., 2010) (Fasting blood glucose)	Based on the cut-off between tertiles 2 and 3 for fasting glucose. The cut-point between tertiles 1 and 2 was considered to be too tight for women with diabetes. Participants had gestational diabetes.	NCC-WCH
5.6 mmol/litre (Farrag, 1987) (Presumed fasting blood glucose)	Women were assigned to 3 different treatment groups. The groups were dichotomised at 5.6 mmol/litre based on the assumption that values were for fasting blood glucose. This assumption is in line with a Cochrane review which included this study.	NCC-WCH
6.1 mmol/litre (Landon et al., 1987) (Mean blood glucose estimate was averaged from fasting and preprandial samples)	Mean capillary blood glucose which was an average of fasting and preprandial glucose, was dichotomised post-hoc according to level of control achieved. This threshold was specified as <110 mg/dl or >110 mg/dl (6.1 mmol/litre). It is unclear whether the value of 110 mg/dl itself is included as optimal control or sub-optimal.	Study
6.4 mmol/litre (Rowan et al., 2010) (2 hour post prandial measurement)	Based on the cut-off between tertiles 2 and 3 for postprandial glucose. The cut-point between tertiles 1 and 2 was considered to be too tight for women with diabetes. Participants had gestational diabetes.	NCC-WCH

Blood glucose threshold (Timing of measurement)	Reason for use of threshold	Applied by study or NCC-WCH technical team?
6.7 mmol/litre and 7.8 mmol/litre (DeMarini et al., 1994) (1.5 hour post prandial measurement)	These values represent the targets assigned to each treatment group for postprandial blood glucose. The target of 6.7 mmol/litre was chosen to represent euglycaemia. The target of 7.8 mmol/litre was chosen to represent standard community care.	Study
7.8 mmol/litre (Combs et al., 1992) (Most of the measurements were taken at 1 hour, but some were between 1.5 to 2 hours post prandial)	According to the target value set for treatment by the study authors of postprandial glucose <7.8 mmol/litre. No rationale was provided for this target.	NCC-WCH
≤ 7.8 mmol/litre and ≤9.7 mmol/litre (Sacks et al., 2006) (Data presented were from a mean blood glucose estimate from pre and 1 hour post prandial samples)	Based on the upper end of the target values women were assigned to in the study. Blood glucose values were based on an average of fasting and postprandial values. The targets were chosen based on previous reports in relation to spontaneous abortions, malformations and perinatal mortality (Rosenn et al., 1994; Sacks et al., 1997).	NCC-WCH

The GRADE profiles for this question are presented in Tables 52 to 58.

Blood glucose threshold (Timing of measurement)	Reason for use of threshold	Applied by study or NCC-WCH technical team?

Table 52: GRADE profile for comparison of fasting blood glucose less than 5.3 mmol/litre versus 5.3 mmol/litre or more in women with gestational diabetes

Number of studies	Number of women		Effect		Quality	Design	Quality assessment				
	Intervention (<5.3 mmol/litre)	Comparator (≥5.3 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Pre-eclampsia											
1 (Rowan et al., 2010)	57/486	59/238	RR 0.47 (0.27 to 0.83)[a]	51 fewer per 1000 (from 16 to 70 fewer per 1000)	Very low[b]	Secondary analysis of RCT data	Serious[1]	No serious inconsistency[2]	Very serious[3]	Serious imprecision[4]	Yes[5]
Large for gestational age											
1 (Rowan et al., 2010)	22/486	23/238	RR 0.48 (0.35 to 0.67)[a]	128 fewer per 1000 (from 81 to 160 fewer per 1000)	Very low[b,c]	Secondary analysis of RCT data	Serious[1]	No serious inconsistency[2]	Very serious[3]	No serious imprecision[6]	Yes[5]

CI confidence interval, RR relative risk
a. Calculated by NCC-WCH technical team.
b. Study quality started as moderate due to the use of secondary analysis of randomised controlled trial data.
c. The study was rated up for large effect size however other serious bias and very serious indirectness in the study design meant that this did not impact on the overall study quality.
1. Selection bias as very strict inclusion/exclusion criteria were used in the original trial.
2. Single study analysis.
3. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc. Dichotomisation to obtain a blood glucose threshold was applied by the NCC-WCH technical team as tertiles of blood glucose levels were used to group results.
4. Confidence interval for the RR crosses RR=0.75.
5. The study was carried out in the Australia and New Zealand. Participants had gestational diabetes. Ethnicity was 51% Caucasian, 21% Polynesian and 28% Asian or other.
6. Rated up for large effect size

Table 53: GRADE profile for comparison of fasting blood glucose less than 5.6 mmol/litre versus 5.6 mmol/litre or more in women with White class diabetes B and C (type 1 diabetes)

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	Intervention (<5.6 mmol/litre)	Comparator (≥5.6 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Maternal hypoglycaemia											
1 (Farrag 1987)	7/16	0/44	RR 39.71 (2.26 to 697.01)[b]	Not calculable	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	No serious imprecision	Yes[7,8]
Pre-eclampsia											
1 (Farrag 1987)	1/16	3/44	RR 0.92 (0.10 to 8.59)[b]	5 fewer per 1000 (from 61 fewer to 518 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6]	Yes[7,8]
Mode of delivery (caesarean section)											
1 (Farrag 1987)	2/16	9/44	RR 0.62 (0.15 to 2.64)[b]	78 fewer per 1000 (from 174 fewer to 335 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6]	Yes[7,8]
Large for gestational age											
1 (Farrag 1987)	0/16	13/44	RR 0.10 (0.006 to 1.68)[b]	266 fewer per 1000 (from 294 fewer to 201 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6]	Yes[7,8]
Perinatal mortality											
1 (Farrag 1987)	0/16	2/44	RR 0.53 (0.03 to 11.14)[b]	21 fewer per 1000 (from 44 fewer to 461 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[6]	Yes[7,8]	

CI confidence interval, RR relative risk

a. Targets were assumed to be for fasting plasma glucose by the NCC-WCH technical team (see point 5).

b. Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.

1. Randomisation methods are not described and group numbers were imbalanced (group A=16, group B=29, group C=15).

2. Single study analysis.

3. Targets assigned to each group were < 5.6mmol/litre for group A, 5.6 to 6.7mmol/litre for group B and 6.7 to 8.9mmol/litre for group C. Numbers of women who achieved targets were not reported however mean blood glucose values were 5.0mmol/litre in group A, 6.1mmol/litre in group B and 8.4mmol/litre in group C.

4. Blood glucose measurements were determined in hospital rather than by self-monitoring by women.

5. It is not clear whether targets assigned were for fasting or postprandial blood glucose. It was assumed by the NCC-WCH technical team that targets were for fasting blood glucose due to the use of low values. This is in line with the conclusion of the Cochrane review which included this study.

6. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.

7. The study was carried out in Saudi Arabia. Participants were White class B or C. Ethnicity was not explicitly reported however all women were Saudi.

8. Dichotomisation of target groups was performed by the NCC-WCH technical team.

Table 54: GRADE profile for comparison of mean capillary blood glucose[a] less than 6.1 mmol/litre[b] in women with White class diabetes B to D

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	Intervention (lower target value)	Comparator (higher target value)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
Mean HbA1c during 3rd trimester											
1 (Landon et al., 1987)	43 Mean=5.9 ± 0.9[c]	32 Mean = 7.5 ± 1.1[d]	NA	MD -1.6 (-2.1 to -1.1)[e]	Very low	Retrospective chart review	Serious[1,2]	No serious inconsistency[3]	Very serious[4,5,6]	No serious imprecision[7]	Yes[8]
Mode of delivery (caesarean section)											
1 (Landon et al., 87)	20/43	16/32	RR 0.93 (0.58 to 1.49)[c]	35 fewer per 1000 (from 210 fewer to 245 more per 1000)	Very low	Retrospective chart review	Serious[1,2]	No serious inconsistency[3]	Very serious[4,5,6]	Very serious[9]	Yes[8]
Large for gestational age											
1 (Landon et al., 1987)	4/43	11/32	RR 0.27 (0.09 to 0.77)[c]	251 fewer per 1000 (from 79 to 313 fewer per 1000)	Very low	Retrospective chart review	Serious[1,2]	No serious inconsistency[3]	Very serious[4,5,6]	Serious[10]	Yes[8]

CI confidence interval, MD mean difference, NA not applicable, RR relative risk

a. Mean capillary blood glucose was calculated from a minimum of 16 weeks (>450 samples) of values from daily fasting and three preprandial (11am, before dinner and at bedtime) sampling throughout the second and third trimesters.

b. The threshold for optimal glucose control was specified as < 110mg/dl or > 110mg/dl. It is unclear whether the value of 110mg/dl itself is included as optimal control or sub-optimal.

c. Values quoted are for HbA1c. Using the Michigan formula (HbA1c=0.9 HbA1 + 0.05) mean HbA1c is 5.4%. It was not possible to convert the standard deviation to HbA1c.

d. Values quoted are for HbA1c. Using the Michigan formula (HbA1c =0.9 HbA1 + 0.05) mean HbA1c is 6.8%. It was not possible to convert the standard deviation to HbA1c.

e. Calculated by NCC-WCH technical team.

1. Selection bias as only two-thirds of admissions of pregnant diabetic women were included in the study; reasons for this were not provided.

2. The cut-off for optimal control of 110mg/dl using mean capillary glucose was specified post-hoc; possible misclassification bias.

3. Single study analysis.

4. Mean blood glucose, which included fasting plasma glucose measurements, was used as a proxy for postprandial glucose.

5. The study measured HbA1 rather than HbA1c. Mean differences are calculated based on HbA1 values.

6. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc.

7. Confidence interval does not span more than one zone. MID calculated by NCC-WCH technical team as 0.63 using sample means and standard deviations.

8. The study was carried out in the United States of America. Participants were White class B to D. Ethnicity was not reported.

9. Confidence interval for the RR crosses the line of no effect and RR=0.75 and RR=1.25.

10. Confidence interval for the RR crosses RR=0.75.

Table 55: GRADE profile for comparison of 2 hour postprandial blood glucose less than 6.4 mmol/litre versus 6.4 mmol/litre or more in women with gestational diabetes

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (< 6.4 mmol/litre)	Comparator (≥ 6.4 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Pre-eclampsia											
1 (Rowan et al., 2010)	19/486	26/238	RR 0.36 (0.30 to 0.43)[a]	70 fewer per 1000 (from 62 to 76 fewer per 1000)	Very low[b,c]	Secondary analysis of RCT data	Serious[1]	No serious inconsistency[2]	Very serious[3]	No serious imprecision[4]	Yes[5]
Large for gestational age											
1 (Rowan et l., 2010)	56/486	59/238	RR 0.46 (0.33 to 0.64)[a]	134 fewer per 1000 (from 89 to 166 fewer per 1000)	Very low[b,c]	Secondary analysis of RCT data	Serious[1]	No serious inconsistency[2]	Very serious[3]	No serious imprecision[4]	Yes[5]

CI confidence interval, MD mean difference, NA not applicable, RR relative risk,

a. Calculated by NCC-WCH technical team.

b. Study quality started as moderate due to the use of secondary analysis of randomised controlled trial data.The study was rated up for large effect size however other serious bias and very serious indirectness in the study design meant that this did not impact on the overall study quality.

1. Selection bias as very strict inclusion/exclusion criteria were used in the original trial.

2. Single study analysis.

3. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc. Dichotomisation to obtain a blood glucose threshold was applied by the NCC-WCH technical team as tertiles of blood glucose levels were used to group results.

4. Rated up for large effect size.

5. The study was carried out in the Australia and New Zealand. Participants had gestational diabetes. Ethnicity was 51% Caucasian, 21% Polynesian and 28% Asian or other.

Table 56: GRADE profile for comparison of strict control of 1.5 hour postprandial blood glucose (less than 6.7mmol/litre) versus customary control (less than 7.8 mmol/litre) in women with type 1 diabetes (White class diabetes B to RT)

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (<6.7 mmol/litre)	Comparator (<7.8 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mean HbA1c during 1st trimester											
1 (Demarini et al., 1994)	68 Mean = 9.4 ± 1.9[a]	69 Mean = 9.4 ± 1.8[a]	NA	MD 0.0 (-0.6 to 0.6)[b]	Very low	Randomised controlled trial	Very serious[1,2,3]	No serious inconsistency[4]	Serious[5]	Very serious[6]	Yes[7]
Mean HbA1c during 2nd trimester											
1 (Demaini et al., 1994)	68 Mean = 7.8 ± 1.4[c]	69 Mean = 7.7 ± 1.4[d]	NA	MD 0.1 (-0.4 to 0.6)[b]	Very low	Randomised controlled trial	Very serious[1,2,3]	No serious inconsistency[4]	Serious[5]	Very serious[8]	Yes[7]

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (<6.7 mmol/litre)	Comparator (<7.8 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mean HbA1c during 3rd trimester											
1 (Demrini et al., 1994)	68 Mean = 7.5 ± 1.2[e]	69 Mean = 7.6 ± 1.1[f]	NA	MD -0.1 (-0.5 to 0.3)[b]	Very low	Randomised controlled trial	Very serious[1,2,3]	No serious inconsistency[4]	Serious[5]	Very serious[9]	Yes[7]

CI confidence interval, MD mean difference, NA not applicable,

a. Values quoted are for HbA1. Using the Michigan formula (HbA1c = 0.9 HbA1 + 0.05) mean HbA1c is 8.5%. It was not possible to convert the standard deviation to HbA1c.

b. Calculated by the NCC-WCH technical team.

c. Values quoted are for HbA1. Using the Michigan formula (HbA1c = 0.9 HbA1 + 0.05) mean HbA1c is 7.1%. It was not possible to convert the standard deviation to HbA1c.

d. Values quoted are for HbA1. Using the Michigan formula (HbA1c = 0.9 HbA1 + 0.05) mean HbA1c is 7.0%. It was not possible to convert the standard deviation to HbA1c.

e. Values quoted are for HbA1. Using the Michigan formula (HbA1c = 0.9 HbA1 + 0.05) mean HbA1c is 6.8%. It was not possible to convert the standard deviation to HbA1c.

f. Values quoted are for HbA1. Using the Michigan formula (HbA1c = 0.9 HbA1 + 0.05) mean HbA1c is 6.9%. It was not possible to convert the standard deviation to HbA1c

1. Randomisation methods were not described and allocation concealment of participants, clinicians and investigators was not reported.

2. Women in the strict control (intervention) group received more frequent care during the study compared with the customary care (control) group.

3. The numbers of women who achieved the designated target values in each treatment group were not reported.

4. Single study analysis.

5. The study measured HbA1 rather than HbA1c. Mean differences are calculated based on HbA1 values.

6. Confidence interval spans all three zones. MID calculated by NCC-WCH technical team as 0.92 using sample means and standard deviations.

7. The study was carried out in the United States of America. Women had type 1 diabetes with White classification ranging from B to RT. Ethnicity was not reported.

8. Confidence interval spans all three zones. MID calculated by NCC-WCH technical team as 0.70 using sample means and standard deviations.

9. Confidence interval spans all three zones. MID calculated by NCC-WCH technical team as 0.57 using sample means and standard deviations.

Table 57: GRADE profile for comparison of 1 to 2 hour postprandial blood glucose of 7.8 mmol/litre or less versus more than 7.8 mmol/litre in women with White class diabetes B to RF

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (≤7.8 mmol/litre)	Comparator (>7.8 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Macrosomia at 29 to 32 weeks' gestation											
1 (Combs et al., 1992)	14/66	18/45	RR 0.53 (0.29 to 0.95)[a]	188 fewer per 1000 (from 20 to 284 fewer per 1000)	Very low	Retrospective review (prospective data)	Serious[1]	No serious inconsistency[2]	Serious[3,4]	Serious[5]	Yes[6]

CI confidence interval, MD mean difference, NA not applicable, RR relative risk,

a. Calculated by NCC-WCH technical team.

1. Selection bias as deliveries before 36 weeks' gestation were excluded.

2. Single study analysis.

3. Participants were not treated to reach specific target values; thresholds for optimal blood glucose were applied post hoc. Results for the association between postprandial blood glucose and macrosomia were reported only at 29 to 32 weeks' gestation based on significance in a regression model were grouped into arbitrary categories. Dichotomisation to obtain a blood glucose threshold was applied by the NCC-WCH technical team based on optimal control as described in the study's methods section.
4. Macrosomia is a proxy for large for gestational age infants.
5. Confidence interval for the RR crosses RR = 0.75.
6. The study was carried out in the United States of America. Participants were White class B to RF. Ethnicity was not reported.

Table 58: GRADE profile for comparison of mean blood glucosea of 7.8 mmol/litre or less versus 9.7 mmol/litre or less in women with type 1 diabetes mellitus

| Number of studies | Number of women | | Effect | | Quality | Design | Quality assessment | | | | Other considerations |
	Intervention (≤7.8 mmol/litre)	Comparator (≤9.7 mmol/litre)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	
HbA1c levels											
1st trimester											
1 (Sacks et al., 2006)	13 Mean = 6.3 ± 0.7	9 Mean = 7.5 ± 1.5	NA	MD -1.2 (-2.32 to -0.08)[b]	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6,7]	Yes[8]
2nd trimester											
1 (Sacks et al., 2006)	13 Mean = 5.6 ± 0.8	9 Mean = 6.1 ± 0.6	NA	MD -0.5 (-1.12 to 0.12)[b]	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6,9]	Yes[8]
3rd trimester											
1 (Sacks et al., 2006)	13 Mean = 5.9 ± 0.6	9 Mean = 6.2 ± 0.8	NA	MD -0.3 (-0.95 to 0.35)[b]	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6,10]	Yes[8]
Mode of delivery (caesarean)											
1 (Sacks et al., 2006)	8/13	6/9	RR: 0.92 (0.49 to 1.73)[b]	53 fewer per 1000 (from 340 fewer to 487 more per 1000)	Very low	Randomised controlled trial	Serious[1]	No serious inconsistency[2]	Very serious[3,4,5]	Very serious[6,11]	Yes[8]

CI confidence interval, MD mean difference, NA not applicable, RR relative risk,

a. Mean blood glucose values were derived from capillary plasma glucose self-monitoring results. Participants used memory based portable glucose meters to test capillary plasma glucose seven times a day, before and 1 hour after the first bite of each meal and at bedtime. Data were downloaded every 1-2 weeks when patients visited the office and were electronically transmitted to a central collection site.
b. Calculated by NCC-WCH technical team.
1. Attrition bias as 31% (4 out of 13) of participants in the less rigid target group were lost to follow-up.
2. Single study analysis.
3. Mean blood glucose, which included fasting plasma glucose measurements, was used as a proxy for postprandial glucose.

4. Women were targeted to achieve blood glucose values within an optimal range therefore no optimal threshold value exists. Upper boundaries of the range are quoted in the GRADE profile.

5. The number of women who achieved the specified target values was not reported.

6. Power calculations required 84 participants per group however only 13 (rigid) and 9 (less rigid) were used. Power was therefore very inadequate and likely caused imprecision.

7. Confidence interval for the MD crosses MD = -0.61. MID calculated by NCC-WCH technical team as 0.61 using sample means and standard deviations.

8. The study was carried out in the United States of America. Participants had type 1 diabetes. Ethnicity was 77% Caucasian, 33% other.

9. Confidence interval for the MD crosses MD = -0.38. MID calculated by NCC-WCH technical team as 0.38 using sample means and standard deviations.

10. Confidence interval for the MD crosses the line of no effect and MD = -0.34 and MD = 0.34. MID calculated by NCC-WCH technical team as 0.34 using sample means and standard deviations.

11. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25.

5.2.5 Evidence statements

5.2.5.1 Fasting blood glucose levels less than 5.3 mmol/litre versus 5.3 mmol/litre or more

One secondary analysis of trial data (n=724) found a reduction in risk of pre-eclampsia (RR 0.47, 95% CI 0.27 to 0.83) and of large for gestational age in babies (RR 0.48, 95% CI 0.35 to 0.67) of women with fasting blood glucose less than 5.3 mmol/litre compared with women with fasting blood glucose of 5.3 mmol/litre or more. The quality of evidence was very low.

5.2.5.2 Fasting blood glucose levels less than 5.6 mmol/litre versus 5.6 mmol/litre or more

One randomised controlled trial (n=60) found an increase in maternal hypoglycaemic episodes (RR 39.71, 95% CI 2.26 to 697.01) in women with fasting blood glucose less than 5.6 mmol/litre compared with women with fasting blood glucose of 5.6 mmol/litre or more. The same study found no evidence of a reduction in risk for pre-eclampsia (RR 0.92, 95% CI 0.10 to 8.59), caesarean delivery (RR 0.62, 95% CI 0.15 to 2.64), large for gestational age (RR 0.10, 95% CI 0.006 to 1.68) or perinatal mortality (RR 0.53, 95% CI 0.03 to 11.14) in women or the babies of women with fasting blood glucose less than 5.6 mmol/litre. The quality of the evidence for these outcomes was very low.

5.2.5.3 Mean capillary blood glucose levels less than 6.1 mmol/litre versus 6.1 mmol/litre or more

One retrospective cohort study (n=75) found a reduction in mean HbA1c levels in the third trimester (MD −1.6, 95% CI −2.1 to −1.1) as well as a reduced risk of large for gestational age (RR 0.27, 95% CI 0.09 to 0.77) in babies of women with mean capillary blood glucose less than 6.1 mmol/litre compared with women with mean capillary blood glucose greater than 6.1 mmol/litre. The same study found no evidence for an effect of mean capillary blood glucose less than 6.1 mmol/litre on risk of caearean section (RR 0.93, 95% CI 0.58 to 1.49). Mean capillary blood glucose was calculated from a minimum of 16 weeks of values from daily fasting and 3 preprandial sampling (11am, before dinner and at bedtime) throughout the second and third trimesters. This amounted to more than 450 samples per patient. The quality of evidence was very low.

5.2.5.4 Postprandial blood glucose levels less than 6.4 mmol/litre versus 6.4 mmol/litre or more

One secondary analysis of trial data (n=724) found a reduction in risk of pre-eclampsia (RR 0.36, 95% CI 0.30 to 0.43) and of large for gestational age (RR 0.46, 95% CI 0.33 to 0.64) in babies of women with postprandial blood glucose less than 6.4 mmol/litre compared with women with postprandial blood glucose of 6.4 mmol/litre or above. The quality of evidence was very low.

5.2.5.5 Postprandial blood glucose levels less than 6.7 mmol/litre versus more than 7.8 mmol/litre

One randomised controlled trial (n=137) found no evidence of a reduction in mean HbA1c levels in the first trimester (MD 0.0, 95% CI -0.6 to 0.6), second trimester (MD 0.1, 95% CI −0.4 to 0.6) or third trimester (MD −0.1, 95% CI −0.5 to 0.3) in women with postprandial blood glucose less than 6.7 mmol/litre compared with women with postprandial blood glucose more than 7.8 mmol/litre. The quality of evidence was very low.

5.2.5.6 Postprandial blood glucose levels 7.8 mmol/litre or less versus more than 7.8 mmol/litre

One retrospective cohort study (n=111) found a reduced risk of large for gestational age (RR 0.53 95% CI 0.29 to 0.95) in babies of women with postprandial blood glucose less than 7.8mmol/litre compared with women with postprandial blood glucose greater than 7.8mmol/litre. The quality of the evidence was very low.

5.2.5.7 Mean blood glucose levels of 7.8 mmol/litre or less versus 9.7 mmol/litre or less

One randomised controlled trial (n=22) found reduced mean HbA1c values during the first trimester (MD −1.2, 95% CI −2.32 to −0.08) in women with mean blood glucose values less than 7.8 mmol/litre compared with women with a mean blood glucose values less than 9.7 mmol/litre. The same study found no evidence of an effect of mean blood glucose on mean HbA1c values during the second (MD −0.5, 95% CI −1.12 to 0.12) or third (MD −0.3 95%, CI −0.95 to 0.35) trimesters or on caesarean section rates (RR 0.92, 95% CI 0.49 to 1.73). Mean blood glucose values were derived from results of capillary plasma glucose self-monitoring performed 7 times a day, before and 1 hour after the first bite of each meal and at bedtime using memor- based portable glucose meters. The quality of the evidence was very low.

No evidence was reported for either shoulder dystocia or NICU length of stay in any of the included studies.

5.2.6 Health economics profile

No health economic advice was identified that compared target ranges for blood glucose in women with type 1, type 2 or gestational diabetes during pregnancy.

This was not prioritised for health economic analysis. This was because although a target may affect the interventions and management used to assist the patient in achieving that target, the target does not incur an opportunity cost.

5.2.7 Evidence to recommendations

5.2.7.1 Relative value placed on the outcomes considered

The guideline development group prioritised pre-eclampsia and maternal hypoglycaemic episodes for maternal outcomes and large for gestational age and shoulder dystocia for neonatal outcomes.

The group noted that data from the HAPO study (HAPO Study Cooperative Research Group et al., 2008) demonstrated a linear relationship between maternal blood glucose and the risk of complications such as macrosomia. Thus, in theory, blood glucose values in women with any form of diabetes should be kept as close to the non-diabetic range as possible. However, the group acknowledged the difficulties of safely achieving this in practice because of the risk of hypoglycaemia.

Therefore, in making recommendations about target values for women with diabetes in pregnancy, the group inclined to use those values for which the evidence showed some benefit. Accordingly, from the evidence they suggested that the following would be reasonable targets:

*   fasting level – less than 5.3 or 5.6 mmol/litre (Rowan et al. [2010] reported a lower incidence of pre-eclampsia and large for gestational age with a target threshold of 5.3 mmol/litre, but Farrag [1987] reported a higher incidence of maternal hypoglycaemic episodes with a target threshold of 5.6 mmol/litre.)
*   1 hour value – less than 7.8 mmol/litre (In a study of women who largely measured the 1 hour values, Combs et al. [1992] reported a lower incidence of large for gestational age with a target threshold of 7.8 mmol/litre.)
*   2 hour value – less than 6.4 mmol/litre (Rowan et al. [2010] reported a lower incidence of pre-eclampsia and large for gestational age with a target threshold of 6.4 mmol/litre.)

5.2.7.2 Consideration of clinical benefits and harms

Ideally, women should strive for blood glucose levels as near to normal as is safely achievable. For women taking insulin and glibenclamide there is a risk of hypoglycaemia and

the guideline development group felt that it would be sensible to provide a limit for the lower level of blood glucose for women on these treatments. However, there was no evidence identified in the review that could inform the group of this limit. The group therefore chose 4.0 mmol/litre because this was the 'safe' lower target value recommended by Diabetes UK. For women on diet and exercise or metformin the risk of hypoglycaemia was very low and the group did not feel that it was necessary to set a lower limit for women on these treatments.

The group commented that as the normal blood glucose values in non-diabetic women change in pregnancy, perhaps the targets ranges for diabetic women should be different at different stages of pregnancy. However, they acknowledged that there were no data to inform such guidance and that the target ranges recommended would inevitably have to apply to the whole of pregnancy. They noted that some of the studies used very short gestational intervals. Targets may have to be adjusted for individual women depending upon their personal circumstances and treatment. Women with gestational diabetes receiving diet and exercise therapy and/or metformin should be able to achieve near normal blood glucose values. That is less likely to be possible in women with type 1 or 2 diabetes or gestational diabetes who are receiving insulin or glibenclamide.

The other concern of setting low or near normal targets for women with diabetes in pregnancy which are difficult to achieve is that it could be setting women up to fail and result in them losing confidence in their ability to self manage their diabetes. This could potentially result in less engagement and worse control, perhaps resulting in worse outcomes.

If a woman presents with gestational diabetes at 30 weeks and is set targets, it may be too late to prevent some poor outcomes and she may still have a large for gestational age baby or develop pre-eclampsia. If a woman has a high blood glucose at 30 weeks it is likely that it was also high at 20 weeks. This is an issue which is especially relevant for women with gestational diabetes. Existing guidance means that diagnosis of gestational diabetes is often not made until the third trimester. By this stage the argument that it is 'too late to affect adverse outcomes' may apply. This concern was specifically expressed in relation to the study by Rowan et al. (2010).

5.2.7.3 Quality of evidence

The outcomes from each study were generally of very low quality. In the study of Combs et al. (1992) the postprandial value of less than or equal to 7.8 mmol/litre was measured at 1 hour in most patients but some women had samples taken between 1 and 2 hours. The authors of the study by Farrag (1987) did not specify the timing of the blood glucose measurements to which targets were related. It was assumed that targets related to fasting blood glucose, given the low values, and in accordance with a Cochrane review (Middleton et al., 2012) which included this study.

5.2.7.4 Other considerations

The inclusion of studies that reported laboratory measured blood glucose was considered by the guideline development group to be valid, even though women would be monitoring capillary samples. Clinical target ranges would have to be based upon capillary blood glucose concentrations.

5.2.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

5.2.9 Research recommendations

22. What is the role of CGM in helping women achieve blood glucose targets in pregnancy?

Why this is important

Continuous glucose monitoring (CGM) is a technology for measuring subcutaneous interstitial fluid glucose concentrations every few minutes. It is often used in conjunction with continuous subcutaneous insulin infusion (CSII) using an insulin pump. In combination, these technologies have been shown to improve glycaemic control by reducing glucose variability and the number and severity of hypoglycaemic episodes in non-pregnant adults. However there have been few systematic studies using the latest real-time devices in pregnant women. One of the main complications of diabetic pregnancy is fetal macrosomia and its associated problems of difficult delivery and neonatal hypoglycaemia. These problems are closely related to mean glucose levels in the late second and third trimesters of pregnancy. However, it remains uncertain whether the main driver for fetal growth is the fasting or post prandial blood glucose or the magnitude of the glycaemic variation. If CGM (± CSII) can be shown to improve glucose control in later pregnancy there is a real prospect of reducing a common and serious complication of diabetic pregnancy. An RCT of CGM versus conventional intermittent capillary blood glucose monitoring in pregnant women is urgently required. A pilot study looking at intermediate outcomes such as the incidence of fasting and postprandial hyperglycaemia and glycaemic variability could be followed with a much larger study exploring macrosomia rates if CGM was shown to be effective in terms of improved blood glucose control.

23. What is the role of telemedicine in helping women achieve blood glucose targets in pregnancy?

Why this is important

These is extensive well documented research to show that good glycaemic control in pregnancy reduces adverse pregnancy outcome such as macrosomia, operative delivery, instrumental delivery, shoulder dystocia, neonatal hypoglycaemia and admission to the neonatal intensive care unit. Research to investigate the role of telemedicine is assisting women in achieving target blood glucose levels is required and needs to explore women's access to healthcare through telemedicine and the acceptability of this method of communication to both the woman and healthcare professionals. An important goal of telemedicine is to improve both the women with pre-existing diabetes and healthcare professional's satisfaction with care. Aspects of satisfaction include acceptance, of the equipment, and the woman healthcare professionals' interaction. Studies are required to examine the clinical outcomes of women using telemedicine compared to women who did not

Randomised controlled trials of support using telemedicine versus conventional support for diabetic women during pregnancy would be the best way of exploring the value of these new technologies.

24. What sequence and/or combinations of therapies best enable women to achieve blood glucose targets?

Why this is important

Tight glycaemic control in pregnancy is necessary to reduce fetal malformation rates and macrosomia. For women with type 1 diabetes this is usually achieved with multiple insulin injections at meal times together with intermediate or long-acting insulin at night (so called basal-bolus or MDI). For women with type 2 diabetes on oral therapy, or gestational diabetes the best sequence and/or combination of treatments is less clear. There is now widespread agreement that metformin is first line treatment but it is unclear whether the addition of glibenclamide or basal or meal-time insulin should be the next therapeutic intervention. An RCT of glibenclamide versus basal versus meal-time insulin would answer this important question. Initially, glycaemic targets would be the intermediate outcome but this could be expanded to look at fetal macrosomia rates and neonatal complications.

25. What are the barriers that women experience to achieving blood glucose targets?

Why this is important

Achieving good blood glucose control both before and during pregnancy in women with pre-existing diabetes is vital for normal fetal development in the first trimester. Good control also helps to prevent macrosomia and other complications in the third trimester in women with pre-existing or gestational diabetes. Whereas many women manage to achieve these targets, a proportion of women continue to find it difficult to do so. A number of factors could be involved, such as health beliefs, a poor understanding of the importance of good blood glucose control, an inability to be able to comply with a demanding regimen of up to 7-times daily blood glucose testing, and the need to adjust insulin dosage. A better understanding of the barriers in this cohort of women is needed so that healthcare professionals can work to overcome them. Robust qualitative studies are needed to explore these barriers, with the aim of improving blood glucose control and fetal outcomes in pregnancy for women with pre-existing diabetes and women with gestational diabetes.

5.3 HbA1c values for women with type 1, type 2 or gestational diabetes during pregnancy – monitoring and target values

5.3.1 Monitoring

5.3.1.1 Review question

What is the effectiveness of HbA1c monitoring in predicting adverse outcomes in women with type 1, type 2 or gestational diabetes during pregnancy?

5.3.1.2 Introduction

In the 2008 guideline a recommendation was made regarding HbA1c monitoring in pregnancy which stated that HbA1c should not be used routinely for assessing glycaemic control in the second and third trimesters of pregnancy. This does not rule out monitoring HbA1c if clinically indicated and is not explicit about whether or not to monitor HbA1c in the first trimester, although this is generally considered to be useful in advising the woman of the risk of adverse pregnancy outcome.

The review question in this update evaluates the effectiveness of monitoring HbA1c in pregnant women with type 1, type 2 or gestational diabetes, specifically in the context of whether the 2008 guideline recommendation not to monitor HbA1c routinely in the second and third trimesters of pregnancy should be changed.

The review also considers the frequency of monitoring HbA1c, whether monitoring HbA1c is more effective than monitoring blood glucose alone and whether different monitoring strategies are appropriate in women with type 1, type 2 and gestational diabetes.

5.3.1.3 Description of included studies

No relevant studies were identified for inclusion in the current review.

5.3.1.4 Evidence profile

There is no GRADE profile as no relevant studies were identified.

5.3.1.5 Evidence statements

No relevant studies were identified for inclusion in this review.

5.3.1.6 Health economics profile

No health economic evidence was identified that addressed the effectiveness of HbA1c monitoring in predicting adverse outcomes in women with type 1, type 2 or gestational diabetes during pregnancy.

This was not prioritised for health economic analysis as the guideline development group considered that any recommendation which departed from current practice would only have a relatively small cost impact and that there would be very limited clinical data to inform such an analysis.

5.3.1.7 Evidence to recommendations

5.3.1.7.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised the following maternal outcomes for this review:
- mode of birth (spontaneous vaginal, operative vaginal, caesarean section [elective or emergency])
- pre-eclampsia (HbA1c may predict this)

The group also prioritised the following neonatal outcomes:
- large for gestational age (however defined in the study, for example using a customised measure based on gestational age and population norms; dichotomous data were preferred)
- neonatal intensive care unit (NICU) length of stay greater than 24 hours
- shoulder dystocia (as a specific example of birth trauma)
- neonatal hypoglycaemia (however defined)
- any congenital abnormality, regardless of gestational age
- mortality

The guideline development group prioritised any congenital abnormalities over preterm birth as an outcome because such abnormalities arise very early in pregnancy.

The group prioritised large for gestational age because babies of women with diabetes who are tested frequently are more likely to be smaller than babies of women who are tested less frequently.

The group recognised that there would be some overlap between NICU length of stay greater than 24 hours and presence of neonatal hypoglycaemia. The group prioritised neonatal hypoglycaemia because they considered that it was a more clinically useful

outcome than the presence of neonatal hyperinsulinaemia or hyper C-peptide-aemia. However, they acknowledged that hyper C-peptide-aemia may be important in defining future research priorities.

5.3.1.7.2 Consideration of clinical benefits and harms
<Insert Note here>

The guideline development group considered that a benefit of HbA1c monitoring is that it represents a retrospective average measure of glycaemic control. They wanted to establish whether HbA1c, particularly first-trimester HbA1c, could be useful (for example for counselling, fetal monitoring during pregnancy and evaluating the likelihood of needing neonatal intensive care).

The group noted several situations where HBA1c testing could be of particular value. For example, results of blood glucose monitoring may not be available in the clinic because women do not always bring their meters or diaries with them. Where this information is not available, knowledge of HbA1c results provides reassurance to clinicians and women in validating women's assertions that their glucose control is stable or improving. Also, where excessive fetal growth is of concern, HbA1c monitoring might highlight a need for more intensive glucose monitoring to enable more informed treatment adjustments or can confirm that there is no need to adjust insulin treatment to control growth if results correspond well to those for blood glucose. Another clinical scenario that the group identified related to late pregnancy. Where a women presents with a normal oral glucose tolerance test (OGTT) but glycosuria or a fetus that is assessed as being large for gestational age for late second trimester, an HbA1c result can be useful to determine whether there has been any glucose intolerance over the past 10 to 12 weeks, notwithstanding the OGTT result.

The group recognised that HbA1c has limitations in pregnancy because of changes in red cell turnover and the frequent occurrence of iron deficiency. Specifically, HbA1c tends to decrease in pregnancy. Also, in iron deficiency anaemia it can be less reliable. However, it can have value in being used as an audit tool of the process of care by checking once in each trimester. It has also been linked in population-based studies to pregnancy outcomes for mother and baby and forms part of the ongoing National Pregnancy in Diabetes audit (Murphy et al., 2013), and can be correlated to other outcomes.

The group was aware that there are alternatives to HbA1c monitoring, such as glycated albumin, fructosamine or 1,5-Anhydroglucitol monitoring. However, these assays are not widely available and there is limited robust data showing any advantage over HbA1c.

5.3.1.7.3 Consideration of health benefits and resource uses

The guideline development group considered whether HbA1c monitoring results would be useful as a biochemical test to determine which women should have a diagnostic OGTT. They concluded that HbA1c could be useful to identify those women with undiagnosed type 2 diabetes and provide an estimate for how long glucose dysregulation may have been present. This might inform discussions around increased surveillance for congenital anomaly if the hyperglycaemic period included embryogenesis. However, they acknowledged that there would be cost implications for more widespread HbA1c monitoring.

5.3.1.7.4 Other considerations

Variation in practice and the guidance from the 2008 guideline is not being followed for a variety of reasons.

The 2008 guideline noted that HbA1c had not been validated as a marker of average glycaemia in the second and third trimesters of pregnancy and because of physiological changes that occur in all pregnant women it could not be recommended for routine assessment of blood glucose control. There is a risk that an observed reduction in HbA1c in women with diabetes during the second and third trimesters of pregnancy might reflect

changes in red cell production or anaemia and would not necessarily indicate improved glycaemic control, and thus could be falsely reassuring. These concerns were the basis for the previous recommendation.

The group acknowledged that is difficult to conduct the study that would suggest target values for HbA1c. However, they were aware of several observational studies in large cohorts of women with pre-existing diabetes where there were associations between increasing levels of HbA1c and worsening outcomes for women and their babies, including stillbirth (Tennant et al., 2014; Glinianaia et al., 2012; Murphy et al., 2011; Murphy et al., 2013). In other words, the group was of the view that although there was no evidence that routine HbA1c testing in pregnancy would be useful in assessing blood glucose control, it was, nonetheless, a marker of risk of adverse outcome and could be of value in practice for that purpose. It is difficult to establish the normal reference ranges for pregnancy because of the impact of anaemia and increased red cell turnover, but the data from the aforementioned observational studies indicates that an HbA1c value in pregnancy above 48 mmol/mol (6.5%) is associated with an increasing risk of adverse outcome.

In the light of these considerations the group decided to recommend that HbA1c should not be used in a diabetic pregnancy to assess glucose control: however, it could be used in specific circumstances to assess the risk in those pregnancies with 48 mmol/mol (6.5%) as a threshold.

Furthermore, the group felt that a high HbA1c at the time of diagnosis in a woman with apparent gestational diabetes in early pregnancy would identify women at increased risk of type 2 diabetes. This was important as the management might be different from that offered to women with gestational diabetes. This might include undertaking retinal and renal screening, greater attention to the results of blood glucose monitoring, with an increased vigilance for the need for pharmacological treatment, and a different monitoring and surveillance strategy after delivery.

5.3.1.8 Key conclusions

The guideline development group noted that HbA1c monitoring in pregnancy was not recommended in the previous guideline. The current guideline development group agreed that there is no evidence to recommend its routine use in pregnancy as a measure of glucose control. It is not currently possible to advocate an alternative measure of average glycaemic control.

The group believed that HbA1c was an indicator of risk of adverse outcome in a diabetic pregnancy, with that risk increasing progressively above 48 mmol/mol (6.5%).

The group also believed that an increased HbA1c at the time of diagnosis of gestational diabetes in early pregnancy raised the possibilty that the woman had previously unrecognised type 2 diabetes.

5.3.1.9 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

5.3.2 Target values

The purpose of this review is to identify target values for HbA1c in women with type 1, type 2 or gestational diabetes during pregnancy. The search for this study included RCTs, systematic reviews and comparative observational studies. Non-comparative observational studies were to be included only if no comparative studies were identified. The same search was used to identify studies for this review and the reviews of target values for blood glucose pre-pregnancy and during pregnancy, target values for HbA1c pre-pregnancy and for blood glucose and HbA1c monitoring during pregnancy.

The guideline development group defined 8 priority outcomes for this review. Maternal

outcomes were:
- mode of birth (spontaneous vaginal, operative vaginal or elective or emergency caesarean section)
- pre-eclampsia
- hypoglycaemic episodes at any time during pregnancy.

Neonatal outcomes were:
- large for gestational age
- neonatal hypoglycaemia
- neonatal intensive care unit (NICU) length of stay greater than 24 hours
- shoulder dystocia
- mortality (defined as perinatal [stillbirth and death up to 7 days after birth] or neonatal [death up to 28 days after birth]).

The original review question in the 2008 guideline was "What are the target ranges for blood glucose during pregnancy?" Studies that examined glycaemic control using blood glucose or HbA1c measurements were included as evidence in the chapter. A more specific approach has been taken in this update. Four separate review questions have been stipulated to examine blood glucose or HbA1c measurements prior to conception and during pregnancy.

Sixteen studies were included in the previous guideline on target values during pregnancy. The majority of these studies examined HbA1c and were considered for inclusion in this review.

5.3.2.1 Review question

What is the target value for HbA1c in women with type 1, type 2 or gestational diabetes during pregnancy?

5.3.2.2 Description of included studies

Four studies met the inclusion criteria for this review. One was a prospective cohort study (Ekbom et al., 2008) and 3 were retrospective cohort studies (Barnes et al., 2013; Mikkelsen et al., 2011; Vaarasmaki et al., 2000). Studies were carried out in Denmark (Ekbom et al., 2008; Mikkelsen et al., 2011), Australia (Barnes et al., 2013) and Finland (Vaarasmaki et al., 2000).

Numbers of participants ranged from 148 to 1695. Women had gestational diabetes (Barnes et al., 2013; Mikkelsen et al., 2011), type 1 diabetes (Ekbom et al., 2008) and type 1 and 2 diabetes (White class B to R) (Vaarasmaki et al., 2000). HbA1c thresholds used as cut-offs for optimal control were 37 mmol/mol (5.5%) (Barnes et al., 2013), 38 mmol/mol (5.6%) (Mikkelsen et al., 2011), 48 mmol/mol (6.5%) (Ekbom et al., 2008) and at different thresholds of either between 20 and 42 mmol/mol (4.0% and 6.0%) or less than 64 mmol/mol (8.0%), depending upon the time period when women were treated (Vaarasmaki et al., 2000). The

first 3 studies used HbA1c, but the latter study used the term 'glycosylated haemoglobin' throughout (Vaarasmaki et al., 2000). The higher value of 64 mmol/mol (8.0%) used in this study was considered to be based on HbA1 due to the time period that data were collected. This value was therefore converted to HbA1c using the Michigan formula. Only 1 of the 4 studies set specific target values for women to achieve and reported the numbers who achieved the targets (Mikkelsen et al., 2011). One of the studies referred to the use of DCCT-aligned (Diabetes Control and Complications Trial) values for HbA1c in 10% of the women included in the study (Ekbom et al., 2008). The remaining 2 studies did not refer to the use of DCCT-alignment.

Of the guideline development group priority outcomes, 2 studies reported evidence for large for gestational age (Barnes et al., 2013; Mikkelsen et al., 2011), 1 for pre-eclampsia, shoulder dystocia and mode of delivery (Mikkelsen et al., 2011), 1 for neonatal hypoglycaemia (Mikkelsen et al., 2011), 1 for maternal hypoglycaemia (Ekbom et al., 2008) and 1 for NICU stay (Vaarasmaki et al., 2000).

5.3.2.3 Evidence profile

GRADE profiles are presented according to HbA1c thresholds. Reasons for the use of each threshold are given in Table 59.

Table 59: HbA1c thresholds for optimal control used in GRADE profiles with reasons for their use

HbA1c threshold	Reason for use of threshold	Type of diabetes	Applied by study or NCC-WCH technical team?
37 mmol/mol (5.5%) (Barnes et al., 2013)	Based on the output of backward logistic regression which aimed to determine significant predictors of large for gestational age.	Gestational diabetes	Study
38 mmol/mol (5.6%) (Mikkelsen et al., 2011)	Based on the treatment goal of care during pregnancy as recommended in Danish clinical guidelines for gestational diabetes.	Gestational diabetes	Study
48 mmol/mol (6.5%) (Ekbom et al., 2008)	Derived from the normal range for the relevant HbA1c assays in non-pregnant individuals used in the study. This was not based on centiles but on previous studies using these assays.	Type 1 diabetes	NCC-WCH
Between 20 and 42 mmol/mol (4.0% and 6.0%) and 64 mmol/mol (8.0%) (Vaarasmaki et al., 2000)	Optimal reference levels in the HbA1c assay between 1986 and 1992 64 mmol/mol (8.0%) and after 1992 20 to 42 mmol/mol (4.0% to 6.0%). The value of 64 mmol/mol (8.0%) is likely to be based on HbA1 rather than HbA1c. Using a standard conversion formula (http://www.med.umich.edu/mdrtc/cores/ChemCore/hemoa1c.htm) the corresponding HbA1c value for an HbA1 of 8.0% is 7.3%.	Type 1 and 2 diabetes (White class B to R)	Study

The evidence for this profile is presented in Tables 60 to 63.

Table 60: GRADE profile for comparison of HbA1c of 37 mmol/mol (5.5%) or less with HbA1c greater than 37 mmol/mol (5.5%) during pregnancy in women with gestational diabetes mellitus

| Number of studies | Number of women/infants | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (≤5.5%)	Comparator (>5.5%)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Large for gestational age (LGA)											
1 (Barnes et al., 2013)	NR	NR	OR 1.38 (1.01 to 1.90)[a]	NA	Very low	Retrospective audit	No serious bias	No serious inconsistency[1]	Serious[2]	Serious[3]	Yes[4,5]

CI confidence interval, NA not applicable, NR not reported, OR odds ratio

a Calculated by study authors using backward logistic regression to identify predictors of LGA.

1 Single study analysis.

2 Participants were not treated to reach specific target values; the threshold for optimal HbA1c were applied based on the results of previous studies indicating the upper limit of normal HbA1c during pregnancy.

3 Confidence interval for the OR crosses OR = 1.25.

4 The study was carried out in Australia. Women had gestational diabetes mellitus. Ethnicity was 36.7% South East Asian, 27.6% Middle Eastern, 22.4% European, 8.6% Indian and Pakistani, 1.9% 5 Samoan, 1.5% non-white African and 1.1% Maori.

Table 61: GRADE profile for comparison of HbA1c of 38 mmol/mol (5.6%) or less with HbA1c greater than 38 mmol/mol (5.6%) during pregnancy in women with gestational diabetes mellitus

| Number of studies | Number of women/infants | | Effect | | Quality | Design | Quality assessment | | | | |
	Intervention (≤5.6%)	Comparator (>5.6%)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Pre-eclampsia											
1 (Mikkelsen et al., 2011)	7/97	3/51	RR 1.23 (0.33 to 4.56)[a]	14 more per 1000 (from 39 fewer to 209 more per 1000)	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	No serious indirectness	Very serious[2]	Yes[3,4]
Mode of delivery (caesarean section)											
1 (Mikkelsen et al., 2011)	32/97	16/51	RR 1.05 (0.47 to 1.72)[a]	16 more per 1000 (from 166 fewer to 226 more per 1000)	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	No serious indirectness	Very serious[2]	Yes[3,4]
Large for gestational age											
1 (Mikkelsen et al., 2011)	18/97	20/51	RR 0.47 (0.27 to 0.81)[a]	208 fewer per 1000 (from 75 to 286 fewer per 1000)	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	No serious indirectness	Serious[5]	Yes[3,4]

Number of studies	Number of women/infants		Effect		Quality	Design	Quality assessment				
	Intervention (≤5.6%)	Comparator (>5.6%)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Shoulder dystocia[b]											
1 (Mikkelsen et al., 2011)	2/97	0/51	RR 2.65 (0.13 to 54.18)[a]	Not calculable	Very low	Retrospective cohort	No serious bias	No serious inconsistency[1]	No serious indirectness	Very serious[2]	Yes[3,4]
Neonatal hypoglycaemia											
1 (Mikkelsen et al., 2011)	4/97	7/51	RR 0.30 (0.15 to 0.60)[a]	96 fewer per 1000 (from 55 to 117 fewer per 1000)	Moderatec	Retrospective cohort	No serious bias	No serious inconsistency[1]	No serious indirectness	No serious imprecision	Yes[3,4]

CI confidence interval, RR relative risk

a. Calculated by the NCC-WCH technical team.

b. Shoulder dystocia was defined as shoulder delivery requiring obstetrical manoeuvres in addition to downward pressure, episiotomy or mild suprapubic pressure.

c .Rated up for large effect size.

1. Single study analysis.

2. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25.

3. The study was carried out in Denmark. Participants had gestational diabetes mellitus. Ethnicity was 57.4% White, 25.0% Middle Eastern, 7.4% Asian and 10.1% other.

4. 97/148 (66%) of women achieved the target of having a last measured HbA1c ≤5.6%.

5. Confidence interval for the RR crosses RR = 0.75.

Table 62: GRADE profile for comparison of HbA1c of 48 mmol/mol (6.5%) or less with HbA1c greater than 48 mmol/mol (6.5%) during pregnancy in women with type 1 diabetes mellitus

Number of studies	Number of women/infants		Effect		Quality	Design	Quality assessment				
	Intervention (≤6.5%)	Comparator (>6.5%)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Maternal hypoglycaemia											
1 (Ekbom et al., 2008)	22/131	11/82	RR 1.25 (0.65 to 2.44)[a]	34 more per 1000 (from 47 fewer to 193 more per 1000)	Very low	Prospective cohort	No serious bias	No serious inconsistency[1]	Serious[2]	Very serious[3]	Yes[4]

CI confidence interval, RR relative risk, NA not applicable

a. Calculated by the NCC-WCH technical team.

1. Single study analysis.

2. Participants were not treated to reach specific target values; thresholds for optimal HbA1c were applied post hoc. Dichotomisation of tertiles was performed by the NCC-WCH technical team.

3. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25.

4. The study was carried out in Denmark. Participants had type 1 diabetes. Ethnicity was White.

Table 63: GRADE profile for comparison of HbA1c between 20 and 42 mmol/mol (4.0% and 6.0%) or less than 56 mmol/mol (7.3%) with HbA1c greater than 42 mmol/mol (6.0%) or 56 mmol/mol (7.3%) or more during pregnancy in women with White class diabetes B to R

| Number of studies | Number of women/infants | | Effect | | | | Quality assessment | | | | |
	Intervention (between 4.0% and 6.0% or <7.3%)	Comparator (>6.0% or ≥7.3%)	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Stay in neonatal unit > 10 days											
1 (Vaarasmaki et al., 2000)	2/48	11/36	RR 0.14 (0.03 to 0.59)[b]	263 fewer per 1000 (from 125 to 296 fewer per 1000)	Very low	Retrospective cohort	Very serious[1,2]	No serious inconsistency[3]	Very serious[4,5,6]	No serious imprecision	Yes[7]

CI confidence interval, RR relative risk, NA not applicable

a. Based on an assumed HbA1 value of 8.0%. This value was converted to HbA1c by the NCC-WCH technical team using the Michigan formula (HbA¬1c = 0.9HbA1 + 0.05).

b. Calculated by the NCC-WCH technical team.

1. Substantial missing data; only 84/296 pregnancies had data available for glycaemic control determined by HbA1c.

2. Optimal HbA1c values changed across the time period of the study from < 7.3% to 4.0 to 6.0%; data for both thresholds were combined by study authors.

3. Single study analysis.

4. Participants were not treated to reach specific target values; thresholds for optimal HbA1c were applied post hoc.

5. This outcome was used as a proxy for NICU stay greater than 24 hours, as specified in the review protocol.

6. The study measured HbA1 rather than HbA1c.

7. The study was carried out in Finland. Participants were White class B to R. Ethnicity was not reported.

5.3.2.4 Evidence statements

5.3.2.4.1 *HbA1c level 37 mmol/mol (5.5%) versus more than 37 mmol/mol (5.5%)*

One study (number not reported) found an increase in the risk of large for gestational age neonates in women with an HbA1c greater than 37 mmol/mol (5.5%) compared with women with an HbA1c less than or equal to 37 mmol/mol (5.5%) (OR 1.38, 95% CI 1.01 to 1.90). The quality of the evidence for this outcome was very low.

5.3.2.4.2 *HbA1c level 38 mmol/mol (5.6%) versus more than 38 mmol/mol (5.6%)*

One study (n=148) found a reduction in risk of being large for gestational age (RR 0.47, 95% 0.27 to 0.81) and of hypoglycaemia (RR 0.30, 95% 0.15 to 0.60) in the neonates of women with gestational diabetes mellitus who obtained a treatment goal of HbA1c of 38 mmol/mol (5.6%) or less compared with those who did not achieve the treatment goal. The quality of evidence for these outcomes was very low and moderate, respectively. The same study found no difference between groups for the outcomes of pre-eclampsia (RR 1.23, 95% CI 0.33 to 4.56), shoulder dystocia (RR 2.65, 95% CI 0.13 to 54.18) or mode of delivery (RR 1.05, 95% CI 0.47 to 1.72). The quality of evidence for these outcomes was very low.

5.3.2.4.3 *HbA1c level 48 mmol/mol (6.5%) versus more than 48 mmol/mol (6.5%)*

One study (n=213) found no difference between groups in the risk of maternal hypoglycaemia in women with type 1 diabetes mellitus whose HbA1c levels were less than or equal to 48 mmol/mol (6.5%) compared with those whose HbA1c levels were greater than 48 mmol/mol (6.5%) RR 1.25 95% CI 0.65 to 2.44). The quality of evidence for this outcome was very low.

5.3.2.4.4 *HbA1c levels 20–42 mmol/mol (4.0% to 6.0%) or less than 56 mmol/mol (7.3%) versus more than 42 mmol/mol (6.0%) or 56 mmol/mol (7.3%)*

One study (n=84) found a reduced risk of neonatal unit stay of longer than 10 days associated with women with White class diabetes B to R who have HbA1c levels of 20–42 mmol/mol (4.0% to 6.0%) or less than 56 mmol/mol (7.3%) (converted from a reported HbA1 value of 8.0%) compared with those who have HbA1c levels greater than 42 mmol/mol (6.0%) or 56 mmol/mol (7.3%) or more (RR 0.14, 95% CI 0.03 to 0.59). The quality of evidence for this outcome was very low.

No evidence was identified for neonatal mortality in any of the studies included in this review.

5.3.2.5 Health economics profile

No health economic evidence was identified that addressed the target value for HbA1c in women with type 1, type 2 or gestational diabetes during pregnancy.

This was not prioritised for health economic analysis because although a target may affect the interventions and management used to assist the patient in achieving that target, a target of itself does not incur an opportunity cost.

5.3.2.6 Evidence to recommendations

5.3.2.6.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised mode of delivery and pre-eclampsia for the maternal outcomes and large for gestational age and shoulder dystocia for the neonatal outcomes.

5.3.2.6.2 Consideration of clinical benefits and harms

The clinical benefits and harms of setting HbA1c targets in pregnancy were not fully clarified by this review, with the 4 studies all having significant limitations and variable findings.

Both the Barnes et al. (2013) study and the Mikkelson et al. (2011) study suggested that a threshold of 37–38 mmol/mol (5.5–5.6%) did reduce the incidence of large for gestational age babies, but in the Mikkelson et al. (2011) study there was no reduction in the incidence of shoulder dystocia. Another apparent fetal/neonatal benefit of this target threshold was a significant reduction of neonatal hypoglycaemia. The guideline development group commented, however, that the population in this study may not have been reflective of all women with gestational diabetes, with the profile being skewed towards the more severe end of the spectrum, and this might explain some of the benefits to the infant. Nevertheless, there were benefits. There was no benefit to the woman in either the incidence of pre-eclampsia or caesarean section rates. But the group commented that this might be influenced by the fact that most of the women were recruited relatively late in pregnancy and the potential for improved glycaemic control improving outcome would be limited, and acknowledged that the incidence of large for gestational age babies was reduced..

The Ekbom et al. (2008) study used a higher target threshold (48 mmol/mol (6.5%) or less) and although no differences in outcomes were found, it was reassuring that the incidence of maternal hypoglycaemia was not increased in the group achieving 'tighter' control. However, it should be acknowledged that 45 mmol/mol (6.3%) is a relatively 'lenient' threshold, being above the upper limit of 'normal' for a person without diabetes. It is possible that if a lower threshold had been used then maternal hypoglycaemia might have occurred.

Finally, the Varaasmaki et al. (2000) study showed a lower incidence of stay greater than 10 days in the NICU. The group questioned the reasons the authors chose this outcome when such a length of stay is an uncommon outcome for infants of diabetic women. The more common outcome is a stay of less than 48 hours for neonatal hypoglycaemia. The paper did not provide the reasons for choosing this outcome nor the indications for NICU admission.

5.3.2.6.3 Consideration of health benefits and resource uses

Obtaining an HbA1c level incurs an opportunity cost, both in terms of laboratory analysis and staff time. There is uncertainty about what would be a normal range of HbA1c in pregnancy and how it may vary across different trimesters. There is a lack of good quality data on the use of HbA1c in pregnancy and therefore its routine use to assess glycaemic control does not currently justify the opportunity cost.

5.3.2.6.4 Quality of evidence

Overall the studies were of very low quality. The reasons for this have been discussed above.

The Mikkelsen et al. (2011) study recruited women late in pregnancy, which limits achievable improvement in outcome. Also, this study seems to include women from the more severe end of the gestational diabetes spectrum, and it cannot be assumed that data would apply to all women with gestational diabetes.

In the Ekbom et al. (2008) study maternal hypoglycaemia did not increase despite tighter control. However, hypoglycaemia was not defined and the chosen HbA1c threshold was not particularly low.

Although the guideline development group decided to retain the Vaarasmaki et al. (2000) study, it was very indirect, both for outcome of interest (the protocol agreed outcome for NICU stay was over 24 hours not 10 days) and differing HbA1c thresholds which were merged in the analysis. Finally, glycaemic control was defined according to values that were

not within the reference range based on the time period when data were collected (1986–92). In the light of these factors, the group decided to not to place too much weight on this study.

5.3.2.6.5 Other considerations

The guideline development group was concerned that normal ranges of HbA1c in pregnancy have not been established and different thresholds probably should be set for different trimesters. But there were no data to inform such a recommendation. Also, HbA1c values are lower if the woman has iron deficiency anaemia.

The review did not look at the use of HbA1c in women with gestational diabetes diagnosed in the first trimester to identify those who might actually have type 2 diabetes. The group was aware that the IADPSG diagnostic criteria suggest that a value of more than 6.5% at the first prenatal visit would identify women with 'overt diabetes'. As a consequence, the group felt that this might provide a specific indication for targeted HbA1c testing.

Given the paucity of good quality data, the guideline development group concurred with the 2008 guideline that HbA1c should not be used routinely to assess glycaemic control in diabetic pregnancies. However, the guideline development group for this guideline agreed, on the basis of their clinical experience and the reasoning above, that selective monitoring of HbA1c can be useful during pregnancy, although healthcare professionals need to be aware of its potential drawbacks. It is not currently possible to advocate an alternative measure of average glycaemic control.

Examples of when the test could be used as an adjunct to assessment of glycaemic control in selected cases included when women do not bring in their glucose monitor, in the absence of extensive home blood glucose monitoring and to motivate or reassure women.

The guideline development group agreed that the HbA1c value at booking was important to inform about the risk of fetal and neonatal outcome. Even if we do not have evidence of the usefulness of HbA1c after the first trimester, measuring HbA1c could be useful to inform the management of diabetes in pregnancy to avoid negative maternal or fetal outcomes.

In view of the lack of evidence about what normal values for HbA1c should be during pregnancy, the guideline development group felt unable to make any recommendation regarding target values for HbA1c.

5.3.2.6.6 Recommendations

The guideline development group did not make any recommendation regarding target values for HbA1c.

5.3.2.7 Research recommendations

26. What are the normal ranges for HbA1c in non-diabetic pregnancy?

Why this is important

HbA1c is an important widely used indicator of glycaemic control, indicating glycaemic control over the preceding 10-12 weeks, and is used outside pregnancy to indicate the quality of glycaemic control in the medium term. HbA1c is lower in pregnancy for a variety of reasons inluding increased red cell turnover and relative iron deficiency. Prospective longitudinal observational studies in women, confirmed by glucose tolerance testing to not have diabetes, documenting the normal ranges of HbA1c in pregnancy in the non-diabetic population are needed. Once these normal ranges for HbA1c during pregnancy are established, that will allow them to be used in assessing the quality of control in women with diabetes.

27. Which is the optimum timing of the post-prandial blood glucose test in pregnancy – 1, 1.5 or 2 hours?

Why this is important

The optimum timing of the post-prandial blood glucose test is the time of the peak blood glucose values following a meal. This result helps to inform insulin does adjustment for the prandial insulin as well as the assessment of overall glycaemic control. The timing of the peak of the blood glucose rise after meals is dependent on a number of factors including gastric emptying times and the glycaemic index of the diet and its fat content. Gastric emptying tends to be slower in pregnancy and in women with diabetic gastroparesis. It is uncertain to what extent changes in gastric emptying effect the timing of the glucose peak after meals throughout pregnancy. Studies need to be performed to determine the optimum time for the post-prandial blood glucose test in pregnancy as to ascertain whether this should be the same for each trimester.

28. What are the barriers to testing blood glucose frequently in pregnancy?

Why this is important

Achieving optimal glycaemic control during pregnancy in women with diabetes lessens the likelihood of adverse outcomes especially with respect to the fetus/newborn. Whilst many women manage to achieve these targets, there is a proportion of women who find it difficult to do so. A number of contributing factors could be involved, such as disbelief in the health benefits, a poor understanding of the importance of good blood glucose control, an inability to be able to comply with the a demanding regime of up to 7-times daily blood glucose testing. A better understanding of the barriers to testing blood glucose in this cohort of women is needed in order that health care professionals to can work with women to overcome them. Robust qualitative studies are needed to explore these barriers, with the aim of improving glycaemic control and fetal outcomes in pregnancy for women with pre-existing diabetes and gestational diabetes.

29. Are other glycosylated molecules better than HbA1c at summarising blood glucose control in pregnancy?

Why this is important

Increasing glycosylated haemoglobin in early pregnancy is associated with an increasing risk of congenital malformations and miscarriage and in late pregnancy with an increased risk of excessive fetal growth and neonatal morbidity. However, it assesses diabetes control over the previous 10-12 weeks and hence anomalous results are sometimes found which do not seem to concur with glycaemic control as observed on a day to day basis. Other molecules are also glycosylated but reflect glucose control over a shorter time period. It may be that these are of more value in advising clinicians about glucose control and hence the risks to the fetus. Prospective observational studies are required which compare glycosylated haemoglobin with other glycosylated molecules, with glucose control being assessed by continuous glucose monitoring and standard maternal and neonatal outcomes being studied.

5.4   Management of diabetes during pregnancy

5.4.1   Description of the evidence

5.4.1.1   Hypoglycaemia

Hypoglycaemia significantly affects maternal quality of life and increases the risk of physical injury. During pregnancy the frequency of hypoglycaemia may increase due to intensification of treatment, an impairment of counter-regulatory hormonal responses and an increased risk of hypoglycaemia unawareness.[214,215] Pregnancy nausea and vomiting can also contribute to hypoglycaemia due to fluctuations in carbohydrate ingestion. [EL = 2+]

A cohort study of 84 pregnant women with type 1 diabetes undergoing intensified treatment[68] found hypoglycaemia requiring third-party assistance occurred in 71% of women, with a peak incidence between 10–15 weeks of gestation. Consequences of maternal hypoglycaemia included several grand mal seizures, five episodes of cerebral oedema, and two road traffic accidents and comminuted fracture of the tibia and fibula. [EL = 2++]

5.4.1.2   Hyperemesis gravidarum

Severe nausea and vomiting in pregnant women with diabetes can lead to ketoacidosis, and DKA during pregnancy carries a risk of fetal death.

Two case studies were identified that reported healthy live births to women with diabetes and hyperemesis gravidarum following treatment with parenteral nutrition.[216,217] One case study reported a fetal death in a woman with hyperemesis gravidarum and DKA following a delay in treatment.[218] [EL = 3]

5.4.1.3   Diabetic ketoacidosis

A case series of 37 women admitted with DKA[219] concluded that vomiting and the use of betamimetic medicines were the primary cause in 57% of cases. Non-adherence to treatment and physician management errors were the primary cause in 24% of cases and contributory in 16%. Common physician management errors included the use of urine instead of blood to monitor maternal glucose control, failure to adhere to pregnancy standards of glucose control and failure to employ home blood glucose monitoring. [EL = 3]

A cohort study of 257 people[220] with DKA admitted to a large urban teaching hospital compared outcomes in people treated by a general physician (n = 224) with those in people treated by a physician with subspecialty training in diabetes (n = 33). People treated by a diabetes specialist had shorter length of stay (3.3 versus 4.9 days, P < 0.0043) and incurred lower hospital charges ($5,463 versus $10,109, P < 0.0001). Plasma glucose in generalist-treated people took longer to fall to less than 11.1 mmol/litre and they had a higher rate of readmission for DKA than the specialist-treated people (6% versus 2%, P = 0.03). [EL = 2+]Rapid-acting insulin analogues

Rapid-acting insulin analogues (aspart and lispro) confer the following benefits compared with regular insulin outside pregnancy:[221]

- fewer episodes of hypoglycaemia
- a reduction in postprandial glucose excursions
- an improvement in overall glycaemic control
- an improvement in patient satisfaction.

These benefits have also been demonstrated in the pregnant population (see Section 3.8).

5.4.1.4 Long-acting insulin analogues

The NICE guideline for the management of type 1 diabetes recommends the long-acting insulin analogue glargine for use outside of pregnancy.[221] However, no clinical trials have as yet been published for their use in pregnancy (see Section 3.9).

5.4.1.5 Four-times-daily versus twice-daily insulin regimens

An open label RCT compared glycaemic control and perinatal outcomes in pregnant women with diabetes using two different insulin regimens.[222] One hundred and thirty-eight women with gestational diabetes and 58 with pre-existing diabetes received insulin four times daily, and 136 women with gestational diabetes and 60 with pre-existing diabetes received insulin twice daily. Glycaemic control was better with the four-times-daily regimen than with the twice-daily regimen. In women with gestational diabetes the four-times-daily regimen resulted in a lower rate of overall neonatal morbidity than the twice-daily regimen. Four-times-daily rather than twice- daily insulin improved glycaemic control and perinatal outcomes without increasing the risks of maternal hypoglycaemia and caesarean section. [EL = 1++]

5.4.1.6 Continuous subcutaneous insulin infusion (insulin pump therapy)

The most widespread method of administering insulin is via subcutaneous insulin injections using a basal/bolus regimen consisting of a basal dose of long-acting insulin, usually administered with a pen before bed, and bolus of rapid-acting insulin given before meals. This is often referred to as a multiple daily injection (MDI) regimen. Insulin can also be administered using CSII (also known as insulin pump therapy). Both regular insulin and rapid-acting insulin can be administered by pump. The potential benefits of CSII are reduced risk of hypoglycaemia, decreased risk of fasting hyperglycaemia and improved adherence as the woman does not have to constantly inject insulin.[223]

NICE guidance for the non-pregnant population concluded that, compared with MDI regimens, CSII results in a modest but worthwhile improvement in blood glucose control and quality of life.[14]

A systematic review[224] investigated the effectiveness of insulin delivery via CSII as compared with MDI regimens for the treatment of diabetes during pregnancy in women with pre-existing diabetes or gestational diabetes. Only two studies were included in the review, neither included women with gestational diabetes. There was a significant increase in mean birthweight associated with CSII as opposed to MDI (two trials, 61 participants, weighted mean difference (WMD) 220.56, 95% CI −2.09 to 443.20). However, taking into consideration the lack of significant difference in rate of macrosomia (birthweight greater than 4000 g; RR 3.20, 95% CI 0.14 to 72.62), this finding was not viewed by the authors as being clinically significant. There were no significant differences in perinatal outcomes between CSII and MDI (perinatal mortality, including stillbirths from 24 weeks of gestation and neonatal deaths up to 7 days of life, RR 2.00, 95% CI 0.20 to 19.91; fetal anomaly, RR 1.07, 95% CI 0.07 to 15.54; gestational age at birth, WMD 0.63, 95% CI −4.87 to 6.13; neonatal hypoglycaemia, RR 1.00, 95% CI 0.07 to 14.64; and SGA, RR 1.55, 95% CI 0.27 to 9.00). Neither were there any significant differences in maternal outcomes between CSII and MDI (caesarean section rate, RR 1.03, 95% CI 0.57 to 1.84; mean maternal HbA1c; 24 hour mean blood glucose level in each trimester; hypoglycaemia; or hyperglycaemia). [EL1+]

Three further RCTs of CSII in women with type 1 diabetes during pregnancy were identified.[225–227] The studies included a total of 200 women. There were no significant differences between groups in glycaemic control or in obstetric or neonatal outcomes. There were four cases of ketoacidosis in women using pumps. This was attributed to catheter occlusion (one case), catheter leakage (one case) and pump failure (one case). Another case was reported but without attribution. [EL = 1++]

One RCT was designed to assess the effect of CSII on retinopathy.[226] This study of 40 women with type 1 diabetes reported progression to proliferative retinopathy in two women using CSII. This was attributed to rapid and significant improvement in glycaemic control. [EL = 1+]

Three cohort studies compared outcomes in women using CSII with those in women using MDI regimens. [EL = 2+][228] [EL = 2+][229] [EL = 2++][230] In each study women were offered pump therapy due to difficulties achieving glycaemic control. All studies reported good glycaemic control and obstetric and neonatal outcomes.

5.4.1.7 Current practice

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that women with type 1 diabetes were more likely to experience recurrent episodes of hypoglycaemia than women with type 2 diabetes (P < 0.001), with 61% (105/171) of women with type 1 diabetes and 21% (25/121) of the women with type 2 diabetes having recurrent episodes of hypoglycaemia.[33] One or more episodes of hypoglycaemia required help in 25% (33/133) of the women with type 1 diabetes and 4% (4/102) of the women with type 2 diabetes. [EL = 3–4]

5.4.2 Existing guidance

The NICE technology appraisal relating to insulin pump therapy (CSII) for people with type 1 diabetes states that insulin pumps can be used in pregnancy even if there is good glycaemic control on MDI regimens.[14]

The Driver and Vehicle Licensing Agency (DVLA) medical rules for drivers do not include any special considerations for diabetes in pregnancy. Fitness to drive is assessed on the basis of the risk of hypoglycaemia, regardless of whether or not the driver is pregnant (see www.dvla.gov.uk/medical. aspx and www.direct.gov.uk/en/Motoring/DriverLicensing/MedicalRulesForDrivers/index.htm) and

https://www.gov.uk/diabetes-driving.

5.4.3 Evidence statement

During pregnancy women with diabetes treated using insulin are at an increased risk of hypoglycaemia and hypoglycaemia unawareness.

Rapid-acting insulin analogues (aspart and lispro) are associated with fewer episodes of hypoglycaemia compared with regular human insulin. When compared with regular human insulin the use of rapid-acting insulin analogues during pregnancy has also been associated with a reduction in postprandial glucose excursions, an improvement in overall glycaemic control and an improvement in patient satisfaction.

Ketoacidosis is a complication that can result in fetal death. Outcomes may be improved with prompt assessment and treatment by a health professional with specialist diabetes training.

RCTs have shown similar outcomes in women using CSII and MDI regimens. Ketoacidosis may result from pump failure. Cohort studies have reported good outcomes in women offered pump therapy because of difficulty achieving glycaemic control using MDI regimens.

5.4.4 From evidence to recommendations

Women and their partners should be informed of the increased risk of hypoglycaemia and hypoglycaemia unawareness during pregnancy, and information about prevention, recognition and treatment (including the provision of a concentrated glucose solution and, if they have type 1 diabetes, glucagon, and education in their use) should be reinforced in

women with insulin- treated diabetes who are pregnant. Women with insulin-treated diabetes should also be advised of the consequences of hypoglycaemia and the dangers associated with driving during periods of hypoglycaemia unawareness. They should be encouraged to carry something that identifies them as having diabetes so they can be treated promptly if disabling hypoglycaemia occurs.

The evidence supports the use of the rapid-acting insulin analogues aspart and lispro in women with diabetes in pregnancy, and also insulin pump therapy (CSII) in women who have difficulty achieving glycaemic control without disabling hypoglycaemia.

Since DKA can be accelerated in pregnancy and is associated with serious maternal and fetal adverse outcomes (including fetal death), the 2008 GDG's consensus view was that current best practice should be followed namely that DKA should be excluded in women with type 1 diabetes who become unwell in pregnancy and pregnant women with DKA should be admitted immediately for level 2[nn] critical care where they can receive medical and obstetric care. However, in addition, the 2014 GDG also noted that, though DKA was primarily a complication of women with type 1 diabetes, there were a number of case reports that indicated that DKA could also occur in women with either type 2 diabetes or gestational diabetes and they felt that the recommendation should not be confined to women with Type 1 diabetes.

5.4.5 Recommendations

Insulin treatment and risks of hypoglycaemia

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.4.6 Research recommendations

30. Do new-generation CSII pumps offer an advantage over traditional intermittent insulin injections in terms of pregnancy outcomes in women with type 1 diabetes? [2008]

[nn] Level 2 critical care is defined as care for patients requiring detailed observation or intervention, including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care.

[oo] For the purpose of this guidance, 'disabling hypoglycaemia' means the repeated and unpredicted occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life.

Why this is important

Randomised controlled trials have shown no advantage or disadvantage of using continuous subcutaneous insulin infusion (CSII) pumps over multiple intermittent insulin injections in pregnancy in terms of glycaemic control or maternal and fetal outcomes. The new generation of CSII pumps (± continuous glucose monitoring – CGM) with more sophisticated technologies enabling more precise insulin dosing offer technological advantages that would make a randomised controlled trial appropriate.

5.5   Continuous glucose monitoring

This section was updated in 2020

5.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.5.1 Research recommendations

The current research recommendations can be found at https://www.nice.org.uk/guidance/ng3

5.6 Retinal assessment during pregnancy

There are two widely used classifications for grading the levels of diabetic retinopathy. The English classification for sight-threatening diabetic retinopathy is used for two-field diabetic retinopathy screening (see the National Screening Committee's diabetic retinopathy

screening programme for England and Wales, available at www.retinalscreening.nhs.uk/). The English classification progresses from no diabetic retinopathy, to background diabetic retinopathy, to pre-proliferative diabetic retinopathy, to proliferative diabetic retinopathy (PDR). The Early Treatment Diabetic Retinopathy Study (ETDRS) classification has provided an evidence base for progression of diabetic retinopathy based on grading of seven-field stereo-photographs. The ETDRS classification progresses from no diabetic retinopathy, to mild non-proliferative diabetic retinopathy (NPDR), to moderate NPDR, to moderately severe NPDR, to severe NPDR, to PDR. The lesions found within the two classifications follow a common language: background diabetic retinopathy is equivalent to mild NPDR and is characterised by increased vascular permeability; pre-proliferative diabetic retinopathy is equivalent to moderate NPDR, moderately severe NPDR and severe NPDR; in PDR the development of new blood vessels can significantly reduce vision. The progression from no diabetic retinopathy to PDR normally occurs over a period of years, but sudden worsening may occur in pregnancy.

Duration of diabetes is known to be an important factor in the progression of diabetic retinopathy and in the development of PDR in people with diabetes. Data from an epidemiological study showed that PDR varied from 1.2% to 67% in people who had had diabetes for less than 10 years and more than 35 years, respectively.[231]

5.6.1 Description of the evidence

A cohort study[232] determined the prevalence of retinopathy characteristically seen in people with diabetes and IGT, and in people with new-onset diabetes of known duration in the Diabetes Prevention Program (DPP) cohort. The DPP recruited and followed people with elevated fasting glucose (5.3–6.9 mmol/litre) and IGT with no history of diabetes other than gestational diabetes that did not persist after pregnancy. A random sample of 302 participants who developed diabetes and those who remained free from diabetes after 3 years follow-up was used for the retinopathy study. Retinopathy consistent with diabetic retinopathy was detected in 12.6% of people with diabetes and 7.9% of people without diabetes (P = 0.03). The study suggests that retinopathy is present in people with elevated fasting glucose and IGT with no known history of diabetes. [EL = 2+]

5.6.1.1 Progression of diabetic retinopathy

Three cohort studies were identified that found pregnancy to be independently associated with progression of diabetic retinopathy.

One study compared 180 women who became pregnant during an RCT of intensive versus conventional treatment of type 1 diabetes with women who did not become pregnant.[233] In the intensive treatment group 693/2950 (23%) non-pregnant women had progression of retinopathy compared with 39/124 (31%) pregnant women (OR 1.62, 95% CI 1.01 to 2.59, P < 0.05). In the conventional treatment group 1742/5605 (31%) non-pregnant women had progression of retinopathy compared with 37/73 (50.3%) pregnant women (OR 2.54, 95% CI 1.59 to 4.03, P < 0.0001). [EL = 2++]

A cohort study compared 60 pregnant women with type 1 diabetes to 80 non-pregnant women with type 1 diabetes.[234] Progression of retinopathy occurred in 10/35 women with pre-existing retinopathy in the pregnant group. There was no progression of retinopathy in the non-pregnant controls (24 had pre-existing retinopathy). [EL = 2+]

A cohort study compared 171 pregnant women with type 1 diabetes to 298 non-pregnant women with type 1 diabetes.[235] A multivariate analysis (pregnancy, HbA1c, blood pressure, number of previous pregnancies and duration of diabetes) found pregnancy to be independently associated with progression of retinopathy (OR 1.8, 95% CI 1.1 to 2.8, P < 0.02). [EL = 2++]

5.6.1.2 Severity of retinopathy at conception

Four studies found progression of retinopathy during pregnancy to be associated with severity of retinopathy at conception.

A cohort study of 155 pregnant women with type 1 diabetes found women with more severe retinopathy at conception were more likely to show progression during pregnancy (χ^2 for trend, $P < 0.001$).[236] The study found progression of two steps or more in 4/39 (10.3%) women with no retinopathy, 8/38 (21.1%) women with microaneurysms only, 5/32 (18.8%) women with mild NPDR and 17/31 (54.8%) women with moderate NPDR. Women with no retinopathy or only microaneurysms at conception did not develop PDR. PDR developed in 2/32 (6%) women with mild NPDR and 9/31 (29%) women with moderate NPDR at conception. [EL = 2++]

A cohort study of 35 women with type 1 diabetes found progression during pregnancy in 3/10 women with no retinopathy at baseline and in 3/20 with background retinopathy (2/20 developed proliferative retinopathy).[237] Diabetic retinopathy deteriorated during pregnancy in all five women with proliferative retinopathy at baseline. [EL = 2+]

A cohort study evaluated 65 women with type 1 diabetes before pregnancy, during each trimester and 12 months postpartum.[238] The study found 38 women had no retinopathy at conception, 28 (74%) showed no progression and ten (26%) progressed to mild NPDR. Twenty-two women had NPDR at conception, 5 (22.5%) showed no progression, 12 (55%) had NPDR progression and 5 (22.5%) progressed to PDR necessitating photocoagulation. The difference in progression of retinopathy between these two groups was statistically significant ($P = 0.0001$). [EL = 2+]

A cohort study followed 154 women with type 1 diabetes.[239] Twenty-three percent (18/78) of women with no retinopathy in the first trimester progressed; 28/68 (41%) women with NPDR in the first trimester progressed; and 5/8 (63%) women with PDR in the first trimester progressed ($P = 0.01$). [EL = 2++]

5.6.1.3 Duration of diabetes

Six cohort studies of women with type 1 diabetes found progression of retinopathy during pregnancy was associated with duration of diabetes.[234,236,238–241]

The effect of duration of diabetes on progression of retinopathy during pregnancy is difficult to separate from the effect of the severity of retinopathy at conception as the two are correlated. A study of 155 pregnant women with type 1 diabetes[236] found that in women with moderate or more severe retinopathy at baseline, retinopathy progressed by two steps or more in 55% of women with 15 years or less of duration of diabetes and 50% of women with more than 15 years of duration of diabetes. However, PDR developed in only 18% of women with 15 years or less of duration of diabetes compared with 39% of women with more than 15 years of duration of diabetes. This suggests that severity of retinopathy at conception is more important than duration of diabetes for the progression of diabetes during pregnancy, but that duration of diabetes may be an important factor in the development of PDR. [EL = 2++]

A recent cohort study of 179 pregnancies in 139 women with type 1 diabetes[241] found progression of retinopathy was significantly increased in women with duration of diabetes of 10–19 years compared with duration less than 10 years (8/80 versus 0/71, $P = 0.007$) and in women with moderate to severe NPDR at booking (6/163 versus 3/10, $P = 0.01$). The study included 20 pregnancies in women with duration of diabetes more than 20 years who had no or mild retinopathy at booking and of these only one progressed. This suggests that severity of retinopathy at conception may be more important than duration of diabetes in the progression of retinopathy during pregnancy. [EL = 2++]

5.6.1.4 Glycaemic control

Seven studies considered the effect of glycaemic control on the progression of diabetic retinopathy during pregnancy.[233,235–239,242] All studies found poor glycaemic control to be associated with progression of retinopathy during pregnancy.

5.6.1.5 Magnitude of improvement in glycaemic control

Three studies[233,237,239] found that a large improvement in glycaemic control in the first trimester was associated with progression of retinopathy. The effect of large improvement of glycaemic control is difficult to separate from poor glycaemic control as women with the largest improvement were those who had poor initial control.[236] [EL = 2++]

Progression of retinopathy following commencement of intensive treatment has also been observed in non-pregnant adults with diabetes.[243–246] In the DCCT study[70,243] involving 1441 people with type 1 diabetes (726 with no retinopathy at baseline) progression of retinopathy was observed at the 6 and/or 12 month visit in 13.1% of people in the intensive group compared with 7.6% in the conventional group (P < 0.001). Among people who had experienced early worsening of retinopathy, 69% in the intensive group and 57% in the conventional group had shown complete recovery by the 18 month visit. Overall people with early worsening of retinopathy in the intensive group had a 74% reduction in the risk of subsequent progression as compared with people with early worsening who received conventional treatment (P < 0.001). [EL = 1++]

Logistic regression incorporating both initial HbA1c and the change between initial HbA1c and 4 month HbA1c found the latter to be the dominant factor for early worsening of retinopathy. There was no evidence that people with more rapid reduction of HbA1c had a greater risk of early worsening of retinopathy than people with more gradual reduction when the reductions were of similar magnitude.[243] [EL = 1++]

5.6.1.6 Hypertension

A cohort study of 154 women with type 1 diabetes examined the effect of hypertension on the progression of retinopathy during pregnancy.[239] Multiple regression found pregnancy-induced hypertension (P = 0.01) and chronic hypertension (P = 0.02) to be associated with progression of retinopathy. [EL = 2++]

A cohort study of 65 pregnant women with type 1 diabetes[238] found systolic blood pressure to be higher in women who showed progression of retinopathy during pregnancy than in those who did not (P < 0.005). [EL = 2++]

5.6.1.7 Postpartum regression

A cohort study followed 154 women with type 1 diabetes through pregnancy to 12 weeks postpartum.[239] Fifty-one women had progression of retinopathy during pregnancy of which seven developed PDR. Thirteen women experienced postpartum regression. None of the women who developed PDR during pregnancy experienced postpartum regression. [EL = 2++]

A cohort study of 65 women with type 1 diabetes were followed until 12 months postpartum.[238] Thirty-eight women had no retinopathy at conception. Of these 28 showed no change during pregnancy. Ten showed mild progression during pregnancy, of which five showed complete postpartum regression. There was no development of PDR in the group with no retinopathy at conception. Twenty-two women had NPDR at conception: five of these women experienced no change during pregnancy; twelve progressed from mild to severe NPDR, of which two showed regression postpartum; five progressed to PDR. [EL = 2+]

5.6.1.8 Laser treatment for diabetic macular oedema

A large multicentre RCT[247] in which people with macular oedema and mild or moderate diabetic retinopathy in one or both eyes were randomly assigned to focal argon laser photocoagulation (754 eyes) or deferred photocoagulation (1490 eyes) showed that focal photocoagulation substantially reduced the risk of visual loss (12% versus 24% at 3 year follow-up). However this RCT did not mention whether pregnant women were included. [EL = 1+] A further report[248] from the RCT described treatment techniques in detail. It defined the concepts of 'clinically significant macular oedema' and 'treatable lesions'. [EL = 3–4]

A subsequent RCT[249] compared eyes selected for early photocoagulation in the first RCT247 by treating with one of four combinations of scatter (panretinal) and focal treatment. It was found that for eyes with macular oedema, focal photocoagulation was effective in reducing the risk of moderate visual loss but that scatter photocoagulation was not. Focal treatment also increased the chance of visual improvement, decreased the frequency of persistent macular oedema and caused only minor visual field losses. [EL = 1+]

An audit by the UK National Diabetic Retinopathy Laser Treatment group[250,251] was conducted in 546 people undergoing their first photocoagulation treatment for maculopathy. At 9 month follow-up, the results showed that 9.2% had a deterioration in visual acuity equivalent to a doubling of the visual angle and 3.3% of eyes had a visual acuity less than 6/60. Improvement in the macular oedema occurred in 64.6% and exudates in 77.3%. [EL = 3–4]

5.6.1.9 Laser treatment for proliferatvie diabetic retinopathy

A study of 55 pregnant women with type 1 diabetes found that progression of retinal disease was arrested with photocoagulation during pregnancy in four women with proliferative retinopathy.[240] [EL = 3]

The Diabetic Retinopathy Study group[252] recommend treatment for control eyes with 'high risk characteristics'. They reported four retinopathy factors that increase the 2 year risk of developing severe visual loss: presence of vitreous or preretinal haemorrhage; presence of new vessels; location of new vessels on or near the optic disc and severity of new vessels. [EL = 3–4]

An RCT[253] that compared photocoagulation with no treatment found that photocoagulation reduced the risk of severe visual loss by 50% or more. The 2 year risk of severe visual loss without treatment outweighed the risk of harmful treatment effects for eyes with new vessels and preretinal or vitreous haemorrhage and for eyes with new vessels on or within one disc diameter of the optic disc (NVD) equalling or exceeding one-quarter to one-third of the disc area, even in the absence of preretinal or vitreous haemorrhage. [EL = 1+]

The UK National Diabetic Retinopathy Laser Treatment audit[251] was conducted on 546 people undergoing their first photocoagulation treatment for maculopathy. At 9 month follow-up neovascularisation had regressed fully in 50.8% of cases with proliferative retinopathy, and there was no change or deterioration in 10.3%. This audit showed that regression of neovascularisation was associated with greater areas of retinal ablation at the initial treatment session. [EL = 3–4]

5.6.1.10 Effect of blood pressure on macular oedema and diabetic retinopathy

A study[254] investigated the relationship between blood pressure and diabetic retinopathy in 249 young people with type 1 diabetes. Retinopathy was present in 63% of young people and hypertension in 2%. The presence of high-normal blood pressure (> 90th percentile but less than 141/90 mm Hg) resulted in a prospectively higher occurrence of retinopathy and of progression of pre-existing retinopathy. [EL 3–4]

A cross-sectional study[255] in Norway of 600 people with a mean age of 19.8 years evaluated the association of various risk factors with retinopathy. In a multiple logistic regression model, age (P = 0.0001), higher mean HbA1c (P = 0.009), duration of diabetes (P = 0.0001) and mean arterial blood pressure (P = 0.0001) were significantly associated with retinopathy. [EL 2++]

A cross-sectional study[256] in the USA of 634 people with type 1 diabetes diagnosed before age 30 years evaluated retinopathy after 14 years. Progression was more likely with higher HbA1c or diastolic blood pressure at baseline, an increase in the HbA1c level and an increase in diastolic blood pressure level from the baseline to the 4 year follow-up. The increased risk of proliferative retinopathy was associated with the presence of hypertension at baseline, whereas the increased risk of a person developing macular oedema was associated with the presence of gross proteinuria at baseline. [EL 2+]

An RCT[257] investigated the effect of tight blood pressure control and risk of microvascular complications in people with type 2 diabetes. After 9 years follow-up the group assigned to tight blood pressure control had a 34% reduction in risk in the proportion of participants with deterioration of retinopathy by two steps (99% CI 11% to 50%, P = 0.0004) and a 47% reduced risk (99% CI 7% to 70%, P = 0.004) of deterioration in visual acuity by three lines of the ETDRS chart. [EL 1++]

A cross-sectional study[258] investigated risk factors related to the incidence and progression of diabetic retinopathy from diagnosis over 6 years in 1919 people with type 2 diabetes. Development of retinopathy (incidence) was strongly associated with baseline glycaemia, glycaemic exposure over 6 years, higher blood pressure and with not smoking. In those who already had retinopathy, progression was associated with older age, male sex, hyperglycaemia (higher HbA1c) and with not smoking. [EL 2++]

A prospective RCT[259] compared the effects of intensive and moderate blood pressure control on the incidence and progression of type 2 diabetic complications in 470 people. At 5.3 years follow-up no difference was found in the incidence between the intensive and moderate groups with regard to the progression of diabetic retinopathy. [EL 1+]

An RCT[260] compared tight blood pressure control (blood pressure less than 150/85) with less tight blood pressure control (blood pressure less than 180/105) and its relationship with diabetic retinopathy in 1148 people with diabetes. At 4.5 years follow-up people allocated to tight blood pressure control were less likely to undergo photocoagulation (RR 0.65, P = 0.03). This difference was driven by a difference in photocoagulation due to maculopathy (RR 0.58, P = 0.02). [EL = 1+]

5.6.2 Current practice

The CEMACH enquiry reported that a detailed retinal assessment was recorded in the woman's notes at least once during pregnancy in 79.9% of women with pre-existing diabetes.[2] The CEMACH case– control study reported that women with poor pregnancy outcome were as likely not to have a retinal assessment during the first trimester or at booking if later (36% [70/194]) than women who had a good pregnancy outcome (27% [49/183], OR 1.4, 95% CI 0.9 to 2.2, adjusted for maternal age and deprivation).[33] Only 55% of the 258 assessments were recorded to have been done through dilated pupils and for 40% of women details about the retinal assessment procedure were not documented. The most common concern noted by the CEMACH enquiry panels over sub-optimal diabetes care in pregnancy was sub-optimal retinal function monitoring and management. [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that women with type 1 diabetes were more likely to have retinopathy than women with type 2 diabetes (P < 0.001), with 36% (50/138) of women with type 1 diabetes and 9% (9/96) of the women with type 2 diabetes having retinopathy in pregnancy.[33] This was a new finding in 26% (13/50) of the women with type 1 diabetes and 56% (5/9) of the women with type 2

diabetes. Of the women with pre-existing retinopathy there was evidence of deterioration in 18% of the women with type 1 diabetes and 11% of the women with type 2 diabetes. Women with type 1 diabetes were more likely to have a retinal assessment compared to women with type 2 diabetes (78% versus 64%, P = 0.02). Where retinopathy was found both groups of women were as likely to be referred to an ophthalmologist (35% versus 44%, P = 0.62). [EL = 3–4]

5.6.3 Existing guidance

The NSF for diabetes recommends full retinal assessment in all women with pre-existing diabetes during the first trimester (or at booking if this is later).[20]

5.6.4 Evidence statement

In some women pregnancy may accelerate progression of diabetic retinopathy. This is more likely in women with more severe diabetic retinopathy, poor glycaemic control and hypertension. Some diabetic retinopathy may regress spontaneously after the woman has given birth.

It is difficult to separate the influence of different factors which have been found to be associated with progression of retinopathy during pregnancy. The magnitude of improvement in glycaemic control is associated with glycaemic control prior to conception (which in turn is associated with duration of diabetes and severity of diabetes at conception). The DCCT found the magnitude, but not the rapidity, of the reduction in HbA1c during the first 6 months of intensive treatment to be an important risk factor for early worsening of diabetic retinopathy. Whether or not the risk of retinopathy progression can be reduced by more gradual reduction in glycaemic control can be resolved only by an RCT.

Evidence supports the use of laser treatment in diabetic macular oedema. Further evidence shows that control of blood pressure has a positive effect on macular oedema and progression of diabetic retinopathy.

5.6.5 From evidence to recommendations

Given the evidence of a rapid change in diabetic retinopathy during pregnancy (because of persistent hyperglycaemia) the GDG's view is that healthcare professionals should err on the side of caution by offering increased frequency of surveillance in the preconception period and throughout pregnancy to women with long-standing poor glycaemic control and pre-proliferative diabetic retinopathy or PDR, and by treating pre-existing diabetic retinopathy before conception.

There is evidence that rapid optimisation of glycaemic control can worsen diabetic retinopathy. However, it is the GDG's view that the benefits to the fetus of good glycaemic control outweigh the risks to the woman (early worsening of diabetic retinopathy). Healthcare professionals should, therefore, encourage improvement in glycaemic control in pregnancy and address ophthalmological complications of diabetes during pregnancy if they occur. In most women, laser treatment can be performed during pregnancy and will reduce the risks of sight loss as a result of progression of diabetic retinopathy. Careful control of blood pressure will also have a positive effect on sight-threatening diabetic retinopathy. Only in very rare circumstances might early birth be considered to reduce the risks of vision loss in pregnancy.

The GDG's view is that retinal assessment during pregnancy for women with diabetes should be conducted in accordance with the recommendations of the National Screening Committee's diabetic retinopathy screening programme (that is, retinal assessment should be performed using digital imaging with mydriasis (dilation of the pupils) using tropicamide). In making its recommendations, the GDG has also noted the report of the CEMACH diabetes

in pregnancy audit, which highlighted that only 55% of women with pre-existing diabetes were documented to have received retinal assessment through dilated pupils.

If diabetic retinopathy is found to be present in early pregnancy, referral should usually be guided by the standard referral criteria (see the National Screening Committee's website), and women should be seen by an ophthalmologist within 4 weeks, except for PDR when urgent referral is required. As with preconception care, if there are concerns in relation to the possible worsening of diabetic retinopathy with imminent improvement of very poor blood glucose control then referral with lesser degrees of retinopathy may be considered.

The recommendations in relation to retinal assessment in the preconception period are presented in Section 3.13.

5.6.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.6.7 Research recommendations

34. Should retinal assessment during pregnancy be offered to women diagnosed with gestational diabetes who are suspected of having pre-existing diabetes?

Why this is important

Women with gestational diabetes may have previously unrecognised type 2 diabetes with retinopathy. At present this is not screened for because of the difficulty in identifying these women amongst the larger group who have reversible and self-limiting gestational diabetes. The benefit of recognising such women is that treatment for diabetic retinopathy is available and can prevent short and long-term deterioration of visual acuity. An observational study of retinal photography assessment in women newly diagnosed with gestational diabetes would determine whether the prevalence is high enough to justify routine screening.

5.7 Renal assessment during pregnancy

Diabetic nephropathy is a progressive disease that can be divided into the following stages:[261] [EL = 4]

- microalbuminuria (incipient nephropathy) – small amounts of albumin are excreted in the urine

- macroalbuminuria or proteinuria (overt nephropathy) – widespread glomerular sclerosis resulting in progressively larger amounts of protein excreted in the urine
- end-stage renal disease – decreasing creatinine clearance, increasing serum creatinine and uraemia.

5.7.1 Description of the evidence

5.7.1.1 Effect of pregnancy on progression of nephropathy

A systematic review[262] considered the effects of pregnancy on diabetic nephropathy. The review included 11 longitudinal studies involving a total of 201 people. Only one study had a non- pregnant control group. The other studies compared the average rate of decline in renal function with the expected rate of decline in the general non-pregnant population of people with diabetic nephropathy. The review found that most studies suggest that pregnancy is not associated with development of nephropathy or with accelerated progression of pre-existing nephropathy, with the exception of women with moderate to advanced disease where pregnancy may accelerate progression to end-stage renal disease. [EL = 2++]

5.7.1.2 Effect of nephropathy on pregnancy outcome

A systematic review[262] which included 11 studies and 681 people found that women with diabetic nephropathy were at increased risk of adverse pregnancy outcomes, in particular fetal growth restriction , chronic hypertension, pre-eclampsia and preterm birth (see Table 66). Pre-eclampsia and preterm birth were associated with incipient nephropathy (microalbuminuria) as well as overt nephropathy. [EL = 1++]

Table 66: Outcome of pregnancy in women with diabetic nephropathy[262]

Outcome	Occurrence (%)
Chronic hypertension	23–77
Pre-eclampsia	15–64
Caesarean section	63–86
Fetal growth restriction	9–45
Birth before 34 weeks	16–45

A cohort study was identified that had been published since the systematic review. The cohort study considered pregnancy outcome in women with type 1 diabetes and microalbuminuria.[263] Of 240 consecutive pregnancies, 203 women (85%) had normal urinary albumin excretion, 26 (11%) had microalbuminuria and 11 (5%) had diabetic nephropathy. In this study normal urinary albumin excretion was defined as less than 30 mg/24 hours, microalbuminuria was defined as urinary albumin excretion 30–300 mg/24 hours and diabetic nephropathy was defined as urinary albumin excretion more than 300 mg/24 hours. The incidence of pre-eclampsia was 6% in women with normal urinary albumin excretion, 42% in women with microalbuminuria and 64% in women with nephropathy (P < 0.001). The incidence of preterm birth (before 34 weeks) was 6% in women with normal urinary albumin excretion, 23% in women with microalbuminuria and 45% in women with diabetic nephropathy (P < 0.001). The incidence of SGA babies was 2% in women with normal urinary albumin excretion, 4% in women with microalbuminuria and 45% in women with diabetic nephropathy (P < 0.001). [EL = 2++]

5.7.1.3 Antihypertensive treatment for microalbuminuria

A cohort study involving 46 women evaluated the impact of antihypertensive treatment with methyldopa in normotensive pregnant women with type 1 diabetes and microalbuminuria.264 The women were similar in terms of age, diabetes duration, pre-pregnancy BMI, HbA1c and

blood pressure, and all were referred before 17 weeks of gestation. The prevalence of preterm birth before 34 weeks of gestation was reduced from 23% to 0% (P = 0.02); the prevalence of preterm birth before 37 weeks of gestation was reduced from 62% to 40% (P = 0.15); and the prevalence of pre-eclampsia was reduced from 42% to 20% (P = 0.11). Perinatal mortality occurred in 4% versus 0%. [EL = 2++]

5.7.2   Current practice

The CEMACH enquiry reported that women who had a poor pregnancy outcome were more likely not to have monitoring for nephropathy (22% [46/209]) than women who had a good pregnancy outcome (13% [26/206], OR 1.9, 95% CI 1.1 to 3.3, adjusted for maternal age and deprivation). In an additional case–control analysis lack of monitoring for nephropathy was associated only with fetal congenital anomaly and not with fetal or neonatal death after 20 weeks of gestation; it is therefore unlikely to have been causative for poor pregnancy outcome. Nephropathy itself was not associated with poor pregnancy outcome. One of the most common concerns noted by the CEMACH enquiry panels over sub-optimal diabetes care in pregnancy was sub-optimal renal function monitoring and management.[33] [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that there was no significant difference in the rate on nephropathy in pregnancy in women with type 1 or type 2 diabetes, with 8% (12/148) of women with type 1 diabetes and 5% (6/119) of the women with type 2 diabetes having nephropathy during their pregnancy.[33] Women with type 1 diabetes were as likely to have monitoring for nephropathy as women with type 2 diabetes (86% versus 79%, P = 0.60). Where nephropathy was found both groups of women were as likely to have a test of renal function (75% versus 50%, P = 0.29). [EL = 3–4]

The CEMACH enquiry did not state an explicit standard of monitoring for nephropathy, but it recommended that appropriate monitoring included testing for microalbuminuria (incipient nephropathy) via protein dipstick testing of urine or serum creatinine.[33] [EL = 3–4]

5.7.3   Existing guidance

The NICE guideline for type 2 diabetes defines microalbuminuria as albumin : creatinine ratio 3.5 mg/mmol or more (for women) or albumin concentration 20 mg/litre or more. Macroalbuminuria is defined as albumin : creatinine ratio 30 mg/mmol or more or albumin concentration 200 mg/litre or more.[8]

The NICE guidelines for type 1 and type 2 diabetes in adults recommend annual testing for nephropathy using urine albumin : creatinine ratio and serum creatinine. It is recommended that people with nephropathy have measurements of urine albumin and serum creatinine levels at each visit.[7,8]

The NICE guidance on "Hypertension in pregnancy" (CG 107) recommends the use of low dose aspirin in women with diabetes to reduce the risk of hypertensive disorders in pregnancy:

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension, [1.1.2.1].

5.7.4 Evidence statement

In the majority of studies pregnancy has not been associated with the development of nephropathy or with accelerated progression of pre-existing nephropathy. Data from three studies suggest that in women with moderate to advanced disease pregnancy may accelerate progression to end- stage renal disease.

All stages of nephropathy, including microalbuminuria, are associated with adverse pregnancy outcomes, especially fetal growth restriction , pre-eclampsia and preterm birth.

A small cohort study suggested that antihypertensive treatment with methyldopa in women with type 1 diabetes and microalbuminuria reduced the risk of preterm birth (before 34 weeks of gestation).

No evidence was identified in relation to thromboprophylaxis in the presence of macro-albuminuria.

5.7.5 From evidence to recommendations

NICE recommends that renal assessment outside pregnancy should use urine albumin : creatinine ratio and serum creatinine. Estimated glomerular filtration rate (eGFR) should not be used during pregnancy as it underestimates the glomerular filtration rate.439 There is no evidence on the optimal assessment schedule during pregnancy. As both microalbuminuria and macroalbuminuria are associated with adverse outcomes the GDG recommends assessment in the preconception period or at the first presentation after conception. All pregnant women should have their urine tested for proteinuria as part of routine antenatal care (see the NICE antenatal care guideline).9 If serum creatinine is abnormal (120 micromol/litre or more) or if total protein excretion exceeds 2 g/day, referral to a nephrologist should be considered.

No evidence was identified in relation to thromboprophylaxis in the presence of macroalbuminuria. The GDG's consensus view is that healthcare professionals should follow best current practice in terms of thromboprophylaxis for women with diabetes and macroalbuminuria (antenatal administration of aspirin for proteinuria less than 5 mg/day and heparin for proteinuria more than 5 mg/day; planned early birth may need to be considered because of the risk of developing pre-eclampsia).

The recommendations in relation to renal assessment in the preconception period are presented in Section 3.14.

Note added for 2015 guideline The guideline development group felt that the diagnostic criteria for severe pre-existing renal disease used in the recommendations should conform to those recommended in the NICE clinical guideline on chronic renal disease. A cohort study was identified that had been published since the systematic review. The cohort study considered pregnancy outcomes in women with type 1 diabetes and microalbuminuria.263 Of 240 consecutive pregnancies, 203 women (85%) had normal urinary albumin excretion, 26 (11%) had microalbuminuria and 11 (5%) had diabetic nephropathy. In this study normal urinary albumin excretion was defined as less than 30 mg per 24 hours, microalbuminuria was defined as urinary albumin excretion 30–300 mg per 24 hours and diabetic nephropathy was defined as urinary albumin excretion more than 300 mg per 24 hours. The incidence of pre-eclampsia was 6% in women with normal urinary albumin excretion, 42% in women with microalbuminuria and 64% in women with nephropathy (p< p0.001). The incidence of preterm birth (before 34 weeks) was 6% in women with normal urinary albumin excretion, 23% in women with microalbuminuria and 45% in women with diabetic nephropathy (p<0.001). The incidence of SGA babies was 2% in women with normal urinary albumin excretion, 4% in women with microalbuminuria and 45% in women with diabetic nephropathy (p<0.001). [EL = 2++]

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A cohort study involving 46 women evaluated the impact of antihypertensive treatment with methyldopa in normotensive pregnant women with type 1 diabetes and microalbuminuria.[264] The women were similar in terms of age, diabetes duration, pre-pregnancy BMI, HbA1c and blood pressure, and all were referred before 17 weeks of gestation. The prevalence of preterm birth before 34 weeks of gestation was reduced from 23% to 0% (P = 0.02); the prevalence of preterm birth before 37 weeks of gestation was reduced from 62% to 40% (P = 0.15); and the prevalence of pre-eclampsia was reduced from 42% to 20% (P = 0.11). Perinatal mortality occurred in 4% versus 0%. [EL = 2++]

5.7.6 Current practice

The CEMACH enquiry reported that women who had a poor pregnancy outcome were more likely not to have monitoring for nephropathy (22% [46/209]) than women who had a good pregnancy outcome (13% [26/206], OR 1.9, 95% CI 1.1 to 3.3, adjusted for maternal age and deprivation). In an additional case–control analysis lack of monitoring for nephropathy was associated only with fetal congenital anomaly and not with fetal or neonatal death after 20 weeks of gestation; it is therefore unlikely to have been causative for poor pregnancy outcome. Nephropathy itself was not associated with poor pregnancy outcome. One of the most common concerns noted by the CEMACH enquiry panels over sub-optimal diabetes care in pregnancy was sub-optimal renal function monitoring and management.[33] [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that there was no significant difference in the rate on nephropathy in pregnancy in women with type 1 or type 2 diabetes, with 8% (12/148) of women with type 1 diabetes and 5% (6/119) of the women with type 2 diabetes having nephropathy during their pregnancy.[33] Women with type 1 diabetes were as likely to have monitoring for nephropathy as women with type 2 diabetes (86% versus 79%, P = 0.60). Where nephropathy was found both groups of women were as likely to have a test of renal function (75% versus 50%, P = 0.29). [EL = 3–4]

The CEMACH enquiry did not state an explicit standard of monitoring for nephropathy, but it recommended that appropriate monitoring included testing for microalbuminuria (incipient nephropathy) via protein dipstick testing of urine or serum creatinine.[33] [EL = 3–4]

5.7.7 Existing guidance

The NICE guideline for type 2 diabetes defines microalbuminuria as albumin : creatinine ratio 3.5 mg/mmol or more (for women) or albumin concentration 20 mg/litre or more. Macroalbuminuria is defined as albumin : creatinine ratio 30 mg/mmol or more or albumin concentration 200 mg/litre or more.[8]

The NICE guidelines for type 1 and type 2 diabetes in adults recommend annual testing for nephropathy using urine albumin : creatinine ratio and serum creatinine. It is recommended that people with nephropathy have measurements of urine albumin and serum creatinine levels at each visit.[7,8]

5.7.8 Evidence statement

In the majority of studies pregnancy has not been associated with the development of nephropathy or with accelerated progression of pre-existing nephropathy. Data from three studies suggest that in women with moderate to advanced disease pregnancy may accelerate progression to end- stage renal disease.

All stages of nephropathy, including microalbuminuria, are associated with adverse pregnancy outcomes, especially fetal growth restriction , pre-eclampsia and preterm birth.

A small cohort study suggested that antihypertensive treatment with methyldopa in women with type 1 diabetes and microalbuminuria reduced the risk of preterm birth (before 34 weeks of gestation).

No evidence was identified in relation to thromboprophylaxis in the presence of macro-albuminuria.

5.7.9 From evidence to recommendations

NICE recommends that renal assessment outside pregnancy should use urine albumin: creatinine ratio and serum creatinine. Estimated glomerular filtration rate (eGFR) should not be used duringpregnancy as it underestimates the glomerular filtration rate.[439] There is no evidence on the optimal assessment schedule during pregnancy. As both microalbuminuria and macroalbuminuria are associated with adverse outcomes the GDG recommends assessment in the preconception period or at the first presentation after conception. All pregnant women should have their urine tested for proteinuria as part of routine antenatal care (see the NICE antenatal care guideline).9 If serum creatinine is abnormal (120 micromol/litre or more) or if total protein excretion exceeds 2 g/day, referral to a nephrologist should be considered.

No evidence was identified in relation to thromboprophylaxis in the presence of macroalbuminuria. The GDG's consensus view is that healthcare professionals should follow best current practice in terms of thromboprophylaxis for women with diabetes and macroalbuminuria (antenatal administration of aspirin for proteinuria less than 5 mg/day and heparin for proteinuria more than 5 mg/day; planned early birth may need to be considered because of the risk of developing pre-eclampsia).

The recommendations in relation to renal assessment in the preconception period are presented in Section 3.14.

NOTE ADDED FOR 2015 GUIDELINE: The GDG felt that the diagnostic criteria for severe pre-existing renal disease used in the recommendations should conform to those recommended in Chronic Renal Disease (NICE Clinical Guideline 182)

5.7.10 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.7.11 Research recommendations

35. Does identification of microalbuminuria during pregnancy offer the opportunity for appropriate pharmacological treatment to prevent progression to pre-eclampsia in women with pre-existing diabetes?

Why this is important

Microalbuminuria testing is available, but it is not performed routinely in antenatal clinics for women with pre-existing diabetes because a place for prophylactic treatment of pre-eclampsia in microalbuminuria-positive women has not been investigated. The benefit of clinically and cost-effective prophylactic treatment would be to significantly improve pregnancy outcomes in this group of women.

5.8 Screening for congenital malformations

5.8.1 Description of the evidence

Women with diabetes have an increased risk of having a baby with a congenital malformation. Major congenital malformations affecting babies of women with diabetes include cardiac, neural tube and genitourinary anomalies. Table 67 lists anomalies associated with diabetes as well as the estimated prevalence and RR compared to women without diabetes, as reported in published studies.[265]

More recent data from the CEMACH enquiry found the prevalence of confirmed major anomalies to be 41.8 per 1000 total births (live and stillborn).[2] Separate rates for babies of women with type 1 diabetes (n = 1707) and type 2 diabetes (n = 652) born between 1 March 2002 and 28 February 2003 are summarised in Table 68.[266] Women with type 2 diabetes were more likely to come from a Black, Asian or Other Minority Ethnic group (type 1 diabetes 9.1%, type 2 diabetes 48.8%). Perinatal mortality in babies of women with diabetes was 31.8 per 1000 births, nearly four times higher than the general maternity population. One hundred and ninety-seven major congenital anomalies were confirmed in 148 babies. The prevalence of major congenital anomaly

Table 67: Detectable major congenital malformations in babies of women with pre-existing diabetes[265]

Group of malformations	Specific malformations	Prevalence per 100 births	Relative risk compared to women without diabetes
Cardiac	Transposition of the great arteries Ventricular septal defect Coarctation of the aorta Atrial septal defect Asymmetric septal hypertrophy	3.0–10.0	3–5
Caudal regression syndrome		0.2–0.5	200
Central nervous system	Neural tube defects (including anencephaly) Microcephaly Isolated hydrocephalus	2.1	2-10
Gastrointestinal	Duodenal atresia Anorectal atresia Hypoplastic left colon	1.0	3
Musculoskeletal system	Talipes Arthrogryposis	0.8–2.4	2–20
Orofacial cleft		1.8	1.5
Urinary tract	Ureteral duplication Cystic kidney Renal dysgenesis	1.7–3.0	5–2

Group of malformations	Specific malformations	Prevalence per 100 births	Relative risk compared to women without diabetes
	Hydronephrosis		

Table 68: Observed and expected prevalence of congenital malformations in babies of women with type 1 and type 2 diabetes (from CEMACH)[266]

Type of malformation	Babies of women with type 1 diabetes, observed (expected)[a]	Babies of women with type 2 diabetes, observed (expected)[a]	Standardised prevalence ratio for babies of women with both type1 and type 2 diabetes (95% CI)
One or more malformations	81 (37)	28 (12.8)	2.2 (1.8 to 2.6)
Neural tube defects	6 (2.4)	4 (0.9)	4.2 (2.0 to 7.8)
Other central nervous system	5 (1.7)	0 (0.6)	1.5 (0.3 to 3.6)
Eye	1 (2.4)	0 (0.9)	1.0 (0.1 to 7.0)
Ear	0 (0.7)	0 (0.3)	–
Congenital heart disease	33 (8.9)	9(3.4)	3.4 (2.5 to 4.6)
Cleft lip and palate	0 (1.3)	0 (0.5)	–
Cleft palate	2 (0.9)	0 (0.3)	1.6 (0.2 to 5.9)
Digestive system	1 (2.6)	2 (1.0)	0.8 (0.2 to 2.5)
Internal urogenital system	9 (6.1)	1 (2.3)	1.2 (0.6 to 2.2)
External genital system	3 (2.5)	2 (0.9)	1.5 (0.5 to 3.4)
Limb	15 (10.2)	4 (3.7)	1.4 (0.8 to 2.1)
Other (non-chromosomal)	6	4	–
Trisomy 21	2	0	–
Other chromosomal	2	2	–

a. Expected rates are based on European Surveillance of Congenital Anomalies (EUROCAT) 2002.267

was 46 per 1000 births in women with diabetes (48 per 1000 births for type 1 diabetes, 43 per 1000 births for type 2 diabetes), more than twice the expected rate. The increase was mainly due to an increase in neural tube defects (4.2-fold) and congenital heart disease (3.4-fold). Anomalies in 65% (71/109) of babies were diagnosed antenatally. Congenital heart disease was diagnosed antenatally in 54.8% (23/42) of babies. Anomalies other than congenital heart disease were diagnosed antenatally in 71.6% (48/67) of babies. [EL = 3–4]

The benefits of screening for congenital malformations include the opportunity for counselling, enabling families time to prepare, allowing antenatal treatment, and ensuring appropriate obstetric management.

According to the NICE antenatal care guideline,[9] all pregnant women should be offered screening for congenital malformations at 18–20 weeks of gestation as part of routine antenatal care. This section considers what additional screening should be offered to women with diabetes.

5.8.2 First-trimester screening for chromosomal anomalies

The NICE antenatal care guideline[9] recommends that all pregnant women should be offered screening for Down's syndrome. Women should understand that it is their choice to embark on screening for Down's syndrome. Screening should be performed by the end of the first trimester (14 weeks of gestation), but provision should be made to allow later screening (up to 20 weeks of gestation) for women booking later in pregnancy. The screening test offered should be the 'combined test' (nuchal translucency (NT), beta human chorionic gonadotropin [β-hCG] and pregnancy-associated plasma protein-A (PAPP-A)) at 11–14 weeks of gestation. At 15–20 weeks of gestation the most clinically effective and cost-effective serum screening test should be offered, namely the 'triple test' or 'quadruple test' (hCG, alpha fetoprotein (AFP), unconjugated estriol (uE3) and inhibin A). The integrated test should not be routinely used as a screening test for Down's syndrome. Information about screening options for Down's syndrome that can be understood by all women, including those whose first language is not English, should be given to women as early as possible and ideally before the booking visit, allowing the opportunity for further discussion before embarking on screening. If a woman receives a screen-positive result, she should have rapid access to appropriate counselling by trained staff. The second-trimester ultrasound scan (at 18–20 weeks of) should not be routinely used for Down's syndrome screening using soft markers. The presence of an isolated soft marker with an exception of increased nuchal fold noted on the routine anomaly scan (at 18–20 weeks of gestation) should not be used to adjust the a priori risk for Down's syndrome. The presence of an increased nuchal fold or two or more soft markers should prompt the offer of fetal medicine referral.

Women with diabetes do not have an increased risk of chromosomal anomalies, however published studies have shown that some biochemical markers tend to be lower in women with type 1 diabetes than in women without diabetes. Therefore, clinical practice has been to make adjustments when calculating the risk of anomalies for women with type 1 diabetes to take account of these differences.

A meta-analysis[268] included published studies of differences in AFP (14 studies, 253 women with type 1 diabetes), uE3 (six studies, 687 women with type 1 diabetes), total hCG (nine studies, 1350 women with type 1 diabetes), free β-hCG (one study, 251 women) and inhibin (three studies, 445 women). The weight-corrected median multiple-of-median (MoM) was 0.92 for AFP, 0.94 for uE3, 0.96 for total hCG, 0.96 for free β-hCG and 1.03 for inhibin (MoM values are ratios of median MoM in women with type 1 diabetes to median MoM in women without diabetes). No CIs or tests of statistical significance were presented in the meta-analysis. [EL = 2+]

Since publication of the meta-analysis, one study has been published on free β-hCG.[269] The study compared 79 women with type 1 diabetes to 16366 women without diabetes. There were no significant differences in weight-corrected free β-hCG (type 1 diabetes MoM 0.87, 95% CI 0.75 to 1.16, women without diabetes MoM 1.00, P = 0.52). [EL = 2+]

Two studies were identified that compared levels of PAPP-A in women with and without diabetes during pregnancy. One study compared 79 women with type 1 diabetes to 93 pregnant women without diabetes.270 Levels of PAPP-A were significantly lower in women with type 1 diabetes (P = 0.024). [EL = 2+]

The second study compared PAPP-A levels in 79 women with type 1 diabetes to those in 16 366 women without diabetes.[269] There was no significant difference in PAPP-A levels (type 1 diabetes MoM 1.02, 95% CI 0.83 to 1.05, women without diabetes MoM 1.01, P = 0.36). [EL = 2+]

One study was identified that compared NT results in 195 women with type 1 diabetes to those in 33 301 women without diabetes.[269] There was no difference in mean NT between the two groups (0.0358 mm versus 0.0002 mm, P = 0.418). [EL = 2++]

5.8.3 Second-trimester ultrasound screening for structural anomalies

The NICE antenatal care guideline9 recommends that 'ultrasound screening for fetal anomalies should be routinely offered, normally between 18 weeks 0 days and 20 weeks 6 days.'

A cohort study compared 130 women with diabetes (85 type 1 diabetes, 45 type 2 diabetes) with 12 169 low-risk pregnant women for the same period.[271] All women had routine ultrasound at 16–24 weeks of gestation. A total of ten major anomalies (7.7%) and three minor anomalies (2.3%) were present in the fetuses of women with diabetes. The incidence of major congenital malformations was greater in the women with diabetes than in the low-risk control group (8% versus 1.4%, P < 0.001). The detection rate was significantly lower in the women with diabetes (30% versus 73%, P < 0.01) and the mean BMI was significantly higher (29 kg/m² versus 23 kg/ m²). Thirty-seven percent (48/130) of scans undertaken in women with diabetes were judged to be unsatisfactory, mainly because of maternal obesity (45/48). The majority (86% [19/22]) of repeat scans were also unsatisfactory. Of the 82 women with diabetes who had satisfactory images, two had congenital malformations. Both were detected antenatally (detection rate 100%). Of the 48 whose image quality was judged to be unsatisfactory there were eight major congenital anomalies. Only one was detected antenatally (detection rate 12.5%). [EL = 2++]

A cohort study considered 432 women with type 1 diabetes who underwent ultrasound screening between 12 and 23 weeks of gestation.[272] The ultrasound included four chambers of the heart and the great vessels. At birth 32 babies had 38 major congenital malformations, 52% (18/32) of which were detected antenatally. There were eight heart anomalies of which five were detected antenatally. All six CNS abnormalities were detected antenatally. The lesions most commonly missed by sonography were ventricular septal defect, abnormal hand or foot, unilateral renal abnormality, and cleft palate without cleft lip. The test performance was: sensitivity 56%, specificity 99.5%, PPV 90%, NPV 97%. [EL = 2++]

In a study of 289 women with diabetes[273] comprehensive ultrasound including a four chamber view undertaken at 18 weeks of gestation by a perinatologist had a test performance for detection of non-cardiac anomalies as follows: sensitivity 59%, specificity 100%, PPV 100%, NPV 98%. The test performance of the standard four chamber view was: sensitivity 33%, specificity 100%, PPV 100%, NPV 97%. In comparison the test performance for echocardiogram was: sensitivity 92%, specificity 99%, PPV 92%, NPV 99%. [EL = 2++]

A cohort study reported on 250 women[274] with pre-existing diabetes who underwent fetal echocardiogram at 20–22 weeks of gestation. Views included the four chamber view, the left ventricular long-axis view with visualisation of the aortic outflow tract, the short-axis view with visualisation of the pulmonary outflow tract and ductus arteriosus, and longitudinal view of the aortic arch. All examinations were undertaken by three experienced ultrasonographers. There were eight cardiac anomalies (3.2%), six of which were detected antenatally by echocardiogram. There was one false-negative result and one false-positive result. One fetus had an apparently normal heart at 21 weeks of gestation but was found to have a small atrial-septal defect at birth. The false positive was a case of perimembranous ventricular-septal defect. The test sensitivity was 85.7% and specificity was 99.5%. [EL = 2++]

A study of 223 women with insulin-requiring diabetes (128 type 1 diabetes, 47 type 2 diabetes, 48 gestational diabetes) considered the utility of different echocardiogram views.[275] There were 11 heart defects, nine of which were detected antenatally. The two missed cases were in women who were obese. Seven defects occurred in women with type 1 diabetes, three in women with type 2 diabetes and one in a woman with insulin-requiring gestational diabetes. The sensitivity of the four chamber view was 73% (8/11) and specificity was 100%. The sensitivity of the four chamber view and aortic outflow tract was 82% (9/11) and the specificity was 100%. Other views did not contribute to detection of a defect. The two missed cases (pulmonary atresia with a ventricular septal defect and an isolated ventricular septal defect) could theoretically have been detected on the four chamber view. [EL = 2++]

One study[276] examined 725 women (with or without diabetes) who had been referred for echocardiogram following a comprehensive anatomy ultrasound that included a four chamber/ left ventricular outflow tract view. The indications for referral included pre-existing diabetes (without additional indication, n = 226), fetal anomaly seen on anatomy ultrasound (n = 130) and family history of congenital heart disease (n = 133). Twenty-nine echocardiograms were reported as abnormal (4%). The indications for referral in these cases were an abnormal four chamber/left ventricular outflow tract view at ultrasound (66%), aneuploidy (14%) other fetal anomaly (17%) and fetal arrhythmia (3%). No abnormal fetal echocardiograms were reported in women with isolated pre-existing diabetes (i.e. with a normal four chamber/left ventricular outflow tract view at ultrasound). [EL = 2++]

5.8.4 Evidence statement

A number of studies have found no significant differences between women with type 1 diabetes and women without diabetes in terms of NT and weight-corrected total hCG, β-hCG and inhibin. On this basis it can be advised that no adjustment is required in these biochemical markers when calculating risks for congenital abnormalities in the fetuses of women with diabetes. A meta-analysis found weight-corrected AFP to be approximately 8% lower in women with type 1 diabetes and weight-corrected uE3 to be 6% lower in women with type 1 diabetes and therefore adjustments should be applied accordingly. Two studies have found conflicting results with regard to levels of PAPP-A. Therefore, until further evidence is available, adjustments should continue to be applied.

A number of well-designed observational studies have found more congenital anomalies are detected antenatally in women with diabetes when antenatal examination includes views of the four chambers of the fetal heart and outflow tracts. No more anomalies are detected with additional views. One study found detection rates were significantly worse in women with diabetes compared with low-risk women. This was largely attributed to obesity in women with diabetes resulting in unsatisfactory images.

5.8.5 Cost-effectiveness

The effectiveness of methods of screening for congenital cardiac malformations in women with diabetes was identified by the GDG as a priority for health economic analysis. The methods and results from the health economic modelling are summarised here; further details are provided in Appendix N.

Women with diabetes are at increased risk of having a baby with a cardiac malformation (the risk being approximately five times that of the general maternity population). Therefore, the GDG considered that this was an area where a different screening programme from that used in routine antenatal care might be justified on health economic grounds. An economic model was used to compare the cost-effectiveness of screening for congenital cardiac malformations using the four chamber plus outflow tracts view versus the four chamber view alone, which represents current practice. The baseline model suggested that the four chamber plus outflow tracts view was highly cost-effective in pregnant women with diabetes with a cost per QALY of approximately £4,000. One-way sensitivity analysis showed that four chamber plus outflow tracts view continued to be cost-effective when parameter values were varied within plausible ranges.

5.8.6 Existing guidance

As noted above, the NICE antenatal care guideline[9] recommends that all pregnant women should be offered ultrasound screening for congenital malformations (ideally at 18–20 weeks of gestation) using the four chamber plus outflow tracts view as part of routine antenatal care. Women should be given information regarding the purpose and implications of the anomaly scan in order to enable them make an informed choice as to whether or not to have the scan. The guideline recommends that all pregnant women should be offered screening

for Down's syndrome and that women should understand that it is their choice to embark on screening for Down's syndrome. If a woman receives a screen positive result, she should have rapid access to appropriate counselling by trained staff.

5.8.7 From evidence to recommendations

A health economic model demonstrated the cost-effectiveness of screening for congenital cardiac malformations based on the four chamber view of the fetal heart and outflow tracts relative to current practice of screening using the four chamber view alone. Data from European Surveillance of Congenital Anomalies (EUROCAT) and published literature suggest that an antenatal diagnosis of TGA may reduce neonatal mortality. These data, together with the higher prevalence of cardiac malformations in pregnant women with diabetes compared to pregnant women without diabetes underpin this result. For this reason the GDG identified screening for congenital cardiac malformations using the four chamber plus outflow tracts view as a key priority for implementation for women with diabetes (this form of screening is recommended as part of routine antenatal care but it does not form a key priority for implementation in the NICE antenatal care guideline9). There may be additional benefits of screening not taken into account in the model, the existence of which would tend to further improve the relative cost-effectiveness of screening based on the four chamber plus outflow tracts view.

The GDG's view is that a specialist cardiac scan should be offered at 22 weeks of gestation only if the results of the four chamber plus outflow tracts view are abnormal or if there is a relevant history of cardiac malformations. This is likely to bring a cost saving to the NHS because there is currently a tendency to offer a specialist cardiac scan to many women with diabetes.

2015 Update: The recommendations relating to screening for congenital malformations were edited by the GDG for the 2015 update to provide greater clarity (see section 5.11.7.5).

5.8.8 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.8.9 Research recommendations

36. How reliable is first-trimester screening for Down's syndrome incorporating levels of pregnancy- associated plasma protein (PAPP-A) in women with pre-existing diabetes?

Why this is important

Several screening tests for Down's syndrome incorporate measurements of PAPP-A. However, two clinical studies have reported conflicting results in terms of whether levels of PAPP-A in women with type 1 diabetes are lower than those in other women. Current practice is to adjust PAPP-A measurements in women with diabetes on the assumption that their PAPP-A levels are indeed lower than those of other women. Further research is, therefore, needed to evaluate the diagnostic accuracy and effect on pregnancy outcomes of screening tests for Down's syndrome incorporating measurements of PAPP-A in women with pre-existing diabetes.

37. How effective is transvaginal ultrasound for the detection of congenital malformations in women with diabetes and coexisting obesity?

Why this is important

Women with diabetes are at increased risk of having a baby with congenital malformations and current recommendations advise detailed ultrasound surveillance of the fetus at 20 weeks. Obstetric ultrasound signals are attenuated by the woman's abdominal wall fat. The incidence of obesity in pregnancy is increasing, and many women with diabetes (particularly women with type 2 diabetes) are obese, and this may limit the sensitivity of abdominal ultrasound screening for congenital malformations. Vaginal ultrasound, in theory, is not affected in this way. However, there is currently no evidence that fetal anatomical surveillance undertaken at about 13 weeks is more effective than abdominal ultrasound at 20 weeks. Comparative studies are, therefore, needed to evaluate the relative diagnostic accuracy of vaginal ultrasound at 13 weeks and abdominal ultrasound 20 weeks in the same group of women with diabetes in pregnancy and coexisting obesity.

5.9 Monitoring fetal growth and wellbeing

5.9.1 Description of the evidence

5.9.1.1 Fetal growth

Women with gestational diabetes and pre-existing diabetes are at increased risk of having a baby with macrosomia (see Sections 4.5 and 5.2). Macrosomia is defined in terms of absolute birthweight (usually more than 4000 g) or birthweight percentile for gestational age (usually ≥ 90th percentile), also referred to as LGA. Macrosomia is a risk factor for shoulder dystocia, brachial plexus injury, asphyxia or prolonged labour, operative delivery and postpartum haemorrhage (see Section 6.3 and Chapter 7).

Women with diabetes are also at risk of having a baby that is SGA. The risks associated with a baby that is SGA are not as well documented as for macrosomia, but at least one study was identified that suggested that babies who were SGA (< 10th percentile for gestational age) have an increased risk of perinatal morbidity and mortality.[277]

There is no clear consensus for monitoring fetal size in pregnant women with diabetes.[278] Clinical assessment of fetal size is by measurement of the symphysis–fundal height. Fetal size can also be measured by sonography. The two main ultrasonic methods for predicting birthweight are estimated fetal weight (EFW) and abdominal circumference of the fetus. EFW uses a combination of parameters, for example, the Hadlock formula[279] uses femur length, biparietal diameter, head circumference and abdominal circumference. Mean errors in estimating fetal weight are between 8% and 15% of actual birthweight.[279] EFW increases the rate of caesarean section in false positives (AGA babies incorrectly diagnosed as LGA).[280,281] Accuracy of estimated fetal weight is worse in women with diabetes[282] and for macrosomic babies.[283]

Compared with babies of women with diabetes who are AGA, LGA babies have accelerated growth of insulin-sensitive tissue such as abdominal wall fat.[284] Abdominal circumference is therefore considered to be a more relevant measure of diabetes-related macrosomia and the risk of shoulder dystocia. Abdominal circumference also has the advantage of being a single measure that is accessible even when the head is engaged in the pelvis.

A systematic review of 63 studies (51 evaluating the accuracy of estimated fetal weight and 12 the accuracy of fetal abdominal circumference) involving 19 117 women pooled data to produce summary receiver operating characteristic (sROC) curves for studies with various test thresholds.[278] Summary likelihood ratios (LRs) for positive and negative test results were generated for an estimated fetal weight of 4000 g and an abdominal circumference of 36 cm for predicting birthweight over 4000 g. The sROC curve area for estimated fetal weight was not different from the area for fetal abdominal circumference (0.87 versus 0.85, P = 0.91). For predicting a birthweight of over 4000 g the summary LR was 5.7 (95% CI 4.3 to 7.6) for a

positive test and 0.48 (95% CI 0.38 to 0.60) for a negative test. For ultrasound fetal abdominal circumference of 36 cm the LR for a positive test for predicting birthweight over 4000 g was 6.9 (95% CI 5.2 to 9.0) and the LR for a negative test was 0.37 (95% CI 0.30 to 0.45). There was no difference in accuracy between estimated fetal weight and abdominal circumference in the prediction of macrosomia at birth. The LRs suggest that both tests are only moderately useful at best. A positive test result is more accurate for ruling in macrosomia than is a negative test for ruling it out. [EL = 1++]

A diagnostic accuracy study compared 31 published formulas for estimated fetal weight in predicting macrosomia (birthweight 4000 g or more) in babies of women with diabetes.[285] One hundred and sixty-five women with pre-existing diabetes or gestational diabetes who had sonograms to estimate fetal weight after 36 weeks of gestation and within 2 weeks of birth were included in the study. Three measures of accuracy were compared: area under the ROC curve relating estimated fetal weight to macrosomia; systematic error; and absolute error. All 31 formulas for estimating fetal weight had similarly poor accuracy for prediction of macrosomia. [EL = 2+]

A cohort study evaluated the reliability of ultrasound estimation of fetal weight in 1117 women (48 with gestational diabetes) with a singleton pregnancy who had undergone ultrasound estimation of fetal weight less than 7 days before a term birth (at or later than 37 weeks of gestation).[286] Both large and normal weight babies of women with diabetes tended to have their weight underestimated. Given that reliability of ultrasound estimation of fetal weight to detect larger babies was poor, the study suggests that ultrasound use in the management of suspected macrosomia should be discouraged. [EL = 2+]

A retrospective cohort study investigated the association between ultrasound fetal biometry and amniotic fluid insulin levels at birth in 93 pregnant women with pre-existing diabetes or IGT.[287] Babies of women with pre-existing diabetes had significantly greater mean growth velocity (1.39, 95% CI 0.43 to 2.23 versus 0.39, 95% CI −01.7 to 0.95, P = 0.04), significantly greater mean estimated fetal weight and greater mean birthweight centile than those with gestational diabetes or IGT. Amniotic fluid insulin levels demonstrated a similar significant difference between women with pre-existing diabetes and those with gestational diabetes or IGT. The study demonstrated that ultrasound measures of fetal size and growth are not sufficiently accurate to predict those babies likely to be at risk from the effects of fetal hyperinsulinaemia. [EL = 2+]

A retrospective cohort study involving 242 pregnant women with IGT evaluated the performance of estimated fetal weight and fetal growth velocity in the prediction of birthweight.[288] The study showed that estimated fetal weight and fetal growth velocity have limited utility in predicting LGA babies. Estimated fetal weight and fetal growth velocity did not predict neonatal hypoglycaemia. [EL = 2+]

A prospective study of 181 women with diabetes (133 pre-existing type 1 diabetes, 48 gestational diabetes) compared the prediction power, at different gestational ages, of clinical and ultrasound measurements for fetal size.[289] Clinical and ultrasound estimates were made at 28, 34 and 38 weeks of gestation or before birth. The study found all measurements were poor predictors of eventual standardised birthweight. Prediction improved with closeness to birth. Adding ultrasound to clinical information improved prediction, but only to a small extent. There was no difference in the prediction power for macrosomia between clinical and ultrasound measurements. [EL = 2++]

5.9.1.2   Fetal wellbeing

Three main tests are used by obstetricians to monitor fetal wellbeing. These are umbilical artery Doppler ultrasound velocimetry, fetal cardiotocography (non-stress test) and the biophysical profile. Monitoring for fetal wellbeing assumes that fetal compromise can be identified and that appropriately timed intervention (induction of labour or caesarean section)

may reduce the risk of perinatal morbidity, admission to neonatal intensive care, asphyxia and fetal death.[290]

Doppler ultrasound

Doppler ultrasound uses sound waves to detect the movement of blood in the umbilical artery. It is used during pregnancy to assess fetus–placenta and/or uterus–placenta circulation.

A systematic review considered the effectiveness of Doppler ultrasound in high-risk pregnancies.[291] The review included 11 studies involving 7000 women. Compared with no Doppler ultrasound, Doppler ultrasound in high-risk pregnancies (especially those complicated by hypertension or presumed impaired fetal growth) was associated with fewer perinatal deaths, fewer inductions of labour (OR 0.83, 95% CI 0.74 to 0.93) and fewer admissions to hospital (OR 0.56, 95% CI 0.43 to 0.72) without adverse effects. [EL = 1++] However, Doppler ultrasound offers no benefits to the low-risk population.[292] [EL = 1++]

Abnormal umbilical Doppler ultrasound results are associated with chronic placental insufficiency, as occurs in pregnancies complicated by pre-eclampsia and fetal growth restriction . Although women with diabetes are at increased risk for these conditions, the majority of adverse outcomes in pregnancies complicated by diabetes are not associated with placental insufficiency.[293] Small studies of women with gestational diabetes or pre-existing diabetes with good glycaemic control have considered the performance of Doppler ultrasound in predicting any adverse pregnancy outcome and have reported low sensitivities [294–297] [EL = 2++ to 2+]

Nonetheless a study has reported that Doppler ultrasound is better than fetal cardiotocography or biophysical profile in pregnant women with diabetes.[298] In this study involving 207 women with diabetes, all three tests were performed concurrently within 1 week of birth. An adverse pregnancy outcome was defined as a pregnancy in which the baby was born before 37 weeks of gestation or had at least one of the following: growth restriction, hypocalcaemia, hypoglycaemia, hyperbilirubinaemia, respiratory distress syndrome or fetal risk requiring caesarean section. There were no perinatal deaths in this series. The performance of the three tests is summarised in Table 69. [EL = 2++]

Table 69: Performance of umbilical artery Doppler ultrasound, fetal cardiotocography and biophysical profile in predicting overall adverse pregnancy outcome; data from Bracero et al. (1996)[298]

	Non-reactive cardio-tocography	Biophysical profile ≤ 6	Umbilical artery systolic : diastolic ratio ≥ 3	Umbilical artery systolic : diastolic ratio ≥ 2.5
Sensitivity	25.3%	8.0%	25.3%	65.3%
Specificity	88.6%	97.0%	96.2%	61.4%
PPV	55.9%	60.0%	79.2%	49.0%
NPV	67.6%	65.0%	69.4%	75.7%
RR	1.7	1.7	2.6	2.0
95% CI	1.2 to 2.5	0.9 to 2.9	1.9 to 3.5	1.4 to 3.0
P value	0.009	0.109	< 0.001	< 0.001

A prospective double-blind randomised study was performed between 28 and 40 weeks of gestation in 92 pregnant women with diabetes to evaluate a random single Doppler ultrasound measurement of the systolic : diastolic ratio of the umbilical artery as a predictor of perinatal outcome in pregnancies complicated by diabetes.[299] The performance of the Doppler ultrasound measurement as a predictor of poor perinatal outcome was: sensitivity 39%, specificity 92%, PPV 54%, NPV 86%. The data suggest that the systolic : diastolic ratio

of the umbilical artery offers no advantage over other well-established tests in the management of pregnancy in women with diabetes. [EL = 1+]

Sixty-five pregnant women with diabetes were examined in a cohort study to evaluate the clinical usefulness of Doppler ultrasound flow velocity waveform analysis in such pregnancies.[300] Umbilical and uterine artery flow velocity waveforms were obtained during the third trimester with a continuous wave Doppler ultrasound device. There was no difference in various clinical and Doppler ultrasound parameters between women with good glycaemic control and those with poor control. In contrast, the clinical and Doppler parameters were significantly different in women with pre-eclampsia than in those without pre-eclampsia, regardless of glycaemic control. There was a weak positive linear correlation (r = 0.30, P < 0.02) between maternal HbA1c and umbilical artery flow velocity waveforms (systolic : diastolic ratio). Proteinuria correlated better with umbilical artery systolic : diastolic ratio (r = 0.49, P < 0.001). The study suggests that Doppler ultrasound flow velocity waveform analysis may be clinically useful only in pregnancies complicated by diabetes and coexisting pre-eclampsia. [EL = 2+]

A prospective cohort study investigated Doppler ultrasound measurement of the fetal umbilical artery velocimetry in 56 women with diabetes, of whom 14 had varying degrees of vascular complications.[301] The mean Doppler ultrasound values were higher in women with diabetes and vasculopathy than in women without diabetes and women with diabetes but no vasculopathy. The third-trimester systolic : diastolic ratio was greater than 3 in almost 50% of women with vasculopathy. A tendency towards adverse outcomes was observed at systolic : diastolic ratios approaching 4. Statistically significant correlations were found between elevated Doppler indices and maternal vasculopathy associated with hypertension and worsening renal insufficiency. Fetal growth restriction and neonatal metabolic complications were also significantly correlated with elevated Doppler indices. The data indicate an increased resistance circuit among women with diabetes and vasculopathy, which may reflect a relative reduction in basal uteroplacental blood flow and the need for cautious interpretation of Doppler indices in these women. [EL = 2+]

Another prospective cohort study was conducted to determine whether fetal aortic velocity waveforms were correlated with fetal outcome in pregnancies complicated by type 1 diabetes.[302] Fetal aortic blood flow was assessed in 30 pregnant women with type 1 diabetes. The babies demonstrated no evidence of fetal distress at birth and there was no relationship between the mean third-trimester fetal aortic systolic : diastolic ratios and perinatal death, preterm deliveries, birthweight, Apgar scores at 1 minute and 5 minutes, or neonatal metabolic abnormalities. The data demonstrate a poor correlation between fetal aortic Doppler waveform analysis and fetal outcome. [EL = 2+]

5.9.1.3 Current practice

The CEMACH enquiry found that 21% of singleton births with a known birthweight had a birthweight of 4000 g or more in women with poor pregnancy outcomes.[33] This was higher than the national average of 11%. A total of 5.7% births were severely macrosomic singleton births (a birthweight of 4500 g or over). The CEMACH enquiry case–control study reported that antenatal evidence of fetal growth restriction was associated with poor pregnancy outcome (OR 2.9, 95% CI 1.4 to 6.3, adjusted for maternal age and deprivation), but antenatal evidence of fetal macrosomia was not (OR 0.8, 95% CI 0.5 to 1.3, adjusted for maternal age and deprivation).[33] Fetal surveillance was sub-optimal for 20% of 37 babies with antenatal evidence of fetal growth restriction and for 45% of 129 babies with antenatal evidence of macrosomia. For babies with antenatal evidence of macrosomia, sub-optimal fetal surveillance was associated with poor pregnancy outcome (OR 5.3, 95% CI 2.4 to 12.0, adjusted for maternal age and deprivation). Additional case–control analysis showed an association with fetal and neonatal death after 20 weeks of gestation, but not with fetal anomaly. [EL = 3–4]

The CEMACH enquiry found no difference in the proportion of women with type 1 or type 2 diabetes with antenatal evidence of macrosomia (P = 0.99) or fetal growth restriction (P = 0.31).[33] [EL = 3–4]

The CEMACH enquiry found that shoulder dystocia was documented in 7.9% of vaginal births. The rate of shoulder dystocia was related to birthweight with 0.9% of babies weighing less than 2500 g, 4.7% of babies 2500–3999 g, 22.0% of babies 4000–4249 g, 25% of babies 4250–4499 g and 42.9% of babies 4500 g or more. The CEMACH enquiry found that Erb palsy occurred in 4.5 per 100 births; this is greater than the incidence of 0.42 per 1000 live births reported in the general population.[2] [EL = 3]

The CEMACH enquiry found 0.9% of singleton babies born to women with type 1 diabetes and 1.3% singleton babies born to women with type 2 diabetes were less than 1000 g; this is higher than the national average for England and Wales (0.5%).[2] [EL = 3]

The main concerns of the enquiry panels regarding surveillance of macrosomic and growth-restricted babies was lack of timely follow-up (affecting approximately 80% of babies). For macrosomic babies, there were also concerns about poor interpretation of ultrasound scans and about actions taken in response to tests. [EL = 3–4]

5.9.2 Evidence statement

The main ultrasonic methods for predicting birthweight (EFW and abdominal circumference) perform similarly in terms of diagnostic accuracy in women with diabetes. However, no clinical studies were identified that compared clinical outcomes using the two methods.

Umbilical artery Doppler ultrasound has better diagnostic accuracy as a test of fetal wellbeing in pregnant women with diabetes than has fetal cardiotocography or biophysical profile. Doppler ultrasound is also a better predictor of adverse maternal and neonatal outcomes, but its effectiveness is limited to high-risk pregnancies defined in terms of fetal growth restriction and/or pre-eclampsia, rather than diabetes per se.

5.9.3 Cost-effectiveness

The effectiveness of methods for monitoring fetal growth and wellbeing in women with diabetes was identified by the GDG as a priority for health economic analysis.

The lack of comparative data in relation to clinical outcomes resulting from ultrasonic methods for assessing fetal growth (for example, fetal abdominal circumference alone versus abdominal circumference plus fetal head circumference) precluded formal cost-effectiveness analysis. The GDG's discussions included consideration of the frequency of ultrasound assessment of fetal growth and the implications for cost-effectiveness. The GDG's view was that three scans should be offered (rather than two): this would allow healthcare professionals to advise women with diabetes on the direction of pregnancy, rather than providing estimates of fetal growth that might be masked by measurement error; it would also allow assessment of the need for, and response to, insulin therapy. Nevertheless, three scans at 4-weekly intervals starting at 28 weeks of gestation was thought to represent a reduction in the frequency of growth scans compared with current clinical practice that would, therefore, bring a cost saving to the NHS.

The clinical evidence in relation to monitoring fetal wellbeing showed that umbilical artery Doppler ultrasound is more effective in predicting adverse outcomes in women with diabetes than fetal cardiotocography or biophysical profile. Given that the clinical effectiveness of Doppler ultrasound is limited to women with other risk factors (notably fetal growth restriction and/or pre-eclampsia), and that current practice involves routine use of Doppler ultrasound to monitor fetal wellbeing in women with diabetes, a recommendation not to monitor fetal wellbeing routinely before 38 weeks of gestation was considered likely to be cost-effective.

5.9.4 Existing guidance

The NICE antenatal care guideline[9] recommends that symphysis–fundal height should be measured and recorded for pregnant women at each antenatal appointment from 24 weeks of gestation. A fetal growth scan to detect SGA unborn babies should be offered to women if the symphysis–fundal height measurement is at least 3 cm less than the gestational age in weeks. Ultrasound estimation of fetal size for suspected LGA unborn babies should not be undertaken in a low-risk population. Doppler ultrasound should not be used to monitor fetal growth during pregnancy. Customised fetal growth charts should not be used for screening for SGA babies.

5.9.5 From evidence to recommendations

In the absence of comparative data on the effectiveness of different methods of ultrasound monitoring of fetal growth, the GDG recommended that fetal growth and amniotic fluid volume (to detect polyhydramnios) should be monitored by ultrasound every 4 weeks from 28 weeks of gestation to 36 weeks of gestation. The GDG's view is that this would represent a change in clinical practice which would effect a reduction in the frequency of monitoring for fetal growth and amniotic fluid volume in women with diabetes and would, therefore, bring a cost saving to the NHS. Fetal growth and amniotic fluid volume should be measured in all women with pre-existing diabetes and gestational diabetes (i.e. even in women with gestational diabetes controlled by diet alone) because of the increased risk of macrosomia.

Evidence shows that monitoring for fetal wellbeing using umbilical artery Doppler ultrasound is a better predictor of pregnancy outcome than fetal cardiotocography and biophysical profile in women with diabetes. However, routine monitoring of fetal wellbeing for women with diabetes is not recommended before 38 weeks of gestation because the effectiveness of Doppler ultrasound is limited to women at risk of fetal growth restriction and/or pre-eclampsia. In making this recommendation the GDG sought to effect a change in clinical practice that would bring a cost saving to the NHS.

5.9.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.9.7 Research recommendations

38. How can the fetus at risk of intrauterine death be identified in women with diabetes?

Why this is important

Unheralded intrauterine death remains a significant contributor to perinatal mortality in pregnancies complicated by diabetes. Conventional tests of fetal wellbeing (umbilical artery Doppler ultrasound, cardiotocography and other biophysical tests) have been shown to have

poor sensitivity for predicting such events. Alternative approaches that include measurements of liquor erythropoietin and magnetic resonance imaging spectroscopy may be effective, but there is currently insufficient clinical evidence to evaluate them. Well-designed randomised controlled trials that are sufficiently powered are needed to determine whether these approaches are clinically and cost-effective.

5.10 Timetable of antenatal appointments

5.10.1 Description of the evidence

No specific searches were undertaken for this section of the guideline. The evidence is drawn from publications identified in searches for other sections.

5.10.1.1 Current practice

The CEMACH diabetes in pregnancy programme provides data on current practice in England, Wales and Northern Ireland in relation to antenatal care, including care plans, for women with type 1 and type 2 diabetes. The enquiry panels classified maternity care during pregnancy as sub-optimal for 58% of women who had poor pregnancy outcomes and 44% of women who had good pregnancy outcomes (OR 1.9, 95% CI 1.2 to 2.8, adjusted for maternal age and deprivation). The two most frequently cited categories for sub-optimal antenatal care were fetal surveillance (monitoring fetal growth and wellbeing; see Section 5.9) and management of maternal risks. Other categories cited included problems with the antenatal diabetes multidisciplinary team. There were no significant differences between women with type 1 and type 2 diabetes in terms of sub-optimal antenatal care.[33] [EL = 3–4]

The enquiry reported that 63% of maternity units in England Wales and Northern Ireland had a full multidisciplinary team comprising an obstetrician, a diabetes physician, a diabetes specialist nurse, a diabetes specialist midwife and a dietitian. There had been an increase in provision of staff over the preceding 8 years, with the availability of a diabetes specialist midwife in the antenatal clinic increasing from 25% to 77% of units, and the availability of a dietitian increasing from 40% to 80% of units. Seventy-five percent of women were reported to have maternity and diabetes care provided in a joint clinic, although only 22% of women were reported to have the entire multidisciplinary team involved in their care.[33] [EL = 3–4]

The CEMACH enquiry panels commented that infrequent clinic appointments, lack of multidisciplinary involvement and communication issues were factors in sub-optimal diabetes care in pregnancy in some of the women in the case–control study.[33] [EL = 3–4]

The CEMACH enquiry recommended that an individualised care plan for pregnancy (and the postnatal period) be used and that the care plan should include, as a minimum:[33]
- targets for glycaemic control
- a schedule for retinal screening
- a schedule for renal screening
- a plan for fetal surveillance during birth
- postnatal diabetes care.

It was recommended that the care plan should be implemented from the beginning of pregnancy by a multidisciplinary team present at the same time in the same clinic. [EL = 3–4]

5.10.1.2 Existing guidance

The NSF for diabetes20 recommends that antenatal care for women with diabetes should be delivered by a multidisciplinary team consisting of an obstetrician, a diabetes physician, a diabetes specialist nurse, a midwife and a dietitian.

The NICE antenatal care guideline9 contains recommendations on the schedule of appointments that should be offered as part of routine antenatal care, including recommendations about what should happen at each appointment.

5.10.2 From evidence to recommendations

The GDG's view is that women with diabetes who are pregnant should be offered immediate contact with a joint diabetes and antenatal clinic, and they should have contact with the diabetes care team for assessment of glycaemic control every 1–2 weeks throughout pregnancy.

The timing and content of antenatal care appointments for women with diabetes should follow the schedule for routine antenatal care appointments recommended in the NICE antenatal care guideline,[9] except where specific additions and/or differences are indicated below to support the recommendations made elsewhere in the guideline. The main differences between routine antenatal care (as specified in the NICE antenatal care guideline)9 and antenatal care for women with diabetes are summarised in Table 70. Ongoing opportunites for accessing information, education and advice should be offered to women with diabetes throughout the antenatal period.

Evidence from the CEMACH enquiry shows that many maternity units have not yet implemented the recommendation in the NSF for diabetes to provide diabetes and maternity care in a joint diabetes/antenatal clinic delivered by a multidisciplinary team. In formulating its recommendations the GDG sought to reinforce the recommendation contained in the NSF for diabetes.

5.10.2.1 First antenatal appointment

The GDG's view is that women with diabetes should be offered confirmation of viability and gestational age at the first antenatal appointment. This is earlier than in routine antenatal care because diabetes is associated with a high rate of miscarriage (see Sections 3.1 and 5.3) and because diabetes can disrupt the menstrual cycle leading to difficulty in determining the timing of ovulation.

Women with pre-existing diabetes may already have attended for preconception care and advice. For these women, the first antenatal appointment provides an opportunity to reinforce information, education and advice in relation to achieving optimal glycaemic control (including   dietary advice). Women who have not attended for preconception care and advice should be offered the corresponding information, education and advice for the first time; a clinical history should seek to establish the extent of diabetes-related complications (including neuropathy and vascular disease); medications for diabetes and its complications should also be reviewed at this time.

Women with pre-existing diabetes who have not had a retinal assessment in the previous 12 months should be offered an assessment at the first presentation in pregnancy (see Section 5.6). Women with pre-existing diabetes who have not had a renal assessment in the previous 12 months should be offered an assessment at the first presentation in pregnancy (see Section 5.7).

All women with diabetes should have contact with the diabetes care team for assessment of glycaemic control every 1–2 weeks throughout the antenatal period (this could include telephone contact) and HbA1c should be used to assess long-term glycaemic control in the first trimester of pregnancy (see Section 5.3).

The GDG's discussions included consideration of screening for Down's syndrome. Screening methods for Down's syndrome in women with diabetes are currently no different to those for women without diabetes, and so the GDG made no specific recommendations in relation to the schedule for screening for Down's syndrome.

The GDG's discussions also included consideration of surveillance for pre-eclampsia. Women with diabetes are at increased risk of pre-eclampsia (see Section 5.7), but methods for surveillance (testing for proteinuria) and management of pre-eclampsia in women with diabetes are no different to those for women without diabetes. The schedule of appointments for routine antenatal care recommended in the NICE antenatal care guideline9 includes testing urine for proteinuria at every appointment, and so the GDG made no specific recommendations in relation to surveillance for pre-eclampsia.

5.10.2.2   16 weeks of gestation

If any retinopathy is present at booking an additional assessment should be made at 16–20 weeks of gestation for women with pre-existing diabetes (see Section 5.6).

5.10.2.3   20 weeks of gestation

Women with diabetes should be offered an ultrasound anatomical examination of the four chamber view of the fetal heart and outflow tracts at 20 weeks of gestation because the diagnostic accuracy is better at 20 weeks of gestation than at 18–19 weeks of gestation (see Section 5.8). The GDG's view is that the routine ultrasound scan for detecting structural anomalies, which should be offered to all pregnant women, should also be performed at 20 weeks of gestation in women with diabetes because it is more convenient for the woman to have both scans at one visit.

5.10.2.4   25 weeks of gestation

No evidence was identified to suggest that antenatal care for women with diabetes should be different to routine antenatal care at 25 weeks of gestation.

5.10.2.5   28 weeks of gestation

Ultrasound monitoring of fetal growth (to detect LGA or SGA babies) and amniotic fluid volume (to detect polyhydramnios) should start at 28 weeks of gestation and continue at 4-weekly intervals (i.e. 32 weeks and 36 weeks; see Section 5.9). Women with pre-existing diabetes who had no diabetic retinopathy at their first antenatal clinic visit should be offered retinal assessment at 28 weeks of gestation (see Section 5.6). Women who have been diagnosed with gestational diabetes as a result of routine antenatal screening enter the care pathway at 28 weeks of gestation (see Section 4.4 and the NICE antenatal care guideline9). They should be offered information about the risks to the woman and the baby that is offered to women with pre-existing diabetes in the preconception period.

5.10.2.6   32 weeks of gestation

Ultrasound monitoring of fetal growth and amniotic fluid volume should be offered at 32 weeks of gestation as part of 4-weekly monitoring (see Section 5.9). It is the GDG's view that, for women with diabetes, the routine investigations that would normally be offered to nulliparous pregnant women at 31 weeks of gestation should instead be offered at 32 weeks of gestation because it is more convenient for the woman to have all the investigations at one visit.

5.10.2.7   34 weeks of gestation

No evidence was identified to suggest that antenatal care for women with diabetes should be different to routine antenatal care at 34 weeks of gestation.

5.10.2.8   36 weeks of gestation

Ultrasound monitoring of fetal growth and amniotic fluid volume should be offered at 36 weeks of gestation as part of 4-weekly monitoring (see Section 5.9). Evidence shows that women with diabetes are likely to give birth soon after 36 weeks of gestation, either through spontaneous labour, elective induction of labour or elective caesarean section to reduce the risk of stillbirth and birth trauma associated with fetal macrosomia (see Section 6.1). Given the evidence, the GDG's view is that women with diabetes should be offered information and advice in relation to intrapartum care and postnatal care at 36 weeks of gestation. The information and advice should cover: timing, mode and management of labour and birth, including options for elective early birth (see Section 6.1); analgesia and anaesthesia (see Section 6.2); changes to hypoglycaemic therapy during and after birth (see Sections 6.3 and 8.1); management of the baby after birth, including early feeding, detection and management of neonatal hypoglycaemia and other diabetes-related complications (see Chapter 7); initiation of breastfeeding and the effect of breastfeeding on glycaemic control (see Section 8.1); and information about contraception and follow-up (see Section 8.2).

5.10.2.9   38 weeks of gestation

Induction of labour, or caesarean section if indicated, should be offered to women with diabetes at 38 weeks of gestation (see Section 6.1). Monitoring of fetal wellbeing should be offered to women with diabetes who are awaiting spontaneous labour.

5.10.2.10   39–41 weeks of gestation

No evidence was identified to suggest that antenatal care for women with diabetes who have not given birth by 40 weeks of gestation should be different to routine antenatal care at 40–41 weeks of gestation. However, evidence shows that many women with diabetes give birth before 40 weeks of gestation (see Section 6.1). Monitoring of fetal wellbeing should be offered to women with diabetes who are awaiting spontaneous labour at 39–41 weeks of gestation.

The GDG's discussions also included consideration of thyroid function in women with diabetes. There was no reason to suppose that women with diabetes required testing for thyroid function.

Table 70: Timetable of antenatal appointments for women with diabetes

Routine antenatal care (NICE antenatal care guideline)[9]	Additional/different care for women with diabetes
First appointment (booking) • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by written information (on topics such as diet and lifestyle considerations, pregnancy care services available, maternity benefits and sufficient information to enable informed decision making about screening tests) • identify women who may need additional care and plan pattern of care for the pregnancy • check blood group and RhD status • offer screening for haemoglobinopathies, anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis • offer screening for asymptomatic bacteriuria • offering screening for Down's syndrome • offer early ultrasound scan for gestational age	First appointment (joint diabetes and antenatal clinic) • if the woman has been attending for preconception care and advice, continue to provide information, education and advice in relation to achieving optimal glycaemic control (including dietary advice) • if the woman has not attended for preconception care and advice give information, education and advice for the first time, take clinical history to establish extent of diabetes-related complications (including neuropathy and vascular disease), and review medications for diabetes and its complicationsOffer retinal assessment for women with pre-existing diabetes. This should be undertaken as soon as possible if an assessment has not

Routine antenatal care (NICE antenatal care guideline)[9]	Additional/different care for women with diabetes
assessment • offer ultrasound screening for structural anomalies (18–20 weeks) • measure BMI, blood pressure and test urine for proteinuria. At the first (and possibly second) appointment, for women who choose to have screening, the following tests should be arranged: • blood tests (for checking blood group and RhD status and screening for haemogloinopathies, anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis) ideally before 10 weeks • urine tests (to check for proteinuria and screen for asymptomatic bacteriuria) • ultrasound scan to determine gestational age using: • crown–rump measurement if performed at 10 weeks 0 days to 13 weeks 6 days • head circumference if crown–rump length is above 84 millimetres Down's syndrome screening using: • nuchal translucency at 11 weeks 0 days to 13 weeks 6 days • serum screening at 15 weeks 0 days to 20 weeks 0 days.	been performed in the last 12 months. • Offer renal assessment for women with pre-existing diabetes if this has not been undertaken in previous 12 months. • contact with the diabetes care team every 1–2 weeks throughout pregnancy for all women with diabetes and assessment of long-term glycaemic control using HbA1c (first trimester only).
16 weeks The next appointment should be scheduled at 16 weeks to: • •review, discuss and record the results of all screening tests undertaken; reassess planned pattern of care for the pregnancy and identify women who need additional care • • b investigate a haemoglobin level of less than 11 g/100 ml and consider iron supplementation if indicated • measure blood pressure and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions, including discussion of the routine anomaly scan; offer verbal information supported by antenatal classes and written information.	16 weeks • Retinal assessment for women with pre-existing diabetes if diabetic retinopathy was present at booking (16–20 weeks). • Early testing of glood glucose or OGTT for women with a history of gestational diabetes and/or ongoing IGT (18–20 weeks).
18–20 weeks • At 18–20 weeks, if the woman chooses, an ultrasound scan should be performed for the detection of structural anomalies. For a woman whose placenta is found to extend across the internal cervical os at this time, another scan at 36 weeks should be offered and the results of this scan reviewed at the 36 week appointment.	20 weeks • Ultrasound scan for detecting structural abnormalities including examination of the fetal heart (four chambers, outflow tracts and three vessels) at 20 weeks..
25 weeks At 25 weeks of gestation, another appointment	25 weeks No additional or different care for women with

Routine antenatal care (NICE antenatal care guideline)[9]	Additional/different care for women with diabetes
should be scheduled for nulliparous women. At this appointment: • measure and plot symphysis–fundal height • measure blood pressure and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.	diabetes.
28 weeks The next appointment for all pregnant women should occur at 28 weeks. At this appointment: • offer a second screening for anaemia and atypical red-cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • offer anti-D to rhesus-negative women • measure blood pressure and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information screening for gestational diabetes.	28 weeks • Start ultrasound monitoring of fetal growth and amniotic fluid volume • Retinal assessment for women with pre-existing diabetes • Women diagnosed with gestational diabetes as a result of routine antenatal screening enter the care pathway.
31 weeks • Nulliparous women should have an appointment scheduled at 31 weeks to: • measure blood pressure and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information • review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care.	32 weeks (not 31 weeks) • Ultrasound monitoring of fetal growth and amniotic fluid volume. • All routine investigations normally scheduled for 31 weeks should also be conducted at 32 weeks.
34 weeks At 34 weeks, all pregnant women should be seen in order to: • offer a second dose of anti-D to rhesus-negative women • measure blood pressure and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information	34 weeks • No additional or different care for women with diabetes

Routine antenatal care (NICE antenatal care guideline)[9]	Additional/different care for women with diabetes
• review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care.	
36 weeks At 36 weeks, all pregnant women should be seen again to: • measure blood pressure and test urine for proteinuria • measure and plot symphysis–fundal height • check position of baby • for women whose babies are in the breech presentation, offer external cephalic version including anaesthetic review/assessment. • review ultrasound scan report if placenta extended over the internal cervical os at previous scan • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.	**36 weeks** • Ultrasound monitoring of fetal growth and amniotic fluid volume. • Offer information and advice about timing, mode and management of labour and birth,
38 weeks Another appointment at 38 weeks will allow for: • measurement of blood pressure and urine testing for proteinuria • measurement and plotting of symphysis–fundal height • information giving, including options for management of prolonged pregnancy, with an opportunity to discuss issues and ask questions; verbal information supported by antenatal classes and written information.	**38 weeks** Induction of labour, or caesarean section if indicated, otherwise await spontaneous labour. • Monitoring of fetal wellbeing if baby not yet born. • 39 weeks • Monitoring of fetal wellbeing if baby not yet born.
40 weeks For nulliparous women, an appointment at 40 weeks should be scheduled to: • measure blood pressure and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.	**40 weeks** • No additional or different care for women with diabetes. • Monitoring of fetal wellbeing if baby not yet born.
41 weeks For women who have not given birth by 41 weeks: • a membrane sweep should be offereda • induction of labour should be offereda • blood pressure should be measured and urine tested for proteinuria • symphysis–fundal height should be measured and plotted	**41 weeks** • No additional or different care for women with diabetes. • Monitoring of fetal wellbeing if baby not yet born.

Routine antenatal care (NICE antenatal care guideline)[9]	Additional/different care for women with diabetes
• information should be given, with an opportunity to discuss issues and ask questions; verbal information supported by written information.	

5.10.3 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.11 Specialist teams

This section was updated in 2015

5.11.1 Review question

What is the effectiveness of specialist teams for pregnant women with diabetes?

5.11.2 Introduction

The objective of this review question is to determine whether specialist care during pregnancy for women with diabetes, as recommended in the 2008 guideline, is effective. Two types of specialist care were investigated by the review: receiving care from a multidisciplinary team compared with standard antenatal care; and receiving care from a centralised hospital compared with care from a peripheral hospital.

5.11.3 Description of included studies

Five studies (2 prospective and 3 retrospective observational studies) were identified for inclusion for this review question (Dunne et al., 2009; Hadden et al., 1999; Owens et al., 2012; Traub et al., 1987; Wilson et al., 2009). One prospective (Owens et al., 2012) and 1 retrospective (Wilson et al., 2009) study compared the use of a multidisciplinary team with standard care. One prospective (Dunne et al., 2009) and 2 retrospective (Hadden et al., 1999; Traub et al., 1987) studies compared the provision of care in a centralised hospital with care given in a peripheral hospital. Of the 2 studies that reported on multidisciplinary teams, 1 included 272 pregnancies without reporting the number of women (Owens et al., 2012) and the other included 96 women who all had gestational diabetes (Wilson et al., 2009). Of the 3 studies that compared centralised and peripheral care, 1 included 104 pregnancies in 84 women (Dunne et al., 2009), another included 856 pregnancies without reporting the number of women (Hadden et al., 1999) and the third included 221 pregnancies in 187 women (Traub et al., 1987).

The guideline development group's priority outcomes that were reported in the studies were:
• mode of birth
• glycaemic control in pregnancy (measured using HbA1C)
• fetal or neonatal mortality
• the number of large for gestational age babies
• length of stay in a neonatal intensive care unit.

The priority outcomes that were not reported in the studies were:
• the number of preterm births
• maternal satisfaction
• initiation of breastfeeding.

5.11.4 Evidence profile

The GRADE profiles for this review question are presented in Tables 71 and 72.

Table 71: GRADE profile for effectiveness of multidisciplinary teams for pregnant women with diabetes

| Number of studies | Number of women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	Receiving care from a multidisciplinary team	Not receiving care from a multidisciplinary team	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Mode of birth											
Vaginal birth (not including assisted birth)											
1 (Wilson et al., 2009)	22/47 (47%)	21/49 (43%)	OR 1.2 (0.5 to 2.6)[a]	39 more per 1000 (from 148 fewer to 234 more)	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[f]
Assisted/instrumental birth (including forceps and ventouse)											
1 (Wilson et al., 2009)	3/47 (6%)	4/49 (8%)	OR 0.8 (0.2 to 3.6)[a]	18 fewer per 1000 (from 68 fewer to 162 more)	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[f]
Caesarean section											
2 (Owens et al., 2012 and Wilson et al., 2009)	135/262 (52%)	81/202 (40%)	OR 1.4 (0.9 to 2.2)[a]	85 more per 1000 (from 20 fewer to 191 more)	Very low	Observational	Serious limitations[g]	No serious inconsistency	No serious indirectness[d]	Serious imprecision[e]	Yes[h]
Glycaemic control in pregnancy											
HbA1C in women with type 1 diabetes in the first trimester											
1 (Owens et al., 2012)	168	104	NA	MD 3 lower (4.5 lower to 1.5 lower)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]
HbA1C in women with type 2 diabetes in the first trimester											
1 (Owens et al., 2012)	168	104	NA	MD 7 lower (8.4 lower to 5.6 lower)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Receiving care from a multidisciplinary team	Not receiving care from a multidisciplinary team	Relative (95% confidence interval)	Absolute (95% confidence interval)							
HbA1C in women with type 1 and type 2 diabetes in the first trimester											
1 (Wilson et al., 2009)	47	49	NA	MD 0 higher (0.3 lower to 0.3 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[l]	Yes[f]
HbA1C in women with type 1 diabetes in the second trimester											
1 (Owens et al., 2012)	168	104	NA	MD 1 lower (1.3 lower to 0.7 lower)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]
HbA1C in women with type 2 diabetes in the second trimester											
1 (Owens et al., 2012)	168	104	NA	MD 5 lower (5.2 lower to 4.8 lower)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]
HbA1C in women type 1 and type 2 diabetes in the second trimester											
1 (Wilson et al., 2009)	47	49	NA	MD 0.2 lower (0.6 lower to 0.2 higher)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[l]	Yes[f]
HbA1C in women with type 1 diabetes in the third trimester											
1 (Owens et al., 2012)	168	104	NA	MD 3 lower (3.3 lower to 2.8 lower)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]
HbA1C in women with type 2 diabetes in the third trimester											
1 (Owens et al., 2012)	168	104	NA	MD 1 higher (0.8 higher to 1.2 higher)[a]	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[k]
HbA1C in women with type 1 and type 2 diabetes in the third trimester											
1 (Wilson et al., 2009)	47	49	NA	MD 0.4 lower (0.7 lower to 0.1 lower)[a]	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[j]	Yes[f]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Receiving care from a multidisciplinary team	Not receiving care from a multidisciplinary team	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Fetal or neonatal mortality											
Perinatal death											
1 (Owens et al., 2012)	1/168 (< 1%)	5/104 (5%)	OR 0.1 (0.0 to 1.0)[a]	42 fewer per 1000 (from 48 fewer to 1 more)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[k]
Stillbirth											
1 (Owens et al., 2012)	2/168 (1%)	4/104 (4%)	OR 0.3 (0.1 to 1.7)[a]	27 fewer per 1000 (from 36 fewer to 24 more)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[k]
Miscarriage											
1 (Owens et al., 2012)	13/168 (8%)	23/104 (22%)	OR 0.3 (0.1 to 0.6)[a]	143 fewer per 1000 (from 74 fewer to 183 fewer)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[m]	Yes[k]
Large for gestational age											
Large for gestational age babies in women with type 1 diabetes											
1 (Owens et al., 2012)	44/168 (26%)	31/104 (30%)	OR 0.8 (0.5 to 1.4)[a]	35 fewer per 1000 (from 126 fewer to 81 more)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[k]
Large for gestational age babies in women with type 2 diabetes											
1 (Owens et al., 2012)	42/168 (25%)	18/104 (17%)	OR 1.6 (0.9 to 3.0)[a]	77 more per 1000 (from 21 fewer to 209 more)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[k]

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Receiving care from a multidisciplinary team	Not receiving care from a multidisciplinary team	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Neonatal intensive care unit stay											
Neonatal intensive care unit admission											
1 (Owens et al., 2012)	94/168 (56%)	63/104 (61%)	OR 0.8 (0.5 to 1.4)[a]	45 fewer per 1000 (from 171 fewer to 71 more)	Very low	Observational	Serious limitations[i]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[e]	Yes[k]
Special care baby unit admission											
1 (Wilson et al2009)	5/47 (11%)	16/49 (33%)	OR 0.3 (0.1 to 0.7)[a]	218 fewer per 1000 (from 62 fewer to 289 fewer)	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[m]	Yes[f]

MD mean difference, NA Not applicable, NC Not calculable, OR odds ratio

a. Calculated by the NCC-WCH based on results reported in the paper

b. It is not clear whether the groups had a comparable body mass index (BMI) at baseline (reported data were conflicting). It is unclear whether there are other potentially confounding factors present

c. Single study analysis

d. Study or studies met population and outcome criteria specified in the review protocol

e. Confidence interval for the OR crosses the line of no effect (OR = 1) and OR = 0.75 and/or OR = 1.25

f. This study was conducted in the UK. In the two groups, 42.6% and 51.0% of the women were white, 38.2% and 34.6% were South Asian. Other ethnicities were not reported. The average age at booking was 31.4 years in one group and 29.7 years in the other group.

g. In one study it was unclear whether the groups had a comparable BMI at baseline (reported data were conflicting).It is unclear whether there are other potentially confounding factors present. In the other study, some of the data contradict what is published in another paper reporting the same study and it is unclear whether there are other potentially confounding factors present. In this study, the multidisciplinary team group also received pre-pregnancy advice, whilst the non-multidisciplinary team group did not.

h. One study was conducted in the UK. In the two groups, 42.6% and 51.0% of the women were white, 38.2% and 34.6% were South Asian. Other ethnicities were not reported. The average age at booking was 31.4 years in one group and 29.7 years in the other group. The other study was conducted in Ireland. The number of women with type 1 diabetes was 52% and 77% in the two groups, and the number of women with type 2 diabetes was 48% and 25% in the two groups. The ethnicity of the women and their average age at booking or birth was not reported in the study.

i. Some of the data contradict that which is published in another paper reporting on the same study. It is unclear whether there are other potentially confounding factors present. The multidisciplinary team group also received pre-pregnancy advice, whilst the non-multidisciplinary team group did not.

j. The confidence interval for the mean difference does not cross the line of no effect

k. Study was conducted in Ireland. In the two groups, 52% and 77% of the women had type 1 diabetes and 48% and 23% of the women had type 2 diabetes. The ethnicity of the women and the age at booking or birth were not reported.

l. The confidence interval for the mean difference crosses the line of no effect (MD = 0) and the minimally important difference (50% of the combined standard deviation of the two groups)

m. The confidence interval for the odds ratio does not cross the line of no effect (OR = 1)

Table 72: GRADE profile for effectiveness of centralised care for pregnant women with diabetes

Number of studies	Number of women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	Centralised care	Peripheral care	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Mode of birth											
Caesarean section											
1 (Traub et al., 1987)	26/60 (43%)	61/100 (61%)	OR 0.5 (0.3 to 0.9)[a]	176 fewer per 1000 (from 15 fewer to 321 fewer)	Very low	Observational	Serious limitations[b]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[e]	Yes[f]
Fetal or neonatal mortality											
Neonatal death											
2 (Hadden, 2009 and Traub et al., 1987)	3/446 (1%)	7/490 (1%)	OR 0.5 (0.1 to 2.0)[a]	7 fewer per 1000 (from 12 fewer to 14 more)	Very low	Observational	Serious limitations[g]	Serious inconsistency[h]	No serious indirectness[d]	Serious imprecision[i]	Yes[j]
Total fetal loss											
2 (Hadden, 2009 and Traub et al., 1987)	58/446 (13%)	53/490 (11%)	OR 1.2 (0.8 to 1.8)[a]	17 more per 1000 (from 21 fewer to 68 more)	Very low	Observational	Serious limitations[g]	No serious inconsistency	No serious indirectness[d]	Serious imprecision[i]	Yes[j]
Miscarriage											
2 (Dunne et al., 2009 and Traub et al., 1987)	10/91 (11%)	27/173 (16%)	OR 0.7 (0.3 to 1.6)[a]	39 fewer per 1000 (from 99 fewer to 71 more)	Very low	Observational	Serious limitations[k]	No serious inconsistency	No serious indirectness[d]	Serious imprecision[i]	Yes[l]
1 (Hadden et al., 2009)	46/386 (12%)	32/390 (8%)	OR 1.5 (0.9 to 2.4)[a]	37 more per 1000 (from 5 fewer to 96 more)	Very low	Observational	Serious limitations[m]	No serious inconsistency[c]	Serious indirectness[n]	Serious imprecision[i]	Yes[o]

| Number of studies | Number of women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	Centralised care	Peripheral care	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Stillbirth											
3 (Dunne et al., 2009; Hadden, 2009; Traub et al., 1987)	9/477 (2%)	15/563 (3%)	OR 0.7 (0.3 to 1.6)[a]	7 fewer per 1000 (from 18 fewer to 16 more)	Very low	Observational	Very serious limitations[p]	No serious inconsistency	No serious indirectness[d]	Serious imprecision[i]	Yes[q]
Perinatal deaths (calculated from neonatal death and stillbirth data reported above)											
3 (Dunne et al., 2009; Hadden 2009; and Traub et al., 1987)	12/477 (3%)	22/563 (4%)	OR 0.6 (0.3 to 1.3)[a]	14 fewer per 1000 (from 27 fewer to 11 more)	Very low	Observational	Very serious limitations[p]	No serious inconsistency	No serious indirectness[d]	Serious imprecision[i]	Yes[q]
Large for gestational age											
1 (Dunne et al., 2009)	5/31 (16%)	16/73 (22%)	OR 0.7 (0.2 to 2.1)[a]	57 fewer per 1000 (from 159 fewer to 148 more)	Very low	Observational	Serious limitations[r]	No serious inconsistency[c]	No serious indirectness[d]	Serious imprecision[i]	Yes[s]
Neonatal intensive care unit stay											
Admission to neonatal unit											
1 (Dunne et al., 2009)	5/31 (16%)	45/73 (62%)	OR 0.1 (0.0 to 0.4)[a]	455 fewer per 1000 (from 256 fewer to 556 fewer)	Very low	Observational	Serious limitations[r]	No serious inconsistency[c]	No serious indirectness[d]	No serious imprecision[e]	Yes[s]

OR odds ratio

a. Calculated by the NCC-WCH based on results reported in the paper.

b. It is unclear whether the groups were comparable at baseline. It is unclear whether there are other potentially confounding factors present.

c. Single study analysis

d. The study/studies met the population and outcome criteria specified in the review protocol

e. The confidence interval of the odds ratio does not cross the line of no effect (OR = 1)

f. Study was undertaken in Northern Ireland. The ethnicity of the women was not reported. The average age in the two groups was 27.5 years and 26.7 years.

g. In one study there are conflicting data reported in the paper, it is unclear if the groups were comparable at baseline, and it is unclear whether there are other potentially confounding factors present. In the other study it is unclear whether the groups were comparable at baseline. It is unclear whether there are other potentially confounding factors present.

h. The I2 value was 33% or greater but less than 66%

i. The confidence interval for the odds ratio crosses the line of no effect (OR = 1) and OR = 0.75 and/or OR = 1.25

j. One study was undertaken in Northern Ireland. The ethnicity of the women was not reported. The average age in the two groups was 27.5 years and 26.7 years. The other study was conducted in Northern Ireland. The ethnicity of the women and their average age at booking or birth was not reported.

k. In one study more women in the central care group received formal pre-pregnancy care and it was unclear whether there are other potentially confounding factors present. In the other study it is unclear whether the groups are comparable at baseline and it is unclear whether there are other potentially confounding factors present.

l. One study was conducted in Northern Ireland. The ethnicity of the women was not reported. The average age of the women in the two groups was 27.5 and 26.7 years. The other study was conducted in Ireland. The ethnicity of the women was not reported. The average age of the women was 33 and 36 years.

m. There are conflicting data reported in the paper, it is unclear if the groups were comparable at baseline, and it is unclear whether there are other potentially confounding factors present.

n. The data was reported in this study as 'Abortion'. It is not clear whether this refers to terminations of pregnancy or spontaneous abortions (or both), however, the figures suggest that this is likely to include miscarriage data. Because of this ambiguity, it was not meta-analysed with the miscarriage data reported in other studies.

o. The study was conducted in Northern Ireland. The ethnicity of the women and their average age at booking or birth was not reported.

p. In one of the studies more women in the central care group received formal pre-pregnancy care than in the peripheral group and it is unclear whether there are other potentially confounding factors present. In another study there are conflicting data reported in the paper, it is unclear if the groups were comparable at baseline, and it is unclear whether there are other potentially confounding factors present. In the third study it was unclear if the groups were comparable at baseline and it is unclear whether there are other potentially confounding factors present.

q. One study was conducted in Northern Ireland. The ethnicity of the women was not reported. The average age of the women in the two groups was 27.5 and 26.7 years. The second study was conducted in Ireland. The ethnicity of the women was not reported. The average age of the women was 33 and 36 years. The third study was conducted in Northern Ireland. The ethnicity of the women and their average age at booking or birth was not reported.

r. More women in the central care group received pre-pregnancy care than in the peripheral group. It is unclear whether there are other potentially confounding factors present.

s. The study was conducted in Ireland. The ethnicity of the women was not reported. The average age of the women was 33 and 36 years.

5.11.5 Evidence statements

5.11.5.1 Multidisciplinary team compared to standard antenatal care

When comparing women cared for in multidisciplinary teams with those receiving standard antenatal care, there were no significant differences in the risk of women having a vaginal birth (1 study, OR 1.2, 95% CI 0.5 to 2.6, n=96), an assisted/instrumental birth (1 study, OR 0.8, 95% CI 0.2 to 3.6, n=96) or caesarean section (2 studies, OR 1.4, 95% CI 0.9 to 2.2, n=464).

There were mixed results for glycaemic control. In the first and second trimester, 1 study (n=272) reported lower mean HbA1c in women with type 1 diabetes (MD −3, 95% CI −4.5 to −0.1 and MD −1, 95% CI −1.3 to −0.7) and in women with type 2 diabetes (MD −7, 95% CI −8.4 to −5.6 and MD −5, 95% CI −5.2 to −4.8) receiving care from a multidisciplinary team. However, a second study of women with type 1 or type 2 diabetes (n=96) reported no differences in mean HbA1c in the first (MD 0, 95% CI −0.3 to 0.3) or second trimester (MD −0.2 95% CI −0.6 to 0.2) among women receiving care from a multidisciplinary team compared with women receiving standard antenatal care.

In the third trimester, 1 study (n=272) reported that mean HbA1c was lower in women with type 1 diabetes (MD −3, 95% CI −3.3 to −2.8) but higher in women with type 2 diabetes (MD 1, 95% CI 0.8 to 1.2) who received care from a multidisciplinary team compared with standard antenatal care. A second study that combined women with type 1 and type 2 diabetes into 1 group reported a significantly lower mean HbA1c in women receiving care from a multidisciplinary team (MD −0.4, 95% CI −0.7 to −0.1).

In terms of fetal and neonatal outcomes, 1 study (n=272) found no difference in the risk of perinatal death (OR 0.1, 95% CI 0.0 to 1.0) or stillbirth (OR 0.3, 95% CI 0.1 to 1.7) in the babies of women receiving multidisciplinary care compared with those receiving standard antenatal care. However, the guideline development group did think that this could have been a function of the small population size. A decreased risk of miscarriage in the group of women receiving care from a multidisciplinary team (OR 0.3, 95% CI 0.1 to 0.6) was reported.

The same study (n=272) reported no differences in the risk of babies being large for gestational age among women with type 1 (OR 0.8, 95% CI 0.5 to 1.4) or type 2 (OR 1.6, 95% CI 0.9 to 3.0) diabetes receiving standard antenatal or multidisciplinary team care, or in the risk of neonatal care unit admission (OR 0.8, 95% CI 0.5 to 1.4). A second study (n=96) did find a reduced risk of special care baby unit admission in the babies of women who received care from a multidisciplinary team compared with those receiving standard antenatal care (OR 0.3, 95% CI 0.1 to 0.7).

The quality of evidence for these outcomes was very low.

5.11.5.2 Centralised care compared to peripheral care

When comparing centralised to peripheral care, 1 study (n=160) reported a reduced risk of caesarean section in the women receiving centralised care (OR 0.5, 95% CI 0.3 to 0.9). No other maternal outcomes were reported.

In terms of neonatal and fetal outcomes, there were no differences reported in the risk of neonatal death (2 studie: n=936, OR 0.5, 95% CI 0.1 to 2.0), fetal loss (2 studies: n=936, OR 1.2, 95% CI 0.8 to 1.8), miscarriage (2 studies: n=264, OR 0.7, 95% CI 0.3 to 1.6; and 1 study: n=776, OR 1.5, 95% CI 0.9 to 2.4), stillbirth (3 studies: n=1040, OR 0.7, 95% CI 0.3 to 1.6), perinatal death (3 studies: n=1040, OR 0.6, 95% CI 0.3 to 1.3) or of babies being large for gestational age (1 study: n=104, OR 0.7, 95% CI 0.2 to 2.1). One study (n=104) found fewer admissions to the neonatal unit for babies born to mothers who received centralised care compared with those who received peripheral care (OR 0.1, 95% CI 0.0 to 0.4).

The quality of evidence for these outcomes was very low.

5.11.6 Health economics profile

A systematic review of the literature did not find any published evidence on the cost effectiveness of specialist teams for pregnant women with diabetes.

This question was initially prioritised for health economic analysis but it was a lower priority than other guideline topics and the clinical evidence was not very strong.

5.11.7 Evidence to recommendations

5.11.7.1 Relative value placed on the outcomes considered

The guideline development group placed an equal value on all of the outcomes, as they each contribute to morbidity and mortality.

5.11.7.2 Consideration of clinical benefits and harms

When comparing women receiving care from a multidisciplinary team with women receiving standard care, glycaemic control (indicated by lower HbA1c) was better in the group of women receiving care from a multidisciplinary team. For fetal outcomes, there were significantly fewer miscarriages and significantly fewer special care baby unit admissions in the group of women who received care from a multidisciplinary team.

When comparing centralised care with peripheral care, there were significantly fewer caesarean sections in the group of women receiving centralised care. There were significantly fewer admissions to the neonatal unit for babies whose mothers who received centralised care.

5.11.7.3 Consideration of health benefits and resource use

The guideline development group accepted that care from a multidisciplinary team was likely to be a more expensive way of delivering services than 'standard care', although the multidisciplinary approach represents current NHS practice. The group believes that a multidisciplinary approach facilitates better communication and care in a complex area of service provision. They therefore are of the view that it is likely to result in better outcomes which will justify any additional costs.

5.11.7.4 Quality of evidence

The quality of the evidence was rated as very low for all reported outcomes considered in the review.

The data could be considered to be limited as 4 out of 5 studies were undertaken in populations that were from the same geographical area (Ireland and Northern Ireland) where there may be less ethnic diversity than that encountered on the UK mainland. The fifth study was from the UK. However, the group felt that the data from all five studies were probably more relevant to the population for which the guidance was intended than studies from other parts of the world. Another limitation is that the majority of the data came from historical cohorts rather than prospective studies. Some studies were poorly reported and the analysis conducted in the papers was not always clearly reported.

5.11.7.5 Other considerations

The guideline development ggroup was aware of the need for effective communication between healthcare professionals, both in the primary and secondary sector, as recommended in the guideline on patient experience.

In the reviewing and updating the table of antenatal appointments recommendation in the original guideline, the guideline development group for this guideline was aware of some inconsistencies between the recommendations regarding the use of ultrasound to screen for structural abnormalities in the original guideline. The relevant recommendations in the original guideline were that women with diabetes should be offered antenatal examination of the 4 chamber view of the fetal heart and outflow tracts at 18–20 weeks and (in Table 5.7) to offer 4 chamber view of the fetal heart and outflow tracts plus scans that would be offered at 18–20 weeks as part of routine antenatal care.

However, Table 5.6 in the original guideline stated that the ultrasound scan for detecting structural anomalies and anatomical examination of the 4 chamber view of the fetal heart plus outflow tracts should occur at 20 weeks. This was on the basis that scanning the fetal cardiac anatomy including the 4 chamber view was better at 20 weeks than 18 weeks.

In the light of this duplication of recommendations and inconsistency in gestational age, the guideline development group felt that it would be better to bring together the separate recommendations about screening for congenital abnormalities (scanning for structural abnormalities in general, scanning the 4 chamber view of the fetal heart and performing the ultrasound scan at 20 weeks, rather than the 18 weeks in non-diabetic pregnancy) into 1 recommendation for greater clarity.The recommendation can be found in Section 5.8.8.

5.11.8   Key conclusions

The evidence was not strong enough to change existing recommendations.

5.11.9   Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

Table 73: Timetable of antenatal appointments

Appointment	Care for women with diabetes during pregnancy*
Booking appointment (joint diabetes and antenatal care) – ideally by 10 weeks	Discuss information, education and advice about how diabetes will affect the pregnancy, birth and early parenting (such as breastfeeding and initial care of the baby).
	If the woman has been attending for preconception care and advice, continue to provide information, education and advice in relation to achieving optimal blood glucose control (including dietary advice).
	If the woman has not attended for preconception care and advice, give information, education and advice for the first time, take a clinical history to establish the extent of diabetes-related complications (including neuropathy and vascular disease), and review medicines for diabetes and its complications.
	Offer retinal assessment for women with pre-existing diabetes unless the woman has been assessed in the last 3 months.
	Offer renal assessment for women with pre-existing diabetes if this has not been performed in the last 3 months.
	Arrange contact with the joint diabetes and antenatal clinic every 1–2 weeks throughout pregnancy for all women with diabetes.
	Measure HbA1c levels for women with pre-existing diabetes to determine the level of risk for the pregnancy.
	Offer self-monitoring of blood glucose or a 75 g 2-hour OGTT as soon as possible for women with a history of gestational diabetes who book in the first trimester.
	Confirm viability of pregnancy and gestational age at 7–9 weeks.
16 weeks	Offer retinal assessment at 16–20 weeks to women with pre-existing diabetes if diabetic retinopathy was present at their first antenatal clinic visit.
	Offer self-monitoring of blood glucose or a 75 g 2-hour OGTT as soon as possible for women with a history of gestational diabetes who book in the second trimester.
20 weeks	Offer an ultrasound scan for detecting fetal structural abnormalities, including examination of the fetal heart (4 chambers, outflow tracts and 3 vessels).
28 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
	Offer retinal assessment to all women with pre-existing diabetes.
	Women diagnosed with gestational diabetes as a result of routine antenatal testing at 24–28 weeks enter the care pathway.
32 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
	Offer nulliparous women all routine investigations normally scheduled for 31 weeks in routine antenatal care.
34 weeks	No additional or different care for women with diabetes.
36 weeks	Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
	Provide information and advice about:
	• timing, mode and management of birth
	• analgesia and anaesthesia

Appointment	Care for women with diabetes during pregnancy*
	• changes to blood glucose-lowering therapy during and after birth • care of the baby after birth • initiation of breastfeeding and the effect of breastfeeding on blood glucose control • contraception and follow-up.
37^{+0} weeks to 38 $^{+6}$ weeks	Offer induction of labour, or caesarean section if indicated, to women with type 1 or type 2 diabetes; otherwise await spontaneous labour.
38 weeks	Offer tests of fetal wellbeing.
39 weeks	Offer tests of fetal wellbeing. Advise women with uncomplicated gestational diabetes to give birth no later than 40^{+6} weeks.
* Women with diabetes should also receive routine care according to the schedule of appointments in the NICE guideline on antenatal care, including appointments at 25 weeks (for nulliparous women) and 34 weeks, but with the exception of the appointment for nulliparous women at 31 weeks. OGTT = oral glucose tolerance test.	

5.12 Preterm labour in women with diabetes

5.12.1 Description of the evidence

5.12.2 Incidence of preterm birth

A prospective cohort study[303] examined the importance of glycaemic control and risk of preterm birth in women with type 1 diabetes who have normoalbuminuria and no pre-eclampsia during pregnancy. Seventy-one women with complete data on HbA1c, insulin dose and albumin excretion rate measured at 12 weeks of gestation and every second week thereafter were recruited and followed. The overall rate of preterm birth was 23%; women who experienced preterm birth had higher HbA1c throughout pregnancy. Regression analysis showed that HbA1c was the strongest predictor of preterm birth from 6–32 weeks of gestation and that the risk of preterm birth was more than 40% when HbA1c was above 7.7% at 8 weeks of gestation. [EL = 2+]

5.12.2.1 Antenatal steroids

Antenatal steroids are administered to women who have a spontaneous or planned preterm birth to accelerate fetal lung development and prevent respiratory distress syndrome. The use of steroids in women with diabetes is associated with a significant worsening of glycaemic control requiring an increase in insulin dose.

Two studies were identified that reported on approaches to increasing insulin in women with diabetes undergoing treatment with antenatal steroids.

The first study reported on a test of an algorithm for improved subcutaneous insulin treatment during steroid treatment (intramuscular administration of betamethasone 12 mg repeated after 24 hours).304 The algorithm was as follows:

- on day 1 (the day on which the first betamethasone injection is given), the night insulin dose should be increased by 25%
- on day 2, all insulin doses should be increased by 40%
- on day 3, all insulin doses should be increased by 40%
- on day 4, all insulin doses should be increased by 20%
- on day 5, all insulin doses should be increased by 10–20%
- during days 6 and 7, the insulin doses should be gradually reduced to their levels before treatment.

The study involved 16 women, eight of whom were treated before the introduction of the algorithm (cohort 1) and another eight who were treated after its introduction (cohort 2). Women in cohort 1 had insulin doses adjusted individually based on the level of blood glucose obtained. The median blood glucose over the 5 days was 6.7 mmol/litre, 14.3 mmol/litre, 12.3 mmol/litre, 7.7 mmol/litre and 7.7 mmol/litre in cohort 1 and 7.7 mmol/litre, 8.2 mmol/litre, 9.6 mmol/litre, 7.0 mmol/litre and 7.4 mmol/litre in cohort 2 (P < 0.05 for days 2 and 3). None of the women developed ketoacidosis or severe hypoglycaemia. [EL = 2+]

The second study reported on the use of a supplementary intravenous sliding scale to indicate the required dosage of supplementary insulin infusion in six women receiving antenatal steroids.[305] The supplementary insulin was in addition to the woman's usual subcutaneous insulin regimen and usual dietary programme. The additional infusion was commenced immediately before the first steroid injection and continued for at least 12 hours after the second injection. If blood glucose levels were too high on the initial regimen (glucose 10.1 mmol/litre or more for 2 consecutive hours) the dosage regimen was moved up to the next level. If the blood glucose level was less than 4 mmol/litre the dosage regimen

was reduced by one level. Data were collected on six women receiving dexamethasone. Significant amounts of supplementary intravenous insulin were required (median dose 74 U, range 32–88 U) in order to achieve glucose control following administration of dexamethasone. Seventy-five percent of all glucose measurements were within 4–10 mmol/litre. [EL = 3]

5.12.2.2 Tocolytic Betamimetics increase agents

Tocolytic agents are used to inhibit uterine contractions. They may help to delay birth and allow women to complete a course of antenatal steroids. Betamimetics have been widely used for tocolysis, although they are no longer recommended as the first choice for general use.[306] blood glucose concentrations[307–309] and several cases of ketoacidosis have been reported in women with diabetes following administration of these medicines (see Section 5.1).[310–314]

5.12.2.3 Current practice

CEMACH undertook a descriptive study of all pregnancies of women with pre-existing diabetes who gave birth or booked between 1 March 2002 and 28 February 2003.2 Of the 3474 women in this study with a continuing pregnancy at 24 weeks of 328 gave birth before 34 weeks of gestation. Thirty-five of these pregnancies resulted in a stillbirth. Of the remaining 293 women, 70.3% received a full course of antenatal steroid therapy. The most common reason given for non-administration of antenatal steroids was birth of the baby before the full course could be given. In a small group of women diabetes was considered a contraindication to antenatal steroid use. [EL = 3]

5.12.3 Evidence statement

The use of antenatal steroids for fetal lung maturation in women with diabetes is associated with a significant worsening of glycaemic control.

Two studies that reported on approaches to modifying insulin dose in women undergoing antenatal steroid treatment showed that glycaemic control could be improved by increasing the insulin dose immediately prior to and during administration of antenatal steroids. However, the two protocols evaluated were only moderately successful in keeping blood glucose levels at the desired level (less than 7 mmol/litre).

Evidence shows that administration of betamimetics to suppress labour induces hyperglycaemia and ketoacidosis.

5.12.4 From evidence to recommendations

The evidence supports the use of increased insulin dose immediately before and during antenatal administration of steroids. Since the two protocols that have been evaluated were only moderately successful in achieving glycaemic control, women receiving additional insulin during administration of antenatal steroids should be closely monitored according to an agreed protocol in case the insulin dose requires further adjustment.

When tocolysis is indicated in women with diabetes an alternative to betamimetics should be used to avoid hyperglycaemia and ketoacidosis.

5.12.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

5.12.6 Research recommendations

There were no research recommendations relating to preterm labour in women with

diabetes.

6 Intrapartum care

6.1 Timing and mode of birth

6.1.1 Mode of birth

6.1.1.1 Description of the evidence

Eight epidemiological studies were identified that examined the effect of diabetes on mode of birth. Eight studies were identified that investigated mode of birth in women with diabetes. Five studies were identified in relation to optimal timing of birth in women with diabetes. Three studies were identified that examined vaginal birth after previous caesarean section (VBAC) in women with diabetes.

6.1.1.2 Effect of diabetes on mode of birth

A retrospective case–control study based on administrative data (n = 776 500) from Canada examined obstetric intervention and complication rates for women with and without pre-existing diabetes.[315] The proportion of women with diabetes in 1996 was 8.42 per 1000 deliveries, but this increased to 11.90 per 1000 deliveries by 2001. The study found that women with pre- existing diabetes were significantly more likely to have caesarean section or induced labour than women without diabetes (P < 0.0001). Pregnancies in women with pre-existing diabetes were also more likely to be complicated by obstructed labour (P = 0.01), hypertension (P < 0.0001), pre-eclampsia (P < 0.0001) and shoulder dystocia (P < 0.0001). However, the study noted marked increases in all these outcomes between 1996 and 2001 in women without diabetes. The study concluded that women with pre-existing diabetes needed close monitoring during pregnancy. [EL = 2−]

A retrospective cohort study (n = 12 303) from the USA examined the relationship of diabetes and obesity on risk of caesarean section.[316] The study found that diet-controlled gestational diabetes (P < 0.0001), insulin-controlled gestational diabetes (P < 0.0001) and pre-existing diabetes (P < 0.0001) were risk factors for having caesarean section. However, multiple regression analysis showed that only pre-existing diabetes was an independent risk factor for having caesarean section. [EL = 3]

A prospective cohort study (n = 166) from the USA examined route of birth of women with gestational diabetes.[317] The study found that 110 women had vaginal births and 56 had caesarean section. Multiple regression analysis showed that maternal nulliparity, fetal position and fetal fat were factors associated with caesarean section. [EL = 3]

A prospective case–control study (n = 3778) from Canada examined the relationship between caesarean section rates and gestational glucose intolerance (3 hour 100 g OGGT).[318] The study identified four groups: negative gestational diabetes (n = 2940), false-positive gestational diabetes (n = 580), untreated borderline gestational diabetes (n = 115) and known treated gestational diabetes (n = 143). Women with gestational diabetes had higher rates of macrosomia (28.7% versus 13.7%, P < 0.001) and caesarean section (29.6% versus 20.2%, P = 0.02). Treatment of gestational diabetes reduced rates of macrosomia (more than 4000 g) to 10.5% compared with 28.7% in the untreated group and 13.7% in the women without diabetes, but caesarean section rates were 33.6% compared with 29.6% in the untreated group and 20.2% in the women without diabetes. Multivariate analysis found that being treated for gestational diabetes was the most significant factor in determining caesarean section (OR 2.1, 95% CI 1.3 to 3.6); untreated gestational diabetes was not a significant risk factor (OR 1.6, 95% CI 0.9 to 2.7). [EL = 2+]

A retrospective case–control study (n = 2924) undertaken in the USA compared the outcomes of macrosomic babies (4000 g or more) with those of babies weighing 3000–3999 g.[319] The rate of injury to the baby during birth was 1.6% for the macrosomic group (RR 3.1, 95% CI 2.5 to 3.8). The study concluded that more research was needed to determine suitable interventions. [EL = 2+]

A prospective cohort study from the USA (n = 53 518) examined the association between perinatal death and presence of gestational diabetes.[320] The study found 33.8 per 1000 perinatal deaths in the group without gestational diabetes and 70.3 per 100) in the group with gestational diabetes. However, the rate in the women without diabetes who had induced labour or caesarean section was 33.2 per 1000 compared with 14.8 per 100 in the women without gestational diabetes who had spontaneous birth. The study also found that babies of women with gestational diabetes who were equal to or greater than the 90 percentile in birthweight were more likely to have retarded lung development (P < 0.005). The study also examined biochemical markers in the placenta, umbilical cord and fetal membranes. Maternal risk factors were not examined and the study was undertaken in 1978 since when the neonatal survival rate has improved. [EL = 3]

A population-based cohort from the UK (n = 11791) examined antenatal risk factors associated with a woman having a caesarean section.[321] The study found that having gestational diabetes increased the risk of having a caesarean section (OR 2.60, 95% CI 1.38 to 4.92), as did pre- existing diabetes (OR 8.50, 95% CI 4.27 to 16.9). However, a number of other factors were also identified, including obstetric history and medical history. Multiple regression showed that diabetes was a risk factor for caesarean section alongside maternal age, previous caesarean section, outcome of last pregnancy, parity, birthweight, neonatal head circumference, gestational age at birth and fetal presentation. However, the study did not examine any health professional- or healthcare-related factors. [EL = 2+]

A cross-sectional study[322] assessed routes of birth and pregnancy outcomes in 10 369 births in the USA. The study showed that diabetes was associated with increased caesarean section, resuscitation of babies with positive pressure ventilation and low Apgar score (less than 3) at 1 minute and 5 minutes. [EL = 3]

6.1.1.3 Regimens for inducing labour and their impact

An RCT (n = 200) from the USA involving women with insulin-requiring diabetes compared the outcomes of active induced labour (accurate measurement of gestational development and induction of labour with intravenous oxytocin, n = 100) with expectant management (close monitoring and insulin treatment, n = 100).[323] Those enrolled had gestational diabetes (n = 187) or pre-existing diabetes (n = 13). There were no differences between the groups at baseline. In the active induction group 70 women had induction of labour, eight had caesarean section and 22 had spontaneous labour. In the expectant management group 49 women had induction, seven had caesarean section and 44 had spontaneous labour. There were significantly more LGA babies in the expectant management group compared with the active induction group (23% versus 10%, P = 0.02). There were three cases of 'mild' shoulder dystocia in the expectant management group and none in the active induction group. The study concluded that active induction of labour at 38 weeks of gestation should be considered in women with insulin- requiring diabetes. [EL = 1+]

A cohort study from Israel (n = 1542) examined the effect of intensive management of diet and three protocols for active elective management of route of birth on outcomes in women with gestational diabetes.[324] The results for the three periods of different protocols were compared (period A, estimated fetal weight for caesarean section more than 4500 g; period B, mean glucose less than 5.8 mmol/litre, estimated fetal weight for caesarean section more than 4000 g, time of elective induction 40 weeks of gestation; period C, mean glucose 5.3 mmol/litre, estimated fetal weight for caesarean section more than 4000 g, time of elective induction 38 weeks of gestation). The results were as follows (period A versus period B

versus period C): macrosomia (more than 4000 g) 17.9% versus 14.9% versus 8.8% (P < 0.05); LGA 23.6% versus 21.0% versus 11.7%(P < 0.05); caesarean section 20.6% versus 18.4% versus 16.2%; shoulder dystocia 1.5% versus 1.2% versus 0.6%; induction of labour 11.0% versus 17.0% versus 35.0%. The study concluded that intensive management of diet and active management of birth were beneficial to women with gestational diabetes and their babies. [EL = 2+]

A case–control study (n = 2604) undertaken in the USA examined the outcome of elective caesarean section due to macrosomia in women with diabetes.[325] The study compared two time periods (before and after introduction of a protocol based on ultrasound estimates of fetal weight, with AGA fetuses being managed expectantly, those more than 4250 g being born via caesarean section, and those LGA but less than 4250 g being born vaginally after induction of labour. Therate of shoulder dystocia was lower in macrosomic babies in the induced group compared with the non-induced group (7.4% versus 18.8%, OR 2.9). The rate of caesarean section was higher postprotocol compared with pre-protocol (25.1% versus 21.7%, P < 0.04). The study recommended the use of ultrasound to estimate fetal weight and using this to determine method of birth. [EL = 2−]

A retrospective cohort study using routinely collected data (n = 108 487) undertaken in the USA examined whether induction of labour increased caesarean section rates in women with diabetes.[326] Women with diabetes were more likely to have a caesarean section than women without diabetes (OR 2.00, 95% CI 1.83 to 2.19). The caesarean section rate was lower in women who had induction of labour than those who did not have induction of labour (OR 0.77, 95% CI 0.50 to 0.89). [EL = 2+]

An RCT (n = 273) undertaken in Israel compared induction of labour with expectant management in the presence of macrosomia (4000–4500 g).[327] At baseline the women in the induction group were significantly older than the expectant management group (30.8 years versus 29.5 years, P = 0.02). There were no significant differences in the mode of birth between the groups (induction of labour group, 91 spontaneous vaginal births, 17 instrumental births and 26 caesarean sections; expectant management group, 91 spontaneous vaginal births, 18 instrumental births and 30 caesarean sections), nor in the mean birthweight (4062.8 g versus 4132.8 g, P = 0.24). There were five cases of shoulder dystocia in the induction group compared with six in the expectant management group. The study concluded that estimated fetal weight between 4000 g and 4500 g should not be considered an indication for inducing birth. However, the study was not explicitly conducted on women with diabetes. [EL = 1+]

An RCT (n = 120) undertaken in the USA compared misoprostol with placebo for inducing birth in women with diabetes.[328] There was no difference between the groups at baseline. The study found no difference between the groups during outpatient observation, time from induction to birth (P = 0.23), total oxytocin dose (P = 0.18) or neonatal characteristics. The study concluded that misoprostol was not beneficial for induction of labour in women with diabetes. [EL = 1+]

A quasi-randomised study (n = 84) undertaken in the USA compared the outcomes of caesarean section (n = 44) and vaginal births (n = 40, 26 spontaneous and 14 induced) in women with gestational diabetes (3 hour 100 g OGTT).[329] The complications recorded for caesarean section versus vaginal birth were: morbidity (9 versus 0), blood transfusions (2 versus 0), wound separation (2 versus 0), macrosomia more than 4000 g (5 versus 3), prematurity by weight (6 versus 5), neonatal infection (1 versus 1), neonatal hypoglycaemia (1 versus 0) and hyperchloraemic acidosis (1 versus 0). The study concluded that there was no advantage to preterm caesarean section in women with gestational diabetes. [EL = 2+]

A case–control study (n = 388) undertaken in the USA examined the risk of wound complication after caesarean section in women with pre-existing diabetes and women without diabetes.330 At baseline women with pre-existing diabetes were more likely to be obese (P < 0.01) and have a positive group B streptococcus status (P < 0.01). During

caesarean section the women with diabetes were more likely to have estimated blood loss above 1000 ml (P < 0.01), postpartum haemorrhage (P = 0.05) and to spend longer in the operating theatre (P = 0.01), but they were less likely to have meconium present (P = 0.01). Women with diabetes were more likely to have wound infection (OR 2.7, 95% CI 1.2 to 6.1), wound separation (OR 6.1, 95% CI 1.8 to 21.2) and wound complications (OR 3.7, 95% CI 1.8 to 7.7). The study concluded that diabetes was a risk factor for wound complications after caesarean section. However, analysis did not take into account baseline and surgical differences between groups. [EL = 2−]

6.1.1.4 Vaginal birth after previous caesarean section

A retrospective case-series (n = 10 110) from the USA examined the success of VBAC in women with previous obstetric complications, including gestational diabetes.[333] Sixty-two percent of women who attempted VBAC were successful. The factors associated with unsuccessful VBAC were birthweight more than 4000 g, cephalopelvic disproportion, prolonged labour, dysfunctional labour, pre-existing diabetes and gestational diabetes, hypertension, induced labour, sexually transmitted disease, fetal distress and breech birth. [EL = 3]

A retrospective cohort study (n = 25 079) from the USA examined whether women with diet-controlled gestational diabetes were at increased risk of failed VBAC compared with women who did not have diabetes.[334] The study involved 13396 women who attempted VBAC. Data on 423 women with diet-controlled gestational diabetes and 9437 women without diabetes were analysed. After controlling for birthweight, maternal age, race, tobacco use, chronic hypertension, hospital setting, labour management and obstetric history, 49% of the women with gestational diabetes and 67% of the women without diabetes attempted VBAC. The study found that gestational diabetes was not an independent risk factor for VBAC. The success rate for attempted VBAC among women with gestational diabetes was 70% compared to 74% for women without diabetes, and the proportion of babies weighing more than 4000 g was 18% compared with 13% (P < 0.05). The VBAC group had more previous pregnancies (3.4 versus 3.1, P < 0.001), different ethnic mix (P < 0.05), different insurance profile (P < 0.001), seen in university hospital (56% versus 42%, P < 0.001), previous vaginal birth or VBAC (40% versus 17%, P < 0.001) and birthweight more than 4000 g (18% v 33%, P < 0.001). Logistic regression analysis showed that age, birthweight, white ethnic origin, induced labour, augmented labour and previous vaginal birth were all predictors of successful VBAC, whilst diet-controlled gestational diabetes and chronic hypertension were not. [EL = 2+]

A retrospective cohort study (n = 428) conducted in the USA compared attempted VBAC in women with gestational diabetes to that in women without diabetes.[332] One hundred and fifty-six women with gestational diabetes were matched with 272 controls. The parities were similar for the two groups, but the women with gestational diabetes were significantly older than the control group (P < 0.001) and more likely to be white or Hispanic (P = 0.006). The study found that those with previous gestational diabetes were more likely to have a future caesarean section (35.9% versus 22.8%, P < 0.001), less likely to have a vaginal birth (64.1% versus 77.2%, P < 0.001) and more likely to have induction of labour (38.5% versus 22.4%, P < 0.001). There was no difference in failure of VBAC in the induced labour group (63.2% versus 68.9%, P = 0.540) but significant difference in failure of VBAC in the spontaneous labour group (18.7% versus 9.5%, P = 0.20). There were no differences for pre-eclampsia, lacerations or shoulder dystocia. The birthweight in the gestational diabetes group was significantly greater than the control (3437.8 g versus 3191.9 g, P = 0.001), but there were no significant differences in outcome Apgar scores or neonatal deaths. [EL = 2+]

No evidence was identified to suggest that the indications for caesarean section in preference to induction of labour are different for women with diabetes compared to women without diabetes.

6.1.1.5 Existing guidance

The NICE induction of labour guideline[12] recommended that women with pregnancies complicated by diabetes should be offered induction of labour before their estimated date for delivery. Although the guideline reported that there were insufficient data clarifying the gestation- specific risk for unexplained stillbirth in pregnancies complicated by diabetes, the GDG that developed the induction of labour guideline considered that it was usual practice in the UK to offer induction of labour to women with type 1 diabetes before 40 weeks of gestation. The induction of labour guideline is currently being updated and induction of labour for women with diabetes is excluded from the scope having been incorporated into the scope for the diabetes in pregnancy guideline.

The NICE intrapartum care guideline[10] contains recommendations in relation to routine intrapartum care, including electronic fetal monitoring.

The NICE caesarean section guideline[13] contains recommendations in relation to caesarean section, including VBAC and provision of information for women.

The NSF for diabetes[20] states: [EL = 4]

'Women with pre-existing diabetes: During labour, a midwife experienced in supporting women with diabetes through labour should be present and an appropriately trained obstetrician should be available at all times. The woman's blood glucose level should be maintained within the normal range in order to reduce the risk of neonatal hypoglycaemia. Continuous electronic fetal heart monitoring should be offered to all women with diabetes during labour and fetal blood sampling should be available if indicated. Arrangements should be in place to enable the rapid transfer of women with diabetes who choose not to deliver in a consultant-led obstetric unit, should difficulties arise.

Women who develop gestational diabetes: In the second and third trimesters of pregnancy, the main risks to the baby are macrosomia (excessive fetal growth), affecting approximately 30% of the offspring of women with type 1 diabetes, and neonatal hypoglycaemia, which occurs in approximately 24% of babies. Jaundice is also more common, but other complications, such as respiratory distress syndrome, hypoglycaemia and polycythaemia, are now rare.

Macrosomia is associated with an increased risk of fetal injury and damage to the birth canal. The risk of macrosomia can be reduced by the achievement of near normal blood glucose levels during the third trimester. Problems during the neonatal period can be reduced by the achievement of tight blood glucose control during labour.

Improving pregnancy outcomes: The rate of shoulder dystocia can be decreased by the use of ultrasound monitoring and elective delivery of those babies weighing over 4250 g. In one study, ultrasound was found to determine accurately the presence or absence of macrosomia in 87% of women scanned.

Diabetic pregnancy is associated with an increased risk of complications during labour and delivery. Close monitoring and prompt intervention can improve outcomes for both the mother and her baby. For example, tight blood glucose control during labour can reduce the risk of neonatal hypoglycaemia and hence reduce the need for admission to a neonatal intensive care unit. However, it should be remembered that some women's experience of a "medicalised" and high-intervention labour and delivery is a negative and frightening one. This need not be the case if they are helped to feel in control, are involved in decision-making and kept informed, and if they are supported by calm and competent professionals.'

6.1.1.6 Evidence statement

Eight studies examined the epidemiology of women with diabetes requiring intervention in the mode of birth. The studies showed that stillbirth and shoulder dystocia were the greatest

risks involved. Diabetes during pregnancy and macrosomia were the greatest risk factors affecting outcome of birth. However, evidence shows that factors related to the behaviour of healthcare professionals and the organisation of health service impact on outcome. For example, caesarean section rates remain high even when diabetes is controlled and macrosomia is not present.

Eight studies investigated different methods of intervening in the mode of birth. There is evidence that fetal weight and risk of stillbirth are the determining factors in whether women with diabetes undergo caesarean section. Caesarean section rates were lower in women who were actively managed with induction of labour, and caesarean section was associated with higher levels of complications and adverse outcomes than vaginal birth. However, the majority of the studies were conducted in the USA where sociocultural and health service factors are different to the UK.

Three studies examined VBAC and showed that birthweight was the main factor in determining success. Women with diabetes were more likely to have unsuccessful VBAC compared to women without diabetes, but diabetes was not a complete contraindication.

6.1.1.7   From evidence to recommendations

Evidence shows that women with diabetes are more likely to undergo induction of labour and/or caesarean section than women without diabetes. The reasons for intervention in the mode of birth in women with diabetes are to prevent stillbirth and shoulder dystocia, which are associated with fetal macrosomia. Healthcare professionals should, therefore, inform women with fetal macrosomia of the risks and benefits of vaginal birth, induction of labour and caesarean section. No evidence was identified to suggest that induction of labour should be conducted differently in women with diabetes compared to other women (including oxytocin protocols and electronic fetal monitoring). Preparation for surgical birth (caesarean section) is considered in Section 6.1.

Evidence shows that diabetes should not be considered a contraindication to attempting VBAC.

6.1.1.8   Recommendations
The current recommendations can be found at www.nice.org.uk/guidance/ng3

6.1.2 Timing of birth

6.1.2.1 Review question
What is the gestational age-specific risk of intrauterine death in pregnancies with type 1, type 2 or gestational diabetes, and the optimal timing of birth?

6.1.2.2 Introduction
The objective of this review question is to determine the optimal timing of birth in women with pregnancies complicated by 1 of the 3 forms of diabetes (type 1, type 2 and gestational diabetes).
The optimal timing of birth has traditionally been determined primarily by the gestational age associated with the minimum mortality rates in the babies of women with diabetes. The main mortality risk associated with expectant management is stillbirth whereas the mortality risk associated with elective birth is neonatal death from preterm delivery. Different outcomes are associated with different approaches to the timing of birth. Where an expectant approach to management is followed, macrosomia, shoulder dystocia and increased incidence of caesarean section are potential associated consequences. In contrast, elective delivery at 37–39 weeks is associated with a higher rate of failed induction of labour, neonatal problems such as respiratory disorders (especially transient tachypnoea of the newborn [TTN]) and admission to NICU.

6.1.2.3   Description of included studies

Six studies were identified for inclusion in this review (Rosenstein et al., 2012; Holman et al., 2014; Eidem et al., 2011; Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010). Four studies included women with gestational diabetes (Rosenstein et al., 2012; Kjos et al., 1993;

Lurie et al., 1996; Alberico et al., 2010), 1 study included women with type 1 diabetes (Eidem et al., 2011) and the sixth included women with Type 1 or Type 2 diabetes (Holman et al., 2014).

One large retrospective study from the USA (Rosenstein et al., 2012) used record linkage to examine mortality rates in babies of women with gestational diabetes compared with those with no diabetes. Three mortality outcomes were examined in the study and were stratified by gestational age: stillbirth, neonatal death and infant death. A second study (Holman et al., 2014) examined data on stillbirth incidence collected from 4 audits of women with pre-existing diabetes conducted in England over 2 time periods and compared these data to stillbirth incidence in all births in England and Wales collected by the Office of National Statistics.

A third study from Norway (Eidem et al., 2011) also used record linkage to examine perinatal mortality rates in babies of women with pregestational type 1 diabetes compared with those without type 1 diabetes. There were no corresponding studies that could be included that examined mortality rates with different severities of diabetes (such as those estimated by HbA1c).

Three further studies compared morbidity and mortality outcomes in women with gestational diabetes who underwent elective delivery or expectant management (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010). One was a randomised controlled trial (RCT) from the USA (Kjos et al., 1993), 1 a prospective cohort study with historical controls from Israel (Lurie et al., 1996) and 1 was a retrospective cohort from Italy (Alberico et al., 2010).

Most women (93.5%) in the RCT (Kjos et al., 1993) and all women in the prospective cohort study (Lurie et al., 1996) had insulin treated gestational diabetes (A2). The retrospective cohort study (Alberico et al., 2010) included women with insulin treated and non-insulin treated gestational diabetes (A1 and A2) and foetal growth acceleration diagnosed at 38 weeks of gestation.

The elective delivery method was active induction of labour in the 38th or 39th gestational week in 3 studies (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010). Two studies required evidence of fetal lung maturity before induction was started (Kjos et al., 1993; Lurie et al., 1996). Up to 3 applications of vaginal prostaglandin were used for cervical ripening in women with low Bishop scores before treatment with intravenous oxytocin to induce labour in the RCT (Kjos et al., 1993). In the prospective cohort study, induction of labour was performed by either intracervical balloon catheter or by prostaglandin gel placement if the cervix was unfavourable or by intravenous oxytocin followed by amniotomy if the cervix was favourable. If fetal weight was estimated to be 4500 g or more, then a caesarean section was performed (Lurie et al., 1996). In the retrospective cohort study, prostaglandin gel was placed vaginally every 6–8 hours until labour started, and if induction did not succeed after 5 attempts, or if fetal distress was suspected, then a caesarean section was performed (Alberico et al., 2010).

Expectant management of pregnancy awaiting spontaneous onset of labour was followed until gestational week 42 in the RCT (Kjos et al., 1993) and beyond reassessment at gestational week 40 (Lurie et al., 1996) or week 40–41 (Alberico et al., 2010) if there were no complications. If spontaneous labour had not occurred by these gestational age limits elective delivery was undertaken. In all 3 studies induction of labour was undertaken if complications arose or, in 1 study, if the pregnancy exceeded 42 weeks of gestation or if the estimated fetal weight was 4200 g or more (Kjos et al., 1993). Caesarean section was

performed if the estimated fetal weight was more than 4250 g in the prospective cohort study (Lurie et al., 1996) and was performed electively if the estimated fetal weight was 4500 g or more in the retrospective cohort study (Alberico et al., 2010).

Data were available for the following outcomes prioritised by the guideline development group:
- mode of birth (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010)
- stillbirth/neonatal death/ perinatal death/infant death (Rosenstein et al., 2012; Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010)
- admission to NICU (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010)
- macrosomia (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010)
- shoulder dystocia (Kjos et al., 1993; Lurie et al., 1996; Alberico et al., 2010).

No data were available in the 6 studies for outcomes regarding maternal complications of delivery, maternal satisfaction/experiences or neonatal intensive care unti (NICU) stay or more than 24 hours.

6.1.2.4 Evidence profile

The GRADE profiles for this review question are presented in Tables 74 to 80.

This section was updated in 2015

Table 74: GRADE profile for incidence of stillbirth by gestational age in pregnancies of women with gestational diabetes compared with women who do not have gestational diabetes

Number of studies	Total number of births in a given week Stillbirths[a]/1,000 deliveries (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with gestational diabetes	In women without gestational diabetes	Relative (95% confidence interval)	Absolute							
At gestational week 36											
1 (Rosenstein et al., 2012)	10445 6.13*	155597 5.43*	1.13 (0.88 – 1.45)*	0.7 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Yes[d]
At gestational week 37											
1 (Rosenstein et al., 2012)	22157 3.38*	340239 2.52*	1.34 (1.06 – 1.70)*	0.86 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 38											
1 (Rosenstein et al., 2012)	44487 1.51*	736413 1.37*	1.10 (0.86 – 1.41)*	0.14 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Yes[d]
At gestational week 39											
1 (Rosenstein et al., 2012)	56085 1.18*	1105279 0.91*	1.30 (1.01 – 1.66)*	0.27 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 40											
1 (Rosenstein et al., 2012)	37819 0.90*	981106 0.74*	1.21 (0.86 – 1.71)*	0.16 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Yes[d]
At gestational week 41											
1 (Rosenstein et al., 2012)	15739 1.21*	510292 0.85*	1.42 (0.90 – 2.25)*	0.36 more per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Yes[d]
At gestational week 42											
1 (Rosenstein et al., 2012)	6296 0.95*	168999 1.15*	0.83 (0.37 – 1.86)*	0.2 fewer per 1000 deliveries*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[f]	Yes[d]

Calculated by NCC from data provided by the author
a. Incidence of stillbirth at a given gestational age was defined as the number of stillbirths at that gestational age per 1000 delivieries

b. The largest ethnic group within the study population was Latin American which is not directly applicable to the UK. The groups were significantly different at baseline for key characteristics. Women with and without gestational diabetes were of significantly different ethnicities and those with gestational diabetes were significantly more likely to have hypertensive disorders than those without gestational diabetes. Gestational age was determined using the date of last menstrual period which is susceptible to inaccuracy as well as recall bias.

c..Confidence interval for the RR crosses crosses the line of no effect and RR = 1.25

d. Country: USA, Ethnicity of women with gestational diabetes N (%): White 52,498 (27.2%), African-American 7,548 (3.9%), Latino 94,682 (49.1%), Asian 35,295 (18.3%), Other 2,877 (1.5%). Ethnicity of women without gestational diabetes N (%): White 1,504,878 (37.7%), African-American 217,883 (5.5%), Latino 1,766,579 (44.2%), Asian 443,980 (11.1%), Other 59,816 (1.5%).

e. Confidence interval for the RR crosses RR = 1.25

f. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25

This section was updated in 2015

Table 75: GRADE profile for incidence of neonatal death by gestational age in the babies of women with gestational diabetes compared with women who do not have gestational diabetes

Number of studies	Number of deliveries Neonatal deaths[a]/10,000 live births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with gestational diabetes	In women without gestationaldiabetes	Relative (95% confidence interval)	Absolute							
At gestational week 36											
1 (Rosenstein et al., 2012)	10375† 10.6 (5.3 - 19.0)	154579† 9.1 (7.7 - 10.8)	1.16 (0.63 to 2.14)*	1.5 more per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 37											
1 (Rosenstein et al., 2012)	22074† 6.8 (3.8 - 11.2)	339187† 6.1 (5.3 - 7.0)	1.11 (0.66 to 1.88)*	0.7 more per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 38											
1 (Rosenstein et al., 2012)	44414† 3.6 (2.1 - 5.9)	735205† 3.9 (3.5 - 4.4)	0.92 (0.56 to 1.53)*	0.3 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 39											
1 (Rosenstein et al., 2012)	56011† 3.4 (2.0 - 5.3)	1104127† 2.8 (2.5 - 3.1)	1.21 (0.76 to 1.92)*	0.6 more per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]

Number of studies	Number of deliveries Neonatal deaths[a]/10,000 live births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with gestational diabetes	In women without gestational diabetes	Relative (95% confidence interval)	Absolute							
1 (Rosenstein et al., 2012)	37779† 2.6 (1.3 - 4.9)	980203† 3.4 (3.1 - 3.8)	0.78 (0.41 to 1.46)*	0.8 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 41											
1 (Rosenstein et al., 2012)	15717† 3.2 (1.0 - 7.4)	509749† 3.6 (3.1 - 4.2)	0.88 (0.36 to 2.14)*	0.4 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 42											
1 (Rosenstein et al., 2012)	6285† 6.4 (1.7 - 16.3)	168769† 4.7 (3.7 - 5.8)	1.36 (0.50 to 3.72)*	1.7 more per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]

NC not calculable

* Calculated by NCC-WCH

† Data provided by author

a. Incidence of infant death was defined as the number of infants born at this gestational age who die within one year of life per 10,000 live births at that same gestational age.

b. The largest ethnic group within the study population was Latin American which is not directly applicable to the UK. The groups were significantly different at baseline for key characteristics. Women with and without gestational diabetes were of significantly different ethnicities and those with gestational diabetes were significantly more likely to have hypertensive disorders than those without gestational diabetes. Gestational age was determined using the date of last menstrual period which is susceptible to inaccuracy as well as recall bias.

c. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25

d. Country: USA, Ethnicity of women with gestational diabetes N (%): White 52,498 (27.2%), African-American 7,548 (3.9%), Latino 94,682 (49.1%), Asian 35,295 (18.3%), Other 2,877 (1.5%). Ethnicity of women without gestational diabetes N (%): White 1,504,878 (37.7%), African-American 217,883 (5.5%), Latino 1,766,579 (44.2%), Asian 443,980 (11.1%), Other 59,816 (1.5%).

e. Confidence interval for the RR crosses the line of no effect and RR = 0.75

This section was updated in 2015

Table 76: GRADE profile for the incidence of infant death by gestational age in the babies of women with gestational diabetes compared with women who do not have gestational diabetes

Number of studies	Number of deliveries Infant deaths[a]/10,000 live births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with gestationaldiabetes	In women without gestationaldiabetes	Relative (95% confidence interval)	Absolute							
At gestational week 36											
1 (Rosenstein et al., 2012)	10,445 19.3 (11.8 - 29.8)	155,597 22.9 (20.6 - 25.4)	0.84 (0.54 - 1.32)	3.6 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 37											
1 (Rosenstein et al., 2012)	22,157 14.0 (9.5 - 19.9)	340,239 18.4 (17.0 - 19.9)	0.76 (0.53 - 1.1)	4.4 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 38											
1 (Rosenstein et al., 2012)	44,487 10.6 (7.8 - 14.1)	736,413 13.3 (12.5 - 14.2)	0.80 (0.59 - 1.06)	2.7 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 39											
1 (Rosenstein et al., 2012)	56,085 8.7 (6.5 - 13.2)	1,105,279 10.7 (10.1 - 11.4)	0.82 (0.61 - 1.08)	2.0 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 40											
1 (Rosenstein et al., 2012)	37,819 9.5 (6.7 - 13.2)	981,106 11.6 (10.9 - 12.3)	0.82 (0.59 - 1.14)	2.1 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[d]
At gestational week 41											
1 (Rosenstein et al., 2012)	15,739 11.5 (6.8 - 18.1)	510,292 12.8 (11.9 - 13.9)	0.89 (0.56 - 1.43)	1.3 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]

Number of studies	Number of deliveries Infant deaths[a]/10,000 live births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with gestational diabetes	In women without gestational diabetes	Relative (95% confidence interval)	Absolute							
At gestational week 42											
1 (Rosenstein et al., 2012)	6,296 9.5 (3.5 - 20.8)	168,999 14.0 (12.3 - 15.9)	0.68 (0.30 - 1.52)	4.5 fewer per 10,000 live births*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]

Calculated by NCC

a. Incidence of stillbirth at a given gestational age was defined as the number of stillbirths at that gestational age per 10,000 ongoing pregnancies

b. The largest ethnic group within the study population was Latin American which is not directly applicable to the UK. The groups were significantly different at baseline for key characteristics. Women with and without gestational diabetes were of significantly different ethnicities and those with gestational diabetes were significantly more likely to have hypertensive disorders than those without gestational diabetes. Gestational age was determined using the date of last menstrual period which is susceptible to inaccuracy as well as recall bias.

c. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25

d. Country: USA, Ethnicity of women with gestational diabetes N (%): White 52,498 (27.2%), African-American 7,548 (3.9%), Latino 94,682 (49.1%), Asian 35,295 (18.3%), Other 2,877 (1.5%). Ethnicity of women without gestational diabetes N (%): White 1,504,878 (37.7%), African-American 217,883 (5.5%), Latino 1,766,579 (44.2%), Asian 443,980 (11.1%), Other 59,816 (1.5%).

e. Confidence interval for the RR crosses the line of no effect and RR = 0.75

This section was updated in 2015

Table 77: GRADE profile for incidence of stillbirth in the babies of women with type 1 and type 2 diabetes compared with all women in England and Wales

Number of studies	Number of deliveries Stillbirth/1000 total births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with type 1 diabetes	In all women in England and Wales	Relative (95% confidence interval)	Absolute							
Stillbirth [a]											
At gestational week 24-27											
1 (Holman et al., 2014)	20 250 (89.8-490.8)	16927† 264 (257.2 – 272.6)	0.95 (0.82 - 1.10)*	14 fewer per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[c]
At gestational week 28-31											
1 (Holman et al., 2014)	49 81.6 (29.5 – 194.6)	31894† 93.5 (90.2 – 96.9)	0.87 (0.66 - 1.16)*	11.9 fewer per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[d]	Yes[c]

Number of studies	Number of deliveries Stillbirth/1000 total births (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other consider ations
	In women with type 1 diabetes	In all women in England and Wales	Relative (95% confidence interval)	Absolute							
At gestational week 32-34											
1 (Holman et al.,)	161 43.5 (20.6 – 87.7)	69930† 34.8 (33.5 – 36.2)	1.25 (0.81 - 1.94)*	8.2 more per 1000*	Very low	Retrospect ive cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Yes[c]
At gestational week 35-36											
1 (Holman et al., 2014)	392 10.2 (3.9 – 26.0)	143609† 13.6 (13.0 – 14.2)	0.75 (0.33 - 1.68)*	3.4 fewer per 1000*	Very low	Retrospect ive cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[f]	Yes[c]
At gestational week 37-38											
1 (Holman et al., 2014)	1185 5.1 (2.3 – 11.0)	670426† 3.5 (3.3 – 3.6)	1.46 (0.37 - 5.66)*	1.6 more per 1000*	Very low	Retrospect ive cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[f]	Yes[c]
At gestational week ≥39											
1 (Holman et al., 2014)	278 10.8 (3.6 – 31.3)	2590083† 1.5 (1.4 – 1.5)	7.2 (1.31 - 39.63)*	9.3 more per 1000*	Very low	Retrospect ive cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[c]

† Data provided by author
*Calculated by NCC-WCH
a. No information a Stillbirth was defined as an infant born after 24 completed weeks of gestation that did not show any signs of life after birth.
b. is provided regarding how gestational age was determined.
c. Country: England (and Wales) No ethnicity details were provided
d. Confidence interval for the RR crosses the line of no effect and RR =0.75
e. Confidence interval for the RR crosses the line of no effect and RR = 1.25
f. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25

This section was updated in 2015

Table 78: GRADE profile for incidence of perinatal mortality in the babies of women with type 1 diabetes compared with women who do not have type 1 diabetes

Number of studies	Number of deliveries Perinatal mortality/1000 (95% CI)		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other considerations
	In women with type 1 diabetes	In women without type 1 diabetes	Relative (95% confidence interval)	Absolute							
Perinatal mortality [a]											
At gestational week 32-34											
1 (Eidem et al., 2011)	85 58.8 (19.4 - 132.0)†	19,594 50.3 (47.3 - 53.5)†	1.17 (0.50 - 2.74)*	8.5 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 35-36											
1 (Eidem et al., 2011)	190 15.8 (3.27 - 45.5)†	39,553 19.0 (17.7 - 20.4)†	0.83 (0.27 - 2.56)*	3.2 fewer per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 37											
1 (Eidem et al., 2011)	152 13.2 (1.60 - 46.7)†	47,517 9.28 (8.44 - 10.2)†	1.42 (0.36 - 5.63)*	3.92 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 38											
1 (Eidem et al., 2011)	225 8.89 (1.08 - 31.7)†	105,234 4.51 (4.12 - 4.94)†	1.97 (0.49 - 7.85)*	4.38 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 39											
1 (Eidem et al., 2011)	245 12.2 (2.53 - 35.4)†	206,321 2.88 (2.66 - 3.12)†	4.25 (1.38 -13.11)*	9.32 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[d]
At gestational week 40											
1 (Eidem et al., 2011)	159 6.29(0.16 - 34.5)†	281,805 2.08 (1.91 - 2.25)†	3.03 (0.43 -21.41)*	4.82 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	Yes[d]
At gestational week 41-45											
1 (Eidem et al., 2011)	1071 29.7 (6.17 - 84.4)†	366,653 2.39 (2.24 - 2.56)†	12.42 (4.06 – 37.93)*	27.31 more per 1000*	Very low	Retrospective cohort	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[d]

† Data provided by author
*Calculated by NCC-WCH
a. Perinatal death was defined as stillbirth (death of the fetus before or during labour) or early neonatal death (death during the first 7 days of life).

b. Gestational age was primarily determined using the date of last menstrual period (LMP) which is susceptible to inaccuracy as well as recall bias. Where LMP information was not available, gestational age was estimated on the basis of ultrasound notes (which are more reliable) although fewer than a third of all births had this data recorded.
c. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25
d. Country: Norway, Ethnicity of women with type 1 diabetes N (%): European origin 99.9%. Ethnicity of women without type 1 diabetes N (%): European origin 94.4%.
European origin was defined as women who are not first or second generation immigrants from a country outside Europe, or from Turkey.

This section was updated in 2015

Table 79: GRADE profile for effectiveness of elective delivery in pregnant women with gestational diabetes compared with expectant management for maternal outcomes

| Number of studies | Number of events/women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	Elective Delivery	Expectant management	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Mode of birth											
Spontaneous vaginal birth											
Vaginal delivery											
1 (Kjos et al., 1993)	75/100 (75%)	69/100 (69%)	RR = 1.09 (0.91 to 1.29)*	62 more per 1000 (from 62 fewer to 200 more)	Low	Randomised trial	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d]
Spontaneous birth											
1 (Lurie et al., 1996)	69/96 (71.9%)	128/164 (75.6%)	RR = 0.92 (0.79 to 1.07)*	62 fewer per 1000 (from 164 fewer to 55 more)	Low	Prospective Cohort	Serious limitations[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[f,g]
1 (Alberico et al., 2010)	36/48 (75%)	39/51 (76%)	RR = 0.98 (0.78 to 1.23)*	15 fewer per 1000 (from 168 fewer to 176 more)	Very low	Retrospective cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	No serious imprecision	Yes[i,j,k]
Operative delivery											
1 (Lurie et al., 1996)	5/96 (5.2%)	9/164 (5.5%)	RR = 0.95 (0.33 to 2.75)*	3 fewer per 1000 (from 37 fewer to 96 more)	Very low	Prospective Cohort	Serious limitations[e]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[f,g]
1 (Alberico et al., 2010)	3/48 (6%)	1/51 (2%)	RR = 3.19 (0.34 to 29.60)	43 more per 1000 (from 13 fewer to 561 more)	Very low	Retrospective cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[i,k]
Caesarean section											
1 (Kjos et al., 1993)	20/89 (22.5%)	12/80 (17.5%)	RR = 1.28 (0.70 to 2.37)*	49 more per 1000 (from 53 fewer to 240 more)	Very low	Randomised trial	Serious limitations[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[c,d,m]
1 (Lurie et al., 1996)	22/96 (22.9%)	31/164 (18.9%)	RR = 1.21 (0.75 to 1.97)*	40 more per 1000 (from 47 fewer to 183 more)	Very low	Prospective Cohort	Serious limitations[d]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[f,g]

| Number of studies | Number of events/women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	Elective Delivery	Expectant management	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Alberico et al., 2010)	9/48 (19%)	11/51 (22%)	RR = 0.87 (0.40 to 1.91)*	52 fewer per 1000 (from 125 fewer to 80 more)	Very low	Retrospective cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[i,k,n,o]
Caesarean section - Subgroup of women with normal BMI (20-25)											
1 (Alberico et al., 2010)	14%	14%	OR = 0.99 (0.2 to 4.91)	NC	Very low	Retrospective cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[i,k]
Caesarean section - Subgroup of women with obesity (BMI ≥30)											
1 (Alberico et al., 2010)	24%	50%	OR = 0.31 (0.04 - 2.14)	NC	Very low	Retrospective cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Very serious imprecision[l]	Yes[i,k]

BMI body mass index, NC Not calculable, RR relative risk

* Calculated by NCC-WCH

a. It is unclear whether an appropriate method of randomisation was used or if the method of allocation to treatment groups was unrelated to potential confounding factors.

b. Confidence interval for the RR crosses the line of no effect and RR = 1.25

c. Study conducted in USA. 187 were diagnosed with insulin dependent gestational diabetes. 13 women were diagnosed with pregestational non-insulin dependent diabetes before pregnancy - 9/13 in elective induction group, 4/13 in expectant management group. All women had no other medical or obstetric complications and were candidates for trial of vaginal delivery (had not had more than 2 previous caesarean sections). No details of ethnicity are given. Onset of labour: In the elective induction group, 22/100 had a spontaneous labour, 70/100 underwent induction of labour and 8/100 had a caesarean delivery without labour (no reasons for this are given). In the expectant management group, 44/100 had a spontaneous labour, 49/100 underwent induction of labour and 7/100 had a caesarean delivery without labour. (One additional woman presented in spontaneous labour with a transverse foetal lie and underwent caesarean section without allowing labour to proceed). The following indications were given for the 49 women who underwent induction of labour - abnormal antenatal testing: 19, ruptured membranes without labour: 8, 42 gestational weeks: 7, poor foetal growth: 4, pregnancy induced hypertension: 3, suspected macrosomia: 1, maternal insistence on delivery: 7

d. Active induction of labour: In pregnancies where gestational age could not be determined with accuracy, amniocentesis was performed to assess foetal lung maturity. Women with 1) accurate estimation of gestational age or 2) evidence of foetal lung maturity (lecithin sphingomyelin ratio ≥ 2.0) were scheduled within 5 days for induction of labour. If foetal lung maturity was not confirmed, amniocentesis was performed again 1 week later. Women continued twice weekly antepartum surveillance and home insulin therapy. Labour was induced with intravenous oxytocin. Women with favourable Bishop scores (<4), unscarred uteri and normal amniotic fluid indices (>5.0cm), up to three applications of vaginal prostaglandin (3mg) were used for cervical ripening before treatment with oxytocin.

Expectant management: Expectant management was daily split-dose insulin treatment and home blood glucose monitoring, weekly antenatal clinic appointments and twice weekly antepartum testing until spontaneous labour occurred. Induction of labour was undertaken if 1) decelerations or nonstress testing or low amniotic fluid volume indicated suspected foetal distress 2) pre-eclampsia occurred, 3) maternal hyperglycaemia or ketonuria occurred 4) estimated foetal weight ≥ 4200g or 5) the pregnancy exceeded 42 gestational weeks. Gestational age in both groups determined by last menstrual period adjusted if ultrasonongraphic estimation (before 22 weeks) indicated a difference of ≥ 10 days.

e. The study used a historic control group who received expectant management. No attempt was made within the design or analysis to balance the comparison groups for potential confounders.

f. Study conducted in Israel. All women had class A2 gestational diabetes. No ethnicity details were given

g. In the first period, unless foetal health was compromised, pregnancy was allowed to progress to spontaneous labour. If the woman was undelivered at 40 gestational weeks a nonstress test and evaluation of cervical status was performed twice weekly and biophysical score once a week. Induction of labour was attempted if one of the following was

met. 1) Ultrasonography estimation of an excessively large foetus (>4000g) 2) Assessment of biophysical score or OCT indicating compromise of foetal health 3) a Bishop score of >6 was obtained Instrumental delivery or caesarean section was perfumed as usually indicated. Elective caesarean section was performed where foetal weight was estimated to be ≥4500g.

In the second period, an amniocentesis was performed to estimate lung maturity and the ratio of lecithin to sphingomyelin (L/S ratio) and phosphatidylglycerol presence were assessed from the amniotic fluid. If the lungs were assessed to be mature and the cervix was unfavourable (Bishop score <6), induction of labour was performed by either intracervical balloon catheter or placement of 0.5mg prostaglandin E2 gel. If the cervix was favourable, intravenous oxytocin was administered followed by amniotomy. If fetal weight was estimated to be ≥4500g by clinical or ultrasound examination, the mother was delivered by caesarean section.

h. It is unclear whether the method of allocation to treatment groups was unrelated to potential confounding factors. There were significantly more very obese women in the elective delivery group compared to the expectant management group although for other major confounding and prognostic factors the groups were comparable at baseline.

i. Study conducted in Italy. No ethnicity data presented. All women had gestational diabetes.

j. 4/51 (8%) women in the expectant management group underwent Induction > 38 weeks for reasons not related to gestational diabetes; 3/4 spontaneous delivery following induction, 1/4 caesarean section

k. Intervention: elective induction of labour was performed by administration of PGE2 gel every 6-8 hours until labour started. If induction did not succeed after 5 attempts then caesarean section was performed.

Control: women in the expectant management group were reassessed at 40-41 gestational weeks by ultrasound. If the estimated foetal weight was >4250g, then a caesarean section was performed, otherwise the patient was observed until spontaneous labour started. Induction was offered if there were any new emerging indications (oligohydramnios, PROM, post-term pregnancy).

For both groups, a caesarean section was performed if foetal distress was suspected.

l. Confidence interval for the RR crosses the line of no effect and RR = 0.75 and RR = 1.25

m. Data are corrected for caesarean section rates in women who had not had a previous caesarean section

n. 9/48 (19%)women in the elective induction group had a caesarean section: 8/9 failed induction, 1/9 foetal distress. 11/51 (22%) women in the expectant management group had a caesarean section:8/11 macrosomia, 2/11 foetal distress, 1/11 following induction>38 weeks

o. A comparison of obese versus normal weight women across study groups demonstrated that obese women were significantly more likely to have a caesarean section (33% versus 14%, p=0.03). A multivariate analysis of women with BMI ≥30 versus women with BMI <30 was performed and the resulting adjusted OR = 3.9 (95% CI 1.2 to 12.8) (adjusted for maternal age, parity, hypertensive disorders and induction of labour at 38 gestational weeks)

This section was updated in 2015

Table 80: GRADE profile for effectiveness of elective delivery in pregnant women with gestational diabetes compared with expectant management for fetal/neonatal outcomes

| Number of studies | Number of events/women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other considerations |
	Elective Delivery	Expectant management	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Stillbirth											
1 (Alberico et al., 2010)	0/48 (0%)	1/51 (2%)	RR = 0.35 (0.01 to 8.48)*	13 fewer per 1000 (from 19 fewer to 147 more)	Very low	Retrospective cohort	Serious limitations[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	Yes[c,d]
Perinatal death											
1 (Kjos et al., 1993)	0/100 (0%)	0/100 (0%)	NC	NC	Low	Randomised trial	Serious limitations[e]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[f,g]

Number of studies	Number of events/women		Effect		Quality	Design	Limitations (risk of bias)	Inconsistency	Indirectness	Imprecision	Other consider ations
	Elective Delivery	Expectant management	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Kjos et al., 1993)	15/100 (15%)	27/100 (27%)	RR = 0.56 (0.32 to 0.98)*	119 fewer per 1000 (from 5 fewer to 184 fewer)	Low	Random ised trial	Serious limitations[e]	No serious inconsistency	No serious indirectness	Serious imprecision	Yes[f,g]
1 (Lurie et al., 1996)	9/96 (9.4%)	30/164 (18.3%)	RR = 0.51 (0.25 to 1.03)*	90 fewer per 1000 (from 137 fewer to 5 more)	Low	Prospect ive Cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Serious imprecision	Yes[i,j,k,l]
1 (Alberico et al., 2010)	6/48 (13%)	11/51 (22%)	RR = 0.58 (0.23 to 1.44)*	91 fewer per 1000 (from 166 fewer to 95 more)	Very low	Retrosp ective cohort	Serious limitations[a]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	Yes[c,d]
Birth weight >4500g											
1 (Kjos et al., 1993)	0/100 (0%)	2/100 (2%)	RR = 0.2 (0.01 to 4.11)*	16 fewer per 1000 (from 20 fewer to 62 more)	Low	Random ised trial	Serious limitations[e]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[f,g]
Shoulder dystocia (with and without consequences for the baby such as trauma, neuromuscular injury)											
1 (Kjos et al., 1993)	0/100 (0%)	3/100 (3%)	RR = 0.14 (0.01 to 2.73)*	26 fewer per 1000 (from 30 fewer to 52 more)	Very low	Random ised trial	Serious limitations[e,m,n]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	Yes[f,g]
1 (Lurie et al., 1996)	1/74 (1.4%)	7/133 (5.3%)	RR = 0.26 (0.03 to 2.05)*	39 fewer per 1000 (from 51 fewer to 55 more)	Very low	Prospect ive Cohort	Serious limitations[h]	No serious inconsistency	No serious indirectness	Very serious imprecisionb	Yes[i,k,o]
1 (Alberico et al., 2010)	0/48 (0%)	0/51 (0%)	NC	NC	Very low	Retrosp ective cohort	Serious limitations[a,n,p]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[c,d]
Admission to NICU											
1 (Alberico et al., 2010)	1/48 (2%)	6/51 (12%)	RR = 0.18 (0.02 to 1.42)*	96 fewer per 1000 (from 115 fewer to 49 more)	Very low	Retrosp ective cohort	Serious limitations[a,n,q]	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	Yes[c,d]
Respiratory disease (including respiratory distress syndrome and transient tachypnoea of the newborn)											
1 (Lurie et al., 1996)	0/96 (0%)	0/164 (0%)	NC	NC	Very low	Prospect ive Cohort	Serious limitations[h,r]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[i,k]

| Number of studies | Number of events/women | | Effect | | Quality | Design | Limitations (risk of bias) | Inconsistency | Indirectness | Imprecision | Other consider ations |
	Elective Delivery	Expectant management	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Neonatal hypoglycaemia											
1 (Kjos et al., 1993)	0/100 (0%)	0/100 (0%)	NC	NC	Low	Random ised trial	Serious limitations[e,s]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Yes[f,g]

NA not applicable, NC not calculable, RR relative risk
*Calculated by NCC-WCH

a. It is unclear whether the method of allocation to treatment groups was unrelated to potential confounding factors. There were significantly more very obese women in the elective delivery group compared to the expectant management group although for other major confounding and prognostic factors the groups were comparable at baseline.

b. Confidence intervals for the estimate of effect cross the line of no effect and either 0.75 and/or 1.25

c. Study conducted in Italy. No ethnicity data presented. All women had gestational diabetes

d. Intervention: elective induction of labour was performed by administration of PGE2 gel every 6-8 hours until labour started. If induction did not succeed after 5 attempts then caesarean section was performed.

Control: women in the expectant management group were reassessed at 40-41 gestational weeks by ultrasound. If the estimated foetal weight was >4250g, then a caesarean section was performed, otherwise the patient was observed until spontaneous labour started. Induction was offered if there were any new emerging indications (oligohydramnios, PROM, post-term pregnancy).

For both groups, a caesarean section was performed if foetal distress was suspected.

e. It is unclear whether an appropriate method of randomisation was used or if the method of allocation to treatment groups was unrelated to potential confounding factors.

f. Study conducted in USA. 187 were diagnosed with insulin dependent gestational diabetes. 13 women were diagnosed with pregestational non-insulin dependent diabetes before pregnancy - 9/13 in elective induction group, 4/13 in expectant management group. No details of ethnicity are given.

g. Active induction of labour: In pregnancies where gestational age could not be determined with accuracy, amniocentesis was performed to assess foetal lung maturity. Women with 1) accurate estimation of gestational age or 2) evidence of foetal lung maturity (lecithin sphingomyelin ratio ≥ 2.0) were scheduled within 5 days for induction of labour. If foetal lung maturity was not confirmed, amniocentesis was performed again 1 week later. Women continued twice weekly antepartum surveillance and home insulin therapy. Labour was induced with intravenous oxytocin. Women with favourable Bishop scores (<4), unscarred uteri and normal amniotic fluid indices (>5.0cm), up to three applications of vaginal prostaglandin (3mg) were used for cervical ripening before treatment with oxytocin.

Expectant management: Expectant management was daily split-dose insulin treatment and home blood glucose monitoring, weekly antenatal clinic appointments and twice weekly antepartum testing until spontaneous labour occurred. Induction of labour was undertaken if 1) decelerations or nonstress testing or low amniotic fluid volume indicated suspected foetal distress 2) pre-eclampsia occurred, 3) maternal hyperglycaemia or ketonuria occurred 4) estimated foetal weight ≥ 4200g or 5) the pregnancy exceeded 42 gestational weeks. Gestational age in both groups determined by last menstrual period adjusted if ultrasonongraphic estimation (before 22 weeks) indicated a difference of ≥ 10 days.

h. The study used a historic control group who received expectant management. No attempt was made within the design or analysis to balance the comparison groups for potential confounders.

i. Study conducted in Israel. All women had class A2 gestational diabetes. No ethnicity details were given

j. One neonate died of severe asphyxia

k. In the first period, unless foetal health was compromised, pregnancy was allowed to progress to spontaneous labour. If the woman was undelivered at 40 gestational weeks a nonstress test and evaluation of cervical status were performed twice weekly and biophysical score once a week. Induction of labour was attempted if one of the following was met. 1) Ultrasonographic estimation of an excessively large foetus (>4000g) 2) Assessment of biophysical score or OCT indicating compromise of foetal health 3) a Bishop score of >6 was obtained Instrumental delivery or caesarean section was performed as usually indicated. Elective caesarean section was performed where foetal weight was estimated to be ≥4500g.

In the second period, an amniocentesis was performed to estimate lung maturity and the ratio of lecithin to sphingomyelin (L/S ratio) and phosphatidylglycerol presence were assessed from the amniotic fluid. If the lungs were assessed to be mature and the cervix was unfavourable (Bishop score <6), induction of labour was performed by either intracervical balloon catheter or placement of 0.5mg prostaglandin E2 gel. If the cervix was favourable, intravenous oxytocin was administered followed by amniotomy. If foetal weight was estimated to be ≥4500g by clinical or ultrasound examination, the mother was delivered by caesarean section.

l. In expectant management group: 15/30 delivered after 40 weeks

m. The outcome is described as mild shoulder dystocia but no definition is given. No incidences of birth trauma - Erg's palsy or bone fracture - in either group

n. It is unclear whether a valid and reliable method was used to determine the outcome

o. The denominators exclude caesarean section deliveries. Definition: failure of the shoulder to be delivered spontaneously after the head due to impaction of the anterior shoulder against the symphysis pubis, as judged by the clinician delivering the foetus. In the expectant management group 5/7 delivered after 40 weeks. 2/7 Erb's palsy, 1/7 clavicular fracture

p. No definition of shoulder dystocia is given

q. No definition of admission to NICU is given

r. The outcome was respiratory distress syndrome, but no definition was given

s. No definition of neonatal hypoglycaemia was given

6.1.2.5 Evidence statements

This section was updated in 2015One retrospective cohort study (n=4,190,953 non anomalous deliveries) reported a trend of falling stillbirth rates from 36 to 40 weeks of gestation and higher rates thereafter in women with and without gestational diabetes. The incidence of stillbirth was higher in babies of women with gestational diabetes compared with those without throughout weeks 36 to 41, but the risk of stillbirth was increased only during weeks 37 (RR 1.13, 95% CI 1.06 to 1.70) and 39 (RR 1.30, 95% CI 1.01 to 1.66) of gestation in women with gestational diabetes compared with those without. In week 42, the incidence of stillbirth was higher in women without gestational diabetes compared with those with gestational diabetes.

The same study found U-shaped trends for the incidence of neonatal and infant death in the babies of women with and without gestational diabetes, which were highest for babies delivered at 36 weeks and which fell to a nadir at 39–40 weeks before rising again at 41 weeks. The neonatal death rate was higher in babies of women with gestational diabetes delivered at weeks 36, 37, 39 and 42 compared with the babies of women without gestational diabetes. However, there were no differences in the risk of neonatal death between the 2 groups at any time point. Although the infant death rates were higher in babies of women without gestational diabetes compared with those with gestational diabetes from 36 to 42 weeks' gestation, there were no differences in the risk of infant death between the 2 groups at any time point..

In the second study (n=3,522,869), the incidence of stillbirth in women with type 1 and type 2 diabetes also demonstrated a U-shaped trend, being highest at 24–27 weeks of gestation, decreasing to a minimum at 37–38 weeks of gestation and then rising at 39 weeks' gestation and later. The incidence of stillbirth in all women in England and Wales similarly decreased from 24 to 27 weeks of gestation but rather than rising, the minimum rate was observed at 39 weeks' gestation and later. When the groups were compared, there were no differences in the risk of stillbirth between the 2 groups at any time point except at 39 weeks' gestation and later, when there was a higher rate in women with type 1 and type 2 diabetes compared with all women in England and Wales (RR 7.2, 95% CI 1.31 to 39.63).

A third retrospective study (n=1,162,399) reported a U-shaped trend for rates of perinatal mortality in babies of women with type 1 diabetes, with the highest risk at a timepoint of 32–34 weeks, dipping to a nadir at week 38 before rising again at 39 weeks. The value at 40 weeks dipped and then rose again at 41–45 weeks. Similarly, rates of perinatal mortality in babies of women without type 1 diabetes was also highest at the 32–34 weeks timepoint, but thereafter fell and plateaued from week 39. The risk of perinatal mortality was higher in babies of women with type 1 diabetes compared with those without type 1 diabetes at week 39 (RR 4.25, 95% CI 1.38 to 13.11) and weeks 41–45 (RR 12.42, 95% CI 4.06 to 37.93).

The evidence for all the above mortality outcomes was of very low quality.

When women with gestational diabetes who had an elective delivery were compared with those who were managed expectantly, there were no differences in these mode of birth outcomes: vaginal delivery, spontaneous vaginal birth, operative deliveries or caesarean section:

- vaginal delivery (RR 1.09, 95% CI 0.91 to 1.29, 1 RCT, n=200)
- spontaneous vaginal birth (2 cohort studies: RR 0.92, 95% CI 0.79 to 1.07, n=260; RR 0.98, 95% CI 0.78 to 1.23, n=99)
- operative deliveries (2 cohort studies: RR 0.95, 95% CI 0.33 to 2.75, n=260; RR 3.19, 95% CI 0.34 to 29.60, n=99)
- caesarean section (1 RCT: RR 1.28, 95% CI 0.70 to 2.37, n=200; and 2 cohort studies: RR 1.21, 95% CI 0.75 to 1.97, n=260; RR 0.87, 95% CI 0.40 to 1.91, n=99).

One study compared the risk of caesarean section in women having an elective delivery with those managed expectantly according to body mass index (BMI) but found no differences in caesarean section risk between groups for women with a normal (20–25) BMI (odds ratio [OR] 0.99, 95% CI 0.2 to 4.91, n=28) or an obese (30 or more) BMI (OR 0.31, 95% CI 0.04 to 2.14, n=78). The evidence for these findings was of low and very low quality.

There were no differences in the risk of stillbirth, perinatal death, shoulder dystocia or NICU admission in the babies of women with gestational diabetes who had an elective delivery compared with those who were managed expectantly:

- stillbirth (1 cohort study: RR 0.35, 95% CI 0.01 to 8.48, n=99)
- perinatal death (1 RCT: RR not calculable [NC], 95% CI NC, n=200; and 1 cohort study: RR NC, 95% CI NC, n=260)
- shoulder dystocia (1 RCT: RR 0.14, 95% CI 0.01 to 2.73, n=200; and 2 cohort studies: RR 0.26, 95% CI 0.03 to 2.05, n=207; RR NC, 95% CI NC, n=99)
- NICU admission (1 cohort study: RR 0.18, 95% CI 0.02 to 1.42, n=99).

The evidence for these findings was of low and very low quality.

With regard to fetal size, 1 RCT found that the risk of macrosomia (defined as birthweight more than 4000 g) was lower in babies of women with gestational diabetes who had an elective delivery compared with those who were managed expectantly (RR 0.56, 95% CI 0.32 to 0.98, n=200) although 2 cohort studies reported no difference in risk of macrosomia (RR 0.51, 95% CI 0.25 to 1.03, n=260; RR 0.58, 95% CI 0.23 to 1.44, n=99). When macrosomia was defined as birthweight more than 4500 g, there was no difference in risk for babies of women who had elective delivery compared with those who were managed expectantly. There were no incidences of respiratory disease (1 cohort study, n=260) or neonatal hypoglycaemia (1 RCT, n=200) reported in the studies that reported these outcomes. The evidence for these findings was of low and very low quality.

6.1.2.6 Health economics profile
This section was updated in 2015

No health economic evidence was found in relation to the optimal timing of birth in pregnancies with type 1, type 2 or gestational diabetes.

De novo analysis was not undertaken for this question.

6.1.2.7 Evidence to recommendations
This section was updated in 2015

6.1.2.7.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised mortality (stillbirth and neonatal death) above morbidity, although such outcomes were rare. If mortality rates were no different at different gestational age thresholds, then differences in morbidity outcomes were taken into account in developing the recommendations.

6.1.2.7.2 *Consideration of clinical benefits and harms*

The main aim and benefit of elective delivery is to lessen the likelihood of a stillbirth late in pregnancy. However, elective delivery at 37 and 38 weeks may be associated with a higher incidence of complications in both the woman (such as failed induction of labour and the need for emergency caesarean section) and the fetus/baby (such as transient tachypnoea of the newborn and the need for NICU admission). In contrast, later delivery may not only increase the likelihood of stillbirth but also increase the incidence of fetal macrosomia and shoulder dystocia.

In all pregnancies complicated by maternal diabetes (of any type) earlier delivery should be considered if there are additional complications in the woman, such as poor glucose control or pre-eclampsia, or in the fetus, such as abnormal fetal growth (large or small for dates) and/or abnormal umbilical artery Doppler recordings and/or biophysical testing.

6.1.2.7.3 Consideration of health benefits and resource uses

A timely spontaneous atraumatic vaginal delivery of a healthy baby that has no neonatal problems is the principle underlying the issue of timing of delivery. However, in practice, identifying this optimum time for the delivery is not easy. It is of note that the main adverse outcomes highlighted by the guideline development group, especially caesarean section for failed induction, maternal and fetal/baby trauma from shoulder dystocia and admission to NICU, were also the outcomes with the highest costs.

6.1.2.7.4 Quality of evidence

The quality of the studies was low or very low. The guideline development group considered there were limitations on the type of data reported for mortality in the studies. For example, the group was of the view that record linkage was likely to be better in Norway than in the USA.

There were no studies comparing expectant management with elective delivery in women with type 1 or type 2 diabetes and although 1 study presented data for mortality rates in women with type 1 or type 2 diabetes, there were no studies examining fetal mortality rates specifically in women with type 2 diabetes.

The group thought the data in the observational record linkage study in women with gestational diabetes were more difficult to interpret, partly because of inconsistencies in the denominator used to evaluate the outcomes. In addition, the group believed that there were very low stillbirth rates in this study. The finding that at week 42 the point estimate of stillbirth was lower for women with gestational diabetes compared with women without was counterintuitive. However, the confidence intervals were very wide and this result was not statistically significant. Furthermore, the guideline development group speculated that this finding, if real, could be ascribed to there being very few women with gestational diabetes who receive prenatal care remaining undelivered at 42 weeks.

Notwithstanding these limitations, the stillbirth rates were significantly higher in women with gestational diabetes than in women without the diagnosis at 37 and 39 weeks. In fact, the absolute stillbirth rate in the women with gestational diabetes fell to a nadir at 40 weeks before rising again thereafter. In light of this, the guideline development group was of the view that in women with gestational diabetes without any maternal or fetal complications, delivery could be delayed until 40 weeks. From a practical point of view the group felt that it would be reasonable that women with gestational diabetes should be offered delivery no later than 39^{+6} weeks so that the delivery could take place no later than in the early part of the 40th week.

The guideline development group noted that infant death rates were higher in women without gestational diabetes. It was noted that this parameter was not the actual infant death rate but a derived statistic and, thus, of uncertain validity. However, if real, the finding could be explained if more women with gestational diabetes were delivered by 40 weeks such that there were fewer babies born to mothers with gestational diabetes who were born at 41 and 42 weeks, when infant mortality rates are higher. The group also acknowledged that infants born to mothers with known gestational diabetes might be at higher risk of short-term morbidities, such that these babies are more likely to undergo more rigorous screening and treatment compared with the general population

The guideline development group noted in the UK study of women with pre-existing diabetes that at all time points rates of stillbirth per 1000 live births were similar in both groups until 39 weeks' gestation and later, when rates were significantly higher in women with type 1 and 2 diabetes compared with all women in England and Wales. The lowest rate of stillbirth was during 37 to 38^{+6} weeks' gestation in women with type 1 and 2 diabetes. The group noted that 'all women in England and Wales' included the small percentage of women with type 1

or 2 diabetes and women with multiple pregnancies, but that this would tend to underestimate the additional risk in women with type 1 and 2 diabetes.

In the study in women with type 1 diabetes, the perinatal mortality rates in women with the disease were higher than those in non-diabetic women from 37 weeks. This difference only became statistically significant from 39 weeks. The guideline development group concluded from the UK study discussed in the previous paragraph that it would be reasonable to offer elective delivery to women with type 1 or type 2 diabetes at 37^{+0} to 38^{+6} weeks. The group felt that offering elective delivery earlier than this would potentially increase the risk of neonatal or longer-term complications.

There were no studies comparing expectant management with elective delivery in women with type 1 or type 2 diabetes. There was no evidence that early delivery reduced the risk of stillbirth in gestational diabetes, but there were RCT data suggesting that delivery at or around 38 weeks reduced the numbers of babies with macrosomia, although this was not translated into a higher incidence of caesarean section or shoulder dystocia in that group. In light of this, and the mortality and stillbirth evidence, the guideline development group recommended earlier delivery where there is evidence of maternal and/or fetal complications, such as ultrasound evidence of macrosomia.

6.1.2.7.5   *Other considerations*

The guideline development group noted that only 1 study was from the UK and the remaining 5 studies came from 4 different countries (USA, Norway, Israel and Italy). Only 2 studies provided details regarding the ethnicities of study populations. In the Norwegian study, 99.9% of women were of European origin and in the record linkage study performed in the USA, approximately one-third of women were Latina. The potential implication of this was that the ethnic profile of the populations could have been quite diverse, limiting the comparability of the populations with, and relevance to, the UK. The group also noted that the protocols differed across studies examining expectant management and elective delivery.

In theory, the guideline development group felt that grouping all types of diabetes together in making the recommendations, as was done in the original guideline, did not allow for the possibility that the risks of late stillbirth could be different between women with type 1, type 2 and gestational diabetes. However, there were limited data available to answer this question. Specifically, there was only 1 observational study of women with type 1 diabetes and that reported perinatal mortality rates by gestational age rather than stillbirth rates. Similarly, there was only 1 observational study of women with gestational diabetes reporting stillbirth rates by gestational age.

The group felt that the evidence justified making separate recommendations regarding the timing of birth for women with type 1 or type 2 diabetes and for women with gestational diabetes.

For women with gestational diabetes, the data from Rosenstein et al. (2012) demonstrated that there was a significant rise in stillbirth rate after 40^{+6} days, whereas the Kjos et al. (1993) study showed that the incidence of babies weighing more than 4000 g rose after 39^{+6} days. Given that avoidance of stillbirth was the philosophy underpinning the timing of delivery, the group felt that in women with uncomplicated gestational diabetes, elective delivery could be delayed until 40^{+6} days.

For women with type 1 or type 2 diabetes the limited data demonstrated that the stillbirth rate rose after 38^{+6} weeks. Thus such women should be offered elective delivery by 38^{+6} weeks. The guideline development group felt that a lower limit should be included in the recommendation to avoid women with uncomplicated type 1 or type 2 diabetes being advised to have an elective preterm delivery with its associated complications for the woman (such as failed induction of labour and caesarean section) and the baby (such as respiratory distress syndrome and admission to the neonatal unit). The data from Holman et al. (2014)

suggested the lower limit of the elective delivery should be 37^{+0} weeks. Thus the group recommended elective delivery for women with uncomplicated type 1 or type 2 diabetes at 37^{+0} to 38^{+6} weeks. In making this recommendation, the group hoped that, in practice, this would result in such women being routinely offered elective delivery nearer 38^{+6} weeks than 37^{+0} weeks.

Finally, the guideline development group was aware that the guideline on antenatal care recommends that women should be offered a discussion and information about labour and birth during the antenatal period. They felt this was especially important in women with diabetes and that this should include a discussion about the reasons why elective delivery would be offered. Ideally they felt this should take place in the third trimester.

6.1.2.8 Key conclusions

This section was updated in 2015

The most important considerations taken into account by the guideline development group in making their decisions about recommendations were:

- Pregnancy in women with diabetes of all types overall is associated with an increased risk of stillbirth compared with non-diabetic pregnancies, and the recommendations relating to timing of birth are primarily aimed at preventing this outcome.
- The group felt it was reasonable to regard type 1 and type 2 diabetes as the same for the purpose of the recommendations. For types 1 and 2 diabetes the group was of the view that, on balance, elective delivery should be offered between 37^{+0} and 38^{+6} weeks.
- Evidence was much less robust that for women with gestational diabetes adverse pregnancy outcomes, apart from mortality, were related to the timing of birth.
- In all pregnancies complicated by pre-existing maternal diabetes (of any type), delivery earlier than 37^{+0} weeks should be considered if there are maternal or fetal complications
- Timing of birth should be discussed with the woman antenatally, ideally during the last trimester.

6.1.2.9 Recommendations
The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

6.1.2.10 Research recommendations

This section was updated in 2015

39. What is the relationship between timing of elective delivery in women with diabetes and the outcome in the baby?

Why this is important

Typically women with all types of diabetes are delivered electively prior to 40 completed weeks, either through induction of labour or planned caesarean section because of the increased risks of stillbirth. While the risk of stillbirth is probably not increased in women with well controlled uncomplicated gestational diabetes compared to the general population, women with type 1 and type 2 diabetes are generally considered to have about a 3-fold increased risk. This increased risk is present from at least 32 weeks. Observational studies demonstrate that preterm delivery is associated with increased risks of neonatal morbidity, separation of mother and baby and difficulties in achieving successful breast feeding. Current fetal surveillance methods have not been found to be of value in predicting fetal demise unless there is fetal growth restriction. There is a need for randomised controlled studies comparing different strategies for the timing of elective delivery, controlled for type of diabetes, which involve additional surveillance in the group being randomised to a delayed delivery.

40. What is the optimum gestation for delivering women with uncomplicated gestational diabetes

Why this is important

It is widely considered that women with gestational diabetes should have labour induced prior to 40 weeks of gestation. Although, in contrast to women with pre-gestational diabetes, there is no convincing evidence that women whose gestational diabetes is managed appropriately are at an increased risk of a still birth, there is evidence to suggest that induction of labour prior to 40 weeks of gestation may reduce the risk of shoulder dystocia. With the increasing incidence of gestational diabetes, at well over 5% in some maternity units, significant pressure is being put on units in dealing with so many inductions. From a woman's perspective induction involves longer hospitalisation and there are additional NHS costs. In addition induction may fail in women having their first babies or can be unnecessarily rapid in those who have had many. Furthermore oxytocin is often used in the induction process and is not without maternal and fetal risks. Accordingly there is a need for studies on women with gestational diabetes, who do not have large babies as assessed by their routine third trimester ultrasound scans, to be randomised into either having labour induced after 38 weeks or to await spontaneous labour.

6.2 Analgesia and anaesthesia

6.2.1 Description of the evidence

Labour and birth can be stressful for any woman. In women with diabetes these stresses may make diabetes more difficult to control, resulting in otherwise preventable morbidities and even mortality. Any interventions during labour and birth should, therefore, be considered carefully in terms of the effect on the woman and the baby. Relevant factors to consider in terms of women with diabetes are glycaemic control, prevention of metabolic disturbances (abnormal acid–base status leading to ketoacidosis) and haemodynamic control (with an emphasis on prevention of hypotension).[335] Additional factors to consider are comorbidities such as neuropathy and obesity, which may complicate obstetric analgesia and anaesthesia.

6.2.1.1 Glycaemic control

No clinical studies were identified in relation to the effects of analgesia or anaesthesia on perioperative glycaemic control in women with diabetes. However, an RCT compared epidural anaesthesia plus general anaesthesia with general anaesthesia alone in people undergoing colorectal surgery for non-metastatic carcinoma.[336] Epidural anaesthesia plus general anaesthesia reduced the perioperative increase in blood glucose compared with general anaesthesia alone (intra-operative glucose production, 8.2 ± 1.9 micromol/kg/min versus 10.7 ± 1.4 micromol/kg.

Min, $P < 0.05$; postoperative glucose production, 8.5 ± 1.8 micromol/kg/min versus 10.5 ± 1.2 micromol/kg/min, $P < 0.05$). Although this was a small study with only eight people without diabetes in each treatment group, it suggests that there may be a benefit in regional anaesthesia for women with diabetes facing caesarean section compared with general anaesthesia. [EL = 1+]

A narrative non-systematic review reported that pain and/or stress following surgery and trauma impairs insulin sensitivity by affecting non-oxidative glucose metabolism.[337] While these observations were not drawn from labouring women with diabetes the suggestion is that glucose regulation can be improved with administration of analgesia (pain relief) in stressful states. [EL = 4]

6.2.1.2 Acid–base status

One cohort study and one case–control study investigated acid–base status (and neonatal Apgar scores) in women with diabetes undergoing elective caesarean section with epidural or spinal anaesthesia.

The cohort study assessed whether epidural anaesthesia in women with diabetes undergoing elective caesarean section was associated with abnormal acid–base and glucose status in the woman and baby compared with epidural anaesthesia in women without diabetes.[338] At birth there were no significant differences between women with diabetes and those without diabetes in terms of arterial blood acid–base status, nor in terms of neonatal umbilical venous or arterial blood acid–base status or neonatal Apgar scores. However, women with diabetes and their babies had a 25–50% reduction in pyruvate concentrations in maternal venous blood and neonatal umbilical venous and arterial blood compared to women without diabetes and their babies ($P = 0.001$). The study suggests that epidural anaesthesia in women with diabetes is associated with normal acid–base status in the mother and baby. [EL = 2+]

The case–control study, which was undertaken in the 1980s, involved ten women with rigidly controlled type 1 diabetes and ten healthy women without diabetes.[335] All the women were scheduled for elective primary or repeat caesarean section using spinal anaesthesia at term.

Dextrose-free intravenous solutions were used for volume expansion before induction of anaesthesia, and hypotension was prevented in all women. There were no significant differences in acid–base values between women with diabetes and those without diabetes, nor between babies of women with diabetes and babies in the control group. Mean maternal artery pH in women with diabetes and women without diabetes were 7.40 (standard error (SE) 0.006) and 7.42 (SE 0.01), respectively. Mean umbilical vein pH in women with diabetes and women without diabetes were 7.33 (SE 0.01) and 7.35 (SE 0.01), respectively. Mean umbilical artery pH in women with diabetes and women without diabetes were 7.27 (SE 0.01) and 7.30 (SE 0.01), respectively. Apgar scores were similar in both groups, with one baby of a woman with diabetes having a score of less than 7 at 1 minute and the remaining 19 babies in both groups having scores of more than 7 at 1 and 5 minutes. The authors of the study suggested that anaesthetics such as nitrous oxide and intravenous agents such as thiopentone are virtually free of metabolic effects and may, therefore, be preferred for women with diabetes. They also suggested that sedatives, narcotic analgesics and muscle relaxants are similarly of benefit to women with diabetes. However, no clinical data were provided to support either of these statements. [EL = 2+]

6.2.1.3 Haemodynamic control

No clinical studies were identified in relation to the effects of analgesia or anaesthesia on perioperative haemodynamic control in women with diabetes.

6.2.1.4 Neuropathy

A retrospective cohort study was identified in relation to the effects of coexisting neuropathy on analgesia and anaesthesia in women with diabetes.[339] The study involved 567 people with pre- existing peripheral sensorimotor neuropathy or diabetic polyneuropathy who were investigated for neurological injury after neuraxial blockade. Two people (0.4%, 95% CI 0.1% to 1.3%) experienced new or progressive postoperative neurological deficits and 65 technical complications occurred in 63 people (11.1%). The most common complications were unintentional elicitation of paraesthesia (7.6%), traumatic needle placement (evidence of blood; 1.6%) and unplanned dural puncture (0.9%). There were no infectious or haematological complications. The study concluded that the risk of severe postoperative neurological injury is high in the population of people with pre-existing neuropathy and healthcare professionals should be aware of this when developing and implementing regional anaesthetic care plans. [EL = 2+]

6.2.1.5 Obesity

No clinical studies were identified in relation to the effects of coexisting obesity on analgesia or anaesthesia in women with diabetes. However, a narrative non-systematic review reported that obesity is a risk factor for obstetric analgesia and anaesthesia.[340] [EL = 4]

No further clinical studies were identified in relation to factors affecting the choice of analgesia or anaesthesia in women with diabetes. However, a narrative non-systematic review suggested that increased risks were associated with general anaesthesia. One risk was that women with diabetes tend to have a higher resting gastric volume (slower gastric emptying) than women without diabetes, increasing the risk of Mendelson syndrome, which results from aspiration of gastric contents into the lungs following vomiting or regurgitation in obstetrical patients.335 Another risk was that irreversible brain damage could occur if hypoglycaemia was allowed to develop during general anaesthesia and surgery. The review also noted the possibility of women with diabetes inadvertently being given glucose orally rather than intravenously, and that irreversible brain damage could occur if hypoglycaemia was allowed to develop during general anaesthesia and surgery. It was also suggested that a delay in returning to consciousness following general anaesthesia could prolong the time before routine metabolic management with insulin could be reinstituted. [EL = 4]

The review also reported that regional anaesthesia (as used for caesarean section), which includes epidural anaesthesia and spinal anaesthesia, carries risks for women with diabetes. In particular it was reported that regional anaesthesia can accentuate haemodynamic distortions in women with diabetes in the presence of polyhydramnios and increased segmental spread of the nerve blockade.335 Vomiting is a consequence of hypotension caused by sympathetic nerve blockade and it may exacerbate metabolic disturbances. For labour analgesia, an epidural nerve blockade may reduce metabolic expenditure and avoid the emetic effects of opioids. [EL = 4]

6.2.2   Existing guidance

The NICE guideline for the management of type 1 diabetes recommends that hospitals ensure that protocols for inpatient procedures and surgical operations are in place and used. Such protocols should ensure that near-normoglycaemia is maintained without the risk of acute decompensation, and that this should normally be achieved through adjustment of intravenous insulin delivery in response to regular blood glucose testing.

6.2.3   Evidence statement

No clinical studies were identified in relation to the effects of analgesia or anaesthesia on perioperative glycaemic control in women with diabetes. A small RCT in people undergoing colorectal surgery showed that epidural anaesthesia plus general anaesthesia reduced the perioperative increase in blood glucose compared with general anaesthesia alone. A narrative non-systematic review suggested that glucose regulation could be improved with administration of analgesia in stressful states.

Two observational studies showed that epidural anaesthesia and spinal anaesthesia are associated with normal acid–base status in women with diabetes undergoing elective caesarean section and with normal acid–base status and Apgar scores in their babies.

No clinical studies were identified in relation to the effects of analgesia and anaesthesia on perioperative haemodynamic control in women with diabetes.

A cohort study showed that neuraxial blockade carries an increased risk of severe postoperative neurological injury in people with pre-existing neuropathy.

No clinical studies were identified in relation to the effects of coexisting obesity on analgesia and anaesthesia in women with diabetes. However, a narrative non-systematic review highlighted that obesity is in itself a risk factor for analgesia and anaesthesia.

6.2.4   From evidence to recommendations

Evidence suggests that epidural anaesthesia and spinal anaesthesia are associated with normal acid–base status in women with diabetes. No evidence was identified to suggest that epidural or spinal anaesthesia should be used any differently (in terms of monitoring, dose or provision of fluids) in women with diabetes, and so the GDG has not made any recommendations specific to epidural or spinal anaesthesia. However, the GDG's discussion included consideration of the possibility of prolonged labour with epidural anaesthesia increasing the risk of DKA. The presence of DKA would alter the management of the need for urgent birth. The GDG's view is that diabetes is not in itself a contraindication to restrict the duration of labour, provided that fluids, blood glucose concentrations, etc., are satisfactory.

Long duration of diabetes, hyperglycaemia and any opioid are thought to slow gastric emptying and increase risks for anaesthesia. Evidence shows that the presence of (symptomatic) autonomic neuropathy in women with diabetes is a risk factor for obstetric anaesthesia. Although no clinical evidence was found specifically in relation to coexisting

diabetes and obesity as risk factors for obstetric anaesthesia, obesity alone has been reported to increase problems with intubation, risk of thromboembolism, stress response with pre-eclampsia and risk of post-epidural neurological problems. It is, therefore, important that anaesthetists have access to a complete medical history including information about the extent of neuropathy (particularly autonomic neuropathy) and obesity to assess fitness for anaesthesia and that monitoring begins before anaesthesia is initiated.

Very few women are likely to undergo general anaesthesia during labour and birth. However, general anaesthesia carries a risk of hypoglycaemia and women recovering from general anaesthesia will lack hypoglycaemia awareness. The woman's need for insulin will decrease significantly after the birth (see Section 8.1) and this can also lead to hypoglycaemia. Regular blood glucose monitoring during anaesthesia is, therefore, recommended for women with diabetes: monitoring should occur at 30 minute intervals to prevent hypoglycaemia remaining undetected and/or untreated for longer periods, and it should continue after the birth until the woman is fully conscious.

6.2.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

6.2.6 Research recommendations

41. What are the risks and benefits associated with analgesia and anaesthesia in women with diabetes?

Why this is important

The increasing number of women with diabetes and the high rate of intervention during birth emphasise the need for clinical studies to determine the most effective methods for analgesia and anaesthesia in this group of women. The research studies should investigate the effect of analgesia during labour, and the cardiovascular effects of spinal anaesthesia and vasopressors on diabetic control.

6.3 Glycaemic control during labour and birth

6.3.1 Description of the evidence

6.3.1.1 Neonatal hypoglycaemia

Neonatal hypoglycaemia can occur for two reasons, with some overlap in individual cases. Some fetuses develop a pattern of hyperinsulinaemia to cope with the regular excessive glucose transfer across the placenta where the maternal diabetes is poorly controlled[122]. As newborns these babies have a persisting autonomous insulin secretion which, in the absence of adequate glucose intake, will lead to severe and prolonged hypoglycaemia. Other babies who have not developed hyperinsulinaemia in fetal life may respond to maternal hyperglycaemia in labour with sufficient insulin production in the 1–2 hours following birth to cause transient hypoglycaemia. In contrast the term baby of a woman without diabetes demonstrates rather sluggish insulin responses to glycaemic stimuli and shows a tendency to relatively high blood glucose levels after feeding in the newborn period.

Eight observational studies were identified that considered the effect of maternal blood glucose control during labour and birth on neonatal blood glucose levels. Four studies involved only women with type 1 diabetes, one study included women with type 1 and type 2 diabetes and one study involved only women with gestational diabetes. All six studies found maternal hyperglycaemia during labour to be associated with neonatal hypoglycaemia.

A retrospective study of 53 babies born to women with type 1 diabetes[342] measured plasma glucose concentrations at birth and 2 hours later. The maternal blood glucose concentration at birth correlated positively with the neonatal blood glucose concentration at birth (r = 0.82, P < 0.001) and negatively with the neonatal blood glucose concentration 2 hours after birth (r = −0.46, P < 0.001). Thirty-seven percent (11/30) of babies born to women whose blood glucose concentration at birth was 7.1 mmol/litre or more developed hypoglycaemia (plasma glucose 1.7 mmol or less). No babies born to women whose blood glucose concentration was less than 7.1 mmol/litre developed hypoglycaemia. Babies with blood glucose concentrations less than 1.7 mmol/litre were treated using intravenous glucose. [EL = 2+]

A prospective study included 122 pregnancies in 100 women with type 1 diabetes.[343] Intravenous glucose and/or insulin was infused during labour to maintain CBG concentrations at 3.9–5.6 mmol/litre. Forty-seven percent (36/76) of babies born to women who had CBG concentrations above 5 mmol/litre before birth developed neonatal hypoglycaemia (less than 1.7 mmol/litre) compared with 14% (6/42) of babies born to women with CBG concentrations less than 5 mmol/litre (P = 0.0003). [EL = 2++]

A prospective study included 233 women with insulin-requiring diabetes (77 with type 1 diabetes, 156 with type 2 diabetes).[344] On the day of birth all women received an intravenous infusion of 10% invert sugar (5% fructose, 5% glucose) at a rate of 125 ml/hour. The rate was adjusted if plasma glucose level was less than 2.8 mmol/litre. Intravenous insulin was administered with an infusion pump at a rate of 1–4 U/hour to maintain plasma glucose concentration at 3.3–5 mmol/ litre. Boluses of 2–5 units of regular insulin were given additionally if the plasma glucose level exceeded 5.5 mmol/litre. The incidence of neonatal hypoglycaemia (plasma glucose concentration less than 1.7 mmol/litre) was 16.5% (38 babies). Babies with plasma glucose concentration less than 1.7 mmol/litre received enteral feeds or intravenous glucose as dictated by their clinical condition. The degree of hypoglycaemia was mild and rarely required admission to intensive care or intravenous treatment. The mean intrapartum blood glucose level was significantly lower in mothers of babies without hypoglycaemia (P < 0.05). The authors reported that the best results were achieved when the desired glucose control was maintained for at least 8 hours before birth. [EL = 2++]

A standardised intravenous protocol for insulin and dextrose therapy in labour and birth was assessed in 25 women with insulin-treated diabetes.[345] Adjustments to insulin infusion rates were determined by trends in blood glucose as well as by absolute concentration. The protocol was as follows:

- nil by mouth until after the birth of the baby
- start intravenous dextrose 10% in 500 ml, 100 ml/hour via IMED® pump
- hourly blood glucose estimation by glucose meter
- insulin infusion by intravenous pump mounted onto the intravenous line, initially at 2 U/ hour when blood glucose more than 7 mmol/litre (50 U human soluble insulin in 50 ml, 0.9% saline, 2 ml/hour)
  - adjust insulin infusion rate to maintain blood glucose 4.0–7.0 mmol/litre according to glucose meter:
  - if less than 4.0 mmol/litre and not rising, then decrease by 1 U/hour to a minimum of
  - 0.5 U/hour
  - if more than 7.0 mmol/litre and not falling, then increase by 0.5 U/hour
- after delivery of the placenta:

    o halve the rate of insulin infusion, to a minimum of 0.5 U/hour

    o adjust as before to maintain blood glucose 4.0–7.0 mmol/litre

    o refer to medical record or contact diabetes team for advice about subcutaneous insulin dose before next main meal

    o stop intravenous fluids and insulin 30 minutes after subcutaneous insulin.

Blood glucose was maintained at 6.0 ± 1.8 mmol/litre for a mean of 6 hours (range 1–29 hours) before birth. Blood glucose at birth was 6.3 ± 2.1 mmol/litre. There was only one case of maternal hypoglycaemia. Neonatal hypoglycaemia (plasma glucose less than 2.0 mmol/litre) occurred in 11 babies. Babies with blood glucose less than 2.0 mmol/litre were all treated routinely with intravenous glucose for 3–24 hours with none showing symptoms of hypoglycaemia. Neonatal blood glucose correlated with maternal blood glucose at birth (r = −0.58, P < 0.01). Introduction of the protocol was associated with a decrease in the incidence of hypoglycaemia in babies born to women with diabetes from 68% to 39% (P < 0.01). [EL = 2++]

A study involving women with type 1 diabetes compared CSII (insulin pump therapy) (n = 28) with constant intravenous insulin infusion (n = 37).[346] Mean blood glucose during labour in women treated using CSII was 4.8 ± 0.6 mmol/litre (range 3.8–5.8). Mean blood glucose in women treated using constant intravenous insulin infusion was 7.2 ± 1.1 mmol/litre (range 5.6– 8.3, P < 0.025). In the constant intravenous insulin infusion group there were eight cases of neonatal hypoglycaemia (less than 1.7 mmol/litre), whereas in the CSII group there were no cases of neonatal hypoglycaemia (P < 0.05). Babies with hypoglycaemia were treated using intravenous glucose. [EL = 2++]

A prospective study of 85 women with gestational diabetes[347] (54 insulin-treated) was undertaken with the aim of assessing a standardised protocol for maintaining glycaemic control during labour and the effect of maternal glycaemic control during labour on neonatal hypoglycaemia (two or more glucose values less than 1.7 mmol/litre). The protocol consisted of: intravenous glucose (8.3 g/hr); intravenous insulin infusion by syringe pump adjusted according to hourly CBG measurements; and urine testing for ketone bodies. The target CBG range for metabolic control was 2.8–6.9 mmol/litre (ideally 3.3–6.1 mmol/litre). Mean CBG during labour was 4.7 ± 1.1 mmol/litre and in 82.3% of women CBG was within the desired range. Five babies developed hypoglycaemia. After logistic regression (HbA1c in third trimester, SGA, preterm birth, insulin treatment) maternal blood glucose in the last 2 hours of labour was associated with neonatal hypoglycaemia (P < 0.05). [EL = 2+]

An observational study[348] compared the effect of a policy change following an intensive effort to improve pre-pregnancy care and advice with a relaxation of targets for blood glucose control during labour. There was no relationship between neonatal blood glucose and HbA1c throughout the third trimester (r = −0.11), mean HbA1c throughout pregnancy (r = 0.10) or HbA1c at booking (r = 0.28). In period 1, neonatal hypoglycaemia was recorded in seven babies (less than 2.2 mmol/ litre; with intravenous glucose used in four), in period 2, neonatal blood glucose was measured as less than 2.2 mmol/litre in 19 babies; with intravenous glucose used in 14). Mean maternal blood glucose at birth was 7.7 ± 3.8 mmol/litre in the group with neonatal blood glucose levels less than 2.2 mmol/litre, compared with 4.9 ± 2.8 mmol/litre in all other women (P = 0.05). When maternal blood glucose was over 10 mmol/litre, the neonatal blood glucose was always low (1.3 ± 0.8 versus 2.5 ± 1.5 for all others; P < 0.02). [EL = 2+]

An observational study of 107 consecutive singleton pregnancies in women with type 1 diabetes[349] measured maternal HbA1c throughout pregnancy, maternal blood glucose throughout labour and birth and neonatal blood glucose. There was a significant negative correlation between neonatal blood glucose and mean maternal blood glucose in labour (r = −0.33, P < 0.001). When maternal blood glucose stayed within the target of 4.0–8.0 mmol/litre there was no relationship with neonatal blood glucose. When maternal blood

glucose was greater than 8.0 mmol/litre, neonatal blood glucose was less than 2.5 mmol/litre, in all except two women. If the maternal blood glucose was above 9.0 mmol/litre neonatal blood glucose was always less than 2.5 mmol/litre. [EL = 3]

6.3.1.2 Fetal distress

Two observational studies were identified that considered the effect of maternal blood glucose control during labour and birth on fetal distress. Both studies found maternal hyperglycaemia during labour to be associated with fetal distress.

A prospective study of 149 babies of women with type 1 diabetes[350] found perinatal asphyxia in 27% (40). Maximum maternal blood glucose during labour was higher in babies with perinatal asphyxia than in those without (9.5 ± 3.7 versus 7.0 ± 3.0, P < 0.0001). Perinatal asphyxia was also associated with gestational age and development of vasculopathy during pregnancy but not with vasculopathy before pregnancy, maternal age, duration of diabetes or White's classification of diabetes. [EL = 2++]

A study compared CSII (28 women with type 1 diabetes) with constant intravenous insulin infusion (37 women with type 1 diabetes).[346] Mean blood glucose during labour in women treated using CSII was 4.8 ± 0.6 mmol/litre (range 3.8–5.8). Mean blood glucose in women treated using constant intravenous insulin infusion was 7.2 ± 1.1 mmol/litre (range 5.6–8.3, P < 0.025). In the constant intravenous insulin infusion group there was acute fetal distress in 27% of cases and a caesarean section rate of 38%. In the CSII group there was fetal distress in 14.3% of cases (P < 0.001) and a caesarean section rate of 25% (P < 0.05). [EL = 2++]

6.3.1.3 Controlling glycaemia during labour and birth

An RCT investigated whether continuous intravenous insulin infusion provided a greater degree of intrapartum maternal glycaemic control in women with gestational diabetes than rotating between glucose-containing and glucose-free intravenous fluids.[351] There was no difference in mean intrapartum maternal CBG levels in the rotating fluids and intravenous insulin groups (5.77 ± 0.48 mmol/litre versus 5.73 ± 0.99 mmol/litre, P = 0.89). Neonatal hypoglycaemia (blood glucose less than 0.6 mmol/litre within the first 24 hours was found to be 6.7% in the rotating group and 19% in the continuous intravenous insulin infusion group, but the difference was not statistically significant. Birthweight, Apgar scores at 1 minute and 5 minutes, respiratory distress, shoulder dystocia, admission to the NICU, and hyperbilirubinaemia were also similar between the two treatments. The study suggests that in women with insulin-requiring gestational diabetes, continuous intravenous insulin infusion and a rotation of intravenous fluids between glucose- containing and glucose-free fluids achieve similar intrapartum glycaemic control. [EL = 1+]

A non-randomised study compared CSII (28 women with type 1 diabetes) with constant intravenous insulin infusion (37 women with type 1 diabetes).[346] Mean blood glucose during labour in women treated using CSII was 4.8 ± 0.6 mmol/litre (range 3.8–5.8). Mean blood glucose in women treated using constant intravenous insulin infusion was 7.2 ± 1.1 mmol/litre (range 5.6–8.3, P < 0.025). However, the lack of randomisation may have meant that women who used CSII during labour and birth were self-selected as those who had better glycaemic control.

6.3.1.4 Current practice

The CEMACH enquiry found sub-optimal glycaemic control during labour and/or birth was not associated with poor pregnancy outcome in women with pre-existing diabetes. Among women with poor pregnancy outcome 49% (79/162) were documented as having sub-optimal control in the first trimester compared with 48% (97/202) of the women with good pregnancy outcome. The enquiry panels identified cases of inappropriate intravenous insulin/dextrose regimen, delay in starting intravenous insulin/dextrose regimen, poor management of sliding

scale, sub- optimal blood glucose monitoring, hypoglycaemia due to clinical practice, poor management of hypoglycaemia and other clinical practice issues in both groups of women.33 [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that 47% of the women with type 1 diabetes and 41% of the women with type 2 diabetes had sub-optimal glycaemic control during labour and birth (P = 0.28). Ten percent of the women with type 1 diabetes and 29% of the women with type 2 diabetes were not given intravenous insulin and dextrose during labour and/or birth (P < 0.001).[33] [EL = 3–4]

6.3.1.5 Existing guidance

The NSF for diabetes recommends tight glucose control during labour to reduce the risk of neonatal hypoglycaemia.[20]

6.3.2 Evidence statement

Eight studies were found that showed that neonatal hypoglycaemia is more likely to occur in babies of women with high blood glucose concentration during labour and birth. Two studies found maternal hyperglycaemia during labour to be associated with fetal distress. Maintaining maternal blood glucose in the range 4–7 mmol/litre during labour and birth reduces the incidence of neonatal hypoglycaemia and reduces fetal distress.

An RCT found continuous intravenous insulin infusion and rotating between glucose-containing and glucose-free intravenous fluids resulted in similar maternal blood glucose levels in women with insulin-requiring gestational diabetes during labour and birth. A non-randomised comparative study found that CSII was associated with better glycaemic control in women with type 1 diabetes during labour and birth than was intravenous insulin infusion. However, the lackof randomisation in the study means that self-selection of CSII by women who were better at controlling their blood glucose cannot be ruled out.

6.3.3 From evidence to recommendations

Evidence shows that maintaining blood glucose in the range 4–7 mmol/litre during labour and birth reduces the incidence of neonatal hypoglycaemia and fetal distress. In formulating their recommendations, the GDG placed a high value on recommending that blood glucose be maintained in this range during labour and birth without being prescriptive about how it is maintained. This leaves the possibility for women who are able to maintain their blood glucose in the range 4–7 mmol/litre using MDI insulin injections or CSII to experience labour and birth without having intravenous insulin regimens. The GDG noted that these options may be associated with greater maternal satisfaction because of the psychological benefits of allowing women to take control of their diabetes during labour and birth, and the practicalities such as permitting greater mobility. However, no clinical studies were identified that evaluated the optimal method of maintaining glycaemic control during labour and birth. In the absence of such evidence the GDG's consensus view was that intravenous dextrose and insulin infusion should be considered for women with type 1 diabetes from the onset of established labour, and that intravenous dextrose and insulin infusion is recommended for women with diabetes whose blood glucose is not maintained between 4–7 mmol/litre.

6.3.4 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

6.3.5 Research recommendations

42. What is the optimal method for controlling glycaemia during labour and birth?

Why this is important

Epidemiological studies have shown that poor glycaemic control during labour and birth is associated with adverse neonatal outcomes (in particular, neonatal hypoglycaemia and respiratory distress). However, no randomised controlled trials have compared the effectiveness of intermittent subcutaneous insulin injections and/or CSII with that of intravenous dextrose plus insulin during labour and birth. The potential benefits of intermittent insulin injections and/or CSII over intravenous dextrose plus insulin during the intrapartum period include patient preference due to the psychological effect of the woman feeling in control of her diabetes and having increased mobility. Randomised controlled trials are therefore needed to evaluate the safety of intermittent insulin injections and/or CSII during labour and birth compared with that of intravenous dextrose plus insulin.

7 Neonatal care

7.1 Initial assessment and criteria for admission to intensive or special care

7.1.1 Description of the evidence

A number of morbidities present in babies born to women with diabetes (including pre-existing type 1 and type 2 diabetes and gestational diabetes). These include fetal macrosomia, infant respiratory distress syndrome, cardiomyopathy, hypoglycaemia, hypocalcaemia, hypomagnesaemia, polycythaemia and hyperviscosity. Hypoxia causes polycythaemia and hyperviscosity.[352] Thrombosis is a rare, but serious, complication necessitating admission to a NICU. Risk factors include maternal diabetes, maternal factors resulting in fetal growth restriction , polycythaemia and the use of intravascular catheters in preterm babies.353 Information on incidence and presentation of thrombosis is very limited and has been gathered mainly from case reports and case series.

While some of the morbidities listed above correct themselves within a period of few hours to a few weeks (e.g. transient tachypnoea normalises within 3 days of birth),[354] it is still important that treatment is provided promptly for those requiring it (e.g. hyaline membrane disease, for which babies may require surfactant, or respiratory and metabolic support).[354]

7.1.1.1 Incidence of neonatal morbidities

A cohort study[355] assessed the effect of rigorous management of type 1 diabetes during pregnancy on perinatal outcome by comparing 78 pregnant women with type 1 diabetes managed prospectively with 78 matched controls who did not have diabetes. The women with diabetes used insulin by infusion pump or split-dose therapy, with the goal of normalising fasting blood sugars and HbA1c. Women with type 1 diabetes had higher rates of preterm birth (31% versus 10%, P = 0.003), pre-eclampsia (15% versus 5%, P = 0.035) and caesarean section (55% versus 27%, P = 0.002). Complications of babies born to women with diabetes included LGA (41% versus 16%, P = 0.0002), hypoglycaemia (14% versus 1%, P = 0.0025), hyperbilirubinaemia (46% versus 23%, P = 0.0002) and respiratory distress (12% versus 1%, P = 0.008). Apgar scores and mortality rates were similar for the two groups. Congenital malformations occurred in 7.7% of babies of women with diabetes and 1.3% of controls (P = 0.05).

The incidence of respiratory distress syndrome and mortality was assessed in a cohort study[356] involving 23 babies selected from a total of 30 babies born to women with diabetes who developed hypoglycaemia after birth. These babies were divided into the following three groups: 12 babies treated with intravenous glucose; seven babies treated with long-acting epinephrine plus intravenous glucose; and four babies treated with long-acting epinephrine only. There were no significant differences in incidence of respiratory distress syndrome or mortality rates between the three groups. [EL = 2+]

A case–control study[357] investigated factors that contribute to neonatal hypoglycaemia in babies of women with diabetes. Timing of blood glucose levels, symptoms of hypoglycaemia and interventions provided were assessed. None of the 66 babies investigated developed symptomatic hypoglycaemia or required intravenous glucose. Nearly all the low blood glucose determinations (less than 1.7 mmol/litre) occurred in the first 90 minutes of life, which is the period of greatest risk of low blood glucose occurring in babies born to women with diabetes. [EL = 2+]

A cross-sectional study[322] assessed routes of delivery and pregnancy outcomes in 10369 births in the USA. Diabetes was associated with increased caesarean section rates,

resuscitation of babies with positive pressure ventilation and low Apgar scores (less than 3) at 1 minute and 5 minutes. [EL = 3]

Another cross-sectional study[358] assessed types and frequencies of complications occurring in babies of women with diabetes. Immediately after birth, babies of women with diabetes were admitted to a NICU and detailed maternal history and physical examination were performed to detect any congenital anomalies. The caesarean section rate was high, as was the rate of birth injuries among those who had vaginal birth. The number of babies with asphyxia, congenital anomalies, hypoglycaemia, hypocalcaemia and hyperbilirubinaemia was high. The overall mortality rate of 7.5% was high. The study recommended that women with diabetes should be offered regular antenatal care to maintain good glycaemic control during pregnancy, the birth should be attended by experienced paediatricians to minimise complications and when there is clinical evidence of macrosomia caesarean section should be offered to reduce birth injuries. [EL = 2−]

7.1.1.2 Neonatal assessment

No clinical studies were identified that addressed the assessments that babies of women with diabetes should undergo. The following evidence is drawn from two narrative non-systematic reviews.[354,359] [EL = 4]

7.1.1.3 Fetal macrosomia

The investigation of birth trauma in macrosomic babies of women with gestational diabetes has been described as necessary. Manifestations included fractures of the clavicle and/or humerus. Brachial plexus (Erb palsy), phrenic nerve or cerebral injuries were also reported. In cases where a fracture is suspected, a chest radiograph may be used to confirm the presence of fractures. The startle reflex could also be used to confirm the presence of fractures, as the baby may show an asymmetric reflex or limited use of the arm on the affected side.[359] As most fractures of this nature heal without treatment, admission to a NICU is probably not necessary. [EL = 4]

7.1.1.4 Respiratory distress

Use of chest radiographs has been suggested for babies displaying signs of respiratory distress syndrome. An enlarged heart or diffuse, fine granular densities are consistent with respiratory distress syndrome. Together with arterial blood gas results, the need for respiratory support and replacement surfactant therapy could be determined. Where left ventricular outflow obstruction was suspected, an echocardiogram was prescribed in order to prevent congestive heart failure.[359] [EL = 4]

7.1.1.5 Polycythaemia

For babies displaying clinical signs of polycythaemia (respiratory distress syndrome, apnoea, hepatomegaly, jitteriness, irritability, seizures, feeding intolerance, hypoglycaemia, decreased urine output), venous haematocrit measurements are indicated.[359] [EL = 4]

7.1.1.6 Hypocalcaemia

Signs and symptoms of hypocalcaemia include coarse tremors, twitching, irritability and seizures. These should indicate monitoring of serum calcium levels. If levels are 1.75 mmol/litre or more, calcium replacement should be started.[359] [EL = 4]

7.1.1.7 Hyperbilirubinaemia

Where there has been lethargy, delayed feeding, polycythaemia and birth trauma, bilirubin levels should be monitored.[359] A review addressing medical concerns in the neonatal period

described jaundice in the first 24 hours of life as pathological and requiring immediate evaluation and therapy as bilirubin in high concentrations is considered a cellular toxin.[354] [EL = 3]

7.1.1.8 Severe asphyxia

If severe asphyxia has occurred at birth, the presence of hypotonia, seizures, poor perfusion and/or absence of respirations in the baby should be assessed to determine whether endotracheal intubation and respiratory support is needed.[359][EL = 4]

7.1.1.9 Hypoglycaemia

The prevention and treatment of neonatal hypoglycaemia is addressed separately in Section 7.2.

7.1.2 Criteria for admission to intensive/special care

7.1.2.1 Amniotic fluid erythropoietin

A case–control study investigated whether chronic fetal hypoxia, as indicated by amniotic fluid erythropoietin (EPO) levels, was associated with neonatal complications in pregnancies complicated by type 1 diabetes.[360] An amniotic fluid sampled for EPO measurement was taken from 157 women with type 1 diabetes who gave birth by caesarean section before the onset of labour (one vaginal birth), either within 2 days of birth or at birth. EPO measurements were compared with those from 19 healthy, non-smoking women delivered by elective caesarean section with an uneventful singleton pregnancy producing a healthy newborn baby. The median amniotic fluid EPO level was significantly higher in the women with diabetes (14.0 mU/ml, range 2.0 to 1975, n = 155) than in control pregnancies (6.3 mU/ml, range 1.7 to 13.7, n = 19; $P < 0.0001$). Amniotic fluid EPO levels above 63.0 mU/ml were considered to indicate fetal hypoxia and these elevated values were observed in 14.1% of the women with diabetes who were divided into three groups: low EPO less than 13.8 mU/ml, intermediate EPO 13.8–63.0 mU/ml and high EPO more than 63.0 mU/ml. Newborn babies in the high EPO group were significantly more likely to be macrosomic ($P = 0.0005$) and acidotic ($P < 0.0001$) and had significantly lower pO2 levels than those in the intermediate and low EPO groups ($P < 0.0001$). Neonatal hypoglycaemia (blood glucose less than 2.0 mmol/litre more than 6 hours after birth; $P < 0.0001$), admission to neonatal intensive care ($P = 0.03$), cardiomyopathy ($P < 0.0001$) and hyperbilirubinaemia ($P = 0.002$) occurred significantly more often in the high EPO group than in the low EPO group. After adjusting for the effects of maternal age, maternal BMI, gestational age at birth, birthweight z-score, last amniotic fluid EPO level and last maternal HbA1c level, amniotic fluid EPO was the only variable to remain independently associated with low umbilical artery pH ($P < 0.0001$) and neonatal hypoglycaemia ($P = 0.002$). Low pO2 at birth was associated with amniotic fluid EPO ($P < 0.0001$) and birthweight z-score ($P = 0.004$). [EL = 2+]

7.1.2.2 Neonatal hypoglycaemia

A prospective cohort study investigated the frequency and risk factors for neonatal hypoglycaemia and long-term outcomes of promptly treated neonatal hypoglycaemia.[361] Of the 4032 babies born in the study hospital, 1023 were admitted to NICU. Ninety-four (9.18%) were evaluated as having hypoglycaemia. Evaluations were performed if symptoms such as hypothermia, apnoea, lethargy, poor feeding or seizures were observed, or if risk factors such as SGA, LGA, preterm birth, sepsis or the mother having diabetes were present. The cohort was followed for 24 months, during which time they were assessed neurologically and developmentally using the Bayley motor and developmental scales. The study found that 51.1% of babies were preterm (37 weeks or less), 34.1% of babies were born to women with pre-existing maternal diabetes or gestational diabetes and 12.8% were SGA. SGA babies

required the longest duration of intravenous dextrose infusion (5.16 days compared with 3.74 days for AGA babies). In 26.6% of the babies no known risk factors for hypoglycaemia were observed. Of the 48 babies undergoing Bayley's psychometric evaluations, two showed a motor deficit at 6 months and one showed a language deficit at 24 months. [EL = 2+]

7.1.2.3 Gestational age, respiratory distress syndrome and higher birthweight

A retrospective cohort study conducted in the USA over a 3 year period acquired data for 530 babies born to 332 women with gestational diabetes and 177 women with type 1 diabetes. The study found 47% (247) of babies were admitted to a NICU.[362] Seventy-six babies had a gestational age of 33 weeks or less, 22 babies had congenital malformations, ten were described as having miscellaneous conditions (apnoea, cardiac arrhythmias, poor feeding or neonatal depression), 103 babies with a gestational age of 34 weeks or more had respiratory distress syndrome and 32 babies had hypoglycaemia as the only diagnosis. For the 182 babies (34%) presenting with respiratory distress syndrome of varying severity, the highest rates (56%) were seen in women with type 1 diabetes which had been diagnosed before the age of 10 years, had had diabetes for 20 years or longer or had complications of diabetes, decreasing to 25% in babies of women with gestational diabetes requiring no insulin. Similarly, babies of women with gestational diabetes requiring no insulin had the lowest representation of LGA babies (25%), while those born to women with type 1 diabetes which had been diagnosed before the age of 10 years and had a duration of 20 years had the highest rate (62%). The frequency of SGA babies was equal among the classes. Seventy-four (14%) of the 530 babies had macrosomia and 57% (42/74) of this group were delivered by caesarean section. Among those delivered by caesarean section, there were 21 cases of hypoglycaemia, three of polycythaemia, one of hypocalcaemia and 12 of hyperbilirubinaemia. Thirty percent of macrosomic babies had respiratory distress syndrome. [EL = 2+]

Blood glucose levels were recorded for 514 babies. One or more hypoglycaemic episodes occurred in 27% (137) of these babies. While 90% of the babies responded rapidly to treatment, 10% had two or more episodes lasting several hours. Neonatal hypoglycaemia was similar among babies born to women with gestational diabetes requiring no insulin (23%), those with gestational diabetes requiring insulin (24%) and those with type 1 diabetes with age of onset 20 years or more, or a duration less of than 10 years with no vascular lesions (25%). The prevalence of neonatal hypoglycaemia was lower in these babies (P < 0.05) than the babies of women with type 1 diabetes with age of onset 10–19 years or duration 10–19 years with no vascular lesions (35%), the babies of women with type 1 diabetes which had been diagnosed before the age of 10 years, and the babies of women who had had diabetes for 20 years or longer or had complications of diabetes (38%). Thirty of the 137 babies with hypoglycaemia were born before 34 weeks of gestation, 55 were LGA, 50 were AGA and two were SGA. Among the 74 babies who were macrosomic, 21 were also hypoglycaemic. Of the 244 babies (46% of total group) assigned to 'well baby nurseries' for routine care and enteral feeding, 32 had hypoglycaemia.

The study found 5% (13) of the 276 babies who had their haematocrit assessed were polycythaemic (haematocrit 0.65 or more). Of the 530 babies, 25% (125) were treated for hyperbilirubinaemia and, of these, 61 were delivered at 33 weeks of gestation or less. The rate of treatment for non- diabetic, full-term babies delivered during the same 2 year period was 5%.

Of the 244 babies admitted to well-baby nurseries for routine care, 18% (43) were then transferred to the NICU (19 with respiratory distress syndrome as the main reason for transfer, 16 for treatment of hypoglycaemia, seven for respiratory distress syndrome plus hypoglycaemia and one for poor feeding). Advanced maternal diabetes and lower gestational age were shown by logistic regression to be the strongest predictors of subsequent NICU care. Logistic regression analysis also showed that after controlling for gestational age and

type of diabetes, breastfed babies were more likely to succeed with routine care and enteral feeding. [EL = 2+]

7.1.2.4 Myocardial hypertrophy and respiratory distress syndrome

A cross-sectional study looked at the association between poorly controlled maternal diabetes and myocardial hypertrophy.[363] Twelve neonates were admitted to NICU with respiratory distress and cardiomegaly. Ten babies were macrosomic and had myocardial hypertrophy as determined by echocardiograph. Two of these babies died from cardiorespiratory failure within 48 hours of birth. Two babies were AGA and had cardiomegaly resulting from ventricular dilation in association with hypoglycaemia and acidaemia. Of the surviving babies, 80% (8/10) had clinical findings suggesting respiratory distress syndrome. The presence of hyaline membranes at autopsy of the other two babies lends support to an association between respiratory distress syndrome and myocardial hypertrophy. [EL = 3]

7.1.2.5 Gestational age and mode of birth

A clinical audit was conducted at the National Women's Hospital in New Zealand364 which serves a multi-ethnic population with a high background prevalence of type 2 diabetes. In total 136 babies of women with diabetes were admitted to NICU. Twenty-nine percent (112/382) of the babies of women with gestational diabetes were admitted and 40% (24/60) of the babies of women with type 2 diabetes were admitted. Fifty-six percent (58/104) of the gestational diabetes was reclassified as normal, IGT or type 2 diabetes after postpartum 75 g OGTTs. Infant outcomes according to maternal antenatal and postpartum diagnoses were recorded. The study found 46% (63/136) babies were delivered preterm (before 37 weeks). Women with gestational diabetes that was reclassified postpartum as IGT or type 2 diabetes accounted for the highest rates of preterm babies (86% [12/14] and 63% [12/19], respectively). The rate of emergency lower segment caesarean section in women with gestational diabetes or type 2 diabetes was 25%. The rate of emergency lower segment caesarean section of women with gestational diabetes or type 2 diabetes whose babies were admitted to NICU was 38% (52/136). When a similar comparison was made for preterm birth the rates were 19% compared with 46% (63/136). The most common indication for admittance to NICU was hypoglycaemia, which was documented in 51% of the babies. This was followed by respiratory distress in 40% of babies. Rates of respiratory distress in the preterm babies and term babies were not significantly different (39% [26/67] versus 43% [31/70], P = 0.34). A third of women with type 2 diabetes antenatally or postpartum had babies weighing more than 4000 g. These birth weights were significantly higher than for the IGT group (P < 0.05) and significantly more common than in the IGT or normal group (P < 0.05). [EL = 2+]

7.1.3 Current practice

The CEMACH enquiry covered neonatal care of term babies born to women with pre-existing type 1 or type 2 diabetes.[33] In the 112 babies selected for the neonatal enquiry that had medical records available, 70 were admitted to a postnatal ward, transitional care unit, stayed on the labour ward or in a maternal dependency unit and 42 were admitted to a NICU for special care. The three main indications for admission to a NICU were a hospital policy of routine admission of healthy babies of women with diabetes 29% (12/42), asymptomatic hypoglycaemia in a healthy baby 26% (11/42) and a clinical need for admission such as poor feeding or respiratory problems 43% (18/42). The enquiry panels assessed that 57% (24/42) of the admissions were unavoidable and that subsequent care of 63% (15) of the babies was compromised, especially in the area of feeding (50%, 12/24 babies). There was evidence of a clear written care plan for 73% (51/70) of babies who remained with their mothers and 57% (24/42) of babies admitted to a NICU. The care plan was not fully followed for 35% (18/51) of babies remaining with their mothers; aspects of the care plan that were not followed included

blood glucose management, feeding and temperature. The enquiry also discussed the importance of early skin-to-skin contact between babies and their mothers (see Section 7.2) and recommended that all units where women with diabetes give birth should have written policy for management of the baby and that the policy should assume that babies will remain with their mothers in the absence of complications. [EL = 3–4]

A 2002 CEMACH audit of units expected to provide maternity care for women with diabetes in England, Wales and Northern Ireland reported that 30% (64/213) had a policy of routinely admitting babies of women with diabetes to the neonatal or special care unit.[32] [EL = 3]

7.1.4 Existing guidance

The NSF for diabetes[20] recommends that 'Neonatal intensive care is only indicated for babies who display persistent hypoglycaemia after 3 hours of age.'

7.1.5 Evidence statement

Five observational studies have reported on the incidence of neonatal morbidity in babies born to women with diabetes. Complications reported in these studies included asphyxia, birth trauma (e.g. shoulder dystocia), congenital malformations, hyperbilirubinaemia, hypoglycaemia, hypocalcaemia, LGA, respiratory distress syndrome and associated mortality.

No clinical studies were identified in relation to neonatal assessment that babies of women with diabetes should undergo, but two narrative non-systematic reviews described the clinical signs of the most frequently occurring neonatal complications in babies of women with diabetes.

A further four observational studies and a clinical audit investigated neonatal complications (including fetal hypoxia, hypocalcaemia, hypoglycaemia, macrosomia, myocardial hypertrophy (hypertrophic cardiomyopathy), polycythaemia and respiratory distress syndrome) and indications for admission to a NICU for babies of women with pre-existing type 1 or type 2 diabetes and gestational diabetes. None of the studies reported incidence of hypoxic ischaemic encephalopathy or hypomagnesaemia, although babies of women with diabetes are believed to be at increased risk of these complications.

One of the observational studies reported that persistent or recurrent hypoglycaemia in the neonatal stage can lead to neurodevelopmental deficits later in life. The authors of the study recommended that high-risk babies be screened at regular intervals in the first 48 hours of life if not being fed, or before the first three or four feedings, and in the presence of clinical signs of hypoglycaemia.

Other observational studies showed that prematurity and birth by emergency caesarean section were predictors for NICU admission in women with type 2 diabetes and those with gestational diabetes. Several of the studies suggested that babies of women with diabetes should be closely monitored and admitted to intensive care only in unavoidable circumstances where there are clinical signs of hypoglycaemia and/or respiratory distress, thus avoiding unnecessary separation of mothers and babies.

The clinical audit reported that the most frequent indications for admission to NICU were hypoglycaemia and respiratory distress syndrome, and one of the observational studies reported that the prevalence of these complications was higher with increasing duration of diabetes.

Cost-effectiveness

The effectiveness of criteria for admission to neonatal intensive/special care for babies of women with diabetes was identified by the GDG as a priority for health economic analysis.

The NSF for diabetes[20] recommends that admission to a NICU should be made only for babies with persistent hypoglycaemia. However, the CEMACH audit reported that 30% of units still routinely admit babies of mothers with diabetes to the neonatal or special care unit and that the most frequent reasons for admission to a NICU were routine policy and asymptomatic hypoglycaemia. Thus no health economic modelling is needed to demonstrate that reinforcing the NSF recommendation, to keep babies with their mothers except when there is a clinical reason to separate them, represents a cost saving to the NHS.

7.1.6 From evidence to recommendations

Evidence shows that birth trauma, congenital malformations (cardiac and central nervous system), hyperbilirubinaemia, hypocalcaemia, hypoglycaemia, hypomagnesaemia, myocardial hypertrophy (hypertrophic cardiomyopathy), neonatal encephalopathy, polycythaemia and hyperviscosity, and respiratory distress (several of which are potentially life-threatening) are more prevalent in babies of women with pre-existing diabetes and gestational diabetes. Healthcare professionals assessing such babies should, therefore, be competent to recognise and manage these conditions and women with diabetes (including gestational diabetes) should be advised to give birth in hospitals where advanced neonatal resuscitation skills are available 24 hours a day.

The GDG's view is that blood glucose testing should be carried out routinely (at 2–4 hours after birth) for babies of women with diabetes because of the risk of complications arising from asymptomatic hypoglycaemia (see Section 7.2). However, blood tests for polycythaemia, hyperbilirubinaemia, hypocalcaemia and hypomagnesaemia, and investigations for congenital heart malformations and cardiomyopathy should be reserved for babies with clinical signs of these complications, thus avoiding unnecessary investigations, which will represent cost savings to the NHS and should provide reassurance for parents.

Babies of women with diabetes should be kept with their mothers unless there is a clinical complication or abnormal clinical signs that warrant admission for intensive or special care, in accordance with the recommendations contained in the NSF for diabetes,[20] thus bringing cost savings to the NHS and maximising the opportunity for early skin-to-skin contact between babies and their mothers and initiation of breastfeeding (see Section 7.2).

Some babies with clinical signs of the conditions listed above may be cared for in a transitional care unit, depending on local guidelines, facilities and care pathways. Where such facilities are unavailable, babies with these conditions should be admitted to a neonatal unit.

Neonatal metabolic adaptation in babies of women with diabetes is generally completed by 72 hours of age. Transfer to community care is not recommended before 24 hours and not before healthcare professionals are satisfied that the baby is maintaining blood glucose levels and has developed good feeding skills because of the risk of recurrent hypoglycaemia in the early neonatal period. Early community midwifery support for these babies should be more intense than average.

7.1.7 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

7.1.8 Research recommendations

There were no research recommendations relating to the initial assessment of babies and criteria for admission to intensive/special care.

7.2 Prevention and assessment of neonatal hypoglycaemia

7.2.1 Description of the evidence

The working definition for neonatal hypoglycaemia is blood glucose less than 2.6 mmol/litre.[193,365,366] This threshold is not used to diagnose the condition, but rather to indicate the level at which intervention (additional feeding and, if this does not reverse the hypoglycaemia, intravenous dextrose) should be considered. It is based on a study that found adverse neurodevelopmental outcomes to be associated with repeated values below this level.[367] The study involved 661 preterm babies and used multiple regression to show that reduced developmental scores were associated independently with plasma glucose concentration less than 2.6 mmol/litre. [EL = 2+]

A consensus statement[368] discussed the definition of neonatal hypoglycaemia. The statement considered term babies, babies with abnormal clinical signs, babies with risk factors for compromised metabolic adaptation, preterm babies and babies receiving parenteral nutrition. Close surveillance should be maintained in babies with risk factors for

compromised metabolic adaptation if the plasma glucose concentration is less than 2.0 mmol/litre; at very low concentrations (1.1–1.4 mmol/litre) an intravenous glucose infusion is indicated to raise the glucose level above 2.5 mmol/litre. [EL = 4]

The characteristics of neonatal hypoglycaemia in babies of women with diabetes are very early onset (first hour after birth), generally asymptomatic, non-recurrent and good response to intravenous dextrose.368

7.2.1.1 Early feeding

Two studies were found that investigated the effect of timing of first feed on blood glucose levels. The studies were undertaken in the 1960s when delaying the initial feed was common.

The first study compared 27 preterm babies allocated to an 'early fed' group (fed with formula from 6 hours of age) with 41 babies fasted for 72 hours.[369] At 72 hours 24/41 babies in the fasted group had blood glucose levels below 1.4 mmol/litre. In the early fed group no babies had blood glucose values below this level. Statistical significance was not reported. [EL = 2+]

The second study compared 118 preterm babies fed at 3 hours with undiluted breast milk with 121 fed at a later stage, usually at 12 hours. There were no cases of symptomatic hypoglycaemia in the early fed group compared with four cases in the later fed group. Blood sugar estimation was introduced in phase three of the trial. The lowest level was less than 1.1 mmol/litre in 5/44 in the 'immediate fed' group compared with 10/54 in the 'later fed' group.[370] Statistical significance was not reported. [EL = 2+]

7.2.1.2 Frequent feeding

One study was identified that looked at the effect of frequency of initial feeds on blood glucose levels.

The study was a cross-sectional study of 156 term babies.[371] A multiple regression analysis with method of feed, between-feed interval, volume of feed and postnatal age as independent variables found only between-feed interval (minutes) to be significantly correlated with blood glucose concentration ($B = -0.003$, $SE = 0.001$, $\beta = -0.32$, $P < 0.05$). [EL = 2+]

7.2.1.3 Breastfeeding

Ten studies were found that had implications for choice of feeding method.

The first study compared 45 breastfed babies with 34 formula-fed babies.[372] The babies were 6 days old and matched for gestation and birthweight. Breastfed babies had significantly higher levels of ketones. [EL = 2+]

The second study compared 71 breastfed babies with 61 formula-fed babies.[371] All babies were term babies less than 1 week old. Breastfed babies had significantly lower mean blood glucose concentration ($P < 0.05$) and significantly higher ketone body concentrations ($P < 0.001$). Breastfed babies had higher total gluconeogenic substrate concentrations ($P < 0.01$). [EL = 2+]

A cohort study investigated the glucose concentration of breast milk of women with diabetes and its relationship with the quality of metabolic control.[373] The study involved 11 women with type 1 diabetes and 11 age-matched women without diabetes. The women with diabetes had intensified insulin treatment and their average HbA1c values were significantly higher than those in women without diabetes ($8.1 \pm 0.9\%$ versus $6.2 \pm 0.5\%$, $P < 0.01$). The glucose concentration of breast milk taken from women with diabetes did not differ from that of women without diabetes (0.68 ± 0.50 versus 0.66 ± 0.55 mmol/litre). No correlation was

found between the maternal blood glucose (HbA1c) and the glucose concentration of breast milk. [EL = 2−]

A prospective cohort study[374] investigated whether children born to women with diabetes were at increased risk of developing obesity and IGT in childhood. A total of 112 children of women with diabetes (type 1 diabetes, n = 83 and gestational diabetes, n = 29) were evaluated prospectively for impact of ingestion of either breast milk from a woman with diabetes or banked donor breast milk from women without diabetes during the early neonatal period (days 1–7 of life) on relative body weight and glucose tolerance at a mean age of 2 years. There was a positive correlation between the volume of breast milk from women with diabetes ingested and risk of overweight at 2 years of age (OR 2.47, 95% CI 1.25 to 4.87). In contrast, the volume of banked donor breast milk from women without diabetes ingested was inversely correlated to body weight at follow-up (P = 0.001). Risk of childhood IGT decreased by increasing amounts of banked donor breast milk ingested neonatally (OR 0.19, 95% CI 0.05 to 0.70). Stepwise regression analysis showed volume of breast milk from women with diabetes to be the only significant predictor of relative body weight at 2 years of age (P = 0.001). The results suggest that early neonatal ingestion of breast milk from women with diabetes may increase the risk of becoming overweight and, consequently, developing IGT during childhood. [EL = 2+]

A prospective cohort study[375] investigated whether intake of breast milk of women with diabetes during the late neonatal period and early infancy influenced subsequent risk of overweight (adipogenic) and IGT (diabetogenic) in children born to women with diabetes. One hundred and twelve children born to women with diabetes were evaluated for influence of ingesting their mother's breast milk during the late neonatal period (second to fourth neonatal week) and early infancy on relative body weight and glucose tolerance in early childhood. Exclusive breastfeeding was associated with increased childhood relative body weight (P = 0.011). Breastfed children of women with diabetes had an increased risk of overweight (OR 1.98, 95% CI 1.12 to 3.50). Breastfeeding duration was also positively related to childhood relative body weight (P = 0.004) and 120 minute blood glucose during an OGTT (P = 0.022). However, adjustment for the volume of breast milk from women with diabetes ingested during the early neonatal period (i.e. the first week of life), eliminated all these relationships with late neonatal breastfeeding and its duration. No relationship was observed between maternal blood glucose in the middle of the third trimester and neonatal outcomes. The study suggests that neither late neonatal breast milk intake from women with diabetes nor duration of breastfeeding has an independent influence on childhood risk of overweight or IGT in children born to women with diabetes. The first week of life appears to be the critical window for nutritional programming in children of ingestion of breast milk from women with diabetes. [EL = 2+]

Another cohort study[376] investigated whether late neonatal ingestion of breast milk might independently influence neurodevelopment in 242 children of women with diabetes. There was no impact of ingestion of breast milk of women with diabetes on psychomotor parameters, but it negatively influenced onset of speaking with children of women with diabetes who were fed solely on breast milk taking the longest time to initiate speech. Adjusting for the amount of breast milk ingested during the early neonatal period weakened the hazard ratio towards non- significance. The data suggest that neonatal ingestion of breast milk of women with diabetes, particularly during the first week of life, may delay speech development, an important indicator of cognitive development. [EL = 2++]

Another cohort study investigated the extent to which early breastfeeding or exposure to cow's milk affected psychomotor and cognitive development in children of women with diabetes.[377] Children of women with diabetes with early breast milk ingestion achieved early psychomotor developmental milestones (lifting head while prone, following with eyes; P = 0.002). However, children who had ingested larger volumes of milk of women with diabetes had a delayed onset in speaking compared to those with lower milk intake (P = 0.002). The data suggest that ingesting larger volumes of milk of women with diabetes may normalise

early psychomotor development in babies of these women, but may delay onset of speaking. [EL = 2++]

A systematic review[378] summarised the clinical evidence relating a short duration of breastfeeding or early cow's milk exposure to the development of type 1 diabetes. People with type 1 diabetes were more likely to have been breastfed for less than 3 months during their infancy (pooled OR 1.43, 95% CI 1.15 to 1.77) and to have been exposed to cow's milk before 4 months (pooled OR 1.63, 95% CI 1.22 to 2.17) compared to those without diabetes. The study suggests that early exposure to cow's milk may be an important determinant of subsequent type 1 diabetes and may increase the risk approximately 1.5 times. [EL = 2++]

Another systematic review[379] evaluated the relationship between early infant diet and the risk of developing type 1 diabetes in later life via a meta-analysis of 17 case–control studies involving 21 039 people who were either breastfed or introduced early to cow's milk. The effect of exposure to breast milk substitutes on developing type 1 diabetes was small. [EL = 2++]

A case–control study investigated the association between the type of feeding in infancy and the development of type 1 diabetes.[380] The study involved 100 children with type 1 diabetes and 100 children without diabetes matched for sex and age. Information on feeding patterns during the first year of life was collected using a questionnaire. A larger proportion of children with diabetes had been breastfed. There was no clear difference between children with diabetes and those without diabetes in terms of duration of breastfeeding (children with diabetes, median duration 3 months; children without diabetes, median duration 2 months). The data do not support the existence of a protective effect of breastfeeding on the risk of type 1 diabetes, or that early exposure to cow's milk and dairy products influences the development of type 1 diabetes. [EL = 2+]

7.2.1.4 Barriers to breastfeeding in women with diabetes in pregnancy

One study was identified that compared breastfeeding initiation and maintenance in 33 women with type 1 diabetes to those of 33 women in a control group and 11 women in a reference sample.[381] The control group consisted of women without diabetes selected using gestational age at delivery, method of delivery, sex of baby and prior lactation experience. The reference group consisted of women without diabetes who were within 90–110% of ideal body weight prior to conception, had uncomplicated pregnancies and delivered vaginally. The study found women with diabetes were more likely to experience difficulties establishing and continuing breastfeeding than control and reference groups. All differences were significant (P < 0.05). The difference between groups was attributed to differences in postpartum care. Hospital protocol placed all babies of women with diabetes in the neonatal unit after birth for monitoring for hypoglycaemia. This meant that women with diabetes saw their babies the least amount of time in the first 3 days postpartum, waited the longest to begin breastfeeding their babies and breastfed their babies fewer times. Other possible contributory factors were that 70% of the women with diabetes had undergone caesarean section and that 30% of the babies of women with diabetes were macrosomic. Women with diabetes cited baby sleepiness as the most common baby- feeding problem. A sleepy baby was not identified as a problem by any of the women in the control group and by only one woman in the reference group. [EL = 2+]

A case–control study[382] investigated factors influencing the initiation and maintenance of breastfeeding in 22 women with type 1 diabetes and 22 women without diabetes. Diabetes was not a principal factor in the decision to breastfeed or bottle-feed for the majority of the women. Women who considered diabetes in their decision to breastfeed had on average 2 years more of education than those who did not (14.82 years versus 12.94 years). Although the women did not perceive diabetes as influencing their breastfeeding experiences, they found that maintaining good control of diabetes required greater effort and flexibility during breastfeeding. [EL = 2+]

7.2.1.5 Banking colostrum before birth

Two publications were identified in relation to production of colostrum from women with diabetes and banking colostrum before birth for use in the neonatal period.

A cohort study compared the composition of macro- and micronutrients in milk from six women with tightly controlled type 1 diabetes (median glycosylated haemoglobin concentrations at parturition of 5.2% (range 4.9–5.3%) and 6 weeks later of 6.1% (range 5.0–6.3%), reference range 5.0–6.4%) with that from five women without diabetes.383 Milk samples were collected halfway through a single breastfeed at days: 3–5 (colostrum); 7, 9 and 10 (transitional milk); and 12, 15, 17, 21, 25, 29 and 35 (mature milk). There were no differences between the two groups in terms of concentrations of macronutrients (triglycerides, lactose and protein), cholesterol, glucose or myoinositol, nor in fatty acid composition. The duration of colostrum lactation was the same for women with diabetes and those without diabetes (3–5 days in both groups). [EL = 2−]

A narrative non-systematic review considered expressing and banking colostrum antenatally for use in the neonatal period.384 The review suggested that women with conditions that may delay breastfeeding and those who wish to lessen known familial health problems for their expected babies (including women with type 1 diabetes or gestational diabetes) would benefit from antenatal expression of colostrum. The risk of nipple stimulation initiating oxytocin release and, therefore, preterm contractions, labour and preterm birth was discussed and a protocol for expressing and storing colostrum was suggested. The review concluded that expressing and storing colostrum is advantageous to babies and confidence building for women and should, therefore, be supported for any condition which healthcare professionals consider to be relevant. [EL = 4]

7.2.1.6 Testing for neonatal hypoglycaemia

A systematic review by the WHO366 found that screening for hypoglycaemia using glucose oxidase-based reagent strips had poor sensitivity and specificity. The report recommended that 'less frequent but more accurate laboratory or ward-based glucose electrode measurements among babies at risk are preferable'.

7.2.1.7 Intravenous dextrose for neonatal hypoglycaemia

There is a consensus that intravenous dextrose should be administered for symptomatic hypoglycaemia and for asymptomatic hypoglycaemia that fails to respond to feeding.366,386,387 However, no clinical studies were identified in relation to evaluation of protocols for the treatment of neonatal hypoglycaemia using intravenous dextrose.

7.2.1.8 Current practice

The CEMACH enquiry33 reported that the opportunity for early skin-to-skin contact after birth was achieved in 29% (30) of the 102 babies whose medical records were available. In eight cases, skin-to-skin contact was not possible due to the condition of the woman and/or the baby. Ninety-five percent of babies remaining with their mothers received their first feed on the labour ward compared with 50% of those admitted to a neonatal unit (P < 0.001). Twenty-six percent (29/112) of women received help with breastfeeding within 1 hour of birth (34% of women on labour wards and 12% of women in the neonatal unit). Thirty-one percent of women whose babies were admitted to the neonatal unit had documented evidence in their medical records that they were shown how to breastfeed and maintain lactation. Infant formula was given at the first feed for 63% (67/106 babies) and this was the first choice for women in 46% (32/70) of cases. Breast milk was the first feed for 50% (34/68) of babies that remained with their mothers and 21% (8/38%) of babies in the neonatal unit (P = 0.001). The first feed given was not the mother's intended type of feed for 28% (27/96) of babies (16% of

women who stayed with their babies and 50% of those admitted to the neonatal unit, P < 0.001). [EL = 3–4]

CEMACH undertook a descriptive study of all pregnancies of women with pre-existing diabetes who gave birth or booked between 1 March 2002 and 28 February 2003.2 The study found that 40.1% of all babies (1382/3451) were fed within 1 hour and 78.8% (2717/3451) by 4 hours. Among term babies 46.5% (1031/2216) were fed within 1 hour and 87.7% (1837/2216) within 4 hours. Exclusive breastfeeding was the choice at birth for 53% (1762/3342) of women with pre-existing diabetes compared with 69% in the general population. At 28 days after birth the proportion of exclusively breastfed babies was 23.8%, half the proportion who had intended to breastfeed at birth. A history of low blood glucose alone was the main reason (36.7%) for giving term babies of women with diabetes supplementary milk or glucose. In 9% of cases babies were given supplementary milk or glucose routinely according to local practice, possibly compromising establishment of breastfeeding. Of the 3451 babies in the study, 83.2% were tested within 6 hours and 47.3% were tested within 1 hour. Testing this early may, however, simply detect the normal drop in blood glucose that can be expected after birth. One-third of term babies were admitted to a neonatal unit for special care. Examining the reasons for admission suggested that many (67%) were avoidable. [EL = 3]

The CEMACH enquiry[33] reported that neonatal blood glucose testing was mainly carried out using reagent strips. It supported the WHO's recommendation that reagent strip testing is unreliable and recommended that when considering the diagnosis of hypoglycaemia at least one laboratory value should be obtained. The enquiry also recommended that women with diabetes should be informed antenatally of the beneficial effects of breastfeeding on metabolic control for them and their babies and that blood glucose testing performed too early should be avoided in well babies without signs of hypoglycaemia. [EL = 3–4]

A standard textbook of neonatology[388] supports this evidence.

7.2.2 Existing guidance

The NSF for diabetes advises that babies born to women with diabetes should be fed as soon as possible after birth.[20] It also recommends breastfeeding for babies of women with diabetes, but that women should be supported in the feeding method of their choice. [EL = 4]

The NICE guideline for routine postnatal care recommends that women should be encouraged to have skin-to-skin contact with their babies as soon as possible after birth and that initiation of breastfeeding should be encouraged as soon as possible after birth and ideally within 1 hour.[11]

7.2.3 Evidence statement

The blood glucose concentration used to guide intervention for neonatal hypoglycaemia (i.e. additional feeding and, if this does not reverse hypoglycaemia, intravenous administration of dextrose) is 2.6 mmol/litre. Close surveillance should be maintained in babies with risk factors for compromised metabolic adaptation if the plasma glucose concentration is less than 2.0 mmol/litre; at very low concentrations (1.1–1.4 mmol/litre) an intravenous glucose infusion is indicated to raise the glucose level above 2.5 mmol/litre.

Two studies showed that early feeding of babies was associated with lower incidence of hypoglycaemia than late feeding (more than 12 hours after birth). However, these studies involved preterm babies who may demonstrate different metabolic adaptation to term babies.

Another study showed between-feeding interval to be correlated with blood glucose levels, suggesting that frequent feeding should be encouraged to prevent neonatal hypoglycaemia.

Three studies relating to choice of infant-feeding method for women with diabetes suggested that: breastfeeding may enhance ketogenesis and that ketones may be an important alternative to glucose for brain metabolism in the neonatal period; breastfeeding babies of women with diabetes was not associated with increased exposure of the babies to high glucose levels; and, where possible, separation of mother and baby should be avoided to enable early feeds, frequent feeds and breastfeeding, with the possibility that supplementary feeding with infant formula may be required for women with diabetes who breastfeed. However, the first of these studies involved 6-day-old babies and therefore has limited relevance to hypoglycaemia in babies of women with diabetes, who are at greatest risk of hypoglycaemia in the first 12 hours.

A further seven observational studies, including two systematic reviews of observational studies, examined associations between feeding method and long-term outcomes. Three of the studies showed that obesity, IGT and impaired cognitive development were associated with ingestion of breast milk from women with diabetes. However, the two systematic reviews, which showed an association between breastfeeding and subsequent development of diabetes, were not specific to children of women with diabetes.

Two studies reported that initiation and maintenance of breastfeeding was more difficult for women with diabetes because of routine separation of babies from their mothers at birth or clinical reasons for separation such as the woman having undergone caesarean section or the baby having macrosomia. Although diabetes was not a major factor in deciding whether to breastfeed, women with diabetes found that maintaining good control of diabetes required greater effort and flexibility during breastfeeding. These findings suggest that, where possible, separation of the mother and baby should be avoided to facilitate early, frequent feeds and breastfeeding. Supplementary feeding with infant formula may be required for women with diabetes who breastfeed.

No clinical studies were identified in relation to the potential benefits of expressing and storing colostrum antenatally for the purposes of supporting early feeding to prevent hypoglycaemia in babies of women with diabetes.

A systematic review by the WHO noted low sensitivity and specificity of reagent strip blood glucose testing to identify neonatal hypoglycaemia and recommended laboratory or ward-based glucose electrode measurements for babies at risk of neonatal hypoglycaemia.

No clinical studies were identified in relation to the evaluation of protocols for treatment of neonatal hypoglycaemia using intravenous dextrose.

7.2.4 From evidence to recommendations

In the absence of high-quality evidence, the GDG's recommendations for the prevention and treatment of neonatal hypoglycaemia are based on group consensus. The GDG's view is that all maternity units should have a local written protocol for the prevention, detection and management of hypoglycaemia in babies of women with diabetes. Breastfeeding is recommended to prevent neonatal hypoglycaemia (by promoting successful metabolic adaptation) alongside other known benefits. Early commencement of breastfeeding is more important in babies of women with diabetes because of the risk of neonatal hypoglycaemia and is encouraged by skin-to-skin contact. Babies of women with diabetes should, therefore, feed as soon as possible after birth and at frequent intervals thereafter. While the target level for blood glucose is 2.6 mmol/litre, the GDG has set the threshold for initiating intravenous administration of dextrose at 2.0 mmol/litre on two consecutive readings, despite maximal support for feeding. Babies of women with diabetes should not be treated with invasive procedures (such as tube feeding or intravenous dextrose) unless they have clinical signs of hypoglycaemia or unless their blood glucose values persist below the threshold for initiating intravenous dextrose.

Blood glucose measurements should be obtained using ward-based glucose electrode or laboratory analysis because these have greater sensitivity and specificity than reagent strip testing. In making this recommendation the GDG noted the findings of the CEMACH enquiry, which reported that reagent strip testing is still commonplace. The GDG's view is that blood glucose should be tested before feeding the baby.

7.2.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

7.2.6 Research recommendations

43. Is systematic banking of colostrum antenatally of any benefit in pregnancies complicated by diabetes?

Why this is important

Babies of women with diabetes are at increased risk of neonatal hypoglycaemia and may need frequent early feeding to establish and maintain normoglycaemia. Additionally, the opportunity for early skin-to-skin contact and initiation of breastfeeding is not always achieved in pregnancies complicated by diabetes because of the increased risk of neonatal complications requiring admission to intensive/special care. Antenatal expression and storage of colostrum may, therefore, be of benefit to babies of women with diabetes. There have been no clinical studies to evaluate the effectiveness of antenatal banking of colostrum in women with diabetes. Randomised controlled trials are needed to determine whether this practice is clinically and cost-effective. Encouraging women with diabetes to express and store colostrum before birth might be viewed as an additional barrier to breastfeeding in this group of women who already have lower breastfeeding rates than the general maternity population. There is also a putative risk of precipitating uterine contractions through antenatal expression of colostrum and an accompanying release of oxytocin. These factors should be explored in the randomised controlled trials.

8 Postnatal care

8.1 Blood glucose control, medicines and breastfeeding

8.1.1 Description of the evidence

Two small cohort studies and a case series were identified that considered the effect of breastfeeding on glycaemic control in women with diabetes. Two cohort studies were identified that considered the effects of oral hypoglycaemic agents on breast milk and infant hypoglycaemia. Factors affecting the choice between breastfeeding and bottle-feeding for babies of women with diabetes are considered in Section 7.2.

8.1.1.1 Insulin

The first cohort study involved 36 women with type 1 diabetes.[389] Breastfeeding was initiated by 15 women in the first 24 hours. At 7 days and 1 month postpartum 28 women were breastfeeding and at 2 months postpartum 24 women were breastfeeding. On discharge from hospital women were prescribed an insulin regimen two-thirds of the third-trimester requirements and advised to adjust pre-meal insulin doses to glycaemic response. Women were advised to keep to regular meal times and eat before the baby's feeding times. If this was not possible, women were advised to have a glass of juice (during the day) or milk (at night). The study compared glycaemic control and insulin requirements of breastfeeding and bottle-feeding women over four periods: preconception, the first 7 days postpartum, the first month postpartum and the second month postpartum. In all women mean blood glucose values were significantly lower during the first week postpartum (6.7 ± 1.1 mmol/litre) than at preconception (7.7 ± 0.9 mmol/ litre) or during the second month postpartum (7.6 ± 1.3 mmol/litre). The percentage of blood glucose readings below 3 mmol/litre did not differ during the four periods. In all women insulin requirements were significantly lower during the first week postpartum (0.56 ± 0.15 U/kg/day) than at preconception (0.68 ± 0.16 U/kg/day) and they remained significantly lower over the first and second months postpartum (0.56 ± 0.15 U/kg/day and 0.56 ± 0.11 U/kg/day, respectively). There was no difference in glycaemic control or insulin requirements between breastfeeding and bottle-feeding women, with the exception of mean blood glucose values during the first week postpartum which reached borderline significance (6.6 ± 0.6 versus 7.0 ± 0.9 mmol/ litre, P = 0.050). Fewer hypoglycaemic episodes in breastfeeding women were associated with breastfeeding sessions (4.0 ± 3.5) than at other times (12.2 ± 7.1, P = 0.002). [EL = 2+]

The second cohort study followed 30 women with type 1 diabetes from birth to 6 weeks postpartum.[390] six women breastfed exclusively, nine women stopped breastfeeding before 6 weeks and 14 women bottle-fed. Insulin dosages did not differ between the three groups. Six week postpartum FBG levels were significantly lower in women who breastfed exclusively (4.6 ± 2.2 mmol/litre) compared with those in women who stopped breastfeeding before 6 weeks (8.1 ± 2.1 mmol/litre) and women who bottle-fed (6.7 ± 1.7 mmol/litre). [EL = 2+]

The case series involved 24 women with type 1 diabetes.[391] of these, 18 established breastfeeding and 16 continued until the 6 week postnatal clinic. Insulin doses were reduced below the pre-pregnancy dose immediately after birth and then adjusted according to blood glucose concentrations. After birth women who breastfed (n = 18) reduced their insulin dose by a mean of 11.6 units (26%) from their pre-pregnancy dose (95% CI 8.9 to 14.3 units, P < 0.001). Women who bottle-fed (n = 6) reduced their insulin dose by a mean of 5.2 units (11.3%) from their pre- pregnancy dose (95% CI 1.1 to 9.3 units, not significant). [EL = 3]

8.1.1.2 Oral hypoglycaemic agents

A cohort study[392] investigated excretion of metformin into breast milk and the effect on nursing babies. Five women with type 2 diabetes and two women without diabetes were started on metformin on the first day after caesarean section. Four women dropped out, leaving only three for analysis. The results are not meaningful and the study is not considered further. [EL = 2−]

Another cohort study[393] investigated whether glibenclamide and glipizide may be excreted into breast milk and whether breastfeeding from women taking these medicines causes infant hypoglycaemia. Eight women who received a single oral dose of 5 mg or 10 mg glibenclamide were studied by measuring drug concentrations in maternal blood and breast milk for 8 hours after the dosing schedule. Another five women treated with 5 mg/day of glibenclamide or glipizide starting on the first day postpartum were assessed by measuring the concentration of the medicines in maternal blood and milk. Infant blood glucose was measured 5–16 days after birth. Neither glibenclamide nor glipizide were detected in breast milk and blood glucose was normal in the three babies (one glibenclamide and two glipizide) who were wholly breastfed. The results suggest that glibenclamide and glipizide are safe and compatible with breastfeeding at the doses investigated. [EL = 2+]

A reference guide to medicines in pregnancy and lactation reports that women taking metformin can breastfeed.[77] The review included evidence from two small observational studies in breastfeeding women which found that metformin is excreted in milk. The average metformin concentration was under 0.3% of the maternal weight-adjusted dose. Both studies concluded that metformin was safe to use during breastfeeding. [EL = 3]

The reference guide reported that acarbose, nateglinide, pioglitazone, rosiglitazone, glibenclamide, glimepiride and glipizide are probably compatible with breastfeeding.[77] Although no studies have investigated their use in women who are breastfeeding, the reference guide suggested nateglinide, pioglitazone and rosiglitazone-related material may be present in low levels in breast milk. The reference guide also suggested that the amount of acarbose available for transfer to breast milk is very small because less than 2% of the acarbose dose is absorbed systemically, and that data on safety during breastfeeding are needed. The reference guide suggested that glimepiride and glipizide are likely to be present in breast milk. [EL = 3]

The reference guide reported that repaglinide, chlorpropamide and tolbutamide are potentially toxic to babies if they are taken by breastfeeding women. Chlorpropamide and tolbutamide are excreted into breast milk. No studies have investigated the use of repaglinide in breastfeeding women, but the reference guide suggested that it may produce skeletal deformities.[77] [EL = 3]

There was no information about gliclazide or gliquidone in the reference guide.

The British National Formulary reports that metformin is present in breast milk and the manufacturer advises women who are breastfeeding to avoid it.[78] The manufacturers of nateglinide, repaglinide, pioglitazone and rosiglitazone advise women who are breastfeeding to avoid them. The manufacturer of acarbose advises women who are breastfeeding to avoid it. Sulphonylureas have a theoretical possibility of causing hypoglycaemia in the baby.

8.1.1.3 Angiotensin-converting enzyme inhibitors

A reference guide to medicines in pregnancy and lactation reported that there are limited data for the use of the ACE inhibitors enalapril and trandolapril, and suggested that they are probably compatible with breastfeeding. There were no data for the use of lisinopril, moexipril hydrochloride, perindopril or quinapril in women who are breastfeeding, but the reference guide suggested that they are probably compatible with breastfeeding. There was no

information about captopril, cilazapril, fosinopril sodium, imidapril hydrochloride or ramipril.[77] [EL = 3]

The British National Formulary reports that quinapril, captopril, fosinopril and lisinopril have been found to be present in breast milk and they should be avoided by women who are breastfeeding. The manufacturers of trandolapril advise pregnant women to avoid it. Cilazapril, imidapril, moexipril, perindopril and ramipril have no information available and so the manufacturer advises women who are breastfeeding to avoid them. The manufacturers state that enalapril is probably present in breast milk in an amount too small to be harmful.[78]

8.1.1.4 Angiotensin-II receptor blockers

A reference guide to medicines in pregnancy and lactation reported that there were no data for the use of ARBs in women who are breastfeeding, but it suggests that they are probably compatible with breastfeeding.[77] [EL = 3]

The British National Formulary states that olmesartan has been found to be present in breast milk and recommends that it should be avoided by women who are breastfeeding. Candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan have no information available so the manufacturers advise women who are breastfeeding to avoid them.[78]

8.1.1.5 Statins

A reference guide to medicines in pregnancy and lactation reported that statins are contraindicated in women who are breastfeeding.[77] Studies have shown that fluvastatin and pravastatin appear in breast milk. No data were available for simvastatin, atorvastatin or rosuvastatin. [EL = 3]

The British National Formulary notes that pravastatin has been found to be present in a small amount in breast milk and should be avoided by women who are breastfeeding. There is no information available for the use of atorvastatin, fluvastatin, rosuvastatin and simvastatin during breastfeeding and women who are breastfeeding are advised to avoid them.[78]

8.1.1.6 Obesity medicines

A reference guide to medicines in pregnancy and lactation reported that there were no data for the use of the obesity drug orlistat in women who are breastfeeding, but that it is probably compatible with breastfeeding. The reference guide reported that there were no data for the use of sibutramine in women who are breastfeeding and it suggests there may be toxicity to the baby. There was no review for rimonabant.[77] [EL = 3]

The British National Formulary recommends that rimonabant be avoided by women who are breastfeeding. The manufacturers of orlistat and sibutramine recommend that they be avoided in women who are breastfeeding, but no further information is given.[78]

8.1.2 Evidence statement

There are no high-quality studies that show that breastfeeding affects glycaemic control. A small cohort study showed that insulin requirements and blood glucose levels fell in all women with diabetes following birth. Blood glucose levels fell only for the first week postpartum. There was no difference between groups in hypoglycaemic episodes, however breastfeeding women were advised to eat a meal or snack before feeds and the small numbers in the study limits comparison between groups.

A small cohort study found lower FBG levels 6 weeks after birth in women who breastfed than in women who bottle-fed or discontinued breastfeeding before 6 weeks.

A case series found a significant reduction in insulin requirements in breastfeeding women following birth, but the study was underpowered to detect a difference in insulin requirements between breastfeeding and bottle-feeding women.

There is limited evidence from two cohort studies and a reference guide in relation to the safety of oral hypoglycaemic agents, ACE inhibitors, ARBs, statins, calcium-channel blockers and obesity medicines in women who are breastfeeding. The reference guide and the manufacturers of the medicines recommend that these preparations are avoided by women who are breastfeeding.

8.1.3 From evidence to recommendations

Given the lack of clinical evidence in relation to the effect of breastfeeding on glycaemic control the GDG's recommendations are based on consensus within the group on best current practice. Women with insulin-treated pre-existing diabetes should, therefore, be advised to reduce their insulin dose immediately after birth and to monitor their blood glucose levels to establish the appropriate dose. Women with insulin-treated pre-existing diabetes who are breastfeeding should be informed that they are at increased risk of hypoglycaemia when breastfeeding and to have a meal or snack available before or during feeds. Women who have been diagnosed with gestational diabetes should discontinue hypoglycaemic treatment immediately after birth.

The safety of oral hypoglycaemic agents, ACE inhibitors, ARBs, statins, and obesity medicines in women who are breastfeeding has not been established. However, it is the GDG's view that women with pre-existing type 2 diabetes who are breastfeeding can resume or continue to take metformin and glibenclamide immediately following birth. Women with diabetes who are breastfeeding should, therefore, continue to avoid any medicines for the treatment of diabetes and its complications that were discontinued for safety reasons in the preconception period.

8.1.4 Recommendations

8.1.5 Blood glucose control, medicines and breastfeeding

The current recommendations can be found at www.nice.org.uk/guidance/ng3

8.1.6 Research recommendations

There were no research recommendations relating to breastfeeding and effects on glycaemic control in women with diabetes.

8.2 Information and follow-up after birth

8.2.1 Description of the evidence

8.2.1.1 Gestational diabetes

In the postnatal period, glucose metabolism in women who have been diagnosed with gestational diabetes may return to normal, or there may be ongoing impaired glucose regulation (IGT or impaired fasting glycaemia) or frank diabetes (including pre-existing type 1 or type 2 diabetes that was unrecognised before pregnancy).[31]

One systematic review and nine additional or subsequent studies examining the likelihood of women who have been diagnosed with gestational diabetes later developing type 1 or type 2 diabetes were identified. Two RCTs and a cross-sectional study on the effect of lifestyle/educational interventions on the development of type 2 diabetes were identified. A further systematic review on the effectiveness of pharmacological and lifestyle interventions

to prevent or delay type 2 diabetes in people with IGT was identified. Two studies on alternatives to a 6 week OGTT for women who have been diagnosed with gestational diabetes were identified.

8.2.1.2 Epidemiology

Women who have been diagnosed with gestational diabetes are likely to have gestational diabetes in future pregnancies. Recurrence rates for gestational diabetes vary between 30% and 84% after the index pregnancy, and the recurrence rate is about 75% in women with a history of insulin- treated gestational diabetes (see Section 4).

A systematic review (28 studies) examined risk factors associated with developing type 2 diabetes in women who had been diagnosed with gestational diabetes.[394] The studies included in the review reported rates of conversion to type 2 diabetes from 2.6% to 70% over periods from 6 weeks to 28 years. The epidemiological data showed that the incidence of type 2 diabetes increased most rapidly in the first 5 years after pregnancy. Fasting glucose levels from OGTTs administered during pregnancy were predictive of developing type 2 diabetes after pregnancy. There was no clear pattern for risk factors such as BMI, maternal age, previous history of gestational diabetes, family history of diabetes or parity. The review highlighted that the included studies varied in ethnicity, length of follow-up and criteria for diagnosis of gestational diabetes and type 2 diabetes and that this made comparison and generalisation of results difficult. The review concluded that women with higher fasting glucose levels during pregnancy may need to be tested for type 2 diabetes more often than current guidelines recommend. [EL = 2+]

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the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

qq At the time of publication (February 2015) glibenclamide was contraindicated for use up to gestational week 11 and did not have UK marketing authorisation for use during the second and third trimesters of pregnancy in women with gestational diabetes. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

A cohort study (n = 753) from Denmark compared the incidence of diabetes after gestational diabetes in a cohort of women with gestational diabetes recruited between 1978 to 1985 (old cohort, n = 151) with a cohort recruited between 1987 and 1996 (new cohort, n = 330).[395] Until 1986, a 3 hour 50 g OGTT was used, whereas afterwards a 75 g OGTT was used. The 1999 WHO criteria were used for classification. Both cohorts were followed up in 2002 (n = 481) with a median follow-up of 9.8 years. The study found that overall 40% (192) of women had type 1 or type 2 diabetes and 27% (130) had impaired glucose regulation (IGT or impaired fasting glycaemia). Comparing the cohorts, 40.9% in the new cohort had type 1 or type 2 diabetes compared with 18.3% in the old cohort. Multiple regression analysis showed that membership of the new cohort, being overweight before pregnancy (BMI 25 kg/m² or more) and IGT postpartum were statistically significant risk factors for developing diabetes (P < 0.05). The study concluded that the incidence of diabetes in the cohort was very high and increasing, and that the increase in BMI in the population seemed to be the main risk factor accounting for this. [EL = 2−]

A cohort study (n = 302) undertaken in Germany examined the risk factors associated with developing diabetes after being diagnosed with gestational diabetes.[396] The study used a 75 g OGTT and the American Diabetes Association criteria for classification. The study found that insulin use during pregnancy, BMI more than 30 kg/m² and serum C-reactive protein at 9 months in 2nd to 4th quartiles were statistically significant predictors of developing diabetes. The study found that having a first-degree relative with diabetes, age, duration of pregnancy, birthweight of child and number of previous pregnancies were not predictive of subsequent diabetes. The study recommended that prospective diabetes assessment and intervention should be considered in women with gestational diabetes who are autoantibody positive, require insulin treatment during pregnancy or who are obese. [EL = 3]

A cohort study using routinely collected data (n = 2956) from Australia examined risk factors for developing diabetes after being diagnosed with gestational diabetes.[397] The study used a 50 g OGTT and the WHO criteria for classification. The study found that 2.0% (58/2956) of women developed diabetes within the first 6 months postpartum. Multivariate analysis found that severity of gestational diabetes, Asian origin and 1 hour plasma glucose were predictive of developing diabetes, but that insulin treatment during pregnancy, BMI, fetal macrosomia, maternal age and booking status (private or not) were not. The study concluded that these risk factors should be taken into account when deciding follow-up care for women with gestational diabetes. Whilst this study included a large number of women the follow-up period was, at most, 6 months. [EL = 3]

A cohort study (n = 278) from Hong Kong compared women with abnormal glucose tolerance test results with those with normal glucose tolerance test results.398 The study used a 75 g OGTT and the WHO criteria for classification. The study found that 29.0% (56/193) of women who had been diagnosed with gestational diabetes had IGT (n = 38) or diabetes (n = 18) by 6 years follow- up compared with 13.8% (5/58 and 3/58, respectively) of women without gestational diabetes. The study found that age, BMI, abnormal OGTT at 6 weeks postpartum, diabetes in a first-degree relative, macrosomia, recurrent gestational diabetes and use of oral contraceptives were not predictive of later developing diabetes. [EL = 3]

A case–control study (n = 70) from Sweden compared the incidence of type 2 diabetes at 15 years follow-up between women who had gestational diabetes and those who did not. The study used the 2 hour 75 g OGTT.399 The study found that 35% (10/28) of women with gestational diabetes had developed type 2 diabetes, whereas none of 52 controls had developed diabetes (P < 0.001). Weight, BMI, fasting blood sugar and HbA1c were all significant predictors of women with gestational diabetes developing diabetes compared to women with gestational diabetes that did not develop diabetes (P < 0.05). The study concluded that better postpartum strategies for control of weight and lifestyle are needed for women who have been diagnosed with gestational diabetes. [EL = 2−]

A case–control study (n = 468, 315 cases and 153 controls) from Sweden compared women with and without gestational diabetes for later development of diabetes.[400] The study used a 2 hour 75 g OGTT and the European Association for the Study of Diabetes criteria for classification. At 1 year follow-up 22% (50/229) of cases and 1.6% (1/60) of controls had developed type 2 diabetes (P < 0.001). Twenty-seven percent (24/90) of women with insulin-treated gestational diabetes and 17% (23/132) women with non-insulin-treated gestational diabetes had 2 hour OGTT values of 7.8–11.0 ml, whereas 20% (18/90) of women with insulin-treated gestational diabetes and 2% (3/132) of women with non-insulin-treated gestational diabetes had 2 hour OGTT values of more than 11.0 mmol/litre, respectively. The study found 2 hour OGTT value and HbA1c at diagnosis were associated with diabetes at 1 year, but BMI, weight increase, estimated fetal weight and birthweight were not associated with developing diabetes. Multiple regression analysis found that the results of OGTT test during pregnancy was predictive for developing diabetes later. [EL = 2+]

A case–control study (n = 870) from Finland compared the incidence of type 1 or type 2 diabetes postpartum in women who had been diagnosed with gestational diabetes (n = 435) with those who had not (n = 435).[401] The study used the Finnish Diabetes Association classification and a 75 g OGTT. Ten percent (43/435) of women in the case group had developed type 1 or type 2 diabetes, whereas none of the women in the control group had developed diabetes. Women treated with insulin during pregnancy were more likely to develop diabetes than those who did not use insulin (P < 0.0001). The women in the control group were significantly younger (27.2 years versus 34.0 years, P < 0.001). Regression analysis showed that age, insulin treatment, positive islet cell antibodies, positive glutamic acid decarboxylase antibodies and being positive for more than one antibody were all predictive of developing diabetes. [EL = 2+]

A cohort study (n = 317) from the USA compared the incidence of type 2 diabetes in Pima Indians who had IGT (75 g) and who were either pregnant or not when the test was undertaken.[402] The study used the WHO criteria for classification and a 75 g OGTT. The study found that 46% (114/244) of non-pregnant women and 23% (17/73) of pregnant women had developed diabetes within the 10 year follow-up period. Using multiple regression analysis the study found that 2 hour plasma glucose, parity and not being pregnant were all statistically significant risk factors in developing diabetes. The authors concluded that IGT outside pregnancy was a stronger predictor of developing diabetes than IGT during pregnancy. This highlights the often transient nature of gestational diabetes. [EL = 2−]

A retrospective case-series (n = 121) from Denmark examined lifestyle changes after pregnancy in women who had been diagnosed with gestational diabetes.[403] The average follow-up period was 24 months. The study found that 19 women had developed diabetes and 22 had IGT. On average the women had gained weight after pregnancy (36 gained weight compared with 18 who lost weight) and they were not exercising as much after pregnancy as before (36 not exercising before pregnancy versus 47 not exercising after pregnancy). However, women had reduced the fat intake in their diets (58 compared with 90 before pregnancy). [EL = 3]

8.2.1.3   Lifestyle interventions

An RCT (n = 3234) undertaken in the USA of people (women and men) with elevated fasting and post-load plasma glucose concentrations compared placebo plus standard advice (n = 1082), metformin plus standard advice (n = 1073) and an intensive lifestyle change programme (n = 1079) in the prevention of development of type 2 diabetes.[404] The intensive lifestyle change programme involved one-to-one meetings over 24 weeks focusing on changing diet, exercise and behaviour plus group sessions to reinforce behaviour. The groups were comparable at baseline. At 2.8 year follow-up the incidence of diabetes in the placebo group was 11 cases per 100 person-years, whereas for metformin it was 7.8 cases per 100 person-years, and for the lifestyle change programme it was 4.8 cases per 100

person-years. The reduction in incidence between the lifestyle change programme group and metformin group was 39% (95% CI 24 to 51), and for women only (n = 2191) the figure was 36% (95% CI 16 to 51). The study shows that intensive lifestyle education reduced the incidence of type 2 diabetes. However, the reduction in development of diabetes for the general population is likely to be greater than those shown in the placebo group because the fact that these people were made aware of the problem is likely to have had some impact. The study involved women and men with an average age of 50.6 years, and it focused on prevention of diabetes rather than management of existing diabetes. The trial was stopped early by the data monitoring committee due to the divergence in the placebo group. Finally no cost data were available to determine the cost-effectiveness of the interventions. [EL = 1+]

An RCT undertaken in Finland (n = 522) in people at high risk of developing type 2 diabetes (relatives with type 2 diabetes, BMI more than 25 kg/m², age 40–65 years and IGT) compared the effect of individualised counselling (n = 265) with standard information provision (n = 257) on the prevention of diabetes, with a mean follow-up of 3.2 years. At 4 year follow-up the cumulative incidence was 11% in the individualised counselling group (95% CI 6% to 15%) and 23% in the standard information group (95% CI 17% to 29%).[405] Cumulative incidence of diabetes in the individualised counselling group was 58% lower than in the standard information group. The study involved women and men with an average age of 55 years with high-risk factors for developing type 2 diabetes, but not specifically women and pregnancy. Therefore, the results may not be applicable to pregnant women. [EL = 1+]

A cross-sectional study[406] examined postpartum patterns of physical activity and related psychosocial factors in women who had been diagnosed with gestational diabetes. The study showed low prevalence of physical activity that was strongly related to social support and self- efficacy. [EL 3]

A systematic review and meta-analysis[407] of 17 RCTs attempted to quantify the effectiveness of pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people (women and men) with IGT. The study showed that lifestyle and pharmacological interventions reduced the rate of progression to type 2 diabetes. Lifestyle interventions seemed to be at least as effective as pharmacological treatment. No separate analyses for women and men were reported. [EL = 1+]

8.2.1.4   Type 1 and type 2 diabetes

No clinical studies were identified in relation to the information and follow-up that should be provided for women with type 1 diabetes and type 2 diabetes in the postnatal period.

The CEMACH enquiry described the postnatal care of women with pre-existing type 1 and type 2 diabetes, emphasising the importance of good communication between maternity and diabetes teams and that maternity staff should have good access to expert advice about glycaemic control.[33] It also commented on: the need for a clear written plan for diabetes management in the woman's medical records; offering information and advice about contraception and the importance of planned pregnancy before the woman is discharged from hospital; and offering women a follow- up diabetes appointment after discharge from hospital to discuss ongoing management of diabetes. The enquiry reported that 17% (31/184) of women who had poor pregnancy outcome and 13% (25/188) of women with good pregnancy outcome had no documented plan for postnatal diabetes management and 73% (280/383) had a follow-up diabetes appointment planned. Women who had a poor pregnancy outcome were more likely not to receive contraceptive advice before being discharged from hospital (44%) than those with a good pregnancy outcome (16%; OR 4.2, 95% CI 2.4 to 7.4, adjusted for maternal age and deprivation). Sixty-six percent (133/203) of the women who had a poor pregnancy outcome and 50% (106/211) of the women who had a good pregnancy outcome were classified as having had sub-optimal postnatal diabetes care and advice (OR 1.8, 95% CI 1.2 to 2.7, adjusted for maternal age and deprivation). The enquiry panels expressed concern specifically about the management of glycaemic control, inadequate plans for care after discharge, lack of contact with the diabetes team and lack of

contraceptive advice for women with pre-existing type 1 and type 2 diabetes postnatally. [EL = 3–4]

The CEMACH enquiry (comparison of women with type 1 and type 2 diabetes) reported that women with type 1 diabetes were as likely to have a written plan for postnatal diabetes management as women with type 2 diabetes (87% versus 87%, P = 0.95) and to receive sub- optimal postnatal diabetes care (53% versus 46%, P = 0.3). Women with type 1 diabetes were more likely to have postnatal contraceptive advice compared to women with type 2 diabetes (85% versus 70%, P = 0.008).[33] [EL = 3–4]

8.2.2 Existing guidance

The NICE postnatal care guideline11 recommends that resumption of contraception should be discussed within the first week of birth.

8.2.3 Evidence statement

Evidence shows that women who have been diagnosed with gestational diabetes are likely to have gestational diabetes in future pregnancies. Recurrence rates of gestational diabetes are between 30% and 84%, with recurrence rates in women with a history of insulin-treated gestational diabetes being about 75%.

Results from a systematic review of epidemiological studies and eight additional or subsequent studies show increasing cumulative incidence of type 2 diabetes in the postnatal period in women who have been diagnosed with gestational diabetes. However, the studies are limited by the variation in data recorded, length of follow-up, high attrition rates at follow-up and differing ethnic and cultural populations. The studies highlight various risk factors or identifiers for developing diabetes after having had gestational diabetes, the main ones being obesity, use of insulin during pregnancy, and results of OGTTs during pregnancy.

A systematic review and two RCTs of lifestyle/education interventions showed that the risk of developing type 2 diabetes could be reduced by either lifestyle or pharmacological interventions. However, these studies were undertaken on a general population at risk of developing diabetes rather than women who had been diagnosed with gestational diabetes. In addition, long-term follow-up would be needed to determine the effectiveness of the programmes.

No clinical studies that evaluated the information and follow-up that should be provided for women with type 1 diabetes and type 2 diabetes in the postnatal period were identified.

8.2.4 From evidence to recommendations

In the postnatal period, glucose metabolism in women who have been diagnosed with gestational diabetes may return to normal, or there may be ongoing impaired glucose regulation (IGT or impaired fasting glycaemia) or frank diabetes (including pre-existing type 1 or type 2 diabetes that was unrecognised before pregnancy). Women who have been diagnosed with gestational diabetes should, therefore, be offered blood glucose testing before they are discharged from hospital to exclude persisting hyperglycaemia.

Women who have been diagnosed with gestational diabetes are likely to develop type 2 diabetes postnatally and so they should be informed of the symptoms of hyperglycaemia. There is evidence that lifestyle/education interventions are effective for people with IGT to prevent progression to type 2 diabetes and, therefore, women who have been diagnosed with gestational diabetes should be offered lifestyle advice and follow-up to have their blood glucose tested at the 6 week postnatal check and annually thereafter.

There is evidence that women who have been diagnosed with gestational diabetes are likely to have gestational diabetes in future pregnancies. In recommending that women who have been diagnosed with gestational diabetes are informed that they are likely to have gestational diabetes in future pregnancies, the GDG is reinforcing the recommendations contained in the NSF for diabetes. There is no clinical evidence to support early self-monitoring of blood glucose (for 1 week) over OGTT in future pregnancies, or vice versa, and

the costs are probably the same. Women who have had gestational diabetes in a previous pregnancy should, therefore, be offered early self-monitoring of blood glucose or OGTT, and a further OGTT if the results are normal (see Section 4.3).

Given that no clinical studies that evaluated the information and follow-up that should be provided for women with type 1 or type 2 diabetes in the postnatal period were identified, the GDG's recommendation is based on the consensus view of the group. Women with pre-existing type 1 or type 2 diabetes should, therefore, be referred back to their routine follow-up arrangements with the diabetes care team. This care should include consideration of the issues identified in relation to preconception care, including the importance of contraception and planning future pregnancies (see Chapter 3).

The phrase 'women who have been diagnosed with gestational diabetes' is used in the recommendations contained in this section to highlight the fact that the gestational diabetes may have resolved immediately postpartum.

8.2.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng3

8.3 Accuracy and timing of postnatal blood glucose testing in women who had gestational diabetes

This section was updated in 2015

8.3.1 Diagnostic accuracy of postnatal tests for glucose intolerance

8.3.1.1 Review question

What is the effectiveness of the following tests in the detection of glucose intolerance after pregnancy in women who have had gestational diabetes (but are not hyperglycaemic before they are transferred to community care):

- fasting plasma glucose (FPG) test
- haemoglobin A1c (HbA1c) test
- 75 g oral glucose tolerance test (OGTT)

where the 75 g OGTT is the 'gold standard' or reference test?

8.3.1.2 Introduction

The objective of this review question is to determine which test should be used in the postnatal period to identify glucose intolerance in women who have had gestational diabetes but are not hyperglycaemic when they are transferred to community care. The 2008 guideline recommended that women who were diagnosed with gestational diabetes should be offered a fasting plasma glucose (FPG) measurement (but not an oral glucose tolerance test [OGTT]) at the 6 week postnatal check and annually thereafter. The need to update this topic in the guideline was partly prompted by concerns that the recommendation was based on a single study conducted using a small sample (122 OGTTs) in a single hospital (Holt et al., 2003).

The term 'glucose intolerance' covers:

- impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT)
- diabetes.

As stated above, the reference standard ('best test') for detecting glucose intolerance outside pregnancy is the 75 g OGTT applied using the World Health Organization (WHO) 1999 diagnostic criteria for IFG, IGT and diabetes:

- IFG defined as FPG 6.1 mmol/litre and above up to less than 7.0 mmol/litre and 2 hour plasma glucose less than 7.8 mmol/litre if measured
- IGT defined as FPG less than 7.0 mmol/litre and 2 hour 7.8 mmol/litre or more and less than 11.1 mmol/litre
- diabetes defined as FPG 7.0 mmol/litre or more or 2 hour 11.1mmol/litre or more.

The tests evaluated as predictors of or alternatives to the 75 g OGTT in this review question are FPG and HbA1c. An HbA1c of 6.5% or more is the WHO recommended cut-off for diagnosing diabetes. Study results relating to evaluation of the diagnostic test accuracy of FPG and HbA1c measurements were eligible for inclusion in the review only if the reference standard (comparator) was the 75 g OGTT applied using the WHO 1999 diagnostic criteria or equivalent. For example, the American Diabetes Association (ADA) 2012 diagnostic criteria for diabetes (but not IFG or IGT) are equivalent to the WHO 1999 diagnostic criteria, and so study results based on the ADA 2012 diagnostic criteria for diabetes were also eligible for inclusion, whereas study results based on ADA 2012 criteria for IFG and IGT were not.

8.3.1.3 Description of included studies

Thirteen studies were identified for inclusion for this review question (Agarwal et al., 2004; Conway & Langer, 1999; Ferrara et al., 2009; Holt et al., 2003; Hunt & Conway, 2008; Joseph et al., 2013; Reichelt et al., 2002; Kitzmiller et al., 2007; Kousta et al., 1999; McClean et al., 2010; Megia et al., 2012; Myers et al., 2014; Reinblatt et al., 2006). Three of the studies (Hunt et al., 2008; Reichelt et al., 2002; Megia et al., 2012) were conducted using a prospective cohort design (1 of these was assumed to be a case-cohort design [Reichelt et al., 2002] but this was not reported clearly in the article). The remaining studies were conducted using a retrospective cohort design. All of the studies used a 75 g OGTT as the reference standard. However, as explained above, only those results that relate to interpretation of the reference standard using the WHO 1999 diagnostic criteria for IFG, IGT and diabetes are presented in this review.

All of the studies evaluated the diagnostic test accuracy of FPG measurements for detecting diabetes postnatally. Four studies (Agarwal et al., 2004; Holt et al., 2003; Reichelt et al., 2002; McClean et al., 2010) also evaluated the diagnostic test accuracy of FPG measurements for detecting IFG and IGT postnatally. One study (Megia et al., 2012) evaluated the diagnostic test accuracy of HbA1c measurements for detecting diabetes postnatally. None of the studies reported evidence for the diagnostic test accuracy of HbA1c measurements in terms of detecting IFG or IGT.

The timing of testing varied, with 7 studies performing testing up to 13 weeks (Agarwal et al., 2004; Conway et al., 1999; Holt et al., 2003; Hunt et al., 2008; Joseph et al., 2013; McClean et al., 2010; Myers et al., 2014) and 1 study testing at more than 1 year (Reichelt et al., 2002). In a further 5 studies the timing of testing overlapped the guideline development group's predefined intervals (Ferrara et al., 2009; Kitzmiller et al., 2007; Kousta et al., 1999; Megia et al., 2012; Reinblatt et al 2006).

8.3.1.4 Evidence profiles

The GRADE profiles for this review question are presented in Tables 81 to 83.

Table 81: GRADE profile for diagnostic test accuracy of fasting plasma glucose at various thresholds between 5.0 mmol/litre and 7.0 mmol/litre to detect impaired glucose tolerance postnatally in women who have had gestational diabetes, compared with the 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirect-ness	Impreci-sion	Other considera-tions
Fasting plasma glucose ≤ 5.0 mmol/litre for detecting IGT												
1 (McClean et al., 2010)	985	14.9 (9.3 to 22.7)[a]	52.4 (51.6 to 53.4)[a]	0.31 (0.19 to 0.49)[a]	1.63 (1.45 to 1.76)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
Fasting plasma glucose ≤ 5.5 mmol/litre for detecting IGT												
1 (McClean et al., 2010)	985	31.6 (23.8 to 40.4)[a]	28.7 (27.7 to 29.9)[a]	0.44 (0.33 to 0.58)[a]	2.38 (2.00 to 2.76)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
Fasting plasma glucose < 6.0 mmol/litre for detecting IGT												
1 (Holt et al., 2003)	122	12.5 (0 to 68.5)[a]	6.3 (5.8 to 8.1)[a]	0.13 (0 to 0.75)[a]	14.00 (3.88 to 17.14)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[i]	Yes[j]
Fasting plasma glucose ≤ 6.0 mmol/litre for detecting IGT												
1 (McClean et al., 2010)	985	54.4 (45.8 to 62.9)[a]	16.9 (15.7 to 18)[a]	0.65 (0.54 to 0.77)[a]	2.70 (2.06 to 3.45)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
Fasting plasma glucose < 6.1 mmol/litre for detecting IGT												
1 (Agarwal et al., 2004)	549	82.1 (73.2 to 89.0)[a]	15.5 (13.9 to 16.7)[a]	0.97 (0.85 to 1.07)[a]	1.15 (0.66 to 1.93)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	No serious imprecision	Yes[k]
1 (Reichelt et al., 2002)	117	76.9 (66.1to 87.2)[a]	14.1 (8.7to 19.2)[a]	0.90 (0.72 to 1.08)[a]	1.64 (0.67 to 3.91)[a]	Very low	Prospective cohort (case-cohort)	Very serious[b,c,d,e,h]	NA	Serious[f]	No serious imprecision	Yes[l]

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsist-ency	Indirect-ness	Impreci-sion	Other considera-tions
Fasting plasma glucose < 7.0 mmol/litre for detecting IGT												
1 (McClean et al., 2010)	985	99.6 (95.4 to 100)[a]	9.7 (9.1 to 9.7)[a]	1.10 (1.05 to 1.11)[a]	0.05 (0 to 0.50)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
1 (Holt et al., 2003)	122	87.5 (43.3 to 100)[a]	2.1 (0.6 to 2.5)[a]	0.89 (0.44 to 1.03)[a]	6.00 (0 to 92.85)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[i]	Yes[j]
1 (Agarwal et al., 2004)	549	99.4 (94.2 to 100)[a]	7.8 (6.9 to 7.9)[a]	1.08 (1.01 to 1.09)[a]	0.08 (0 to 0.84)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	No serious imprecision	Yes[k]
1 (Reichelt et al., 2002)	117	98.8 (90.6 to 100)[a]	10.8 (6.6 to 11.4)[a]	1.11 (0.97 to 1.13)[a]	0.12 (0.00 to 1.43)[a]	Very low	Prospective cohort (case-cohort)	Very serious[b,c,d,e,h]	NA	Serious[f]	No serious imprecision	Yes[l]

IGT impaired glucose tolerance, NA not applicable, NC not calculable
a. Calculated by the NCC-WCH technical team from data reported in the article
b. The selection criteria were not clearly reported
c. The reference standard was not independent of the index test
d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Country: UK, Ethnicity of population: South Asian-Pakistani, Bangladeshi or Indian (71%), White European (26%), not reported (4%)
h. Some clinical data available when the test is used in practice were not available when test results were interpreted
i. Confidence interval for sensitivity was wider than 40 percentage points
j. Country: UK, Ethnicity of population: White (86%), Asian (14%)
k. Country: United Arab Emirates (UAE), Ethnicity of population: Arabs (78.8%), Indian National (20.5%)
l. Country: Brazil, Ethnicity of population: not reported

Table 82: GRADE profile for diagnostic test accuracy of fasting plasma glucose at various thresholds between 5.1 mmol/litre and 7.0 mmol/litre to detect diabetes postnatally in women who have had gestational diabetes, compared to the 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Fasting plasma glucose ≥ 5.1 mmol/litre for detecting diabetes												
1 (McClean et al., 2010)	985	99.1 (94.3 to 100)[a]	49.2 (48.6 to 49.3)[a]	1.95 (1.84 to 1.97)[a]	0.02 (0.00 to 0.12)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
Fasting plasma glucose ≥ 5.6 mmol/litre for detecting diabetes												
1 (McClean et al., 2010)	985	97.2 (91.7 to 99.3)[a]	74.7 (74.0 to 74.9)[a]	3.84 (3.53 to 3.96)[a]	0.04 (0.01 to 0.11)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
1 (Myers et al., 2014)	629	76	91	3.8[a]	0.03[a]	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[t]	Yes[h]
Fasting plasma glucose ≥ 6.0 mmol/litre for detecting diabetes												
1 (Holt et al., 2003)	122	87.5 (31.5 to 100)[a]	93.8 (91.9 to 94.2)[a]	14.00 (3.88 to 17.14)[a]	0.13 (0 to 0.75)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,i]	NA	Serious[f]	Serious[j]	Yes[k]
1 (Joseph et al., 2013)	148	94.4	90.4	9.8[a]	0.06[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	Serious[t]	Yes[l]
Fasting plasma glucose ≥ 6.1 mmol/litre for detecting diabetes												
1 (McClean et al., 2010)	985	89.9 (82.9 to 94.5)[a]	88.5 (87.6 to 89.0)[a]	7.80 (6.68 to 8.63)[a]	0.11 (0.06 to 0.20)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
1 (Reichelt et al., 2002)	117	88.9 (53.2 to 99.4)[a]	88.9 (85.9 to 89.8)[a]	8.00 (3.78 to 9.71)[a]	0.13 (0.01 to 0.55)[a]	Very low	Prospective cohort (case-cohort)	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[i]	Yes[m]
1 (Myers et al., 2014)	629	90	91	10.4[a]	0.11[a]	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[t]	Yes[h]

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Fasting plasma glucose ≥ 7.0 mmol/litre for detecting diabetes												
1 (Ferrara et al., 2009)	5524	25.0 (7.3 to 52.4)[a]	NC	NC	NC	Very low	Retrospective cohort	Very serious[c,d,e,o]	NA	Serious[f]	Very serious[p]	Yes[q]
1 (Conway & Langer 1999)	179	85.7 (57.2 to 98.2)[a]	NC	NC	NC	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	Very serious[p]	Yes[r]
1 (Agarwal et al., 2004)	549	72.0 (64.4 to 72.0)[a]	100 (NC)[s]	> 1000 (NC)	0.28 (0.28 to 0.36)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[t]	Yes[n]
1 (Hunt & Conway 2008)	400	30.8 (12.7 to 30.8)[a]	100 (NC)[q]	> 1000 (NC)	0.69 (0.69 to 0.88)[a]	Very low	Prospective cohort	Very serious[b,c,d,e,o]	NA	Serious[f]	Serious[t]	Yes[u]
1 (Kitzmiller et al., 2007)	527	16.0 (6.5 to 16.0)[a]	100 (NC)[q]	> 1000 (NC)	0.84 (0.84 to 0.94)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	Serious[t]	Yes[v]
1 (Reinblatt et al., 2006)	275	46.2 (33.3 to 46.2)[a]	100 (NC)[q]	> 1000 (NC)	0.54 (0.54 to 0.68)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,w]	NA	Serious[f]	Serious[r]	Yes[x]
1 (McClean et al., 2010)	985	76.8 (72.8 to 77.3)[a]	99.9 (99.4 to 100)[a]	> 1000 (129.87 to > 1000)[a]	0.23 (0.23 to 0.27)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	No serious imprecision	Yes[g]
1 (Reichelt et al., 2002)	117	88.9 (59.8 to 88.9)[a]	100 (NC)[q]	> 1000 (NC)	0.11 (0.11 to 0.41)[a]	Very low	Prospective cohort (case-cohort)	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[j]	Yes[m]
1 (Kousta et al., 1999)	165	75.0 (61.4 to 76.9)[a]	99.6 (97.1 to 100)[a]	211.50 (21.47 to > 1000)[a]	0.25 (0.23 to 0.40)[a]	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	No serious imprecision	Yes[y]

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Holt et al., 2003)	122	62.5 (17.0 to 75.0)[a]	99.6 (98.1 to 100)[a]	150.00 (8.81 to > 1000)[a]	0.38 (0.25 to 0.85)[a]	Very low	Retrospective cohort	Very serious[b,c,d,e,h]	NA	Serious[f]	Serious[j]	Yes[k]
1 (Megia et al., 2012)	364	58.3 (27.7 to 84.8)[a]	NC	NC	NC	Very low	Prospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	Very serious[p]	Yes[x]
1 (Myers et al., 2014)	629	76	91	8.4	0.26	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[t]	Yes[h]

NA not applicable, NC not calculable

a. Calculated by the NCC-WCH technical team from data reported in the article

b. The selection criteria were not clearly reported

c. The reference standard was not independent of the index test

d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

g. Country: UK, Ethnicity of population: South Asian-Pakistani, Bangladeshi or Indian (71%), White European (26%), not reported (4%)

h. Country: UK, Ethnicity of population: White (17%), Black (16.1%), Asian (40.7%), Other (26.3%)

I. Some clinical data available when the test is used in practice were not available when test results were interpreted

j. Confidence interval for sensitivity was wider than 40 percentage points

k. Country: UK, Ethnicity of population: White (86%), Asian (14%)

l. Country: UK, Ethnicity of population: White (90%), Asian (6%), Afro-Caribbean (2%), Southeast Asian (2%)

m. Country: Brazil, Ethnicity of population: not reported

n. Country: United Arab Emirates (UAE), Ethnicity of population: Arabs (78.8%), Indian National (20.5%)

o. The whole sample or a random selection of the sample did not receive verification using the reference standard

p. The difference between the upper and lower confidence limits is greater than 40 percentage points for sensitivity and the confidence interval for specificity could not be calculated

q. Country: USA, Ethnicity of population: Non-Hispanic White (28%), African American (3.2%), Asian (31.3%), Hispanic (27.1%), Other (5.6%), Unknown (4.8%)

r. Country: USA, Ethnicity of population: not reported

s. The specificity was fixed at 100% as all the 2 hour 75 g oral glucose tolerance tests (OGTTs) with negative test results (fasting plasma glucose (FPG) < 7.0 mmol/litre and 2 hour plasma glucose < 11.1 mmol/litre) will necessarily have an FPG < 7.0 mmol/litre which means it is not possible to have a false positive result. Specificity treated as 99.999% instead of 100% to calculate LR+

t. Confidence interval for sensitivity and/or specificity could not be calculated

u. Country: USA, Ethnicity of population: Mexican American (94%)

v. Country: USA, Ethnicity of population: Asian Indian (15%), Far East Asian (18%), Southeast Asian (29%), Hispanic (18%), Non-Hispanic White: European, Russian or middle eastern origin (20%)

w. The spectrum of participants was not representative of the women who will receive the test in practice

x. Country: Canada, Ethnicity of population: not reported

y. Country: UK, Ethnicity of population: European (35%), South Asian from India, Sri Lanka or Bangladesh (29%), Afro-Caribbean (17%), Other/mixed origin (19%)
z. Country: Spain, Ethnicity of population: European (91.5%), Arabic (5.5%), Hispanic (1.6%), Others (1.4%)

Table 83: GRADE profile for diagnostic test accuracy of HbA1C at thresholds from 5.3% to 47 mmol/litre 6.5% to detect diabetes postnatally in women who have had gestational diabetes, compared to the 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
HbA1C ≥ 5.3% for detecting diabetes												
1 (Megia et al., 2012)	364	91.7 (NC)	72.4 (NC)	3.33 (NC)	0.11 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.4% for detecting diabetes												
1 (Megia et al., 2012)	364	75.0 (NC)	82.7 (NC)	4.33 (NC)	0.30 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.5% for detecting diabetes												
1 (Megia et al., 2012)	364	66.7 (NC)	88.1 (NC)	5.59 (NC)	0.38 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.6% for detecting diabetes												
1 (Megia et al., 2012)	364	41.7 (NC)	92.1 (NC)	5.24 (NC)	0.63 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.7% for detecting diabetes												
1 (Megia et al., 2012)	364	41.7 (NC)	96.3 (NC)	11.29 (NC)	0.61 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.8% for detecting diabetes												
1 (Megia et al., 2012)	364	41.7 (NC)	98.9 (NC)	36.55 (NC)	0.59 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 5.9% for detecting diabetes												
1 (Megia et al., 2012)	364	33.3 (NC)	100 (NC)	> 1000[h] (NC)	0.67 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]

Number of studies	Number of women with postnatal test	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Quality	Design	Limitations	Inconsistency	Indirect-ness	Impreci-sion	Other considera-tions
HbA1C ≥ 6.0% for detecting diabetes												
1 (Megia et al., 2012)	364	25.0 (NC)	100 (NC)	> 1000[h] (NC)	0.75 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]
HbA1C ≥ 6.5% for detecting diabetes												
1 (Megia et al., 2012)	364	16.7 (NC)	100 (NC)	> 1000[h] (NC)	0.83 (NC)	Very low	Prospective	Very serious[a,b,c,d]	NA	Serious[e]	Very serious[f]	Yes[g]

NA not applicable, NC not calculable

a. The reference standard was not independent of the index test

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. The selection criteria were not clearly reported

e. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

f. Confidence interval for both sensitivity and specificity could not be calculated

g. Country: Spain, Ethnicity of population: European (91.5%), Arabic (5.5%), Hispanic (1.6%), Others (1.4%)

h. Specificity treated as 99.999% instead of 100% to calculate LR+

8.3.1.5 Evidence statements

All evidence included in this review was of very low quality.

Most of the included studies relating to FPG and HbA1c measurement reported diagnostic test accuracy in terms of sensitivity and/or specificity. Likelihood ratios for positive and negative test results (LR+ and LR−, respectively) were reported less frequently, although in many cases the data reported in the articles were sufficient to allow calculation of the likelihood ratios (albeit without confidence intervals [CIs]).

8.3.1.5.1 *Fasting plasma glucose to detect glucose intolerance*

There was no evidence from 4 cohort studies (n=117, n=122, n=549, n=985) of a strongly predictive FPG threshold for detecting IGT, but a level less than 7.0 mmol/litre was moderately useful for ruling out IGT.

8.3.1.5.2 *Fasting plasma glucose to detect diabetes*

The 13 cohort studies (6 studies n=100-300, 5 studies n=301–400, 1 study n=985, 1 study n=5524) that used FPG to detect diabetes reported a range of cut-offs, from 5.1 mmol/litre to 7.0 mmol/litre. In general, and as expected, higher FPG cut-offs provided a useful test for ruling in diabetes and a less useful test for ruling out diabetes, while lower FPG cut-offs provided a useful test for ruling out diabetes and a less useful test for ruling in diabetes. A cut-off of 6.0 mmol/litre appeared to provide the best balance between ruling in and ruling out diabetes, with the evidence showing that FPG of 6.0 mmol/litre or above is a very useful test for ruling in diabetes, and FPG below 6.0 mmol/litre is a moderately useful test for ruling out diabetes.

8.3.1.5.3 *HbA1c to detect glucose intolerance*

The available evidence for using HbA1c measurements to detect glucose intolerance is derived from a single cohort study (n=364) that reported HbA1c cut-offs ranging from 5.3% to 47 mmol/litre (6.5%). A value greater than or equal to 5.7% was very useful for ruling in diabetes. HbA1c was not useful for ruling out diabetes.

No data were reported for using HbA1c to detect IGT or IFG.

8.3.1.6 Health economics profile

No health economic evidence was found in relation to postnatal testing for glucose intolerance.

The method of postnatal testing for the detection of glucose intolerance after pregnancy in women who have had gestational diabetes was initially prioritised for health economic analysis. However, no formal health economic analyses was undertaken as it was ultimately decided that there were more important priorities within the guideline, as the review did not produce evidence and recommendations that would lead to a marked change in current practice or previous NICE guidance.

8.3.1.7 Evidence to recommendations

8.3.1.7.1 *Relative value placed on the outcomes considered*

The guideline development group also prioritised the timing at which testing should be undertaken (that is, the interval between the woman giving birth and postnatal testing for glucose intolerance).

An emphasis was placed on likelihood ratios rather than sensitivity, specificity or predictive values, as there is a recognised and objective system for using them to assess the usefulness of a given test.

8.3.1.7.2   Consideration of clinical benefits and harms

The reported results show an expected trade-off between reducing the rate of false positive test results (that is, reducing the misclassification of women without diabetes as having the condition) and increasing the rate of false negative test results (that is, increasing the misclassification of women with diabetes as not having the condition).

The potential harms from being falsely diagnosed with diabetes include psychological stress to the woman, unnecessary screening (for example for retinopathy), changes to costs of items such as travel and life insurance, and the potential of metformin being inappropriately prescribed (although this could be a benefit if it delays progress from IGT to diabetes).

The potential harms from not being correctly diagnosed with diabetes include not taking up lifestyle advice, a lack of early surveillance for complications (such as retinopathy) and identification of treatable cardiovascular risk factors (for example from serum lipid and blood pressure measurements).

FPG appears to be better than HbA1c for detecting diabetes. FPG was not useful for detecting IGT. No data are reported regarding the use of HbA1c for detecting IGT or IFG.

As FPG is not useful for detecting IGT, and it is not known if HbA1c is useful for detecting IGT, a 75 g OGTT is still needed so that women with IGT are not missed.

8.3.1.7.3   Consideration of health benefits and resource uses

HbA1c might be preferred by women on grounds of convenience. HbA1c is a single test without the need for fasting so it can be done at any time, whereas the FPG requires women to fast prior to testing, which may be difficult or inconvenient if the woman is breastfeeding or has to travel far to get to her appointment. If this additional inconvenience of FPG affects uptake of the test, then population detection rates would be less than those suggested by the diagnostic accuracy data.

However, the HbA1c is a more expensive test and appears to have a lower diagnostic accuracy than FPG in the detection of diabetes. Furthermore, there may be constraints on timing when using HbA1c as it reflects blood glucose levels over the preceding few weeks (up to 12 weeks). So if the sample is taken close to the pregnancy when the woman had gestational diabetes, the values may be falsely high for the postnatal period.

In addition to diagnostic accuracy, the timing of the test may also have a bearing on the cost effectiveness of postnatal testing. The cost effectiveness of postnatal detection ultimately depends on the additional long-term benefits derived from detection in the postnatal period over and above detection at the annual review.

8.3.1.7.4   Quality of evidence

All of the reported evidence was of very low quality.

None of the study papers reported a return to euglycaemia following birth. HbA1c data were reported in only 1 study, which had few cases of confirmed diabetes. The timing of the HbA1c test in that study was undertaken at varying intervals between 2 and 12 months. Therefore, the guideline development group felt that the chance of the results reflecting, in part, glucose haemostasis during the latter stages of the pregnancy complicated by gestational diabetes was low and more likely to reflect the non-pregnant state.

8.3.1.7.5 *Other considerations*

The populations included in the IGT studies are mainly women who would be considered to be ethnic minorities in England and Wales. It is not clear how applicable the results of these studies are to the UK population.

The guideline development group noted that FPG levels of 7.0 mmol/litre or higher and 6.1 mmol/litre or higher are the diagnostic thresholds for diabetes and IFG respectively, as derived from the oral glucose tolerance test, which was the reference standard used in this review.

Because FPG is used as part of the diagnosis of diabetes, the expected sensitivity and specificity of using 7.0 mmol/litre or above to detect diabetes should be 100%. However, this is not the case in the reported evidence.

False negatives are reported in all of the studies that use an FPG cut-off of 7.0 mmol/litre, which affects the calculated sensitivity of the tests. If any of true positives, false positives, false negatives or true negatives were equal to zero, a value of 0.5 was added to the values so that a likelihood ratio could be calculated. This affected the calculated specificity of the tests.

The evidence shows that an FPG threshold of greater than or equal to 6.0 mmol/litre is highly predictive of diabetes. The guideline development group believed these women should undergo a confirmatory test. This test could be a second FPG, HbA1c or 75 g OGTT. (The WHO has concluded that HbA1c can be used as a diagnostic test for diabetes).

An FPG value less than 6 mmol/litre is very useful for excluding diabetes. However, the group believes such women should continue with their lifestyle and dietary advice because they are at high risk of developing future glucose intolerance.

The group was aware that in 2011 the WHO recommended an HbA1c diagnostic threshold for type 2 diabetes of 48 mmol/mol (6.5%). However, the WHO did not provide specific guidance on HbA1c criteria for people at increased risk of type 2 diabetes. The group noted that a report from a UK expert advisory group on the implementation of WHO guidance recommended using HbA1c values between 42 mmol/mol and 47 mmol/mol (6.0–6.4%) to indicate that a person was at high risk of type 2 diabetes. Importantly, that expert group recognised that there is a continuum of risk across a range of subdiabetic HbA1c levels and that people with an HbA1c below 42 mmol/mol (6.0%) may also be at risk (John et al., 2012). Given this acknowledgement that values lower than 42 mmol/mol (6.0%) were indicative of risk and the finding in the review undertaken for this question that 39 mmol/mol (5.7%) was associated with a positive likelihood ratio of 11.23 for the diagnosis of diabetes ('a very useful test') the guideline development group felt this lower value of 39 mmol/mol (5.7%) would represent a more useful threshold for screening and was based on evidence. They acknowledged that other factors may impact on HbA1c values in the postnatal period, including anaemia and the associated reactive erythropoiesis, breastfeeding and altered iron stores.

Finally, the guideline development group was of the view that if the postnatal test result (FPG or HbA1c) suggested the woman was at increased risk of developing type 2 diabetes, then they should be managed in accordance with the NICE guideline on preventing type 2 diabetes: risk identification and interventions for individuals at high risk.

8.3.1.8 **Key conclusions**

FPG is a more useful test than HbA1c for detecting diabetes than HbA1c, but for convenience and other reasons, HbA1c may be preferable.

FPG cannot be used to reliably diagnose IGT.

There are no available data for the accuracy of using HbA1c to detect IGT or IFG.

If HbA1c was used, then 39 mmol/mol (5.7%) represented the threshold for an increased risk of diabetes.

8.3.1.9 Recommendations

All recommendations are collated in 8.3.2.9.

8.3.1.10 Research recommendations

All research recommendations are in 8.3.2.9.

8.3.2 Timing of postnatal tests for glucose intolerance

8.3.2.1 Review question

What is the optimal timing of postnatal testing for the detection of glucose intolerance after pregnancy in women who have had gestational diabetes (but are euglycaemic before they are transferred to community care)?

8.3.2.2 Introduction

The objective of this review question is to determine when testing should be undertaken postnatally to identify glucose intolerance in women who have had gestational diabetes but are euglycaemic when they are transferred to community care. The 2008 guideline recommended that women who were diagnosed with gestational diabetes should be offered a fasting plasma glucose (FPG) measurement (but not an oral glucose tolerance test [OGTT]) at the 6 week postnatal check, and annually thereafter. The effectiveness of offering a test coinciding with the postnatal check at 6 weeks is one aspect of postnatal testing being revisited through this review question. Additionally, although the question refers to 'postnatal' testing, the term postnatal is interpreted more broadly than the standard 6 week postnatal period to allow consideration of studies that evaluate testing at 12 weeks after the birth or later. Moreover, the guideline scope is broad enough to allow the guideline development group to consider recommending testing annually after pregnancy, as in the 2008 guideline.

Studies that were eligible for inclusion in the review were those that determined the incidence of glucose intolerance at specified intervals after pregnancy through an HbA1c measurement in women who were euglycaemic before they were transferred to community care. Additionally, studies that determined the incidence of glucose intolerance using an FPG measurement or a 75 g OGTT were eligible for inclusion, provided the WHO 1999 diagnostic criteria for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and/or diabetes or equivalent, were used. (IFG is defined as FPG of 6.1 mmol/litre and above but less than 7.0 mmol/litre and 2 hour plasma glucose less than 7.8 mmol/litre if measured; IGT is defined as FPG less than 7.0 mmol/litre and 2 hour FPG of 7.8 mmol/litre and above but less than 11.1 mmol/litre; and diabetes is defined as FPG of 7.0 mmol/litre and above, or 2 hour FPG 11.1 mmol/litre or more). For example, the American Diabetes Association (ADA) 2012 diagnostic criteria for diabetes (but not IFG or IGT) are equivalent to the WHO 1999 diagnostic criteria, and so studies that used the ADA 2012 diagnostic criteria for diabetes were also eligible for inclusion. These were the same study test inclusion criteria as in the review question relating to diagnostic accuracy of postnatal tests.

A single systematic search was undertaken to cover both review questions relating to postnatal testing for glucose intolerance (diagnostic test accuracy and timing).

8.3.2.3 Description of included studies

Fifty-one studies were identified for inclusion for this review question (Aberg et al., 2002; Agarwal et al., 2004; Albareda et al., 2003; Albareda et al., 2004; Anderberg et al., 2011; Buchanan et al., 1998; Chew et al., 2012; Conway & Langer 1999; Costa et al., 2000;

Ekelund et al., 2010; Ferrara et al., 2009; Gingras et al., 2013; Holt et al., 2003; Hossein-Nezhad et al., 2009; Hunt & Conway 2008; Jacob Reichelt et al., 2002; Jang et al., 2003; Joseph et al., 2013; Katon et al., 2012; Katreddy et al., 2013; Kerimoglu et al., 2010; Kim et al., 2011; Kitzmiller et al., 2007; Kousta et al., 1999; Krishnaveni et al., 2007; Kwak et al., 2013; Kwong et al., 2009; Lauenborg et al., 2004; Lawrence et al., 2010; Lee et al., 2008; Lin et al., 2005; Lobner et al., 2006; Malinowska-Polubiec et al., 2012; McClean et al., 2010; Megia et al., 2012; Myers et al., 2014; Noussitou et al., 2005; Ogonowski & Miazgowski 2009; Pallardo et al., 1999; Pallardo et al., 2003; Reinblatt et al., 2006; Retnakaran et al., 2009; Rivas et al., 2007; Rivero et al., 2008; Saucedo et al., 2012; Schaefer-Graf et al., 2002; Schaefer-Graf et al., 2009; Stasenko et al., 2010; Tam et al., 2007; Vambergue et al., 2008; Xiang et al., 2010). Thirteen of the studies were those identified for inclusion for the review question relating to diagnostic accuracy of postnatal tests (Agarwal et al., 2004; Conway & Langer 1999; Ferrara et al., 2009; Holt et al., 2003; Hunt & Conway 2008; Jacob Reichelt et al., 2002; Joseph et al., 2013; Kitzmiller et al., 2007; Kousta et al., 1999; McClean et al., 2010; Megia et al., 2012; Myers et al., 2014; Reinblatt et al., 2006) while the remaining studies reported incidence data only.

Of the 51 included studies:

- 24 were prospective cohort studies (Anderberg et al., 2011; Buchanan et al., 1998; Ekelund et al., 2010; Gingras et al., 2013; Hossein-Nezhad et al., 2009; Hunt & Conway 2008; Jang et al., 2003; Kim et al., 2011; Krishnaveni et al., 2007; Kwaket al., 2013; Lin et al., 2005; Lobner et al., 2006; Megia et al., 2012; Ogonowski & Miazgowski 2009; Pallardo et al., 1999; Pallardo et al., 2003; Jacob Reichelt et al., 2002; Retnakaran et al., 2009; Rivas et al., 2007; Rivero et al., 2008; Saucedo et al., 2012; Schaefer-Graf et al., 2009; Vambergue et al., 2008; Xiang et al., 2010)
- 24 were retrospective cohort studies (Aberg et al., 2002; Agarwal et al., 2004; Albareda et al., 2003; Albareda et al., 2004; Conway & Langer 1999; Costa et al., 2000; Ferrara et al., 2009; Holt et al., 2003; Joseph et al., 2013; Katon et al., 2012; Katreddy et al., 2013; Kerimoglu et al., 2010; Kitzmiller 2007; Kousta et al., 1999; Kwong et al., 2009; Lauenborg et al., 2004; Lawrence et al., 2010; McClean et al., 2010; Myers et al., 2014; Noussitou et al., 2005; Reinblatt et al., 2006; Schaefer-Graf et al., 2002; Stasenko et al., 2010; Tam et al., 2007)
- 2 were case-control studies (Lee et al., 2008; Malinowska-Polubiec et al., 2012).
- 1 was a cross sectional study (Chew et al., 2012).

Any definition of gestational diabetes was accepted for this review. Of the studies that reported the criteria used to define gestational diabetes, 5 studies (Holt et al., 2003; Kousta et al., 1999; McClean et al., 2010; Ogonowski & Miazgowski 2009; Tam et al., 2007) used the WHO 1999 criteria using a 75 g OGTT. However, the cut-off reported in 1 of these studies (Tam et al., 2007) did not exactly match the WHO criteria. In another study (Kousta et al., 1999), which recruited women from 5 London hospitals, some hospitals used the WHO 1999 criteria and elsewhere gestational diabetes was diagnosed when the area under the plasma glucose curve exceeded 43 mmol/litre/h during a 3 hour 75 g OGTT. A further 9 studies (Aberg et al., 2002; Anderberg et al., 2011; Chew et al., 2012; Ekelund et al., 2010; Joseph et al., 2013; Kwong et al., 2009; Myers et al., 2014; Rivero et al., 2008; Schaefer-Graf et al., 2009) also employed a 75 g OGTT but results were not interpreted according to the WHO criteria. The majority of the remaining studies used a 50 g challenge test followed by a 100 g 3 hour OGTT to diagnose gestational diabetes.

The type of postnatal test undertaken was:

- a 75 g 2 hour OGTT in 37 studies (Aberg et al., 2002; Albareda et al., 2003; Albareda et al., 2004; Anderberg et al., 2011; Chew et al., 2012; Buchanan et al., 1998; Conway & Langer 1999; Costa et al., 2000; Ekelund et al., 2010; Gingras et al., 2013; Hossein-Nezhad et al., 2009; Jang et al., 2003; Joseph et al., 2013; Katon et al., 2012; Katreddy et al., 2013; Kim et al., 2011; Kitzmiller et al., 2007; Krishnaveni et al., 2007; Kwak et al., 2013; Lauenborg et al., 2004; Lin et al., 2005; Lobner et al., 2006; Malinowska-Polubiec et al., 2012; McClean et al., 2010; Myers et al., 2014; Noussitou et al., 2005; Ogonowski

& Miazgowski 2009; Pallardo et al., 1999; Pallardo et al., 2003; Retnakaran et al., 2009; Rivas et al., 2007; Rivero et al., 2008; Saucedo et al 2012; Schaefer-Graf et al., 2002; Schaefer-Graf et al., 2009; Tam et al., 2007; Xiang et al., 2010),

- a FPG or 75 g OGTT in 6 studies (Hunt et al., 2008; Kerimoglu et al., 2010; Kwong et al., 2009; Lawrence et al., 2010; Stasenko et al., 2010; Vambergue et al., 2008)
- both an FPG and 75 g OGTT in 6 studies (Agarwal et al., 2004; Holt et al., 2003; Jacob-Reichelt et al., 2002; Kousta et al., 1999; Megia et al., 2012; Reinblatt et al., 2006)
- an FPG only in 2 studies (Ferrara et al., 2009; Lee et al., 2008).

Two studies, 1 of which performed a 75 g OGTT (Kim et al., 2011) and the other an FPG and 75 g OGTT (Megia et al., 2012) also carried out an HbA1c test.

Where possible, the timing at which testing was performed was categorised according to 3 arbitrary, but predefined, intervals after pregnancy. The categories, which were chosen by the guideline development group as being practicable in terms of implementation, related to testing performed at:

- 0–13 weeks after the birth
- more than 13 weeks after the birth and up to 1 year
- more than 1 year after the birth.

Twenty-seven studies performed testing in only 1 of the time intervals specified by the guideline development group. Nineteen of these performed testing at up to 13 weeks (Agarwal et al., 2004; Conway & Langer 1999; Hunt & Conway 2008; Holt et al., 2003; Hossein-Nezhad et al., 2009; Jang et al., 2003; Joseph et al., 2013; Katreddy et al., 2013; Kerimoglu et al., 2010; Kwak et al., 2013; Lauenborg et al., 2004; Lawrence et al., 2010; Lee et al., 2008; McClean et al., 2010; Myers et al., 2014; Ogonowski & Miazgowski 2009; Rivero et al., 2008; Retnakaran et al., 2009; Saucedo et al., 2012); 1 study performed testing between 13 weeks and up to 1 year (Aberg et al., 2002) and the remaining 6 studies performed testing at more than 1 year (Anderberg et al., 2011; Gingras et al., 2013; Krishnaveni et al., 2007; Kwak et al., 2013; Jacob Reichelt et al., 2002; Tam et al., 2007; Vambergue et al., 2008; Xiang et al., 2010).

Four studies examined postnatal testing of glucose tolerance in more than one of the time intervals specified by the guideline development group. One study performed testing at up to 13 weeks and twice between 13 weeks and 1 year (Saucedo et al., 2012; performed testing at 6 weeks, 6 months and 1 year) and reported the cumulative incidence at each of the time points. The second performed testing at 1 year, 2 years and 5 years (Ekelund et al., 2010). This study performed a 75 g OGTT unless diabetes was diagnosed in the previous test and therefore reported incidence in those tested at a given time point and not cumulative incidence. However, a greater proportion of women seemed to have returned at 5 years than at 2 years. The third study was cross-sectional and reported 75 g OGTT results of women with previous gestational diabetes selected using randomly samples from a hospital database (Chew et al., 2012). The duration from the index pregnancy ranged from 3 months to 15 years. The last study carried out on one occasion in a group of women in the first 6 months after delivery (Lawrence et al., 2010). The timing appears to be arbitrary. The study presented the data in 3 time intervals after delivery: 7 days to 6 weeks, 6 to 12 weeks and at more than 12 weeks and up to 6 months. The first two of these time points fall with the first predefined interval specified by the guideline development group (0–13 weeks). The third overlaps the group's predefined interval (more than 13 weeks to up to 1 year).

In a further 21 studies the timing of testing overlapped the group's predefined intervals (Buchanan et al., 1998; Costa et al., 2000; Ferrara et al., 2009; Katon et al., 2012; Kim et al., 2011; Kitzmiller et al., 2007; Koustaet al., 1999; Kwong et al., 2009; Lawrence et al., 2010; Lin et al., 2005; Lobner et al., 2006; Malinowska-Polubiec et al., 2012; Megia et al., 2012; Noussitou et al., 2005; Pallardo et al., 1999; Pallardo et al., 2003; Reinblatt et al., 2006;

Rivas et al., 2007; Schaefer-Graf et al., 2002; Schaefer-Graf et al., 2009; Stasenko et al., 2010).

Of the 51 studies reporting incidence data, only 1 study documented a return to euglycemia in the immediate days following delivery and before discharge from hospital (Lobner et al., 2006).

8.3.2.4 Evidence profile

The GRADE profiles for this review question are presented in Tables 84 to 95.

Table 84: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at up to 13 weeks after birth

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Hunt & Conway 2008)	707	288	4-6 weeks	4.5% (13/288)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Holt et al., 2003)	152	122	6 weeks	2.5% (3/122)	2.5% (3/122)	3.3% (4/122)	Very low	Retrospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]
1 (McClean et al., 2010)	1189	985	6 weeks	11.1% (109/985)	11.6% (114/985) [IGT and IFG: 5.3% (52/985)]	10.3% (101/985)	Very low	Retrospective cohort	Very serious[a,b,d,e]	NA	Serious[f]	Serious[g]	Yes[k]
1 (Rivero et al., 2008)	125	109	6 weeks	17.4% (19/109)	NR	NR	Very low	Prospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[l]
1 (Saucedo et al., 2012)	100	52	6 weeks	17.3% (9/52)	NR	NR	Very low	Prospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[m]
1 (Joseph et al., 2013)	258	147	6 weeks	5.4% (8/147)	14.2% (21/147)	15.6% (23/147)	Very low	Retrospective cohort	Very serious[a,c,d,e]	NA	Serious[f]	Serious[g]	Yes[n]
1 (Katreddy et al.,2013)	408	203	6 weeks	3.5% (7/203)	NR	5.4% (11/203)	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[o]
1 (Myers et al., 2014)	NR	629	median 44 days (IQR 42-50)	4.8% (30/629)	NR	NR	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[p]
1 (Agarwal et al., 2004)	1641	549	4-8 weeks	9.1% (50/549)	15.3% (84/549)	5.5% (30/549)	Very low	Retrospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[q]
1 (Jang et al., 2003)	392	311	6-8 weeks	15.1% (47/311)	NR	NR	Very low	Prospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[r]
1 (Lauenborg et al., 2004)	753	481	2 months	35.6% (171/481)	IGT/IFG: 27.0% (130/481)	NR	Very low	Retrospective cohort	Very serious[c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[s]
1 (Kwak et al., 2013)	NR	843	2 months	12.5% (105/843)	NR	NR	Very low	Prospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[t]

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirect-ness	Imprecision	Other considerations
1 (Ogonowski & Miazgowski 2009)	855	318	5-9 weeks	1.3% (4/318)	NR	NR	Very low	Prospective cohort	Very serious[a,c,d,e]	NA	Serious[f]	Serious[g]	Yes[u]
1 (Kerimoglu et al., 2010)	78	10	6-12 weeks	50.0% (5/10)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[v]
1 (Retnakaran et al., 2009)	NR	284	3 months	3.2% (9/284)	NR	1.1% (3/284)	Very low	Prospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[w]
1 (Conway & Langer 1999)	1017	179	4-13 weeks	7.8% (14/179)	NR	NR	Very low	Retrospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[x]

, IFG impaired fasting glucose, IGT impaired glucose tolerance, NA not applicable, NR not reported

a. The selection criteria were not clearly reported

b. The whole sample or a random selection of the sample did not receive verification using the reference standard

c. The reference standard was not independent of the index test

d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

g. Total number of events less than 300 for each form of glucose intolerance

h. Other considerations: Country: USA, Ethnicity of population: Mexican American (94%)

I. Some clinical data available when the test is used in practice was not available when test results were interpreted

j. Country: UK, Ethnicity of population: White (86%), Asian (14%)

k. Country: UK, Ethnicity of population: South Asian-Pakistani, Bangladeshi or Indian (71%), White European (26%), not reported (4%)

l. Country: Brazil, Ethnicity of population: NR

m. Country: Mexico, Ethnicity of population: NR

n. Country: UK Ethnicity of population: White (90%), Asian (6%), Afro-Caribbean (2%), Southeast Asian (2%)

o. Country: UK Ethnicity of population: White (70%) and Other racial groups (Asian: 50, Afro-Caribbean: 2, others: 9)(30%)

p. Country: UK Ethnicity of population: White (17%), Black (16.1%), Asian (40.7%), Other (26.3%)

q. Country: United Arab Emirates (UAE), Ethnicity of population: Arabs (78.8%), Indian National (20.5%)

r. Country: Korea, Ethnicity of population: Korean women

s. Country: Denmark, Ethnicity of population: Danish population

t. Country: Korea Ethnicity of population: Not reported

u. Country: Poland, Ethnicity of population: White (100%)

v. Country: Turkey, Ethnicity of population: NR

w. Country: Canada, Ethnicity of population: White - In those with IGT by American Diabetes Association (ADA) only (85.7%), In those with GDM by ADA only (74.5%). Asian-In those with IGT by ADA only (6.1%), In those with GDM by ADA only (17.6%). Other-In those with IGT by ADA only (8.2%), In those with GDM by ADA only (7.8%)

x. Country: USA, Ethnicity of population: NR

Table 85: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose test or oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at up to 13 weeks after birth

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other consider ations
1 (Hunt & Conway 2008)	707	112	4-6 weeks	4.5% (5/112)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Holt et al., 2003)	152	122	6 weeks	1.6% (2/122)	NR	NR	Very low	Retrospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]
1 (Lee et al., 2008)	868	620	6 weeks	11.5% (71/620)	NR	NR	Very low	Retrospective case control	Very serious[a,c,d,e,k]	NA	Serious[f]	Serious[g]	Yes[l]
1 (Agarwal et al., 2004)	1641	549	4-8 weeks	6.6% (36/549)	NR	9.3% (51/549)	Very low	Retrospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[m]
1 (Hossein-Nezhad et al., 2009)	114	98	6-12 weeks	8.1% (8/98)	NR	NR	Very low	Prospective cohort	Very serious[a,c,d,e]	NA	Serious[f]	Serious[g]	Yes[n]
1 (Kerimoglu et al., 2010)	78	27	6-12 weeks	7.4% (2/27)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[o]

NA not applicable, NR not reported
a. The selection criteria were not clearly reported
b. The whole or random selection of the sample did not receive verification using the reference standard
c. The reference standard was not independent of the index test
d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Total number of events less than 300 for each form of glucose intolerance
h. Country: USA, Ethnicity of population: Mexican American (94%)
I. Some clinical data available when the test is used in practice was not available when test results were interpreted
j. Country: UK, Ethnicity of population: White (86%), Asian (14%)
k. Unclear whether all clinical data available when the test is used in practice was available when test results were interpreted

l. Country: Korea Ethnicity of population: NR
m. Country: United Arab Emirates (UAE), Ethnicity of population: Arabs (78.8%), Indian National (20.5%)
n. Country: Iran Ethnicity of population: NR; Country: Turkey, Ethnicity of population: NR

Table 86: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose test or oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed on more than one occasion between birth and 13 weeks

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limita-tions	Inconsist-ency	Indirectness	Imprecision	Other consider ations
1 (Lawrence et al., 2010)	11,825	2596	7 days to <6 weeks	0.6% (16/2596)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Lawrence et al., 2010)	11,825	2728	6-12 weeks	1.0% (27/2728)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]

NA not applicable, NR not reported
a. The whole sample or a random selection of the sample did not receive verification using the reference standard
b. The reference standard was not independent of the index test
c. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
d. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
e. Uninterpretable, indeterminate or intermediate test results were not reported
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Total number of events less than 300 for each form of glucose intolerance
h. Country: USA Ethnicity of population: Hispanic (53%), Black (4%), Asian/Pacific Islander (22%), Other/unknown (1%), Non-Hispanic white (20%)

Table 87: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at more than 13 weeks and up to 1 year

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Saucedo et al., 2012)	100	52	6 months	Cumulative incidence: 32.7% (17/52)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[f]
1 (Aberg et al., 2002)	315	229	1 year	9.2% (21/229)	NR	NR	Very low	Retrospective cohort	Very serious[a,c,g,h]	NA	Serious[d]	Serious[e]	Yes[i]
1 (Saucedo et al., 2012)	100	52	1 year	Cumulative incidence: 48.1% (25/52)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[f]
1 (Ekelund et al., 2010)	174	123	1 year	12.2% (15/123)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[j]

NA not applicable, NR not reported

a. The reference standard was not independent of the index test

b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

d. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

e. Total number of events less than 300 for each form of glucose intolerance

f. Country: Mexico, Ethnicity of population: NR

g. The selection criteria were not clearly reported

h. Some clinical data available when the test is used in practice was not available when test results were interpreted

i. Country: Sweden, Ethnicity of population: NR

j. Country: Sweden, Ethnicity of population: In those with Normal Glucose Tolerance at 5 years postpartum 59% Swedish, in those with Impaired Glucose Tolerance-Impaired Fasting Glucose at 5 years postpartum 26% Swedish, in those with Diabetes at 5 years postpartum 42% Swedish

Table 88: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at more than 1 year

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirect-ness	Imprecision	Other considerations
1 (Anderberg et al., 2011)	298	160	1-2 years	10.6% (17/160)	23.8% (38/160)	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[g]
1 (Ekelund et al., 2010)	159	85	2 year	8.2% (7/85)	NR	NR	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[h]
1 (Xiang et al., 2010)	NR	72	15-30 months	At a median follow-up of 72 (12-142) months: 43.1% (31/72)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d,i]	NA	Serious[e]	Serious[f]	Yes[j]
1 (Gingras et al., 2013)	215	178	At a mean 3.5±1.9 years	18% (32/182)	NR	NR	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[k]
1 (Kwak et al., 2013)	738	370	At a median 49 months (IQR 30-82)	23.8% (88/370)	NR	NR	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[f]	Serious[g]	Yes[m]
1 (Krishnaveni et al., 2007)	41	35	5 years	37.1% (13/35)	IGT/IFG: 31.4% (11/35)	NR	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[m]
1 (Ekelund et al., 2010)	152	112	5 years	12.5% (14/112)	24.1% (27/112)	3.6% (4/112)	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[h]
1 (Vambergue et al., 2008)	466	209	6 years	NR	13.4% (28/209)	NR	Very low	Prospective cohort	Very serious[a,b,c,d,o]	NA	Serious[e]	Serious[f]	Yes[p]

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirect-ness	Imprecision	Other considerations
1 (Jacob Reichelt et al., 2002)	159	117	4-8 years	7.7% (9/117)	NR	NR	Very low	Prospective cohort (case-cohort)	Very serious[a,b,c,d,i]	NA	Serious[e]	Serious[f]	Yes[q]
1 (Tam et al., 2007)	134	67	7-10 years	9.0% (6/67)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[r]

IFG impaired fasting glucose, IGT impaired glucose tolerance, NA not applicable, NR not reported

a. The selection criteria were not clearly reported

b. The reference standard was not independent of the index test

c. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

d. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

e. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

f. Total number of events less than 300 for each form of glucose intolerance

g. Country: Sweden, Ethnicity of population: Swedish (58%), European except Swedish (16%), Non-European (27%)

h. Country: Sweden, Ethnicity of population: In those with NGT at 5 years postpartum 59% Swedish, in those with IGT-IFG at 5 years postpartum 26% Swedish, in those with Diabetes at 5 years postpartum 42% Swedish.

i. Some clinical data available when the test is used in practice was not available when test results were interpreted

j. Country: USA, Ethnicity of population: All Hispanic women

k. Country: Canada, Ethnicity of population: Non-Hispanic white (94.6%), Other (5.4%)

l. Country: Korea Ethnicity of population: Not reported

m. Country: India Ethnicity of population: NR

o. The whole sample or a random selection of the sample did not receive verification using the reference standard

p. Country: France, Ethnicity of population: In subjects with normal glucose tolerance at follow-up 95.4% French, in subjects with IFG at follow-up 85.7% French, in sujects with IGT at follow-up 72.1% French, in subjects with Diabetes at follow-up 75.8% French.

q. Country: Brazil, Ethnicity of population: NR

r. Country: Hong Kong, Ethnicity of population: All Chinese women

Table 89: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose test applied using the World Health Organization 1999 diagnostic criteria – testing performed at more than 1 year

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Vambergue et al., 2008)	466	295	6 years	18.0% (53/295)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Jacob Reichelt et al., 2002)	159	117	4-8 years	6.8% (8/117)	NR	NR	Very low	Prospective cohort	Very serious[a,c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]

NA not applicable, NR not reported

a. The selection criteria were not clearly reported

b. The whole sample or a random selection of the sample did not receive verification using the reference standard

c. The reference standard was not independent of the index test

d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

g. Total number of events less than 300 for each form of glucose intolerance

h. Country: France, Ethnicity of population: In subjects with normal glucose tolerance at follow-up 95.4% French, in subjects with Impaired fasting glucose at follow-up 85.7% French, in subjects with Impaired glucose tolerance at follow-up 72.1% French, in subjects with Diabetes at follow-up 75.8% French

i. Some clinical data available when the test is used in practice was not available when test results were interpreted

j. Country: Brazil, Ethnicity of population: NR

Table 90: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at more than one time interval to one year or more

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Saucedo et al., 2012)	100	52	6 weeks	17.3% (9/52)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[f]

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Saucedo et al., 2012)	100	52	6 months	Cumulative incidence:32.7% (17/52)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[f]
1 (Saucedo et al., 2012)	100	52	1 year	Cumulative incidence:48.1% (25/52)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[f]
1 (Ekelund et al., 2010)	174	123	1 year	12.2% (15/123)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[g]
1 (Ekelund et al., 2010)	159	85	2 year	8.2% (7/85)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[g]
1 (Ekelund et al., 2010)	152	112	5 years	12.5% (14/112)	24.1% (27/112)	3.6% (4/112)	Very low	Prospective cohort	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[g]
1 (Chew et al., 2012)	342	170	1-5 years	8.8% (15/170)	15.9% (27/170)	NR	Very low	Cross sectional	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[h]
1 (Chew et al., 2012)	342	94	6-10 years	22.3% (21/94)	7.5% (7/94)	NR	Very low	Cross sectional	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[h]
1 (Chew et al., 2012)	342	78	11-15 years	21.8% (17/78)	10.3% (8/78)	NR	Very low	Cross sectional	Very serious[a,b,c]	NA	Serious[d]	Serious[e]	Yes[h]

NA not applicable, NR not reported
a. The reference standard was not independent of the index test
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
e. Total number of events less than 300 for each form of glucose intolerance
f. Country: Mexico, Ethnicity of population: Not reported
g. Country: Sweden, Ethnicity of population: Not reported
h. Country: Malaysia Ethnicity of population: Not reported

Table 91: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose or 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – testing performed at more than one time interval up to 6 months after birth

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsist-ency	Indirect-ness	Imprecision	Other considerations
1 (Lawrence et al., 2010)	11825	2596	7 days to <6 weeks	0.6% (16/2596)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Lawrence et al., 2010)	11825	2728	6-12 weeks	1.0% (27/2728)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Lawrence et al., 2010)	11825	533	>12 weeks to 6 months	4.3% (23/533)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]

NA not applicable, NR not reported
a. The reference standard was not independent of the index test
b. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
c. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
d. The whole sample or a random selection of the sample did not receive verification using the reference standard
e. Uninterpretable, indeterminate or intermediate test results were not reported
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Total number of events less than 300 for each form of glucose intolerance
h. Country: USA Ethnicity of population: Hispanic (53%), Black (4%), Asian/Pacific Islander (22%), Other/unknown (1%), Non-Hispanic white (20%)

Table 92: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a using a 75 g oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – timing of testing overlaps the predefined categories

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Schaefer-Graf et al., 2002)	4041	1636	1-4 months	14.1% (230/1636)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Diabetes:Serious[f] IGT/IFG: No serious imprecision	Yes[g]
1 (Rivas et al., 2007)	169	117	2-4 months	18.8% (22/117)	NR	11.97% (14/117)	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[h]
1 (Kitzmiller et al., 2007)	NR	527	6-21 weeks	4.7% (25/527)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[i]
1 (Buchanan et al., 1998)	233	122	1-6 months	9.8% (12/122)	NR	NR	Very low	Prospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[j]
1 (Reinblatt et al., 2006)	1350	275	6 weeks to 6 months	9.5% (26/275)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d,k]	NA	Serious[e]	Serious[f]	Yes[l]
1 (Albareda et al., 2003)	982	696	6 weeks or after cessation of breast feeding, whichever occurred later.	At 6 years: 5.6% (39/696)	At 6 years: 8.8% (61/696)	At 6 years: 3.6% (25/696)	Very low	Retrospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[m]
1 (Albareda et al., 2003)	982	696	6 weeks or after cessation of breast feeding, whichever occurred later.	At 11 years: 13.8% (NR/NR)	NR	NR	Very low	Retrospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[m]

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Pallardo et al., 2003)	1350	838	3-6 months	3.6% (30/838)	NR	7.8% (65/838)	Very low	Prospective cohort	Very serious[a,b,c,d,n]	NA	Serious[e]	Serious[f]	Yes[o]
1 (Noussitou et al., 2005)	159	74	6.4-45 weeks	10.8% (8/74)	16.2% (12/74)	NR	Very low	Retrospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[p]
1 (Schaefer-Graf et al., 2009)	1184	605	13 weeks (median), within 1 year	5.5% (33/605)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[q]
1 (Megia et al., 2012)	NR	364	Within 1 year, 6 weeks-3 months n=260 (71%) 4-6 months n=69 (19%) 7 months-1 year n=35 (10%)	3.3% (12/364)	NR [IGT, IFG or both: 24.5% (89/364)]	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[r]
1 (Lin et al., 2005)	235	127	1-19 months	13.4% (17/127)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[s]
1 (Katon et al., 2012)	536	277	3-111 weeks	5.4% (15/277)	NR	NR	Very low	Retrospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[t]
1 (Kim et al., 2011)	NR	54	6 weeks-36 months	9.3% (5/54)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[u]
1 (Kousta et al., 1999)	192	165	1-86 months	15.2% (25/165)	29.7% (49/165)	4.2% (7/165)	Very low	Retrospective cohort	Very serious[b,c,d]	NA	Serious[e]	Serious[f]	Yes[v]
1 (Malinowska-Polubiec et al., 2012)	NR	155	6 months-10 years	14.8% (23/155)	30.0% (31/155)	18.1% (28/155)	Very low	Retrospective case control	Very serious[b,c,d,n]	NA	Serious[e]	Serious[f]	Yes[w]

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Lobner et al., 2006)	NR	302x	9 months, 2, 5, 8 and 11 years	At 8 years: 52.7% (55/105)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	No serious indirectness	Serious[f]	Yes[y]

IFG impaired fasting glucose, IGT impaired glucose tolerance, NA not applicable, NR not reported

a. The selection criteria were not clearly reported

b. The reference standard was not independent of the index test

c. Unclear whether index test results were interpreted without knowledge of the results of the reference standard

d. Unclear whether reference standard results were interpreted without knowledge of the results of the index test

e. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care

f. Total number of events less than 300 for each form of glucose intolerance.

g. Country: USA, Ethnicity of population: NR

h. Country: Venezuela, Ethnicity of population: NR

i. Country: USA, Ethnicity of population: Asian Indian (15%), Far East Asian (18%), Southeast Asian (29%), Hispanic (18%), Non-Hispanic white, White: European, Russian or middle eastern origin (20%)

j. Country: USA, Ethnicity of population: All Latino women

k. The spectrum of participants was not representative of the patients who will receive the test in practice

l. Country: Canada, Ethnicity of population: NR

m. Country: Spain, Ethnicity of population: All Spanish women

n. Some clinical data available when the test is used in practice was not available when test results were interpreted

o. Country: Spain, Ethnicity of population: All White women

p. Country: Switzerland, Ethnicity of population: White (51%)

q. Country: Germany, Ethnicity of population: White (100%)

r. Country: Spain, Ethnicity of population: European (91.5%), Arabic (5.5%), Hispanic (1.6%), Others: 1.4%

s. Country: Taiwan, Ethnicity of population: NR

t. Country: USA, Ethnicity of population: White (38%), African-American (18%), Hispanic (32%), Asian Indian (10%), Other (2%)

u. Country: USA, Ethnicity of population: Non-Hispanic white (73%), Asian (11%), African American (11%)

v. Country: UK, Ethnicity of population: European (35%), South Asian from India, Pakistan, Sri Lanka or Bangladesh (29%), Afro-Caribbean (17%), Other/mixed origin (19%)

w. Country: Poland, Ethnicity of population: White 100%

x. 302 women participated in follow-up, cumulative drop-out rate was 21% by 5 years

y. Country: Germany, Ethnicity of population: NR

Table 93: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose test applied using the World Health Organization 1999 diagnostic criteria – timing of testing overlaps the predefined categories

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Reinblatt et al., 2006)	1350	275	6 weeks-6 months	4.4% (12/275)	NR	2.5% (7/275)	Very low	Retrospective cohort	Very serious[a,b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Ferrara et al., 2009)	14,448	5524 (screened 1995-2006)	6 weeks-1 year	3.5% (191/5524)	NR	NR	Very low	Retrospective cohort	Very serious[c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]
1 (Ferrara et al., 2009)	14,448	564 (screened 1995-1997)	6 weeks-1 year	5.7% (32/564)	NR	NR	Very low	Retrospective cohort	Very serious[c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]
1 (Ferrara et al., 2009)	14,448	2381 (screened 2004-2006)	6 weeks-1 year	3.4% (80/2381)	NR	NR	Very low	Retrospective cohort	Very serious[c,d,e,i]	NA	Serious[f]	Serious[g]	Yes[j]
1 (Costa et al., 2000)	NR	120	2-12 months	NR	NR	3.3% (4/120)	Very low	Retrospective cohort	Very serious[b,c,d,e,k]	NA	Serious[f]	Serious[g]	Yes[l]
1 (Megia et al., 2012)	NR	364	Within the first year 6 weeks-3 months n=260 (71%) 4-6 months n=69 (19%) 7 months-1 year n=35 (10%)	1.9% (7/364)	NR	NR	Very low	Prospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[m]
1 (Kousta et al., 1999)	192	165	1-86 months	11.5% (19/165)	NR	10.9% (18/165)	Very low	Retrospective cohort	Very serious[c,d,e]	NA	Serious[f]	Serious[g]	Yes[n]

NA not applicable, NR not reported
a. The spectrum of participants was not representative of the patients who will receive the test in practice
b. The selection criteria were not clearly reported

c. The reference standard was not independent of the index test
d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Total number of events less than 300 for each form of glucose intolerance
h. Country: Canada, Ethnicity of population: NR
i. The whole or random selection of the sample did not receive verification using the reference standard
j. Country: USA, Ethnicity of population: Non-Hispanic white (28%), African-American (3.2%), Asian (31.3%), Hispanic (27.1%), Other (5.6%), Unknown (4.8%)
k. Some clinical data available when the test is used in practice was not available when test results were interpreted
l. Country: Spain, Ethnicity of population: White (100%)
m. Country: Spain, Ethnicity of population: European (91.5%), Arabic (5.5%), Hispanic (1.6%), Others (1.4)
n. Country: UK, Ethnicity of population: European (35%), South Asian from India, Pakistan, Sri Lanka or Bangladesh (29%), Afro-Caribbean (17%), Other/mixed origin (19%)

Table 94: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a fasting plasma glucose test or oral glucose tolerance test applied using the World Health Organization 1999 diagnostic criteria – timing of testing overlaps the predefined categories

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other consider ations
1 (Kwong et al., 2009)	909	438[a]	6 weeks-6 months	3.2% (14/438)	NR	NR	Very low	Retrospective cohort	Very serious[b,c,d,e]	NA	Serious[f]	Serious[g]	Yes[h]
1 (Lawrence et al., 2010)	11,825	533	>12 weeks to 6 months	4.3% (23/533)	NR	NR	Very low	Retrospective cohort	Very serious[c,d,e,l,j]	NA	Serious[f]	Serious[g]	Yes[k]
1 (Stasenko et al., 2010)	745	251	<=6 months	2.0% (5/251)	NR	NR	Very low	Retrospective cohort	Very serious[b,c,d,e,l]	NA	Serious[f]	Serious[g]	Yes[m]

NA not applicable, NR not reported
a. 95% OGTT, 5% FPG
b. The selection criteria were not clearly reported.
c. The reference standard was not independent of the index test.
d. Unclear whether index test results were interpreted without knowledge of the results of the reference standard.
e. Unclear whether reference standard results were interpreted without knowledge of the results of the index test.
f. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
g. Total number of events less than 300 for each form of glucose intolerance
h. Country: Canada, Ethnicity of population: White (56.4%), Non-White (43.4%)
i. The whole sample or a random selection of the sample did not receive verification using the reference standard

j. Uninterpretable, indeterminate or intermediate test results were not reported
k. Country: USA Ethnicity of population: Hispanic (53%), Black (4%), Asian/Pacific Islander (22%), Other/unknown (1%), Non-Hispanic white (20%)
l. Unclear if the whole sample or a random selection of the sample received verification using the reference standard
m. Country: USA Ethnicity of population: White (27%), African-American (7%), Latina (7%), Asian (59%)

Table 95: GRADE profile for incidence of glucose intolerance (diabetes, impaired glucose tolerance or impaired fasting glucose) detected postnatally in women who have had gestational diabetes using a HbA1C test applied using the World Health Organization 1999 diagnostic criteria – timing of testing overlaps the predefined categories

Number of studies	Number of potential participants	Number of women with postnatal test	Timing of postnatal test	Incidence of diabetes	Incidence of impaired glucose tolerance	Incidence of impaired fasting glucose	Quality	Design	Limita-tions	Inconsist-ency	Indirect-ness	Imprecision	Other consider ations
HbA1C ≥5.6%													
1 (Megia et al., 2012)	NR	364	Within the first year 6 weeks-3 months n=260 (71%) 4-6 months n=69 (19%) 7 months-1 year n=35 (10%)	0.5% (2/364)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[g]
HbA1C ≥5.7%													
1 (Kim et al., 2011)	NR	54	6 weeks-36 months	46.3% (25/54)	NR	NR	Very low	Prospective cohort	Very serious[a,b,c,d]	NA	Serious[e]	Serious[f]	Yes[h]

NA not applicable, NR not reported
a. The selection criteria were not clearly reported
b. The reference standard was not independent of the index test
c. Unclear whether index test results were interpreted without knowledge of the results of the reference standard
d. Unclear whether reference standard results were interpreted without knowledge of the results of the index test
e. Study did not document a return to euglycaemia in the immediate days following birth and before transfer to community care
f. Total number of events less than 300 for each form of glucose intolerance
g. Country: Spain, Ethnicity of population: European (91.5%), Arabic (5.5%), Hispanic (1.6%), Others (1.4%)
h. Country: USA, Ethnicity of population: Non-Hispanic white (73%), Asian (11%), African American (11%)

8.3.2.5 Evidence statements

All evidence included in this review was of very low quality.

8.3.2.5.1 *Testing performed at up to 13 weeks after the birth*

Using a 75 g OGTT and assessed using the WHO 1999 diagnostic criteria:

- Diabetes was detected in a median percentage of 8.5% of women (range 1.3% to 50.0%). Of the 16 cohort studies that reported data for diabetes (2 studies population less than 100; 6 studies n=100–300; 5 studies n=301–600; 3 studies n=601–1000), 1 study (n=985) mainly comprising UK ethnic minority population (South Asian women) detected diabetes in 11.1% and another study (n=549) predominantly including Middle Eastern women detected diabetes in 9.1% of the study population.
- IGT was detected in a median percentage of 12.9% of women (range 2.5% to 15.3%). Of the 4 studies that reported data for IGT (n=122, n=147, n=549, n=985), 1 study (n=985) mainly comprising of a UK ethnic minority population (South Asian women) detected IGT in 11.6% and another study (n=549) predominantly including Middle Eastern women detected IGT in 15.3% of the study population.
- IFG was detected in a median percentage of 6.9% of women (range 1.1% to 15.6%). Of the 6 cohort studies that reported data for IFG (n=122, n=147, n=203, n=284, n= 549, n=985), 1 study (n=985) mainly comprising UK ethnic minority population (South Asian women) detected IFG in 10.3% and another non-UK study (n=549) predominantly including Middle Eastern women detected IFG in 5.5% of the study population.

For this time interval, the median percentage of women taking up an offer of a 75 g OGTT was 49.8% (range 13% to 87%; number of women offered the test ranged from 78 to 1641).

Using an FPG measurement of at least 7.0 mmol/litre (the threshold based on the 75 g OGTT applied using the WHO 1999 diagnostic criteria):

- Diabetes was detected in a median percentage of 7.0% of women (range 1.6% to 11.5%).
- Of the 6 cohort studies that reported data for diabetes (n=27, n=98, n=112, n=122, n=620, n=549), 1 study (n=549) mainly comprising Middle Eastern women detected diabetes in 6.6%.
- IFG was detected in a median percentage of 9.3% of women (single non-UK study mainly comprising Middle Eastern women).

No results were reported for the detection of IGT because IGT cannot be detected using FPG alone. At this time interval, the median percentage of women taking up an offer of an FPG was 53% (range: 16% to 86%; number of women offered the test ranged from 78 to 1641).

Using an FPG or 75 g OGTT measurement applied using the WHO 1999 criteria in the cohort study (n=5324) where glucose tolerance was tested on more than one occasion in the first 13 weeks after birth, diabetes was detected in 0.6% of women tested up to 6 weeks (n=2596) and 1.0% of women tested between 6 and 12 weeks (n=2728). This was not a high risk population in terms of ethnicity. Though these data come from a single study, that study categorised women based on the timing of their first test and so the same women were not tested at more than one time point. No evidence was identified for inclusion at the other time intervals of interest to the guideline development group, nor for detection of either IGT or IFG using this test. At this time interval, the median percentage of women taking up an offer of an FPG or 75 g OGTT was 22.5% (range: 22% to 23%; number of women offered the test was 11,825).

No evidence was identified for inclusion relating to testing for diabetes, IGT or IFG using an HbA1c measurement at up to 13 weeks after the birth.

8.3.2.5.2 *Testing performed at more than 13 weeks and up to 1 year after the birth*

Using a 75 g OGTT applied using the WHO 1999 diagnostic criteria, diabetes was detected in a median percentage of 22.5% of women (range 9.2% to 48.1%) in 4 cohort studies (n=52, n=52, n=123, n=229). These studies did not represent high risk populations in terms of ethnicity. No evidence was identified for inclusion relating to testing for IGT or IFG at more than 13 weeks and up to 1 year. At this time interval, the median percentage of women taking up an offer of a 75 g OGTT was 61.5% (range: 52% to 73%; number of women offered the test ranged from 100 to 315).

Using an FPG measurement only, no evidence was identified for inclusion relating to testing for diabetes or IFG at more than 13 weeks and up to 1 year. IGT cannot be detected using FPG alone.

No evidence was identified for inclusion relating to testing for diabetes, IGT or IFG using an HbA1c measurement at more than 13 weeks and up to 1 year after the birth.

8.3.2.5.3 *Testing performed at more than 1 year after the birth*

Using a 75 g OGTT applied using the WHO 1999 diagnostic criteria:
- Diabetes was detected in a median percentage of 12.5% of women (range 7.7 to 43.1%). Of the 9 cohort studies (4 studies population less than 100; 3 studies n=100–200; remaining studies n=209 and n=370) that reported data for diabetes, 1 study from India (ethnicity percentages not reported) detected diabetes in 37.1% of women.
- IGT was detected in a median percentage of 23.8% of women (range 13.4% to 24.1%). None of the 3 cohort studies (n=112, n=160, n=209) that reported data for IGT provided evidence from high risk populations in terms of ethnicity.
- IFG was detected in a median percentage of 3.6% of women (in 1 cohort study; n=112). This evidence did not come from a high risk population in terms of ethnicity.

At this time interval, the median percentage of women taking up an offer of a 75 g OGTT was 54% (range: 45% to 85%; number of women offered the test ranged from 41 to 466).

Using an FPG measurement of at least 7.0 mmol/litre (that is, the threshold based on the 75 g OGTT applied using the WHO 1999 diagnostic criteria), diabetes was detected in a median percentage of 12.4% of women (range 6.8% to 18.0%). Neither of the 2 cohort studies (n=117, n=295) that reported data for diabetes provided evidence that related to a high risk population in terms of ethnicity. No evidence was identified for inclusion relating to testing for IFG at more than 1 year. IGT cannot be detected using FPG alone. At this time interval, the median percentage of women taking up an offer of an FPG measurement was 68.5% (range: 63% to 74%; number of women offered the test ranged from 159 to 466).

No evidence was identified for inclusion relating to testing for diabetes, IGT or IFG using an HbA1c measurement at more than 1 year after the birth.

8.3.2.5.4 *Testing performed at more than one time interval*

Using a 75 g OGTT applied using the WHO 1999 diagnostic criteria, the incidence of diabetes was 17.3% at 6 weeks, increasing to 32.7% at 6 months and 48.1% at 1 year (cumulative incidence) in 1 cohort study (n=52). This evidence apparently did not come from a high risk population in terms of ethnicity. At all 3 time points, the proportion of women taking up an offer of a 75 g OGTT was 52% (the number of women offered the test was 100).

Using a 75 g OGTT applied using the WHO 1999 diagnostic criteria, diabetes was detected in 12.2%, 8.2% and 12.5% of women tested at 1 year (n=123), 2 years (n=85) and 5 years (n=112) respectively in 1 cohort study. This study performed a 75 g OGTT unless diabetes was diagnosed in the previous test. IGT and IFG were detected respectively in 24.1% and 3.6% of women tested at 5 years in this same study (n=112). This evidence did not relate to

a high risk population in terms of ethnicity. At each of the time points, the proportion of women taking up an offer of a 75 g OGTT was 71%, 53% and 74% respectively (the number of women offered the test was 174, 159 and 152 respectively).

Using a 75 g OGTT applied using the WHO 1999 diagnostic criteria, diabetes was detected in 1 cross-sectional study in 8.8%, 22.3% and 21.8% of women and IGT detected in 15.9%, 7.6% and 10.3% of women at the following intervals after the index pregnancy: 1–5 years (n=170), 6–10 years (n=94) and 11–15 years (n=78) respectively. The study was performed in Malaysia but the ethnicity of participants was not reported.

Using an FPG or 75 g OGTT measurement applied using the WHO 1999 criteria, evidence from 1 cohort study demonstrated that diabetes was detected in 0.6%, 1.0% and 4.3% of women tested at: 7 days to 6 weeks (n=2596); at 6 to 12 weeks (n=2728) and at more than 12 weeks up to 6 months (n=533) respectively . This study categorised women based on the timing of their first test and so different sub-populations were tested at the 3 different time points. Therefore, this study was not strictly speaking a longitudinal study. This evidence did not relate to a high risk population in terms of ethnicity. At each of the time points, the proportion of women taking up an offer of an FPG or 75 g OGTT was 22%, 23% and 5% respectively (the total number of women offered the test was 11,825 divided between the 3 time points).

No evidence was identified for inclusion relating to testing for diabetes, IGT or IFG using an HbA1c measurement at more than one of the guideline development group's predefined time intervals.

8.3.2.5.5 *Testing performed at overlapping time intervals*

For studies using a 75 g OGTT overlapping the predefined timing of test intervals:

- Diabetes was detected in 3.3% to 52.7% of women tested at times ranging from 3 weeks to 10 years.
- IGT was detected in 16.2% to 30.0% of women tested at times ranging from 1 to 86 months.
- IFG was detected in 4.2 to 18.1% of women tested at times ranging from 1 month to 10 years.

The median percentage of women taking up an offer of a 75 g OGTT was 52% (range: 20% to 86%; number of women offered the test ranged from 159 to 4041).

For studies using an FPG measurement but overlapping the predefined timing of test intervals:

- Diabetes was detected in 1.9% to 11.5% of women tested at times ranging from 1 month to 86 months in 4 cohort studies (n=165, n=275, n=364, n=2381–5524).
- IFG was detected in 2.5% to 10.9% of women tested at times ranging from 1 month to 86 months in 3 cohort studies (n=120, n=165, n=275).

The median percentage of women taking up an offer of an FPG measurement was 20% (range: 4% to 86%; number of women offered the test ranged from 192 to 14,448).

For studies using an FPG or 75 g OGTT measurement but overlapping the predefined timing of test intervals, diabetes was detected in 2.0% to 4.3% of women tested before 6 months in 3 cohort studies (n=251, n=438, n=533). No evidence was identified for inclusion relating to testing for IFG or IGT. The median percentage of women taking up an offer of an FPG or 75 g OGTT test was 34% (range: 5% to 48%; number of women offered the test ranged from 745 to 11,825).

For studies using an HbA1c measurement but overlapping the predefined timing of test intervals, diabetes was detected in a median percentage of 0.5% of women tested between 6

weeks and 1 year using a HbA1c threshold of 5.6% or more in 1 cohort study (n=364) and a median percentage of 46.3% of women tested between 6 weeks and 36 months using a HbA1c threshold of 5.7% or more in another cohort study (n=54). The proportion of women taking up an offer of an HbA1c measurement could not be calculated (the number of women offered the test was not reported).

8.3.2.6 Health economics profile

A systematic review of the literature did not find any health economic evidence relating to the optimal timing of postnatal testing for the detection of glucose intolerance after pregnancy in women who have had gestational diabetes.

The optimal timing of testing for glucose intolerance after pregnancy in women who have had gestational diabetes was initially prioritised for health economic analysis. However, no formal health economic analyses was undertaken as it was thought that any recommendation would have a relatively small cost and health impact in the context of any postnatal test and annual review.

8.3.2.7 Evidence to recommendations

8.3.2.7.1 *Relative value placed on the outcomes considered*

The guideline development group prioritised incidence of diabetes, IFG and IGT diagnosed at different time intervals in the postnatal period according to WHO 1999 criteria in order to determine the optimal timing of testing after pregnancy to identify women at risk of developing diabetes.

8.3.2.7.2 *Consideration of clinical benefits and harms*

The advantages of a correct positive diagnosis of postnatal diabetes are that appropriate, timely management to control glucose levels can be started. The guideline development group noted that up to 40% more women will be diagnosed with type 2 diabetes using a 75 g OGTT compared to an FPG alone up to 13 weeks postpartum. Moreover, it is not possible to diagnose IGT without a 75 g OGTT and the group felt that making such a diagnosis was important because although it is probably not a serious condition in itself at the time of diagnosis, these women are at higher risk of type 2 diabetes in later life and their identification provided an opportunity to motivate them to undertake lifestyle changes before type 2 diabetes was diagnosed and possibly delay its development. However, the group accepted the practical difficulties and poor acceptability of a 75 g OGTT and recognised that the evidence from this review shows that at best about 50% women diagnosed with gestational diabetes take up the offer of a 75 g OGTT postpartum.

The main advantage of a correct negative diagnosis is that it gives reassurance to the woman about her current status with regard to glucose regulation and avoids unnecessary interventions. However, the guideline development group noted that this group of women remain at high risk of type 2 diabetes and therefore require an annual test for diabetes, given the conclusions and recommendation about long-term timing of screening below.

A consequence of a false positive diagnosis is that it may result in the use of unnecessary interventions to gain tighter control of glucose regulation and also increases stress to the woman and her family.

The guideline development group believed that when a woman receives a false negative diagnosis, the lack of prompt effective treatment would, in turn, increase the likelihood of poor outcomes for the woman.

8.3.2.7.3 *Consideration of health benefits and resource uses*

In addition to diagnostic accuracy, the timing of the test may have a bearing on the cost effectiveness of postnatal testing. It is recommended that women with gestational diabetes should be followed up annually due to their increased life-time risk of glucose intolerance.

There is potentially a trade-off in the timing of postnatal testing, as a longer interval would detect more cases but earlier testing would facilitate earlier treatment, which takes the form of weight control, diet and exercise. However, it should also be noted that the additional treatment 'window' provided by early detection is relatively short, given that the women are also being reviewed annually.

8.3.2.7.4 Quality of evidence

One of the 2 studies included in the 2008 guideline was also included in this update review. Although a more comprehensive review was undertaken in this update, the quality of the evidence was rated as very low for all reported outcomes considered in the review.

Fifty studies did not document a return to euglycaemia postnatally. It is possible that women may have been checked for euglycaemia but this is not clearly reported. Therefore, the guideline development group assumed that the women included in these studies were euglycaemic.

Four studies examined postnatal testing of glucose tolerance in more than 1 of the time intervals specified by the guideline development group and may therefore be more useful to draw conclusions from. The first of these studies (Saucedo et al., 2012) performed testing at 6 weeks, 6 months and 1 year and reported the cumulative incidence at each of the time points. The second study performed testing at 1 year, 2 years and 5 years (Ekelund et al., 2010). This study performed a 75 g OGTT unless diabetes was diagnosed in the previous test and therefore reported incidence in those tested at a given time point and not cumulative incidence. However, a greater proportion of women seemed to have returned at 5 years than at 2 years. The third study (Chew et al., 2012) reported 75 g OGTT results in women who were at an interval from the index pregnancy of either 1–5 years, 6–10 years and/or 11–15 years. The prevalence of diabetes was highest in those tested at 6–10 years from the index pregnancy and plateaued in those women 11–15 years from the index pregnancy. The fourth study (Lawrence et al., 2010) reported 75 g OGTT results carried out on one occasion in a group of women in the first 6 months after delivery. The timing appears to be arbitrary. The study presented the data in 3 time intervals after delivery: 7 days to 6 weeks; 6 to 12 weeks; and at more than 12 weeks and up to 6 months. The first 2 of these time points fall with the first predefined interval specified by the guideline development group (0–13 weeks). The third overlaps the group's predefined interval (more than 13 weeks to up to 1 year). Again, the evidence for all 3 of these studies was of very low quality.

A large number of studies did testing on a single occasion but at any time in a wide interval and were therefore considered to be not particularly useful for answering this review question. This may direct future research to be aimed at studying multiple time points or in a tighter time interval to produce more meaningful results.

8.3.2.7.5 Other considerations

The guideline development group noted that some of the studies included in the review reported data from ethnic groups that are considered to be at high risk of diabetes. The majority of these studies were conducted outside the UK but 2 studies reported data from ethnic minority populations within the UK.

As described in the previous section, the group noted that the evidence demonstrated that a fasting blood glucose was a better test for identifying women at risk of diabetes postnatally, yet they recognised they had to be pragmatic and practical and hence gave the option of a fasting plasma glucose test (with the flexibility for this to be performed at any time between 6 and 13 weeks) or a non-fasting HbA1c. However, they felt that they could not offer the same flexibility of timing for women who had an HbA1c test rather than a fasting blood glucose. On the one hand, although the evidence demonstrated that an HbA1c taken between 6 and 13 weeks after birth identified some women with type 2 diabetes, delaying the test until 13 weeks avoided the theoretical possibility that an earlier test may actually reflect hyperglycaemia present in the pregnancy. On the other hand, recommending that women should have the HbA1c test 'after 13 weeks' could be interpreted as the test being done at

any time up to the first annual check, leading to an unacceptable delay in diagnosis. Thus, the guideline development group recommended that the HbA1c test be undertaken at 13 weeks postpartum.

The group noted that all but one of the studies reporting incidence data did not explicitly document a return to euglycaemia in the immediate days following birth and before discharge. It is not clear from these studies if all women were tested to exclude persisting hyperglycaemia before they were transferred to community care, as recommended in the 2008 guideline. The group believes that it is important these women should be offered a blood glucose test to exclude persisting hyperglycaemia before they are transferred to community care. Women who do not become euglycaemic after birth are very likely to have type 2 diabetes and should be referred to the diabetes care team for ongoing care and management.

Finally, on the basis of the recommendations in the NICE guideline on preventing type 2 diabetes for individuals at high risk, the guideline development group felt there should be a recommendation about offering women lifestyle advice (including weight control, diet and exercise) based on the evidence that women who had gestational diabetes were at greater risk of developing type 2 diabetes in later life.

8.3.2.8 Key conclusions

The guideline development group recognised that the rate of diabetes detected by performing a 75 g OGTT between 13 weeks and 1 year postnatally is almost double the rate of detection compared with performing a 75 g OGTT up to 13 weeks postnatally in the same population. No data relating to FPG alone were found. Therefore, the group recommended that women who have been diagnosed with gestational diabetes who became euglycaemic before discharge from hospital should be offered a test to determine whether their glucose regulation continues to be normal. This test should be performed ideally between 6 weeks and 13 weeks postnatally. The group recognised that for practical reasons this test might be performed at the 6 week postnatal check. However, women may not find this timing convenient, given the pressures of looking after their relatively newborn baby. Furthermore, some areas are now dispensing with the formal 6 week postnatal check. The guideline development group also agreed that this group of women remain at high risk of diabetes and require an annual test. Therefore, the guideline development group recommended that these women should be tested annually after their first postnatal test.

The guideline development group acknowledged that women do not respond positively to the offer of a postnatal diabetes test and recognised the need for national surveillance on the uptake of the postnatal tests for diabetes, as well as documenting the reasons for any poor uptake.

The group also recognised the importance of encouraging further research to determine if a diagnosis of IGT encourages the adoption of lifestyle changes postnatally in women who have had gestational diabetes.

8.3.2.9 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng3

8.3.2.10   Research recommendations

44. What is the efficacy of HbA1c as a diagnostic test for detecting impaired glucose tolerance in the postnatal period?

Why this is important

It is known that for some women with gestational diabetes, hyperglycaemia persists postnatally, hence postnatal testing is important. Current recommendations support testing with a fasting blood sugar, so it is inevitable that impaired glucose tolerance, which is not detected by a fasting blood sugar, will not be diagnosed. HbA1c is used as a diagnostic test outside pregnancy, and has potential advantages over fasting blood glucose in that women do not need to fast for the test, and reflects long term average glycaemic control rather than just a single fasting glucose. However, it is not known if HbA1c would be an effective test postnatally with sufficient sensitivity and specificity to be a useful diagnostic test. This would be undertaken by a comparative study of HbA1c and oral glucose tolerance testing in a group of women who had gestational diabetes.

45. What is the optimal timing of an HbA1c test for detecting diabetes and/or glucose intolerance in the postnatal period?

Why this is important

It is known that for some women with gestational diabetes, hyperglycaemia persists postnatally, hence postnatal testing is important . Gestational Diabetes is also a strong risk factor for the development of type 2 diabetes in later life, with that risk increasing over time from the index pregnancy. HbA1c is influenced by red cell turnover, hence is potentially affected by pregnancy, blood loss at delivery and lactation. Thus if used as a diagnostic test in the postnatal period, the test could be misleading, with false negative results for women, for example, who are or have been anaemic. Furthermore, if the test is undertaken too close to the end of pregnancy, abnormalities might reflect glucose intolerance during pregnancy rather than those persisting after the pregnancy. However, early diagnosis and treatment of type 2 diabetes persisting beyond pregnancy reduces the long term risk of complications from diabetes. An observational comparative study would need to be undertaken in a group of women who have had gestational diabetes and testing their glucose tolerance with both an oral glucose tolerance test and an HbA1c at 3, 6, 9 and 12 months to establish when, how

uu Note that the threshold for defining a moderate risk of developing type 2 diabetes postnatally for women who have had gestational diabetes is different from that given in NICE guideline on preventing type 2 diabetes, because of the different populations.

vv Note that the threshold for defining a high risk of developing type 2 diabetes postnatally for women who have had gestational diabetes is different from that given in NICE guideline on preventing type 2 diabetes, because of the different populations

frequently and with which test glucose tolerance testing should be undertaken in the first year after the pregnancy.

46. What is the best test for detecting impaired glucose intolerance in the immediate postpartum period?

Why this is important

It is known that some women diagnosed with gestational diabetes have pre-existing undiagnosed type 2 or occasionally type 1 diabetes. Some of these women, if untreated would develop clinically significant hyperglycaemia in the post-partum period. Identification of these women should therefore take place, before the woman is discharged from hospital with advice to discontinue home blood glucose monitoring. The timing and nature of the test to identify these women needs to be established, to prevent unnecessary tests and anxiety for the majority of women whilst appropriately identifying women who need to continue with long term therapy. An observational study would be undertaken in the first 48h after birth in a group of women who had gestational diabetes diagnosed during the pregnancy. A formal 75g oral glucose tolerance test undertaken would be used to determine which test would provide the best diagnostic information.

47. Why women do not engage with postnatal glucose tolerance testing? Surveillance of uptake in the postnatal test for diabetes

Why this is important

Women diagnosed with GDM in pregnancy have been shown to be at significantly higher risk of type 2 diabetes. Diagnosing type 2 diabetes relatively promptly in the post-partum period has potential health benefits to both the mother in that type 2 diabetes often does not present clinically until serious vascular complications have become established. There has been some research that has highlighted that women who do not attend the post-partum oral glucose tolerance test for the detection of type 2 diabetes are older, higher parity. Further contributory factors are the lack of knowledge of healthcare professionals related to the importance of post-partum screening and fragmentation or care.

The barriers and facilitators to women with GDM accessing and attending for post-partum screening are not understood therefore research is required to explore the reasons why women do not attend their post-partum screening test and investigate the policies and processes for screening in with the primary care setting.

It is anticipated that qualitative studies will be the best methodological approach for this research.

48. Does the diagnosis of IGT influence the uptake of life style changes after birth in a woman with previous GDM

Why this is important

Many studies have demonstrated an association between gestational diabetes mellitus and future development of Type 2 Diabetes. As the population of women diagnosed with gestational diabetes increases, there is the likelihood of a comparable incidence of Type 2 Diabetes later in their life. Lifestyle interventions have been shown to prevent or delay the deterioration in blood glucose tolerance. Women diagnosed with gestational diabetes are offered glucose tolerance testing at 6-13 weeks after birth and those found to have persistent impaired glucose tolerance are offered lifestyle modifications. These lifestyle changes may be easier to adopt at this time, compared to a woman who has not had recent experience of pregnancy, as the modifications may be similar to those employed in the antenatal period, along the mothers motivation to lose her ' baby weight'. Adopting lifestyle modifications in the prevention of type 2 diabetes is multifactorial and requires significant behavioural changes.

Many studies have focused on lifestyle changes in isolation. Identifying elements that promote change in the postnatal period may be applied to the general population with qualitative observational studies would contribute to a greater understanding of factors that in turn could lead to increased compliance with such interventions.

49. Are there effective long-term pharmacological interventions that can be recommended postnatally for women who have been diagnosed with gestational diabetes to prevent the onset of type 2 diabetes?

Why this is important

Gestational diabetes is one of the strongest risk factors for the subsequent development of type 2 diabetes: up to 50% of women diagnosed with gestational diabetes develop type 2 diabetes within 5 years of the birth. There are some data suggesting that changes in diet and exercise, with or without metformin, can prevent type 2 diabetes developing in non-pregnant middle-aged people with glucose intolerance, but there are no studies specifically in women with a past history of gestational diabetes. There is thus an urgent need to investigate what interventions may delay or prevent type 2 diabetes developing in this high-risk population of women. Undertaking a formal randomised controlled trial involving long-term outcomes is often not feasible in practice. However, it would be possible to have a quasi- randomised study comparing 2 populations of women with similar demographic profiles who had gestational diabetes. One population would be encouraged at their annual check to follow a specific diet and exercise regime and those in the other population would not. The incidence of the development of type 2 diabetes in the 2 groups at 5, 10 and 20 years would be compared.

9 Health economics

This section was updated in 2015

9.1 Review of the literature

A global search for health economic evidence covering the complete guideline identified 1757 articles. After reviewing titles and abstracts, 52 papers were obtained. Two publications were unavailable as full papers.

A total of 32 studies were excluded because they were not economic evaluations, did not consider the right population for this guideline or had already been included in the previous guideline. Twenty studies were included in the literature review (see Appendix L) and are described in Table 96.

9.1.1 General screening for gestational diabetes

One study (Round et al., 2011) explored the cost–utility of 8 screening strategies based on a woman's hypothetical individual risk of gestational diabetes: 2 hour 75 g oral glucose tolerance test (OGTT); fasting plasma glucose (FPG); random blood glucose (RBG); 1 hour 50 g glucose challenge test (GCT); FPG plus OGTT; RBG plus OGTT; GCT plus OGTT. Results suggest that the individual risk of disease determines which strategy is most likely to be cost effective. Using a willingness-to-pay (WTP) threshold of £20,000 per quality adjusted life year (QALY), a 'no screening/treatment' strategy was found to be cost effective when the gestational diabetes risk is less than 1%. For a gestational diabetes risk between 1.0% and 4.2%, FPG followed by OGTT was most likely to be cost effective and for gestational diabetes risk more than 4.2% a 'universal OGTT' strategy was most likely to be cost effective. Sensitivity analysis suggested that test acceptance rates (that is, the rate of women who have been invited for screening and actually have a test performed) alter which strategy becomes the most cost effective.

A cost effectiveness analysis of 6 screening strategies for gestational diabetes (random glucose measurement, fasting glucose measurement, 50 g GCT, risk factor assessment, risk factor assessment combined with a 50 g GCT, universal screening with an OGTT) evaluated the costs and effects at different times during the pregnancy against no screening (van Leeuwen et al., 2009). Health benefits were measured as a composite outcome of neonatal death, shoulder dystocia and birth trauma. From the perspective of the healthcare system, costs were calculated per prevented serious perinatal complication. All screening strategies were associated with lower risk for serious perinatal complications. Incremental cost effectiveness ratios (ICER) ranged from €23,479 per prevented neonatal complication (risk factor assessment combined with 50 g GCT) to €37,037 (GCT in all women).

Finally, another study assessed the cost effectiveness of screening for gestational diabetes in India and Israel compared with no screening (Marseille et al., 2013). The 'gold standard' for screening for gestational diabetes was the 75 g, 2 hour OGTT, while sensitivity analysis used 100 g, 3 hour OGTT. Inputs into their cost effectiveness model included cost of screening and related gestational diabetes costs, prevalence, adverse event risk and intervention efficacy. Outcomes in the cost effectiveness analysis were measured using disability-adjusted life years (DALY) where 1 DALY equals 1 year of healthy life lost. The cost per DALY averted was 1,626 international dollars in India and 1,830 international dollars in Israel compared with no screening. These values are defined as highly cost effective by the World Health Organization (WHO) DALY thresholds. However, the results were sensitive to the incidence of type 2 diabetes mellitus and the costs and effectiveness of postpartum intervention. Nonetheless, the authors argued that their results showed the benefits of providing screening and management of gestational diabetes where screening has not been previously been provided.

9.1.2 Effectiveness of interventions

A decision analytic model (Mission et al., 2012c) was developed to compare the cost effectiveness of treating patients versus not treating in the USA. They considered patients in HAPO (Hyperglycemia and Adverse Pregnancy Outcome) Category 5 (top 3–12% of fasting glucose levels) which is consistent with diagnosis of marginal patients according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations. Pre-eclampsia, mode of delivery, maternal death, macrosomia, shoulder dystocia, brachial plexus injury (permanent and transient), hypoglycaemia, hyperbilirubinemia and neonatal death were included as maternal and neonatal outcomes. Treating patients was found to be cost effective at a cost of US$44,203 per QALY. A one-way sensitivity analysis suggested that treatment remained cost effective when it met 64% of its reported efficacy.

The same authors also conducted an economic evaluation for patients in HAPO Category 4 (top 12–23% of fasting glucose levels) (Mission et al., 2013). This category is below the cutoff for gestational diabetes using IADPSG guidelines. The same outcomes were used as for an earlier study (Mission et al., 2012b). Treating this category of patients was not found to be cost effective at a cost of US$102,324 per QALY.

Another study from the US compared treating versus not treating mild gestational diabetes from a societal perspective (Ohno et al., 2011). Maternal outcomes included pre-eclampsia, shoulder dystocia, caesarean versus vaginal delivery and maternal death; neonatal outcomes included macrosomia (more than 4000 g), brachial plexus injury (permanent or transient), hypoglycaemia, admission to a neonatal intensive care unit, hyperbilirubinemia and neonatal death. In the base case analysis, treatment was found to be cost effective (below a WTP threshold of US$100,000) at US$20,412 per QALY. Sensitivity analyses showed that treatment remained cost effective when the incremental cost to treat was less than US$3,555 or when the reported efficacy was at least 49% (at baseline cost).

A Netherlands study (Oostdam et al., 2012) evaluated whether the FitFor2 exercise program during pregnancy was cost effective compared with standard care in preventing gestational diabetes. The study was undertaken from a societal perspective, taking into account losses in productivity. The sample was based on a randomised controlled trial (RCT), with health related quality of life measured using the EuroQol-5D and QALYs calculated. Clinical outcomes included maternal fasting blood glucose levels, insulin sensitivity and infant birth weight. The results of their economic evaluation found that the twice weekly exercise programme for pregnant women at risk of gestational diabetes was not cost effective compared with standard care for any of the outcomes considered. The authors reported an ICER of −€46,791 per QALY, although negative ICERs are meaningless in decision-making as it can indicate that an intervention dominates or is dominated.

The cost effectiveness of lifestyle counselling as a prevention for gestational diabetes was assessed in a clustered RCT in Finland (Kolu et al., 2013). Their primary outcome of effectiveness was mean birth weight, the 15D questionnaire that can be used to generate QALYs and a 0–10 Visual Analogue Scale to measure perceived health of the pregnant woman. They reported an ICER of €7 per gram of birth weight avoided. They stated that lifestyle counselling was not cost effective on any of their outcome measures compared with usual care.

A recent study (Nguyen et al., 2014) compared the cost effectiveness of 'group prenatal care' with 'individual prenatal care' for women with pre-gestational type II diabetes mellitus (the authors give no details about the differences in the two types of care). A decision analytic model was built with outcomes including preterm birth, neurodevelopment disability, intrauterine fetal demise, neonatal mortality and pre-eclampsia. The authors found that group prenatal care dominated individual prenatal care and remained cost effective at a WTP threshold of US$100,000 per QALY gained, with costs of US$11,000 higher for group prenatal care remaining cost effective at this threshold.

A decision analysis model was developed to determine if labour induction at 38 weeks of gestation was cost effective when compared with expectant management for pregnant women with insulin-requiring diabetes mellitus (Nayeri et al., 2014). Risks accounted for were caesarean delivery, pre-eclampsia, neonatal demise, shoulder dystocia and transient and permanent brachial plexus injuries. An ICER of US$20,069 per QALY gained was found for induction of labour. The results were sensitive to neonatal demise, neonatal respiratory distress and shoulder dystocia, although the authors concluded that induction of labour at 38 weeks of gestation was cost effective compared with expectant management under a wide range of circumstances.

An Australian study included a cost-consequence analysis comparing the treatment of women with mild gestational diabetes by dietary advice, blood glucose monitoring and required insulin therapy with routine pregnancy care from a health system perspective (Moss et al., 2007). Based on data from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial, the incremental cost per additional serious perinatal complication (defined as 1 or more of the following: death, shoulder dystocia, bone fracture, nerve palsy) prevented was estimated as AU$27,503. The incremental cost per perinatal death prevented was calculated as AU$60,506 and AU$2,988 per life-year saved.

Finally, a study from Brazil considered a cost-benefit analysis of hospitalisation compared with outpatient care for pregnant women with pregestational and gestational diabetes or with mild hyperglycemia (Cavassini et al., 2012). Inpatients were treated by diet and insulin, while outpatients were treated by diet alone. Costs from prenatal, childbirth and neonatal stages are accounted for, while benefits include hospital days avoided during pregnancy as well as indirect benefits from productivity gains from reduced maternal and perinatal mortality. For both populations, they found that the benefits exceeded the costs, with the outpatient group having more than 5 times the benefit to the cost. The sample size for the study was small (n=50) and without the indirect benefits of increased productivity, neither options were beneficial in terms of cost.

9.1.3 Diagnostic criteria

Five studies described the implications of the new, more inclusive screening criteria proposed by the IADPSG to diagnose gestational diabetes using a 75 g OGTT at 24–28 weeks of gestation (Werner et al., 2012; Munigoti et al., 2011; Gillespie et al., 2012; Mission et al., 2012a; Mission et al., 2012b).

A decision analysis model was developed to assess the cost effectiveness of IADPSG criteria for the diagnosis of gestational diabetes (Werner et al., 2012). Comparing the 3 strategies of no screening, current practice (1 hour 50 g GCT between 24 weeks and 28 weeks followed by 3 hour 100 g OGTT) or screening according to IADPSG criteria, their results suggest that the IADPSG recommendations are cost effective with an ICER of US$20,336 per QALY. The results remained robust in sensitivity analyses. Excluding long-term maternal health benefits from the analysis suggested that the IADPSG strategy was no longer cost effective within a WTP threshold of US$100,000.

The effects of criteria proposed by WHO and IADPSG in clinical practice were compared by Munigoti et al. (2011). Among women with high risk pregnancies, 7.5% satisfied the WHO criteria, 16.4% the IADPSG criteria for the diagnosis of gestational diabetes. Adopting the IADPSG criteria was associated with a predicted reduction in maternal and perinatal adverse outcomes: gestational age (0.7%); caesarean section rate (0.6%); pre-eclampsia/gestational hypertension (0.5%); and shoulder dystocia (0.2%). The average treatment cost for gestational diabetes was calculated as £1,087 per affected pregnancy, the total cost of the mentioned averted adverse outcomes as £12,037. The total additional costs of adopting the IADPSG criteria of £54,005 was estimated to equal £12 per pregnancy or £79 per high risk pregnancy.

Based on information gained from the ATLANTIC DIP dataset, an Irish study (Gillespie et al., 2012) assumed an increased prevalence of gestational diabetes of 12.4% (compared with a previously observed prevalence of 2.6%) for the cohort to estimate the costs of universal screening for gestational diabetes in Ireland associated with the new IADPSG diagnostic criteria. The average cost per case detected was calculated as €351 and the cost per case detected and treated €9,325 compared with a cost per undetected and untreated case of €5,385.

Another Irish paper (Gillespie et al., 2013) also explored the independent effects of gestational diabetes mellitus on maternity care and costs in the ATLANTIC DIP dataset. Gestational diabetes led to higher levels of caesarean section and higher levels of neonatal admission, and costs of care were 34% higher than non-gestational diabetes pregnancies (€6,092 versus €4,028). Other significant contributors to costs were obesity, maternal age older than 30 years, first pregnancy and delivery before term. This study showed the potential savings for the healthcare service that could be accrued from preventing gestational diabetes..

A study compared the additional costs accruing from a diagnosis of gestational diabetes with women who do not develop gestational diabetes in a cluster-randomised trial (Kolu et al., 2012). The results from this study were comparable with those in another study (Gillespie et al., 2013), as total healthcare costs were 25% higher for women with gestational diabetes (€6,432 versus €5,143). Inpatient visits were associated with a 44% increase in cost and a 49% increase in costs within a neonatal intensive care unit. The authors suggested lifestyle counselling could provide a means for reducing secondary care costs. This study was addressed in the previous section (see Section 9.1.2) on the effectiveness of interventions (Kolu et al., 2013).

The cost effectiveness of screening using the 2 hour OGTT compared with the 50 g 1 hour GCT (followed by a 3 hour OGTT) with a threshold of 140 mg/dl using IADPSG criteria was evaluated in a US setting (Mission et al., 2012b). The baseline assumptions included a detection rate of 4% for the 50 g 1 hour OGCT and an additional 15% of patients diagnosed with gestational diabetes using the new criteria. The 2 hour OGTT was estimated to be more costly (US$2943 per patient versus US$2,819), but more effective (56.954 versus 56.951 QALYs gained), which resulted in an ICER of USD 50,630 per QALY. A one-way sensitivity analysis suggested that a diagnostic approach using the IADPSG criteria remained cost effective (within a WTP threshold of US$100,000) provided that at least an additional 1.7% of patients were diagnosed and treated for gestational diabetes.

A different cost effectiveness study in a US setting (Mission et al., 2012a) confirmed the cost effectiveness of the 2 hour OGTT with an ICER of US$61,503 per QALY from a societal perspective (using a willingness to pay threshold of US$100,000 per QALY). Sensitivity analyses suggested that the model remained robust in most cases. For the extended screening under the IADPSG criteria to be cost effective, an additional 2.04% of patients needed to be diagnosed with gestational diabetes, the cost of the 2 hour OGTT had to be less than US$175.74, the cost of treatment less than US$1,971 and the treatment needed to meet more than 74.9% of its reported treatment efficacy.

9.1.4 Detecting glucose intolerance after pregnancy in women with history of gestational diabetes

A study from the USA (Kim et al., 2007) calculated the cost per case detected for postpartum screening in women with a history of gestational diabetes. The study population was a cohort of women with a history of gestational diabetes who had normal 6 week postpartum OGTTs. Screening strategies included FPG, 2 hour OGTT and HbA1c in annual, 2 year and 3 year testing intervals. Screening by means of OGTT resulted in lower costs per case detected and had a higher detection rate than FPG or HbA1c for all testing intervals and in most sensitivity

analyses. For all screening strategies, a longer screening interval was associated with lower costs per case detected and lower detection rates compared with more frequent testing.

9.1.5 Health economics profile

Table 96 summarises the health economic studies identified as relevant for this review.

Table 96: Profile of health economics studies

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	ICER	
General screening for gestational diabetes							
Marseille et al. (2013)	Potentially serious limitations[1]	Partially applicable[15,16]	Novo Nordisk A/S funded study	194-76 International dollars	0.12-0.042 DALYs averted	1,626 International dollars (India) 1,830 International dollars (Israel)	One-way and multivariate sensitivity analysis 3 h 100 g OGTT
Round et al. (2011)	Minor limitations[2]	Directly applicable[17]	Incremental analysis: OGTT relative to the next best strategy (FPG+OGTT) NCC-WCH employees are co-authors on paper	£13	0.0004	£94,285 (1% GD risk); £29,308 (3%); £16,312 (5%)	Probabilistic sensitivity analysis (probability that a strategy is cost-effective at given WTP/QALY)
van Leeuwen et al. (2009)	Potentially serious limitations[3]	Partially applicable[15,18]	Decision model; comparison – no screening. Composite outcome of neonatal death, shoulder dystocia and birth trauma. Healthcare perspective.	Not given	Not given	Range of €23,479 to €37,037 For 6 screening strategies comapred to no screening	Unknown

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	ICER	
Effectiveness of interventions							
Cavassini et al. 2012	Potentially serious limitations[4]	Partially applicable[15,19]	Both treatments cost-beneficial including productivity costs. Not cost-beneficial otherwise. No conflicts of interest reported	Not applicable	Not applicable	n/a	None undertaken
Kolu et al. (2013)	Potentially serious limitations[5]	Partially applicable[15,20]	Poor understanding of CEAC output. Not cost-effective. No competing interests	€475	0.008 (based on the 15D utility instrument)	€62,285	Bootstrapping and CEAC reported
Mission et al. (2012c)	Potentially serious limitations[6]	Partially applicable[15,21]	Not reported how utilities were estimated from clinical outcomes. Discounted at 3%. No referral to conflicts of interest	US$757.33	0.0171	US$44,203	One-way sensitivity analysis (treatment efficacy)
Mission et al. (2013)	Potentially serious limitations[6]	Partially applicable[15,22]	Not clear how utilities were generated. Discounted at 3%. No referral to conflicts of interest.	US$ 1146	0.0110	US$ 104,324	One-way sensitivity analysis (treatment effect)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects	ICER	
Moss et al. (2007)	Potentially serious limitations[7]	Partially applicable[15,23]	Costs to women outside of health care included. No competing interests declared.	AU$ 60,506	2.2 1.0 20.25	AU$ 27,503 AU$ 60,506 AU$ 2,988	No sensitivity analysis
Nayeri et al. (2014)	Potentially serious limitations[8]	Partially applicable[15,24]	Not clear how costs and utilities were generated. No referral to conflicts of interest	US$ 20.69	0.0010	US$ 20,069	Univariate sensitivity analysis
Nguyen et al. (2014)	Potentially serious limitations[8]	Partially applicable[15,25]	No referral to conflicts of interest	US$ 64	0.1168	Group care dominates	Univariate sensitivity analysis
Ohno et al. (2011)	Potentially serious limitations[9]	Partially applicable[15,26]	No referral to conflicts of interest	US$456	0.0222	US$20,412	One-way (all probabilities, costs, utilities) and multivariate sensitivity analyses
Oostdam et al. (2012)	Potentially serious limitations[9]	Partially applicable[15,27]	No competing interests declared.	€986	−0.005	Exercise program dominated	Human capital approach versus friction cost for productivity losses
Diagnostic criteria							
Werner et al. (2012)	Potentially serious limitations [10]	Partially applicable[15,28]	No conflict of interest declared	Total: US$1,256.34	Total: 0.0618	US$20,336	• Base case analysis limited to perinatal outcomes, excluded potential long-term maternal benefits

| Study | Limitations | Applicability | Other comments | Incremental | | | Uncertainty |
				Costs	Effects	ICER	
							• one-way sensitivity analyses • multivariate sensitivity analyses
Munigoti et al. (2011)	Potentially serious limitations [11]	Partially applicable[29]	No referral to conflict of interest.	£12 per pregnancy £79 per high risk pregnancy	n/a	n/a	Not reported
Gillespie et al. (2012)	Potentially serious limitations [12]	Partially applicable[15,30]	No referral to conflict of interest.	€351 cost per case detected €9,325 Cost per case detected and treated	n/a	n/a	95% confidence intervals reported around costs
Gillespie et al. (2013)	Potentially serious limitations[13]	Partially applicable[15,31]	Effects are for women with a diagnosis of GDM No conflicts of interest declared.	Costs of care were 34% higher.	Emergency caesarean section (odds ratio [OR] 1.75 [95% CI 1.08–2.81]), levels of neonatal unit admission (3.14 [2.27–4.34]),		95% confidence intervals reported around cost and odds ratio outcomes
Mission et al. (2012b)	Potentially serious limitations[6]	Partially applicable[15,33]	No referral to conflict of interest.	US$124.50	0.0025	US$50,630	One-way sensitivity

| Study | Limitations | Applicability | Other comments | Incremental | | | Uncertainty |
				Costs	Effects	ICER	
							analyses: • different baseline GDM rates, • rates of GDM diagnosis under new IADPSG criteria
Mission et al. (2012a)	Potentially serious limitations[9]	Partially applicable[15,34]	No referral to conflict of interest	US$123	0.0020	US$61,503	One-way sensitivity analyses: • additional GDM diagnoses • cost of 2 h OGTT, • cost to treat GDM, • efficacy of treatment
Detecting glucose intolerance after pregnancy in women with history of gestational diabetes							
Kim et al. (2007)	Potentially serious limitations [14]	Partially applicable[15,35]	OGTT every 3 years lowest cost per case detected US$388				Sensitivity analysis undertaken on parameters

GDM gestational diabetes, IADPSG International Association of the Diabetes and Pregnancy Study Groups, QALY quality adjusted life year, OGTT oral glucose tolerance test, WTP willingness to pay
1. DALYs reported. WTP threshold used may not be most efficient use of these resources
2. Original paper does not report ICER, focus on how cost-effectiveness varied with individual risk; range of unique ICERs for each different risk level presented graphically as a probabilistic cost-effectiveness threshold.
3. No ICER reported; cost per prevented neonatal complication; Incremental analysis between screening strategies not undertaken; No sensitivity analysis reported.
4. Societal perspective CBA; Small sample size; No sensitivity analysis undertaken
5. Societal perspective. No account of long-term benefits from intervention
6. Conference abstract; Not clear perspective or calculation of cost and utilities
7. Outcomes on cost per perinatal complication prevented, perinatal death prevented, life year saved
8. Conference abstract; Not clear perspective or calculation of cost and utilities
9. Societal perspective.

10. No indirect cost or disutility associated with stress of GDM diagnosis considered

11. Conference abstract; no ICER reported; additional cost per pregnancy/high risk pregnancy

12. Cost comparison only; cost per case detected and treated versus undetected and untreated case

13. Cost comparison only

14. No ICER reported; cost per case detected

15. Question relevant, setting outside of UK

16. Lifetime model screening versus no screening with 2 hour 75 g OGTT. Diverse settings (Israel, India).

17. Eight screening strategies: 2 hour 75 g OGTT, FPG, RBG, 1 hour 50 g GCT, FPG + OGTT, RBG + OGTT, GCT + OGTT

18. Six screening strategies: random glucose measurement, fasting glucose measurement, 50 g glucose challenge test, risk factor assessment, risk factor assessment combined with 50 g glucose challenge test (all followed with OGTT if indicated), and universal screening with OGTT

19. Hospitalization versus outpatient care for GDM+ pregnant women in Brazil.

20. Lifestyle counselling to prevent GDM in clustered randomised trial in Finland.

21. Treatment versus no treatment of HAPO category 5 (i.e. top 3-12% of fasting glucose levels, above new threshold).

22. Treatment versus no treatment of HAPO category 4 (i.e. top 12-13% of fasting glucose levels, below new threshold)

23. Treating mild GDM by dietary advice, blood glucose monitoring and insulin therapy versus routine pregnancy care

24. Labour induction at 38 weeks compared to expectant management for insulin-requiring diabetes mellitus

25. Group prenatal care versus individual prenatal care

26. Treatment versus no treatment of mild GDM

27. Exercise program versus standard care during pregnancy to prevent GDM

28. Screening according to IADPSG criteria versus current standard (1 hour 50 g GCT)

29. Impact of adopting the IADPSG for diagnosing GDM in women with high risk pregnancies after initial screening. Not a CUA.

30. Cost of universal screening for GDM using IADPSG

31. Independent effects of GDM on maternity care and costs

32. Health care costs of GDM with high-risk women

33. 2 hour OGTT versus 50 g 1 hour GCT

34. 2 hour OGTT versus 1 hour GCT

35. Fasting plasma glucose versus 2 hour OGTT vs. glycated hemoglobin

9.2 Cost-effective diagnostic threshold for gestational diabetes

9.2.1 Introduction

The diagnostic thresholds for gestational diabetes generate considerable clinical controversy. Diagnostic criteria were first developed 50 years ago (O'Sullivan et al., 1964) but it is perhaps only during the last 10 years, following the landmark ACHOIS study (Crowther et al., 2005), that it has been widely accepted that treatment of gestational diabetes confers a treatment benefit. The first NICE antenatal care guideline (2004), for example, concluded there was insufficient evidence of a treatment benefit to recommend screening for gestational diabetes and the US Preventative Task Force observed that "no properly controlled trial has examined the benefit of universal screening or selective screening compared to routine care without screening" (US Preventive Services Task Force, 1996).

It was in the context of some of this uncertainty that the HAPO observation study (HAPO Study Cooperative Research Group, 2008) was established "to clarify the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus". The results of this study suggested strong associations between maternal blood glucose levels and a number of adverse pregnancy outcomes, and it was found that these associations existed at blood glucose levels below the diagnostic threshold for diabetes.

In the aftermath of the HAPO study, the IADPSG recommended new consensus diagnostic criteria for gestational diabetes (IADPSG, 2010). These criteria were adopted by the American Diabetic Association, a number of national diabetic associations and the WHO. However, the criteria they propose have not been universally accepted and controversy remains (Cundy et al., 2014; Waugh et al., 2010).

9.2.1.1 Arguments for the IADPSG diagnostic criteria

As noted above, previous criteria for the diagnosis of gestational diabetes were developed 50 years ago and had remained largely unchanged in that time. Yet those criteria were intended to identify pregnant women who would be at risk of diabetes in the future rather than reducing the risk of adverse maternal and neonatal outcomes in the index pregnancy. Two intervention studies (Crowther et al., 2005; Landon et al., 2009) and the HAPO observational study (HAPO Study Cooperative Research Group, 2008) all suggested that adverse pregnancy outcomes were associated with less severe degrees of hyperglycaemia than would be considered diagnostic using WHO 1999 criteria and speculated that treatment benefits might occur below the old diagnostic thresholds. The proponents of the IADPSG criteria acknowledged that the prevalence of gestational diabetes is likely to increase as a result but argue that this criticism presupposes that there is some acceptable lower prevalence. They also pointed out that gestational diabetes is an increasing problem with pregnancy more frequently occurring at older ages and in women with a higher mean body mass index (BMI).

The IADPSG criteria reflected the deliberations and consensus of many experts (Moses, 2010) and the view that there was a need for an internationally agreed set of criteria. To settle on a precise diagnostic threshold was difficult as the HAPO study did not show a threshold or inflection point where risks increased sharply. It has also been pointed out that in the HAPO study there were significantly better outcomes in those with no plasma glucose values above the IADPSG thresholds than in those with one or more plasma glucose values above the IADPSG threshold.

9.2.1.2 Arguments against the IADPSG diagnostic criteria

The threshold developed by IADPSG was based on results of an observational study. However, it did not prove causation or show that treatment would lead to improved outcomes (Holt et al., 2011). In particular, not all the women who would be diagnosed with gestational diabetes using the new IADPSG criteria would have met the inclusion criteria for intervention studies and therefore it is not known what, if any, benefits would result from intervening in a group with 'milder' disease (Cundy et al., 2014).

The arbitrariness of the threshold, which was determined where the odds of a number of outcomes were 1.75 times the odds at the mean OGTT blood glucose value for fasting, 1 hour and 2 hour samples, has been criticised (Cundy et al., 2014).

That the new IADPSG criteria are likely to increase the number of women diagnosed with gestational diabetes is not contested. Critical commentators note that having a label of gestational diabetes may lead to a medicalistion of the pregnancy, which could have an adverse impact on the pregnancy experience for women who are often asymptomatic. It has been suggested that a diagnosis results in more glucose monitoring, more clinic visits, greater monitoring of the woman and the fetus and a higher chance of intervention in the birth itself. These commentators are concerned at how many extra women will have their pregnancy affected this way. Finally, the additional diagnoses of gestational diabetes will have a large impact on resource use and service delivery.

9.2.1.3 The health economic approach

In addressing the health economic analysis of the IADPSG diagnostic criteria, it would be appropriate to refer to the six sequential stool guaiac protocol which was proposed by the American Cancer Society for the screening of colonic cancer and critically reviewed (Neuhauser et al., 1975). That review suggested that by failing to consider the marginal value of each test, the protocol resulted in incremental costs of a cancer case detected by the sixth test being more than 20,000 times the average cost of detection.

Health economic considerations have not informed the new diagnostic criteria for gestational diabetes. In principle, the marginal costs and benefits of a 0.1 mmol/litre change in diagnostic threshold could be considered to derive an optimum or efficient level where healthcare benefits are delivered at an acceptable level of cost.

In reality, there may be practical difficulties with such an approach. For example, the existing evidence base may make it difficult to assess the marginal costs and benefits of small changes in blood glucose levels, although the HAPO study is important in this respect. Second, it would make sense to have an internationally agreed threshold for gestational diabetes but costs and disease prevalence will vary across different healthcare settings and therefore there is unlikely to be a unique threshold which can be considered universally cost effective.

Nevertheless, that does not mean that the health economic approach should be abandoned as it can arguably produce more transparent and efficient diagnostic criteria than approaches which do not consider the additional costs of testing and treatment weighed explicitly against expected health gains.

Due to the importance of this clinical issue and a lack of consensus, the diagnostic threshold for gestational diabetes was selected as a high priority for economic analysis in the health economic plan drawn up for this guideline update. The model that was developed to assess the cost effectiveness (or cost utility) of different diagnostic thresholds for gestational diabetes is described below.

9.2.2 Methods

A decision analytic model was developed in Microsoft Excel™ as part of a cost utility analysis to compare 13 different diagnostic thresholds for gestational diabetes using the OGTT in pregnant women of 24–28 weeks of gestation. The population on which the diagnostic thresholds were to be applied could be either unselected or selected, for example by using existing NICE screening criteria.

A diagnostic threshold is only important if used as a guide to future management and therefore the option of no treatment was added as a 14th comparator with no requirement for a diagnostic test. All 14 comparators are listed in Table 97. For all diagnostic thresholds diagnosis follows a Boolean odds ratio (OR) logic with disease classed as present if any one of the blood glucose readings in an OGTT equals or exceeds the relevant threshold.

Table 97: Diagnostic threshold comparators

Threshold name	Fasting blood glucose	One hour blood glucose	Two hour blood glucose
WHO 1999	7.0	-	7.8
IADPSG 1.75 (incl 1 hour)	5.1	10.0	8.5
IADPSG 1.75	5.1	-	8.5
IADPSG 1.50	5.0	-	7.9
IADPSG 2.00	5.3	-	9.0
5.3/WHO 2 hour	5.3	-	7.8
5.4/WHO 2 hour	5.4	-	7.8
5.5/WHO 2 hour	5.5	-	7.8
5.6/WHO 2 hour	5.6	-	7.8
5.3/IADPSG 2 hour	5.3	-	8.5
5.4/IADPSG 2 hour	5.4	-	8.5
5.5/IADPSG 2 hour	5.5	-	8.5
5.6/IADPSG 2 hour	5.6	-	8.5
No treatment	NA	NA	NA

IADPSG International Association of the Diabetes and Pregnancy Study Groups, NA not available, WHO World Health Organization
a. IADPSG 1.75 (incl 1-hour) exactly represents the new IADPSG diagnostic criteria. The diagnostic thresholds for fasting plasma glucose, one-hour plasma glucose and two-hour plasma glucose are determined by the glucose value at which the odds for birth weight, cord c-peptide and percent body fat > 90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values in the HAPO study
b. IADPSG 1.75 is similar to the published IADPSG diagnostic criteria but making a diagnosis based on either a fasting plasma glucose or a two-hour plasma glucose as is common practice in England and Wales. A two-point test rather than a three-point test
c. IADPSG 1.50 is the same as for IADPSG 1.75 but uses odds of 1.5 times the odds of outcomes at mean glucose values
d. IADPSG 2.0 is as for other IADPSG two-point test criteria but using an odds ratio of 2.0

A schematic of the model decision tree is shown in Figure 1. In all comparators, with the exception of 'No treatment', a cost of OGTT is incurred. However, different comparators vary in terms of the population they identify as having disease, with implications for numbers treated and concomitant differences in maternal and neonatal outcomes arising from treatment.

Figure 1: Model Schematic
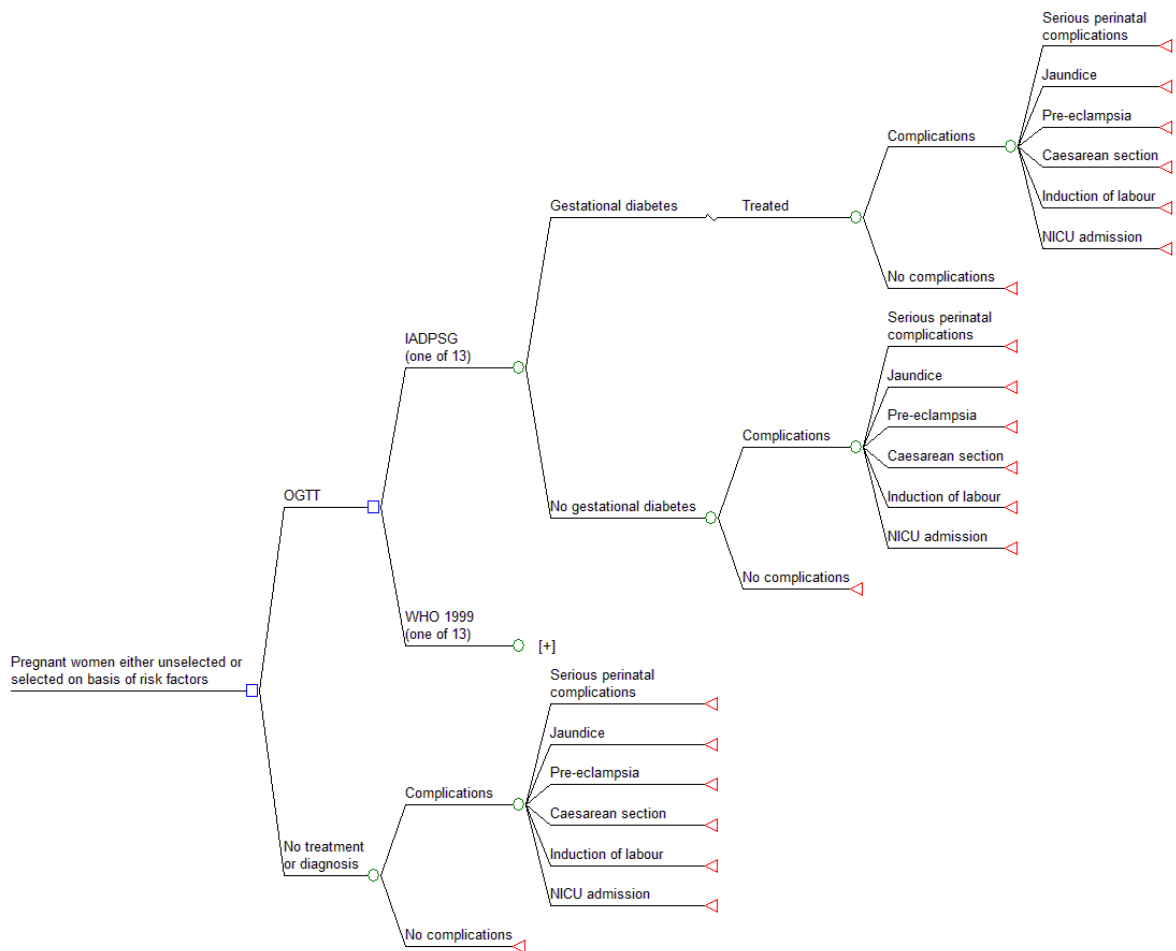
IADPSG International Association of the Diabetes and Pregnancy Study Groups, NICU neonatal intensive care unit, OGTT oral glucose tolerance test, WHO World Health Organization

The modelling approach follows the NICE Reference case unless otherwise stated.

9.2.2.1 The model population (patient level data)

It is common practice in health economics to model a hypothetical patient cohort. If we had followed such an approach then a key model parameter would have been the detection rate of different diagnostic thresholds. Although there are some studies which have addressed this for the new IADPSG criteria (Moses et al., 2011), such data are not available to assess the impact on detection rates of more marginal changes in diagnostic thresholds.

Therefore, the NCC-WCH put out a 'call for evidence' in order to get anonymised OGTT results from various centres in England and Wales in women being tested for gestational diabetes. Centres that submitted data were also asked to identify the process by which women were selected for testing. Before submitting data, centres were asked to check they had permission to send this data, from the relevant Caldicott Guardian for example.

In total, 14 data submissions were received, although data could not be used from 1 centre as it included only those with a confirmed diagnosis. Table 98 list the centres which responded to the call for evidence, along with various characteristics of the submitted datasets.

Table 98: Datasets submitted for gestational diabetes diagnostic threshold cost effectiveness model

Centre	OGTT fasting value	OGTT 1 hour value	OGTT 2 hour value	Number of patients	Patient selection	Other variables
HAPO (4 centres)[a]	Yes	Yes	Yes	6221	HAPO inclusion criteria	Full dataset collected for HAPO study
Norwich[b]	Yes	Yes	Yes	12,755	Largely NICE risk factor screening	No
Colchester	Yes	No	Yes	159	NICE risk factor screening	Risk factors present
East & North Herts[c]	Yes	No	Yes	1622	Largely NICE risk factor screening	No
Hartlepool	Yes	No	Yes	50	NICE risk factor screening	Risk factors present
North Tees	Yes	No	Yes	229	NICE risk factor screening	Risk factors present
King's College (London)	Yes	No	Yes	576	NICE risk factor screening	Risk factors present
Leeds	Yes	No	Yes	1235	NICE risk factor screening	Reason for test
Maidstone & Tonbridge Wells	Yes	No	Yes	111	NICE risk factor screening	Reason for test
Oldham[d]	Yes	No	Yes	6740	NICE risk factor screening	Gestational age
Warrington	Yes	No	Yes	296	NICE screening criteria plus 2 positive episodes of glycosuria	No
Worcester	Yes	No	Yes	290	Largely NICE risk factor screening	Reason for test
Southampton	Yes	No	Yes	1973	Largely NICE risk factor screening	No
Sheffield	Yes	No	Yes	3253	NICE risk factor screening	No

Centre	OGTT fasting value	OGTT 1 hour value	OGTT 2 hour value	Number of patients	Patient selection	Other variables
Atlantic DIP	Yes	Yes	Yes	6308	Atlantic DIP study inclusion criteria	Full dataset collected for Atlantic DIP study

HAPO Hyperglycemia and Adverse Pregnancy Outcome, OGTT oral glucose tolerance test
a. The HAPO dataset was taken from the UK (Manchester and Belfast) and Australian (Brisbane and Newcastle) centre that participated in the HAPO study (HAPO Study Cooperative Research Group, 2008). See the HAPO study for further details on the characteristics of this dataset
b. The Norwich dataset was collected between 2008 and February 2014
c. The East & North Herts data was collected between 2008 and 2014
d. Oldham data was collected from 1993-94; 1997-2002; 2008-2013

Multivariate logistic regression analysis was undertaken to predict a baseline risk for a number of outcomes for each patient based on their OGTT results (see Section 9.2.2.3). Then, for any given diagnostic threshold, the effect of treatment on risk would be calculated if the patients' OGTT results indicated a diagnosis of gestational diabetes (See section 9.2.2.8)[ww].

9.2.2.2 Modelling patient baseline risk

9.2.2.2.1 *Model outcomes*

The model estimated baseline risk for the following outcomes:
- shoulder dystocia
- caesarean section
- jaundice (requiring phototherapy)
- pre-eclampsia
- induction of labour
- neo-natal intensive care (NICU) admission

This list was a pragmatic one, reflecting 'hard' physical outcomes that had been assessed in important intervention trials (Crowther et al., 2005; Landon et al., 2009) and were therefore potentially amenable to some treatment effect, and outcomes reported in the HAPO study exhibiting a gradient of risk across blood glucose values and therefore of relevance to the setting of a diagnostic threshold.

The ACHOIS study used 'serious perinatal complications', a composite measure including shoulder dystocia, as its primary outcome and shoulder dystocia accounted for almost 80% of the serious perinatal complications in that study. It therefore was used as a proxy for serious perinatal complications in the model which is the key source of differences in health state utility in the model. Outcomes such as large for gestational age and macrosomia could

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[ww] The original intention was to produce a separate 'scenario analysis' for each dataset and, given the data submissions, it was thought this would reflect the wide differences in prevalence that exist across England and Wales. Data was not to be pooled across the datasets due to heterogeneity in patient selection and because such pooled data could not necessarily be considered representative of England and Wales as a whole.
In each scenario analysis, the original intention was for the model to calculate a baseline risk for a number of outcomes for each patient based on their OGTT results. However, the issue arose as to whether the fasting or 2 hour plasma glucose should be used. A model that predicted an individual's risk based on a single blood glucose value was problematic as 2 patients with an identical 2 hour blood glucose value and a different fasting blood glucose value would have an identical predicted risk in the 2 hour blood glucose model but a different predicted risk in the fasting glucose model. Therefore, a multivariate approach was used which could utilise all blood glucose values in a single model.
The logistic regression was undertaken using the HAPO (4 centres) dataset as this was the dataset for which outcome data was available. The HAPO study utilised a 3-point OGTT and all 3 measures were used as covariates in the regression analysis. This meant that only the Norwich and HAPO (4 centres) datasets could be used in the model as they were the only datasets for which 3-point OGTT values were available.

be considered as intermediate markers of a risk of shoulder dystocia, in which case they are made somewhat redundant by data on the endpoint outcome of interest.

Biochemical markers such as cord blood c-peptide levels were not modelled despite their role as surrogates for fetal insulin production, the key mechanism in the pathogenesis of fetal disease. To model this outcome it would be necessary to have a natural history model capable of mapping the marker onto 'hard' health outcomes. Given that such markers would be expected to be associated with macrosomia and concomitant shoulder dystocia it seems reasonable to focus instead on the hard outcomes for which the data exists.

The other included outcomes primarily have an important impact on 'downstream' costs and are not used to modify health state utility. There were a number of outcomes that were not included because it was thought that the data could be compromised by double counting. For example, the costs arising from respiratory distress syndrome and preterm birth would largely be captured by NICU admissions. Furthermore, 1 of the intervention studies (Landon et al., 2009) failed to demonstrate any treatment benefit for those outcomes.

9.2.2.3   Multivariate prediction model to estimate baseline risk

The implication of the HAPO data was that increasing blood glucose values (fasting, 1 hour and 2 hour) were associated with worse pregnancy outcomes. For a model based on patient level data containing, as a minimum, blood glucose values it was decided that it was best to estimate the baseline risk at the patient level using a multivariate prediction model which included blood glucose values as predictors.

Stepwise logistic regression was undertaken in SPSS™ in order to predict an individual patient risk for each of the 6 outcomes listed in Section 9.2.2.2. The logistic regression used the HAPO (4 centres) dataset which, in addition to OGTT results, included many other variables as well as relevant outcome data. The initial regression analysis used the same covariates that were used in the regression models used in the HAPO study to adjust for possible confounders (HAPO Study Cooperative Research Group, 2008). Stepwise logistic regression involved the backward elimination of blood glucose variables with non-significant coefficients, as this can improve the model in terms of prediction. Blood glucose variables with non-significant coefficients are eliminated one at a time, with the variable eliminated from the next iteration being that with lowest probability of significance (highest p-value). After elimination the regression analysis is repeated with the remaining set of covariates. Elimination was only undertaken if a blood glucose coefficient was non-significant and therefore only 1 blood glucose covariate was left in the final iteration for all outcomes apart from induction of labour which had 2 significant blood glucose variables remaining after the final iteration. The spreadsheet model is configured to allow the user to use any of the regression analyses produced at each step for purposes of sensitivity analysis. For the base case deterministic analysis the regression model with all non-significant blood glucose variables eliminated was used.

An alternative stepwise logistic regression analysis was undertaken where fasting, 1 hour and 2 hour blood glucose values were the only explanatory variables included in the regression. Again, this analysis was undertaken using the HAPO (4 centres) dataset. It was thought that blood glucose values generally served as reasonable proxies for other covariates. If that is the case then the predictive ability of blood glucose level could be underestimated with the inclusion of other covariates. However, it is noted that omitted variable bias could potentially be an issue with this approach. As with the regression analyses utilising non-blood glucose covariates, the stepwise logistic regression involved the elimination of blood glucose variables with non-significant coefficients. The number of blood glucose variables remaining after the elimination process varied between outcomes (1 blood glucose variable remained for shoulder dystocia, NICU admission and jaundice; 2 blood glucose variables remained for caesarean section and pre-eclampsia; no elimination was necessary for induction of labour leaving all 3 blood glucose variables in the regression).

Again, the spreadsheet model allows the regression models produced at any of the steps to be selected. In the base case analysis the regression models using just blood glucose variables was only used in an evaluation of the Norwich patient dataset, as this data only consisted of values for the 3-point OGTT. Datasets consisting of only a fasting blood glucose and 2 hour blood glucose could not be analysed as the 1 hour blood glucose variable was not eliminated for all outcomes.

As described above there were 2 types of regression which are categorised as:

- all covariates
- blood glucose covariates only

The logistic regression models developed for each of the 6 outcomes are shown in Tables 99 to 104. The actual number of regression models for each outcomes depends on the number of variables that were eliminated due to insignificant coefficients. There is a maximum of 3 regression analyses for each type (all covariates, blood glucose covariates only).

Table 99: Logistic regression models to predict neonatal shoulder dystocia

| Variable | Co-efficient (standard error) | | | | | |
| | Models with blood glucose covariates | | | Models with all covariates | | |
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Centre (1)[a]	-	-	-	1.151 (0.424)	1.141 (0.424)	1.151 (0.423)
Centre (2)[a]	-	-	-	0.562 (0.491)	0.561 (0.491)	0.505 (0.489)
Centre (3)[a]	-	-	-	1.622 (0.472)	1.632 (0.472)	1.604 (0.472)
Age_OGTT	-	-	-	−0.022 (0.024)	−0.024 (0.024)	−0.023 (0.024)
BMI_OGTT	-	-	-	−0.011 (0.024)	−0.013 (0.024)	−0.006 (0.023)
Smoker	-	-	-	−0.477 (0.409)	−0.491 (0.409)	−0.480 (0.409)
Drinker	-	-	-	−0.107 (0.317)	−0.100 (0.317)	−0.101 (0.317)
Family history DM	-	-	-	−0.008 (0.187)	0.002 (0.185)	−0.006 (0.184)
GA_OGTT[b]	-	-	-	−0.114 (0.092)	−0.116 (0.092)	−0.111 (0.091)
Neonate gender	-	-	-	−1.316 (0.292)	−1.318 (0.292)	−1.321 (0.292)
Family history HBP	-	-	-	-	-	-
Maternal UTI	-	-	-	-	-	-
Mean blood pressure	-	-	-	−0.007 (0.015)	−0.007 (0.015)	−0.006 (0.015)
Hospital admission before delivery	-	-	-	0.175 (0.267)	0.171 (0.267)	0.173 (0.266)
Paritycat (1)[c]	-	-	-	−0.108 (0.420)	−0.117 (0.420)	−0.118 (0.420)

Variable	Co-efficient (standard error)					
	Models with blood glucose covariates			Models with all covariates		
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Paritycat (3)[c]	-	-	-	−0.013 (0.399)	−0.022 (0.399)	−0.026 (0.399)
Paritycat (2)[c]	-	-	-	0.469 (0.414)	0.454 (0.413)	0.456 (0.412)
Fasting blood glucose[d]	0.166 (0.110)	0.137 (0.107)	-	0.151 (0.112)	0.130 (0.110)	-
1 hour blood glucose[d]	−0.152 (0.163)	-	-	−0.138 (0.165)	-	-
2 hour blood glucose[d]	0.265 (0.151)	0.179 (0.120)	0.267 (0.097)	0.222 (0.152)	0.145 (0.120)	0.223 (0.100)
Constant	−4.475 (0.122)	−4.471 (0.122)	−4.467 (0.122)	1.139 (3.508)	1.268 (3.045)	0.925 (3.025)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infection

a. Centre coefficients are dummy variables to capture participating centre. When all Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle

b. GA_OGTT – gestational age at time of OGTT

c. Paritycat – dummy variables for parity or missing parity data Each paritycat (parity category) variable is set to either 1 or 0. If the women has carried no pregnancies (the reference category) to a viable gestational age they will all be set to 0 in the regression model. If she has carried 1 previous pregnancy to a viable gestational age then Paritycat(1) = 1. If she has carried 2 or more pregnancies to a viable gestational age then Paritycat(2)=1. If the data is missing then Paritycat(3)=1

d. Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for shoulder dystocia arising from a 1 SD mmol/litre change in blood glucose

Table 100:   Logistic regression models to predict caesarean section

Variable	Co-efficient (standard error)				
	Models with blood glucose covariates		Models with all covariates		
	Model 1	Model 2	Model 3	Model 4	Model 5
Centre (1)[a]	-	-	−0.495 (0.092)	−0.495 (0.092)	−0.494 (0.092)
Centre (2)[a]	-	-	−0.114 (0.100)	−0.110 (0.099)	−0.099 (0.098)
Centre (3)[a]	-	-	−0.692 (0.141)	−0.690 (0.140)	−0.681 (0.140)
Age_OGTT	-	-	0.034 (0.007)	0.034 (0.007)	0.034 (0.007)
BMI_OGTT	-	-	0.039 (0.007)	0.039 (0.007)	0.039 (0.007)
Smoker	-	-	−0.292 (0.106)	−0.292 (0.106)	−0.304 (0.106)
Drinker	-	-	−0.025 (0.087)	−0.025 (0.087)	−0.028 (0.087)
Family history DM	-	-	0.052 (0.057)	0.052 (0.057)	0.050 (0.057)
GA_OGTT[b]	-	-	0.004 (0.029)	−0.004 (0.029)	0.004 (0.029)

| Variable | Co-efficient (standard error) | | | | |
| | Models with blood glucose covariates | | Models with all covariates | | |
	Model 1	Model 2	Model 3	Model 4	Model 5
Neonate gender	-	-	−0.205 (0.071)	−0.205 (0.071)	−0.205 (0.071)
Family history HBP	-	-	-	-	-
Maternal UTI	-	-	-	-	-
Mean blood pressure	-	-	0.003 (0.004)	0.002 (0.004)	0.003 (0.004)
Hospital admission before delivery	-	-	0.510 (0.079)	0.510 (0.079)	0.514 (0.079)
Paritycat (1)[c]	-	-	-	-	-
Paritycat (2)[c]	-	-	-	-	-
Paritycat (3)[c]	-	-	-	-	-
Fasting blood glucose[d]	0.053 (0.040)	-	−0.009 (0.044)	-	-
1 hour blood glucose[d]	0.119 (0.048)	0.138 (0.046)	0.101 (0.051)	0.098 (0.049)	0.144 (0.037)
2 hour blood glucose[d]	0.113 (0.046)	0.123 (0.046)	0.071 (0.048)	0.069 (0.048)	-
Constant	−1.433 (0.035)	−1.435 (0.035)	−3.509 (0.950)	−3.495 (0.947)	−3.518 (0.947)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infection

a. Centre coefficients are dummy variables to capture participating centre. When all Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle

b. GA_OGTT - gestational age at time of OGTT

c. Paritycat - dummy variables for parity or missing parity data

d. Blood glucose values are 'standardised' - so the exponential of the coefficient represents the odds ratio for caesarean section arising from a 1 SD mmol/litre change in blood glucose

Table 101: Logistic regression models to predict neonatal intensive care unit admissions

| Variable | Co-efficient (standard error) | | | | | |
| | Models with blood glucose covariates | | | Models with all covariates | | |
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Centre (1)[a]	-	-	-	0.889 (0.159)	0.889 (0.159)	0.894 (0.159)
Centre (2)[a]	-	-	-	1.400 (0.163)	1.401 (0.161)	1.393 (0.161)
Centre (3)[a]	-	-	-	1.163 (0.191)	1.163 (0.191)	1.153 (0.190)
Age_OGTT	-	-	-	0.012 (0.009)	0.012 (0.009)	0.013 (0.009)
BMI_OGTT	-	-	-	0.024 (0.009)	0.024 (0.009)	0.025 (0.009)
Smoker	-	-	-	0.201 (0.130)	0.201 (0.130)	0.209 (0.130)

	Co-efficient (standard error)					
	Models with blood glucose covariates			Models with all covariates		
Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Drinker	-	-	-	−0.023 (0.117)	−0.023 (0.117)	−0.025 (0.117)
Family history DM	-	-	-	0.038 (0.069)	0.038 (0.069)	0.033 (0.069)
GA_OGTT[b]	-	-	-	−0.052 (0.038)	−0.052 (0.038)	−0.050 (0.038)
Neonate gender	-	-	-	−0.302 (0.094)	−0.302 (0.094)	−0.304 (0.094)
Family history HBP	-	-	-	-	-	-
Maternal UTI	-	-	-	-	-	-
Mean blood pressure	-	-	-	0.006 (0.006)	0.006 (0.006)	0.006 (0.006)
Hospital admission before delivery	-	-	-	0.792 (0.097)	0.792 (0.097)	0.794 (0.097)
Paritycat (1)[c]	-	-	-	−0.474 (0.148)	−0.474 (0.148)	−0.474 (0.148)
Paritycat (2)[c]	-	-	-	−0.493 (0.157)	−0.493 (0.157)	−0.490 (0.157)
Paritycat (3)[c]	-	-	-	−0.086 (0.135)	−0.086 (0.135)	−0.084 (0.135)
Fasting blood glucose[d]	−0.025 (0.050)	-	-	−0.003 (0.054)	-	-
1 hour blood glucose[d]	0.078 (0.064)	0.068 (0.061)	-	0.082 (0.067)	0.081 (0.064)	-
2 hour blood glucose[d]	0.167 (0.060)	0.161 (0.059)	0.208 (0.041)	0.107 (0.063)	0.107 (0.061)	0.159 (0.045)
Constant	−2.375 (0.046)	−2.375 (0.046)	−2.374 (0.046)	−3.061 (1.243)	−3.056 (1.239)	−3.181 (1.236)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infection
a. Centre coefficients are dummy variables to capture participating centre. When all Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle
b. GA_OGTT - gestational age at time of OGTT
c. Paritycat - dummy variables for parity or missing parity data
d. Blood glucose values are 'standardised' - so the exponential of the coefficient represents the odds ratio for caesarean section arising from a 1 SD mmol/litre change in blood glucose

Table 102:   Logistic regression models to predict jaundice

	Co-efficient (standard error)					
	Models with blood glucose covariates			Models with all covariates		
Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Centre (1)[a]	-	-	-	0.410 (0.157)	0.407 (0.157)	0.407 (0.157)
Centre (2)[a]	-	-	-	0.420 (0.173)	0.440 (0.171)	0.449 (0.171)

| Variable | Co-efficient (standard error) | | | | | |
| | Models with blood glucose covariates | | | Models with all covariates | | |
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Centre (3)[a]	-	-	-	−0.332 (0.259)	−0.322 (0.259)	−0.315 (0.259)
Age_OGTT	-	-	-	−0.005 (0.011)	0.005 (0.011)	0.005 (0.011)
BMI_OGTT	-	-	-	−0.009 (0.012)	−0.012 (0.011)	−0.011 (0.011)
Smoker	-	-	-	−0.093 (0.162)	0.092 (0.162)	0.082 (0.161)
Drinker	-	-	-	−0.508 (0.163)	−0.510 (0.163)	−0.514 (0.163)
Family history DM	-	-	-	−0.060 (0.094)	−0.058 (0.094)	−0.060 (0.094)
GA_OGTT[b]	-	-	-	−0.077 (0.047)	−0.078 (0.047)	−0.078 (0.047)
Neonate gender	-	-	-	−0.115 (0.113)	−0.116 (0.113)	−0.116 (0.113)
Family history HBP	-	-	-	-	-	-
Maternal UTI	-	-	-	-	-	-
Mean blood pressure	-	-	-	0.018 (0.007)	0.018 (0.007)	0.018 (0.007)
Hospital admission before delivery	-	-	-	0.865 (0.116)	0.866 (0.116)	0.867 (0.116)
Paritycat (1)[c]	-	-	-	−0.380 (0.185)	−0.381 (0.185)	−0.382 (0.185)
Paritycat (2)[c]	-	-	-	−0.526 (0.200)	−0.528 (0.201)	−0.526 (0.200)
Paritycat (3)[c]	-	-	-	0.078 (0.165)	0.079 (0.165)	0.078 (0.165)
Fasting blood glucose[d]	−0.063 (0.061)	-	-	−0.055 (0.066)	-	-
1 hour blood glucose[d]	0.199 (0.078)	0.174 (0.073)	0.237 (0.052)	0.192 (0.079)	0.174 (0.076)	0.216 (0.056)
2 hour blood glucose[d]	0.102 (0.072)	0.174 (0.073)	-	0.073 (0.074)	0.060 (0.072)	-
Constant	−2.850 (0.057)	−2.848 (0.057)	−2.846 (0.057)	−2.014 (1.526)	−1.906 (1.521)	−1.927 (1.522)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infection

a. Centre coefficients are dummy variables to capture participating centre. When all Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle

b. GA_OGTT – gestational age at time of OGTT

c. Paritycat – dummy variables for parity or missing parity data

d. (glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for jaundice requiring phototherapy arising from a 1 SD mmol/litre change in blood glucose

Table 103:   Logistic regression models to predict pre-eclampsia

| Variable | Co-efficient (standard error) | | | | |
| | Models with blood glucose covariates | | Models with all covariates | | |
	Model 1	Model 2	Model 3	Model 4	Model 5
Centre (1)[a]	-	-	−0.800 (0.193)	−0.797 (0.193)	−0.784 (0.192)
Centre (2)[a]	-	-	−0.277 (0.202)	−0.278 (0.202)	−0.308 (0.200)
Centre (3)[a]	-	-	−0.667 (0.278)	−0.673 (0.278)	−0.685 (0.278)
Age_OGTT	-	-	−0.011 (0.015)	−0.010 (0.015)	−0.009 (0.015)
BMI_OGTT	-	-	0.097 (0.012)	0.098 (0.011)	0.101 (0.011)
Smoker	-	-	−0.569 (0.246)	−0.564 (0.246)	−0.556 (0.245)
Drinker	-	-	−0.168 (0.194)	−0.169 (0.194)	−0.170 (0.194)
Family history DM	-	-	0.006 (0.127)	0.001 (0.127)	−0.004 (0.127)
GA_OGTT[b]	-	-	−0.096 (0.059)	−0.095 (0.059)	−0.092 (0.059)
Neonate gender	-	-	0.174 (0.147)	0.174 (0.147)	0.173 (0.147)
Family history HBP	-	-	0.230 (0.150)	0.232 (0.150)	0.233 (0.150)
Maternal UTI	-	-	0.721 (0.211)	0.725 (0.211)	0.734 (0.211)
Mean blood pressure	-	-	-	-	-
Hospital admission before delivery	-	-	-	-	-
Paritycat (1)[c]	-	-	−0.292 (0.240)	−0.293 (0.240)	−0.291 (0.240)
Paritycat (2)[c]	-	-	−0.703 (0.271)	−0.703 (0.271)	−0.701 (0.271)
Paritycat (3)[c]	-	-	0.023 (0.224)	0.024 (0.224)	0.026 (0.224)
Fasting blood glucose[d]	0.183 (0.068)	0.201 (0.065)	0.062 (0.078)	0.077 (0.074)	-
1 hour blood glucose[d]	0.083 (0.098)	-	0.065 (0.104)	-	-
2 hour blood glucose[d]	0.150 (0.090)	0.196 (0.072)	0.195 (0.096)	0.229 (0.079)	0.272 (0.067)
Constant	−3.455 (0.075)	−3.453 (0.075)	−3.107 (1.855)	−3.164 (1.853)	−3.370 (1.842)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infection

a. Centre coefficients are dummy variables to capture participating centre. When all Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle

b. gestational age at time of OGTT

c. Paritycat – dummy variables for parity or missing parity data

d. Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for pre-eclampsia arising from a 1 SD mmol/litre change in blood glucose

Table 104: **Logistic regression models to predict induction of labour**

| Variable | Co-efficient (standard error) | | |
| | Model with blood glucose covariates | Models with all covariates | |
	Model 1	Model 2	Model 3
Centre (1)[a]	-	−0.476 (0.077)	−0.476 (0.077)
Centre (2)[a]	-	−0.333 (0.087)	−0.337 (0.085)
Centre (3)[a]	-	−0.384 (0.110)	−0.387 (0.109)
Age_OGTT	-	0.006 (0.006)	0.006 (0.006)
BMI_OGTT	-	0.039 (0.006)	0.039 (0.006)
Smoker	-	0.051 (0.082)	0.051 (0.082)
Drinker	-	0.079 (0.072)	0.079 (0.072)
Family history DM	-	0.016 (0.048)	0.016 (0.048)
GA_OGTT[b]	-	0.011 (0.024)	0.011 (0.024)
Neonate gender	-	−0.038 (0.059)	−0.038 (0.059)
Family history HBP	-	-	-
Maternal UTI	-	-	-
Mean Blood Pressure	-	0.008 (0.004)	0.008 (0.004)
Hospital admission before delivery	-	0.608 (0.066)	0.608 (0.066)
Paritycat (1)[c]	-	−0.363 (0.101)	−0.363 (0.101)
Paritycat (2)[c]	-	−0.193 (0.105)	−0.193 (0.105)
Paritycat (3)[c]	-	0.141 (0.094)	0.141 (0.094)
Fasting blood glucose[d]	0.079 (0.033)	0.009 (0.037)	-
1 hour blood glucose[d]	−0.093 (0.041)	−0.111 (0.043)	−0.108 (0.041)
2 hour blood glucose[d]	0.100 (0.040)	0.094 (0.041)	0.096 (0.041)

	Co-efficient (standard error)		
	Model with blood glucose covariates	**Models with all covariates**	
Variable	**Model 1**	**Model 2**	**Model 3**
Constant	−1.032 (0.029)	−3.037 (0.796)	−3.050 (0.794)

BMI body mass index, DM diabetes mellitus, HBP high blood pressure, UTI urinary tract infectio
a. Centre coefficients are dummy variables to capture participating centre. When all the Centre dummies are set to zero the model predicts Belfast outcomes. Centre (1) is set to 1 for Manchester, Centre (2) is set to 1 for Brisbane and Centre (3) is set to 1 for Newcastle
b. GA_OGTT – gestational age at time of OGTT
c. Paritycat – dummy variables for parity or missing parity data
d. Blood glucose values are 'standardised' – so the exponential of the coefficient represents the odds ratio for induction of labour arising from a 1 SD mmol/litre change in blood glucose

9.2.2.4   Costs

The costs used in the model can be broken down into 3 categories: costs of the OGTT; costs relating to treatment/management; and costs arising from neonatal and maternal outcomes. Costs are not discounted because they are all assumed to occur within 12 months of diagnosis. Costs are based on the 2013 price year unless otherwise stated.

9.2.2.4.1   *OGTT costs*

In the model all patients accrue the costs of an OGTT apart from in the 'No treatment' comparator. A bottom-up or 'ingredients based' approach was adopted to obtain a cost for a 2 point and 3 point OGTT[xx].

The costs of the test comprised the laboratory test costs for each blood sample, the costs of the glucose solution and the costs of staff time in administering the OGTT. Although practice will not be the same everywhere, it was assumed that as part of the test it would be necessary to provide some explanation of the test, obtain patient consent, prepare the glucose solution, take blood samples and inform the patient of the result. The blood tests are often taken by a healthcare assistant but a diabetic specialist nurse or midwife will often be responsible for explaining the test and informing the woman of the test result. After consultation with the guideline development group, it was assumed that a 2 point OGTT will take 20 minutes of a healthcare assistant's time and 5 minutes of a nurses' time. It was additionally assumed that a 3 point OGTT will take an additional 5 minutes for a healthcare assistant compared with a 2 point OGTT.

The unit costs used to calculate the cost of an OGTT in the model are given in Table 105.

Table 105:   OGTT unit costs

Item	Cost	Source
Health care assistant Band 3[a]	£25 per hour	Curtis (2013)
Nurse Band 6[b]	£49 per hour	Curtis (2013)
Laboratory costs 2 sample OGTT	£8.00	An NHS hospital trust personal communication (2014)
Laboratory costs 3 sample OGTT	£12.00	An NHS hospital trust personal communication (2014)
Glucose solution	£1.64	Joint Formulary Committee (2014)

OGTT oral glucose tolerance test
a. A cost per hour is not provided for a Band 3 post but a mean basic annual pay of £16,522 is reported. This is 52% of the mean basic annual pay reported for a Band 6 qualified nursing, midwifery and health visiting staff and so the cost per hour for a healthcare assistant Band 3 is estimated as 52% of the hourly cost of a Band 6 nurse
b. The hourly cost of a Band 6 nurse is based on a cost per hour as opposed to a cost per patient hour, which assumes that only 41% of a nurse's time is spent in direct contact with patients. It is assumed that the nurses time input reflects all OGTT related activity and not just patient contact time.

[xx] Historically a fasting blood glucose and 2 hour post glucose challenge blood glucose have been used to make a diagnosis of gestational diabetes (2 point). However, in the new IADPSG diagnostic criteria a diagnosis can additionally be made using a 1 hour post glucose challenge blood glucose (3 point)

Cost of the 2 sample OGTT is:

$$(£25 \times (\tfrac{20}{60})) + (£49 \times (\tfrac{5}{60})) + £8 + £1.64 = £22.06$$

Cost of the 3-sample OGTT is:

$$(£25 \times (\tfrac{25}{60})) + (£49 \times (\tfrac{5}{60})) + £12 + £1.64 = £28.14$$

9.2.2.4.2 Gestational diabetes treatment cost

It was assumed that there are 90 days of treatment from the time of diagnosis to the time of birth. First line treatment is a trial of diet, the success of which was assumed in the model to be able to be assessed 10 days from diagnosis. The model additionally made the simplifying assumption that any transition from diet to hypoglycaemic therapy would be made once this 10 day assessment was made.

In line with the previous NICE guideline, the model assumed that in women who have not achieved a sufficient reduction in blood glucose during the 10-day trial of diet, the first line hypoglycaemic therapy is insulin.

Throughout treatment the patient is expected to undertake self-monitoring of blood glucose (SMBG) which requires some instruction. In addition, healthcare professionals will be required to spend time providing dietary advice, a key component of treatment with diet, as well as carrying out dietary assessment at the end of the 10-day trial period and insulin instruction in those patients who do not achieve sufficient reduction in blood glucose on diet alone. For women on insulin treatment, the guideline development group agreed that it was reasonable to assume that 20 units of rapid-acting insulin and 10 units of intermediate-acting insulin was a typical daily dose.

The time of healthcare professionals for these various activities used in the model to cost treatment are shown in Table 106. The model assumed that dietary advice and assessment would be undertaken by a dietician and SMBG and insulin instruction provided by a Band 7 nurse.

Table 106: Healthcare professional time input

Activity	Time (minutes)	Source
SMBG instruction	30	Guideline development group
Dietary advice	30	Guideline development group
Dietary assessment	15	Guideline development group
Insulin instruction	45	Guideline development group

In line with the guideline recommendations, the model costed SMBG on the basis of testing 4 times a day, unless the woman is on insulin in which case a test frequency of 7 times a day is used.

The model assumed, in line with NICE guidance, that a diagnosis of gestational diabetes leads to an increase in antenatal monitoring compared with a low risk pregnancy. Specifically, the costing includes 3 additional ultrasound scans and 3 additional hospital appointments.

The unit costs used in calculating treatment costs are shown in Table 107.

Table 107:   Treatment unit costs

Item	Cost	Standard error	Source
Band 7 nurse[a]	£139 per hour	-	Curtis (2013)
Band 7 dietician[b]	£47 per hour	-	Curtis (2013)
Antenatal standard ultrasound scan[c]	£130	£4.37	NHS Reference Costs (2012/13) Currency code NZ21Z
Antenatal appointment[c]	£89	£3.42	NHS Reference Costs (2012/13) Currency code WF01A
Rapid acting insulin (aspart)	£0.02	-	Joint Formulary Committee (2014)
Intermediate insulin (isophane)	£0.01	-	Joint Formulary Committee (2014)
Needles[d]	£0.13	-	NHS Drugs Tariff July 2014
Lancets[e]	£0.03	-	NHS Drugs Tariff July 2014
SMBG strips[f]	£0.20	-	Joint Formulary Committee (2014)

a. The cost of a Band 7 nurse is based on cost per hour of patient contact team. This costing is based on a nurse spending 41% of their work-time in direct contact with patients. The timings in this analysis relate to direct contact with patients
b. The cost of a Band 7 dietician is based on cost per hour as no breakdown is given on how time is allocated
c. It is assumed that the sample means of NHS Reference Costs are normally distributed for the purposes of probabilistic sensitivity analysis
d. Needles based BD Micro-Fine™ Ultra 4mm/32 gauge priced at £12.69 for a pack of 100
e. Lancets based on BD Micro-Fine+ 0.20mm/33 gauge priced at £3.16 for a pack of 100
f. Strip based on Accu-Check™ Active priced at £9.95 for a pack of 50

The total cost of treatment can be broken down into the following categories:

Dietary instruction and assessment

$$(£47 \times (\tfrac{30}{60})) + (£139 \times (\tfrac{15}{60})) = £58.25$$

Insulin instruction and use

The model assumes that 64% of patients require insulin therapy at the end of the diet trial period (see Section 9.2.2.6) which lasts for a period of 80 days.

$$((£139 \times (\tfrac{45}{60})) + (80 \times ((20 \times £0.02) + (10 \times £0.01) + (4 \times £0.13)))) \times 0.64 = £118.94$$

SMBG instruction and testing

$$(£139 \times (\tfrac{30}{60})) + (90 \times 4 \times (£0.20 + £0.03)) + (0.64 \times (80 \times 3 \times (£0.20 \times £0.03))) = £187.63$$

More intensive antenatal care

$$3 \times (£130 + £89) = £657$$

Thus the total cost of treatment, the sum of these component categories, is £1022.

9.2.2.4.3   *Calculating standard errors for NHS Reference Costs for use in probabilistic sensitivity analysis (PSA)*

NHS Reference Costs give a mean cost and an upper and lower quartile range. They also provide data on the number of data submissions on which these summary statistics are based. We have developed a spreadsheet tool which estimates parameters for a probabilistic sensitivity analysis. The 'front end' of this is shown in Figure 2.

Figure 2: User interface for spreadsheet tool to estimate NHS Reference Cost parameters for a probabilistic sensitivity analysis
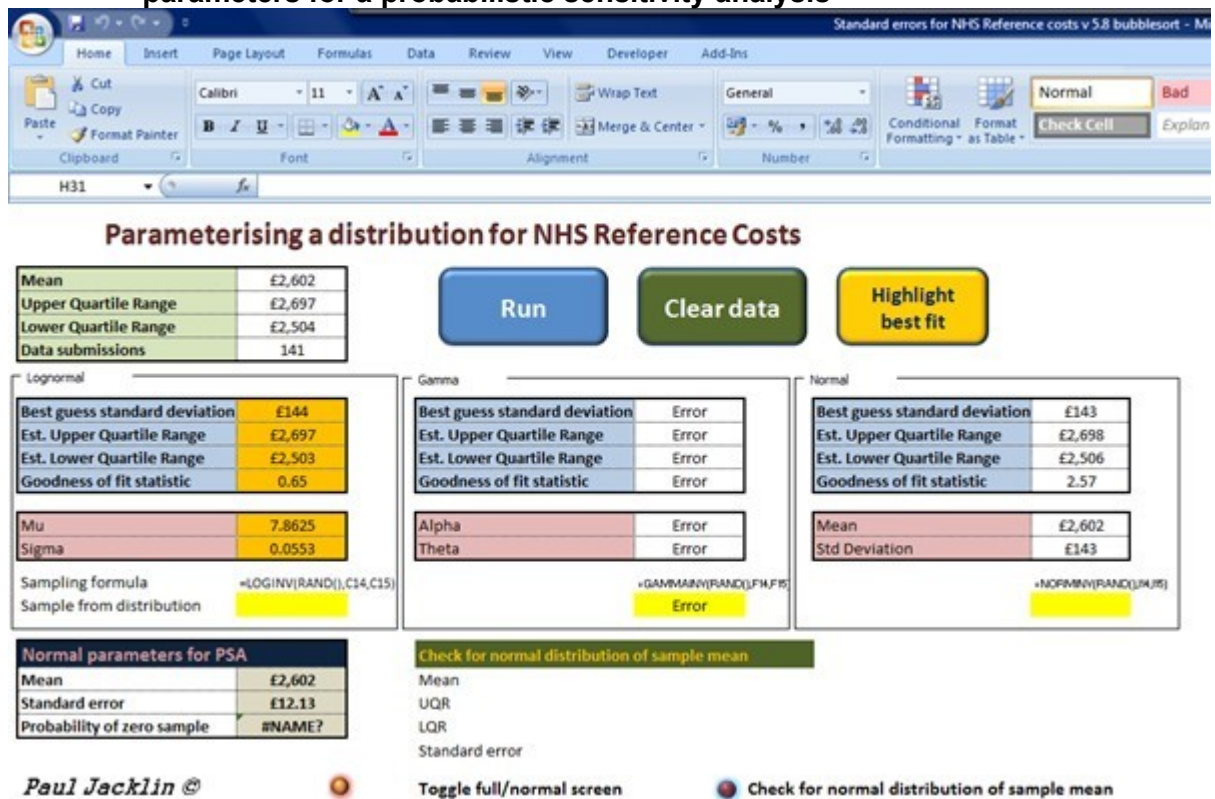
Source: Spreadsheet tool used to estimate PSA parameters for NHS Reference Costs

The user is asked to input the mean, upper quartile range, lower quartile range and number of data submissions for the NHS Reference Cost to be sampled as part of a probabilistic sensitivity analysis. The user then hits the 'Run' button and is asked for a low and high value for standard deviation (for example £50 and £450). The user is then asked how many different standard deviations they wish to fit. The default assumes that the user will wish to try standard deviations at £1 intervals, and therefore in the example with a low standard deviation of £50 and a high standard deviation of £450, a total of 401 different standard deviations will be 'fitted'.

The spreadsheet tool estimates which distribution best fits the population distribution out of log-normal, gamma or normal. For each distribution a 'goodness of fit' statistic is calculated for each fitted standard deviation. For each distribution and standard deviation the model calculates the inverse of the cumulative probability density function at a probability of 0.25 and 0.75, in order to indicate the actual upper and lower quartile range associated with the fitted distribution. The goodness of fit statistic is then estimated by summing the square[yy] of the difference between the actual upper quartile range and the upper quartile range of the fitted distribution and the actual lower quartile range and the lower quartile range of the fitted distribution. The fitted distribution which has the lowest goodness of fit statistic is that which has the closest fit to the NHS Reference Cost data. This is done for the 3 types of distribution and the distribution which has the lowest goodness of fit is deemed to be the one that best matches the NHS Reference Cost. The best fit distribution therefore has a best fit standard deviation.

Most NHS Reference Costs have a number of data submission points (over 100 is common) and therefore it is reasonable to assume, according to central limit theorem, that the

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[yy] The difference is squared because goodness of fit is not affected by whether the difference is positive or negative

sampling distribution is approximately normally distributed. Therefore, the PSA parameters estimated from the spreadsheet tool are normal distribution with a mean equal to the NHS Reference Cost mean and a standard error given by the best fit standard deviation divided by the square root of the number of data submissions.

9.2.2.4.4 *Outcome related or 'downstream' costs*

Treatment of gestational diabetes is potentially worthwhile because it has been shown to reduce the risk of certain adverse outcomes. As well as affecting health related quality of life, these outcomes often have associated costs and therefore reductions in these outcomes may produce some resource savings which may, to some extent, offset the costs of screening, diagnosis and treatment. Conversely, there may be some potentially adverse effects of treatment, such as hypoglycaemia, and the risk of certain events may be increased.

Therefore, to ascertain the full opportunity costs of the intervention it was important that any savings or costs associated with changed outcomes be taken into account within the analysis. The costs used within the model are shown in Table 108.

Table 108:   Outcome related costs

Outcome	Cost	Standard Error	Source
Severe hypoglycaemiaa,b	£629	-	NHS Reference Costs (2012/13) Currency code ASS02 Currency code KB01C Currency code KB01D Currency code KB01E Currency code KB01F
Admission to neonatal intensive care unit (NICU)c	£1118	£35	NHS Reference Costs (2012/13) Currency code XA01Z
Induction of labourc,d	£329	£72	NHS Reference Costs (2012/13) Currency code NZ30C Currency code NZ31C
Caesarean sectionc	£884	£86	NHS Reference Costs (2012/13) Currency code NZ30C Currency code NZ50C
Neonatal deathc,e	£767	£39	NHS Reference Costs (2005/06) Currency code N01
Shoulder dystociac	£1256	£125	NHS Reference Costs (2012/13) Currency code PB02Z
Birth traumac	£1256	£125	NHS Reference Costs (2012/13) Currency code PB02Z
Serious perinatal complicationf,g	£1219	n/a	Calculated
Phototherapy	£810	£72	NHS Reference Costs (2012/13) Currency code JC47B
Pre-eclampsiah,i	£4656	-	NICE (2010)*

* Hypertension in pregnancy. NICE Clinical Guideline 107 (2010)
a. The costs of severe hypoglycaemia are derived from the cost of an ambulance and a weighted average of A&E costs for diabetes with hypoglycaemic disorders
b. Probabilstic sensitivity analysis was not undertaken on the costs of severe hypoglycaemia because it affects approximately only 1% of treated patients and therefore has a negligible impact on the overall costs associated with any comparator diagnostic threshold
c. It is assumed that the sample means of NHS Reference Costs are normally distributed for the purposes of probabilistic sensitivity analysis
d. The costs of induction of labour and caesarean section are the costs over above those incurred in a normal vaginal delivery in woman with a non-elective long stay admission and with CC score 0
e. There is no longer an NHS Reference Cost for a neonatal death so an older version was used. The cost was then uprated to 2012/13 prices using the HCHS index (Resource Planning and Acquisition team, Department of Health)
f. The cost of serious perinatal complication is a weighted average of the costs of shoulder dystocia, birth trauma and neonatal death. See Section 9.2.3.7 for weights used in the calculation
g. The probabilistic sensitivity analysis does not require the costs of serious perinatal complications to be sampled separately as it is a weighted average cost of other costs that are sampled in each simulation

h. The cost of pre-eclampsia was uprated to 2012/13 prices using the HCHS index (Resource Planning and Acquisition team, Department of Health)
i. Probabilistic sensitivity analysis was not undertaken for the costs of pre-eclampsia as no data existed on the dispersion or variation from the point estimate. This value was varied as part of a sensitivity analysis

9.2.2.5 Clinical effectiveness

In a decision analytic model, probability parameters are used to determine the expected pay-offs (costs and QALYs in this case) associated with different decision alternatives. In Section 9.2.2.3 the method by which the baseline risk or probability for each patient was estimated for a number of outcomes was described. For each different diagnostic threshold comparator, the model determined whether a patient's blood glucose values were such that they would be diagnosed with gestational diabetes and treated or not. If the patient is not treated then the patient experiences the baseline risk for those outcomes. However, if the patient is treated then a relative risk is applied to the baseline risk to obtain a treated probability for different outcomes. We followed a published study (Round et al., 2011) in using pooled relative risks from 2 randomised controlled studies (Crowther et al., 2005; Landon et al., 2009) unless otherwise stated, both of which investigated treatment efficacy of gestational diabetes using a similar trial protocol. The relative risks used in the model are shown in Table 109.

Table 109: Relative risks from treating gestational diabetes

Outcome	Relative risk	Standard error log relative risk	Distribution	Source
Shoulder dystocia	0.41	0.314	Log-normal	Crowther et al. (2005); Landon et al. (2009)
Caesarean section	0.88	0.068	Log-normal	Crowther et al. (2005); Landon et al. (2009)
NICU[a]	0.77	0.194	Log-normal	Landon et al. (2009)
Jaundice requiring phototherapy	0.84	0.139	Log-normal	Crowther et al. (2005); Landon et al. (2009)
Pre-eclampsia[b]	0.46	0.345	Log-normal	Landon et al. (2009)
Induction of labour	1.17	0.069	Log-normal	Crowther et al. (2005); Landon et al. (2009)

NICU neonatal intensive care unit
a. Crowther (2005) reported on admission to neonatal nursery rather than NICU but given the high numbers involved the guideline development group considered that NICU admission as reported in Landon (2009) better reflected practice in England and Wales
b. The risks of pre-eclampsia reported in Crowther (2005) seem high in both groups and therefore a decision was made to just use the results of Landon (2009) for this outcome

The primary outcomes in both the randomised studies were composites of serious perinatal complications. This model calculated both a cost and QALY decrement associated with serious perinatal complications. It was noted that shoulder dystocia accounted for 73% of all serious perinatal complications in Landon et al. (2009) and Crowther et al. (2005). This proportion was similar in both intervention and control arms of the studies. Therefore a multiplier of 1.37 was used to estimate both baseline and treated risk of serious perinatal complications from the risk of shoulder dystocia[zz].

[zz] $1 \div 0.73 = 1.37$

9.2.2.6 Other event probabilities

Most of the chance nodes in the model relate to the baseline and treatment risk of various outcomes. However, there are a small number of other probabilities used in the model which influence the expected cost associated with different parameters. First, there is the probability that patients are able to remain on diet treatment alone without the need for hypoglycaemic therapy. Second, for those on hypoglycaemic therapy there is assumed to be a risk of hypoglycaemia and concomitant risk of hospitalisation due to that hypoglycaemia.

Data supplied from the guideline development group members was used to assess the likely transition to hypoglycaemic therapy after initiating diet treatment. This data provided by the group is summarised in Table 110 and the model assumed that the mean of women remaining on diet and exercise only from these data would be the proportion in the model who did not require hypoglycaemic treatment.

Table 110:   Treatment of women with gestational diabetes by the end of pregnancy

NHS Hospital Trust	Diet & exercise only	Metformin only	Insulin with or without metformin
Central Manchester University Hospitals	47%	11%	42%
South Tees Hospitals	31%	40%	25%
City Hospitals Sunderland	35%	40%	25%
Norfolk and Norwich University Hospital	30%	19%	51%

The source for parameter estimates relating to hypoglycaemia was the same as used in the previous NICE guidance (NICE, 2008; Round et al., 2011).

The model's other event probabilities are summarised in Table 111.

Table 111:   Other event probabilities

Event	Probability	Source
Not requiring hypoglycaemic therapy	36%	Guideline development group, mean of those remaining on diet and exercise in Table 110
Hypoglycaemia given that the woman is taking insulin	20%	Langer et al. (2000)
Severe hypoglycaemia given that the woman has hypoglycaemia	5%	NICE (2008)

9.2.2.7 Quality adjusted life years

In the model a QALY decrement is attached to serious perinatal complications. The method to estimate the QALY loss associated with a serious perinatal complication is the same as that followed in previous studies (NICE, 2008; Round et al., 2011).

In deriving the QALY loss from a serious perinatal complication, an annual discount rate of 3.5% was applied in line with NICE methods (NICE, 2012). An individual QALY loss was attached to the individual components of a serious perinatal complication. A weighting was then applied according to the relative frequency of these outcomes across Crowther et al. (2005) and Landon et al. (2009) in order to ascertain a weighted average for a serious perinatal complication as shown in Table 112.

Table 112:   QALY loss from serious perinatal complications

Complication	Weight	QALY	Source
Neonatal death/stillbirth	0.08	25	Calculated
Shoulder dystocia	0.73	0.2	Culligan et al., 2005
Birth trauma	0.20	0.2	Culligan et al., 2005

The QALY from a neonatal death is a reasonable approximation of the discounted QALY from a life expectancy of 80 years lived in perfect health.

$$\sum_{n=0}^{79} \frac{1.0}{1.035^n} = 27.6$$

The QALY loss from shoulder dystocia and birth trauma is relatively small as less than one-fifth of infants affected suffer any long-term morbidity as a result. For both shoulder dystocia and birth trauma the QALY loss was estimated from the QALY loss associated with brachial plexus injuries, one of the most important fetal complications of shoulder dystocia, affecting 4–16% of cases (Clements 2001; Maternal and Child Health Research Consortium, 1998; RCOG, 1999). Most of these resolve without disability, with permanent brachial plexus dysfunction occurring in less than 10% of cases (Gherman et al., 1998). Therefore, the model assumed that 84% of shoulder dystocia cases would incur no brachial plexus injury. Of the 16% who incurred a brachial plexus injury, it was assumed that 10% of them would have a permanent brachial plexus dysfunction.

Culligan et al., 2005 estimated a health-state utility of 0.6 for permanent brachial plexus injury (mild to moderate, and including quality of life of mother and child) and a health state utility of 0.99 for brachial plexus injuries that resolve within 2 months. Thus the QALY loss associated with shoulder dystocia and birth trauma is estimated as follows[aaa]:

$$(\sum_{n=0}^{79} \frac{0.4}{1.035^n} \; x \; 0.016) + 0.01 \; x \; \frac{2}{12} \; 0.144 = 0.179$$

This was rounded up to 0.2 QALYs.

The overall weighted QALY loss of a serious perinatal complication was calculated as:

$$(0.08 \times 25) + (0.73 \times 0.2) + (0.20 \times 0.2) = 2.2$$

Maternal health state utility

In the base case analysis maternal utility during pregnancy was not included. However, the model does allow maternal utility to be considered as part of analysis incorporating data that was collected in the ACHOIS study (Crowther et al., 2005). The maternal health state utility during pregnancy was assumed to last 90 days, the approximate time from testing for gestational diabetes and birth. The postpartum period was assumed to be 3 months. The model assumes that maternal health state utility is determined according to whether

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[aaa] The terms within parenthesis estimate the QALY loss from permanent brachial plexus injury. The health state utility associated with permanent brachial plexus injury has been estimated as 0.6 (Culligan et al., 2005) and therefore an upper-bound estimate of the health state utility loss, based on perfect health, is 0.4. The lifetime QALY loss of this is given by summing the discounted health state utility loss over the patient's remaining life expectancy, 80 years in this case (years 0–79). However, it is assumed that only 16% of shoulder dystocia results in brachial plexus injury and only 10% of brachial plexus injuries results in permanent disability, or 1.6% of cases of shoulder dystocia. Therefore, the lifetime QALY loss associated with a permanent brachial plexus is multiplied by 0.016 to give the weighted average loss across all cases of shoulder dystocia. The terms outside parenthesis give the weighted average QALY loss due to non-permanent brachial plexus injury which is estimated to have a health state utility loss of 0.01 experienced over a period of 2 months.

treatment is given or not and is independent of plasma glucose values. Table 113 gives the model default values for maternal health state utility values.

Table 113: Maternal health state utility parameters[a]

Category	Health state utility	Standard Error	Distribution
Pregnancy treated	0.72	0.025	Beta
Pregnancy not treated	0.70	0.024	Beta
Postpartum treated	0.79	0.022	Beta
Postpartum not treated	0.78	0.022	Beta

a. The ACHOIS Study (Crowther et al., 2005)

9.2.2.8 Sensitivity analysis

Probabilistic sensitivity analysis was undertaken to assess how sensitive results were to parameter uncertainty arising from sampling variation. Coefficients in the regression model were sampled using the Cholesky decomposition method which allows for the correlation between coefficients to be maintained. A common criticism made of probabilistic sensitivity analysis is that sampled parameters are often assumed to be independent. Clearly, that is often not the case (for example sensitivity and specificity) and in this model it would be expected that there was some correlation between blood glucose parameters as a minimum.

If the covariance structure between parameters is known then it is possible to correlate then by taking correlated draws from a multivariate normal distribution. A regression analysis provides this structure through the variance–covariance matrix. The Cholesky decomposition of this matrix is another matrix which, when multiplied by its transpose, gives the variance–covariance matrix. This Cholesky decomposition matrix is then used to generate a vector of correlated variables, calculated using a vector of mean parameter values added to independent standard normal variates multiplied by the Cholesky decomposition matrix.

In addition, one-way sensitivity analysis was undertaken on a small number of parameter values where there was important uncertainty, the cause of which was not the result of random error.

9.2.3 Results

9.2.3.1 Implications for diagnosis in changing from WHO 1999 criteria to IADPSG (1.75) criteria

Compared with WHO 1999 diagnostic criteria for gestational diabetes, IADPSG (1.75) criteria has a lower fasting threshold and a higher 2 hour threshold. Clearly, there are some women who would be diagnosed as having gestational diabetes using either criteria. However, in addition there will some women diagnosed with gestational diabetes using IADPSG fasting criteria who would not be diagnosed using WHO 1999 criteria. Conversely, there are women who would be diagnosed on the basis of a WHO 1999 2 hour blood glucose value who no longer get a label of gestational diabetes using IADPSG criteria. The trade-off this involves is indicated in the Venn diagram shown in Figure 3 for the Southampton dataset.

Figure 3: Women diagnosed with gestational diabetes per 1000
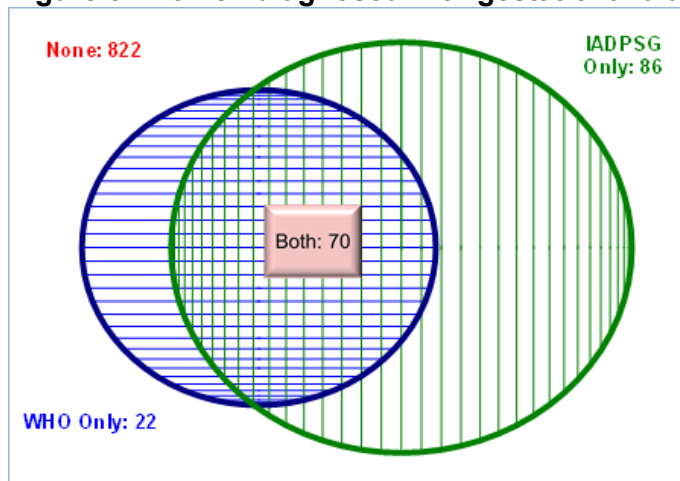
In economic terms, the key issue is whether the benefits in the additional diagnoses made using the IADPSG criteria only more than offset the losses in patients who would have been diagnosed using WHO 1999 criteria. It need not necessarily follow that because IADPSG has identified more patients that the benefits in newly diagnosed patients offset the losses in previously diagnosed patients, as their risk of adverse outcomes is unlikely to be identical. It should be noted, though, that on average patients 'missed' by one of the diagnostic criteria will have less severe gestational diabetes then the group who would be identified by either criteria. By implication, those identified by both criteria have a higher average fasting blood glucose than patients diagnosed using IADPSG criteria and, similarly, patients identified by both criteria have a higher average 2 hour blood glucose than those only identified using WHO 1999 criteria. However, even if the benefits in those now diagnosed did outweigh the losses in those no longer diagnosed, resource scarcity requires that this additional benefit can be achieved at an acceptable cost.

In the Venn diagram in Figure 3 it can be seen that IADPSG (2-point criteria) does classify more patients as having gestational diabetes than would be the case using WHO 1999 criteria. In Figures 4 and 5, the detection rate for WHO 1999 and 2-point IADPSG (1.75) criteria is compared across all the datasets. Additionally, for the HAPO dataset the additional detection arising from the addition of a 1 hour post glucose challenge result to the 2-point OGTT is also compared.

Figure 4: Numbers detected using WHO 1999 and IADPSG (1.75) criteria in various populations
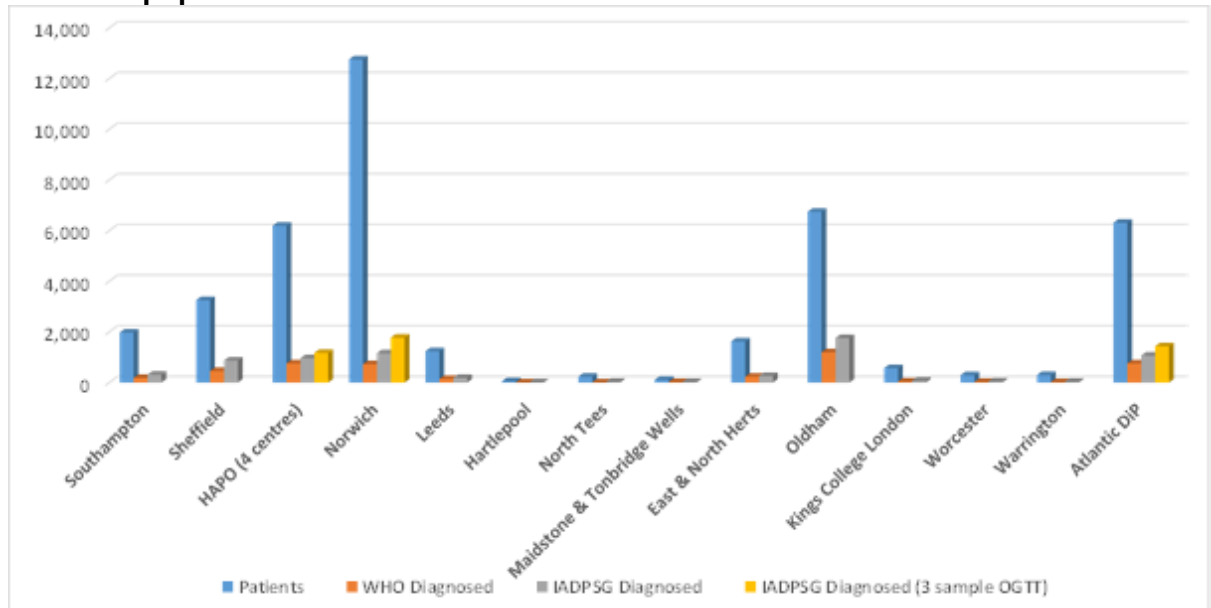
Source: Data submitted as part of call for evidence for this guideline

Figure 5: Percentage detected using WHO and IADPSG (1.75) criteria in various populations
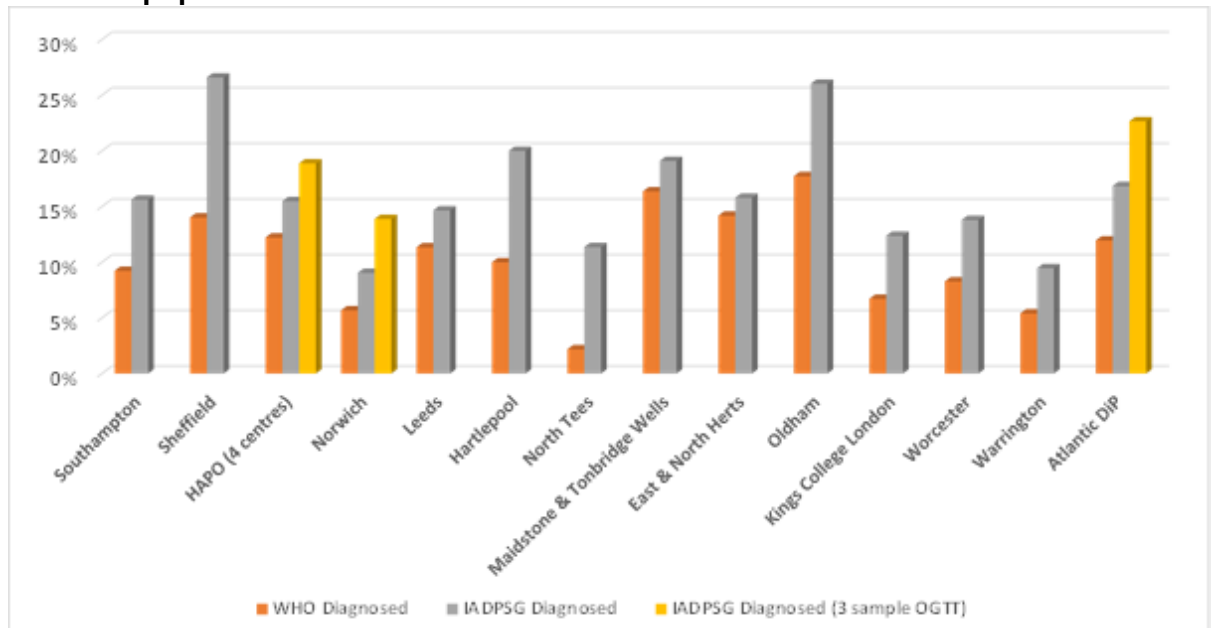
Source: Data submitted as part of call for evidence for this guideline

It should be noted that, with the exception of the HAPO (4 centres) data, these detection rates cannot be interpreted as a measure of disease prevalence. However, they do strongly suggest that IADPSG (1.75) will lead to a marked increase in the measured prevalence of gestational diabetes compared with WHO 1999 criteria.

They also suggest that a change to IADPSG (1.75) criteria would have a considerable impact on service delivery clinics in England and Wales using NICE based risk factor screening and WHO 1999 criteria, with detection rates increasing from 11% (East and North Herts) to 420% (North Tees). However, the increase may not be quite as dramatic as suggested, as the view

and practice of the guideline development group was that most centres in England and Wales will initiate treatment on a lower fasting value than used in the WHO 1999 criteria.

This model considered other diagnostic thresholds besides WHO 1999 and IADPSG (1.75) criteria and these are shown graphically in Figure 6. This shows that there is a broader range of trade-off to be made than a consideration of WHO 1999 and IADPSG (1.75) alone would imply. In other words, WHO 1999 criteria and IADPSG (1.75) criteria have a certain implication in terms of which women will be detected as a result of a fasting or 2 hour value. However, other thresholds can be used which lead to more or less women detected as a result of a fasting or 2 hour value.

Figure 6: Detection rates across data submissions for all diagnostic thresholds considered in the model

Source: Data submitted as part of call for evidence for this guideline

9.2.3.2   Cost effectiveness Norwich population

The deterministic analysis presented below is for the Norwich dataset using the stepwise regressions with backward elimination. The results are shown in Table 114 and Figure 7.

Table 114:   Incremental cost effectiveness of alternative diagnostic thresholds (Norwich)

Threshold	Cost[a]	QALY[a]	ICER
No treatment	£0	0.00	-
Fasting 5.6/2 hour 8.5	£711,023	18.71	Extended dominance
Fasting 5.5/2 hour 8.5	£762,704	19.91	Extended dominance
Fasting 5.4/2 hour 8.5	£846,382	21.79	Extended dominance
WHO 1999	£847,518	24.16	£35,076
IADPSG 2.00	£865,789	21.21	Dominated

Threshold	Cost[a]	QALY[a]	ICER
Fasting 5.3, 2 hour 8.5	£943,378	23.98	Dominated
Fasting 5.6, 2 hour 7.8	£983,368	27.32	£43,079
Fasting 5.5, 2 hour 7.8	£1,029,444	28.32	£45,890
Fasting 5.4, 2 hour 7.8	£1,106,687	29.99	£46,346
Fasting 5.3, 2 hour 7.8	£1,193,936	31.85	£46,822
IADPSG 1.75	£1,215,489	29.81	Dominated
IADPSG 1.50	£1,610,432	40.02	£50,979
IADPSG 1.75 (incl 1 hour)	£1,757,385	42.47	£60,068

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectivenesss ratio, QALY quality adjusted life year, WHO World Health Organization
a. Cost and QALYs calculated relative to no treatment

Figure 7: Graph to illustrate cost and QALYs of the different diagnostic thresholds in the Norwich dataset
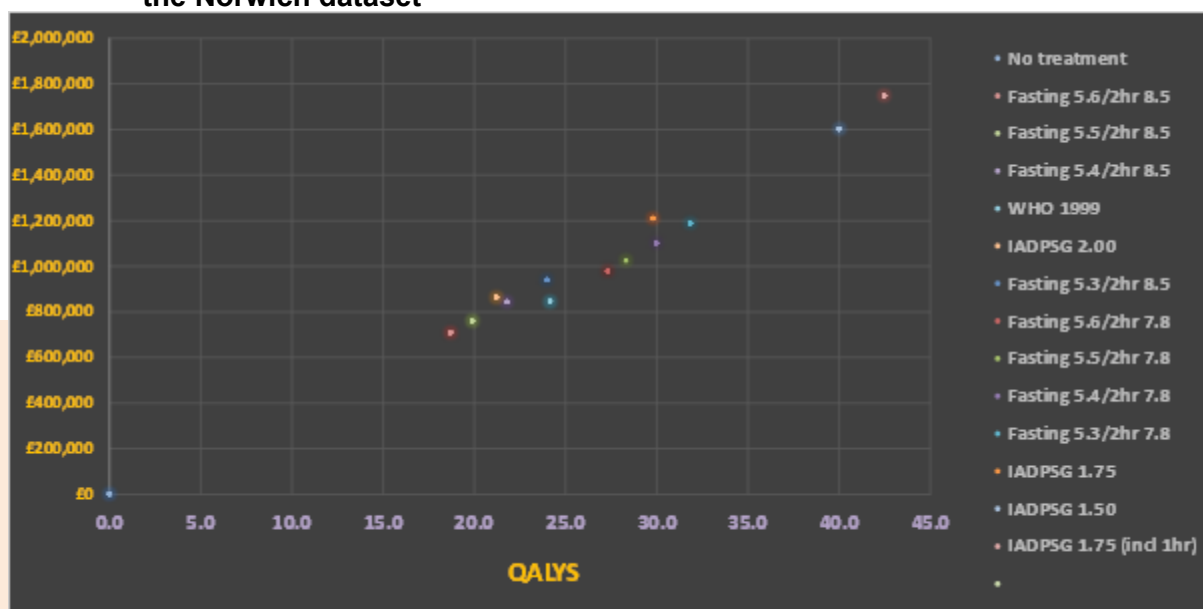
Source: Data submitted as part of call for evidence for this guideline

The differences in outcomes influencing these results are shown in Table 115 and Figure 8.

Table 115: Clinical outcomes in Norwich dataset analysis

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
No treatment	0	132	182	2333	1,005	699	346	3173
Fasting 5.6, 2 hour 8.5	568	125	173	2315	989	692	325	3202
Fasting 5.5, 2 hour 8.5	629	125	172	2313	988	691	323	3205
Fasting 5.4, 2 hour 8.5	727	124	171	2311	986	690	321	3209
WHO 1999	724	124	170	2310	984	690	323	3208
IADPSG 2.00	748	125	171	2311	986	690	320	3210
Fasting 5.3, 2 hour 8.5	840	124	170	2308	984	689	318	3214

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
Fasting 5.6, 2 hour 7.8	888	122	168	2305	981	688	318	3216
Fasting 5.5, 2 hour 7.8	942	122	168	2304	980	687	317	3219
Fasting 5.4, 2 hour 7.8	1032	122	167	2302	978	686	315	3223
Fasting 5.3, 2 hour 7.8	1133	121	166	2299	976	685	312	3227
IADPSG 1.75	1153	122	167	2300	978	685	312	3228
IADPSG 1.50	1608	118	162	2288	968	681	303	3249
IADPSG 1.75 (incl 1 hour)	1771	117	161	2283	965	677	301	3253

CS caesarean section, Dx diagnosed, IOL induction of labour, NICU neonatal intensive care unit admissions, SD shoulder dystocia, SPC serious perinatal complications,

Figure 8: Graph to show clinical outcomes in analysis of Norwich dataset
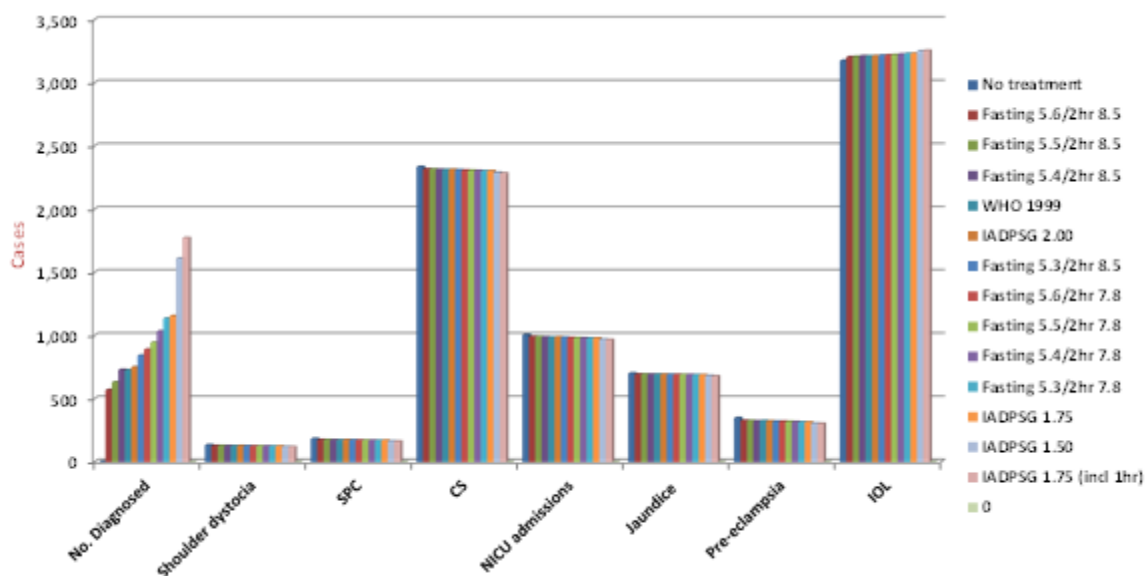
Source: Data submitted as part of call for evidence for this guideline

Using a willingness to pay threshold of £20,000 or £30,000 per QALY, a strategy of no testing and no treatment would be cost effective. The WHO 1999 strategy is closest to being cost effective at a £30,000 per QALY willingness to pay threshold.

9.2.3.3 Cost effectiveness HAPO (4 centres) population

The deterministic analysis presented below is for the HAPO (4 centres) dataset using the stepwise regressions with backward elimination. The results are shown in Table 116 and graphically in Figure 9.

Table 116: Incremental cost effectiveness of alternative diagnostic thresholds (HAPO)

Threshold	Cost[a]	QALY[a]	ICER
No treatment	£0	0.00	-
Fasting 5.6, 2 hour 8.5	£524,920	18.68	£28,103

Threshold	Cost[a]	QALY[a]	ICER
Fasting 5.5, 2 hour 8.5	£557,408	19.70	£31,736
IADPSG 2.00	£579,718	18.90	Dominated
Fasting 5.4, 2 hour 8.5	£593,771	20.67	Extended dominance
Fasting 5.3, 2 hour 8.5	£667,934	22.58	Extended dominance
WHO 1999	£734,309	25.19	£32,244
Fasting 5.6, 2 hour 7.8	£799,806	27.02	Extended dominance
Fasting 5.5, 2 hour 7.8	£827,154	27.81	£35,482
Fasting 5.4, 2 hour 7.8	£855,491	28.51	£39,946
IADPSG 1.75	£904,465	28.04	Dominated
Fasting 5.3, 2 hour 7.8	£921,369	30.07	£42,305
IADPSG 1.75 (incl 1 hour)	£1,086,287	32.57	Extended dominance
IADPSG 1.50	£1,284,018	38.22	£44,485

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectivenesss ratio, QALY quality adjusted life year, WHO World Health Organization
a. Cost and QALYs calculated relative to no treatment

Figure 9: Graph to illustrate cost and QALYs of the different diagnostic thresholds in the HAPO dataset
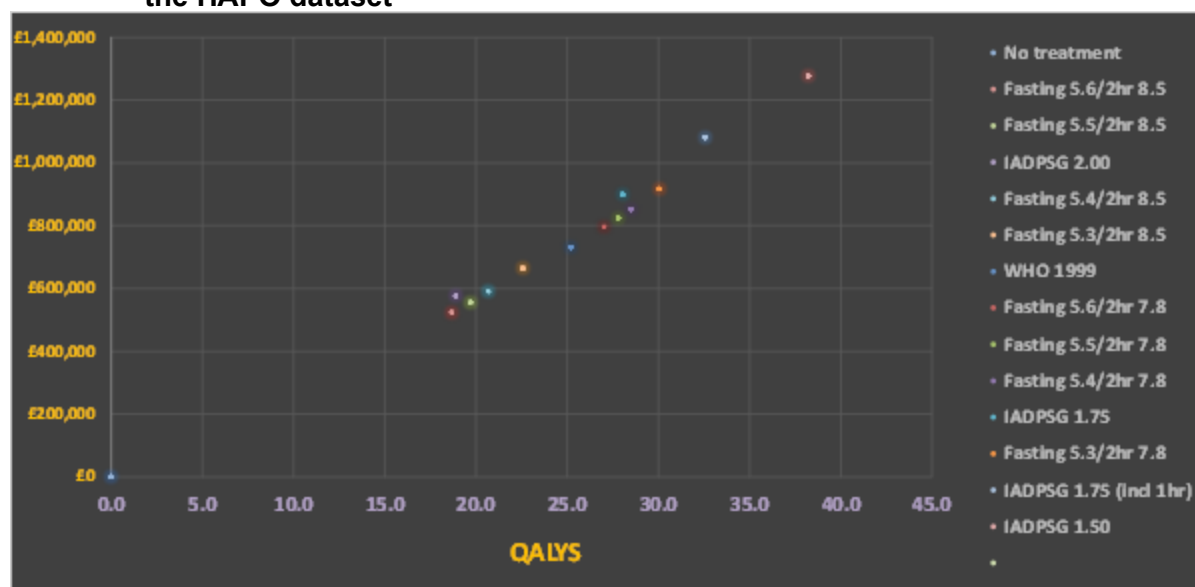
Source: Data submitted as part of call for evidence for this guideline

The differences in outcomes influencing these results are shown in Table 117 and Figure 10.

Table 117: Clinical outcomes in HAPO dataset analysis

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
No treatment	0	73	100	1,224	533	345	201	1,621
Fasting 5.6, 2 hour 8.5	504	66	91	1,209	519	338	183	1,645
Fasting 5.5, 2 hour 8.5	543	66	91	1,207	518	338	182	1,647
IADPSG 2.00	569	66	91	1,207	518	338	182	1,649
Fasting 5.4, 2 hour 8.5	589	66	90	1,206	517	337	181	1,649

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
Fasting 5.3, 2 hour 8.5	676	65	90	1,204	515	336	179	1,653
WHO 1999	755	64	88	1,202	512	336	177	1,657
Fasting 5.6, 2 hour 7.8	837	64	87	1,199	510	335	175	1,662
Fasting 5.5, 2 hour 7.8	869	63	87	1,198	509	334	174	1,663
Fasting 5.4, 2 hour 7.8	904	63	87	1,197	509	334	173	1,665
IADPSG 1.75	955	63	87	1,196	509	334	172	1,667
Fasting 5.3, 2 hour 7.8	981	63	86	1,195	507	333	171	1,668
IADPSG 1.75 (incl 1hr)	1,165	62	85	1,190	505	331	168	1,676
IADPSG 1.50	1,399	60	82	1,184	499	329	163	1,688

CS caesarean section, Dx diagnosed, IOL induction of labour, NICU neonatal intensive care unit admissions, SD shoulder dystocia, SPC serious perinatal complications

Figure 10:   Graph to show clinical outcomes in analysis of HAPO dataset
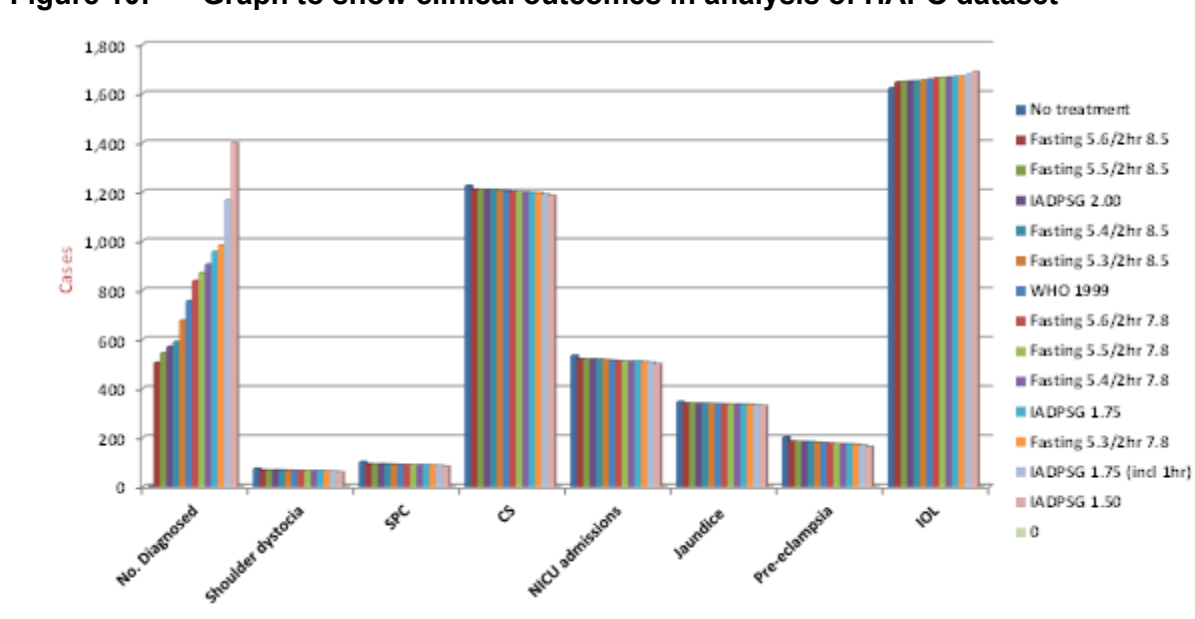
Source: Data submitted as part of call for evidence for this guideline

Using a willingness to pay threshold of £20,000 per QALY then a strategy of no testing and no treatment would be cost effective. A fasting glucose threshold of 5.6 mmol/litre and a 2 hour post glucose threshold of 8.5 mmol/litre is the cost-effective diagnostic threshold using a more permissive £30,000 per QALY willingness to pay threshold.

9.2.3.4   Cost effectiveness HAPO (4 centres) screening with NICE risk factors

The deterministic analysis presented below is for the HAPO (4 centres) dataset using patients who would be offered an OGTT using the NICE risk factors of ethnicity, BMI and family history of diabetes mellitus[bbb]. As with the other datasets, the patient's baseline risk for

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[bbb] The dataset did not include previous gestational diabetes or macrosomia, other risk factors which form part of NICE risk factor screening

different outcomes was estimated using stepwise logistic regression with backward elimination. The results are shown in Table 118 and graphically in Figure 11.

Table 118: Incremental cost effectiveness of alternative diagnostic thresholds (HAPO with risk factor screening)

Threshold	Cost[a]	QALY[a]	ICER
No treatment	£0	0.00	-
Fasting 5.6, 2 hour 8.5	£388,442	16.25	£23,902
Fasting 5.5, 2 hour 8.5	£419,027	17.25	Extended dominance
Fasting 5.4, 2 hour 8.5	£448,231	18.06	Extended dominance
IADPSG 2.00	£456,456	17.21	Dominated
WHO 1999	£505,039	20.43	£27,928
Fasting 5.3, 2 hour 8.5	£513,111	19.86	Dominated
Fasting 5.6, 2 hour 7.8	£560,419	22.11	£32,943
Fasting 5.5, 2 hour 7.8	£585,864	22.87	£33,313
Fasting 5.4, 2 hour 7.8	£608,834	23.49	£36,819
Fasting 5.3, 2 hour 7.8	£667,249	24.96	£39,958
IADPSG 1.75	£685,943	24.20	Dominated
IADPSG 1.75 (incl 1 hour)	£802,203	27.58	Extended dominance
IADPSG 1.50	£927,274	31.43	£40,172

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectivenesss ratio, QALY quality adjusted life year, WHO World Health Organization
a. Cost and QALYs calculated relative to no treatment

Figure 11: Graph to illustrate cost and QALYs of the different diagnostic thresholds in a HAPO subset selected with NICE risk factors
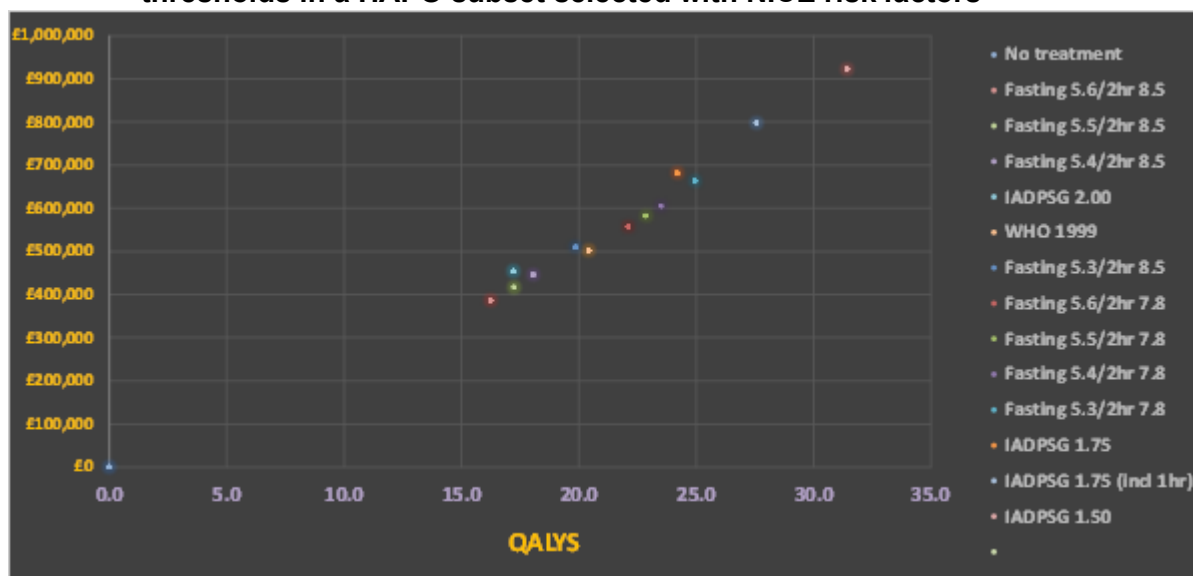
The differences in outcomes influencing these results are shown in Table 119 and Figure 12.

Table 119: Clinical outcomes in risk factor HAPO subset analysis

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
No treatment	0	49	67	759	345	219	146	974

Threshold	Dx	SD	SPC	CS	NICU	Jaundice	Pre-eclampsia	IOL
Fasting 5.6, 2 hour 8.5	413	43	59	745	332	213	130	995
Fasting 5.5, 2 hour 8.5	450	43	59	744	331	213	129	996
Fasting 5.4, 2 hour 8.5	488	42	58	743	330	212	128	999
IADPSG 2.00	494	43	59	743	331	212	128	999
WHO 1999	558	41	57	741	328	212	126	1,002
Fasting 5.3, 2 hour 8.5	565	42	57	741	329	212	126	1,002
Fasting 5.6, 2 hour 7.8	629	41	56	739	326	211	123	1,006
Fasting 5.5, 2 hour 7.8	659	41	56	738	326	210	123	1,007
Fasting 5.4, 2 hour 7.8	688	40	56	737	325	210	122	1,009
Fasting 5.3, 2 hour 7.8	757	40	55	735	323	209	120	1,012
IADPSG 1.75	774	40	55	735	324	209	120	1,013
IADPSG 1.75 (incl 1hr)	912	39	54	731	321	207	117	1,019
IADPSG 1.50	1,063	38	52	727	317	206	113	1,027

CS caesarean section, Dx diagnosed, IOL induction of labour, NICU neonatal intensive care unit admissions, SD shoulder dystocia, SPC serious perinatal complications

Figure 12:   Graph to show clinical outcomes in analysis of HAPO subset

Using a willingness to pay threshold of £20,000 per QALY a strategy of no testing and no treatment would be cost effective. The WHO 1999 diagnostic criteria is cost effective using a £30,000 per QALY willingness to pay threshold.

9.2.3.5 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis the regression analysis was based on blood glucose covariates only with backward elimination of variables with non-significant coefficients. Due to the model run time, a smaller number of Monte Carlo simulations were run with all the diagnostic strategies. However, for illustrative purposes a larger number of simulations were run for the HAPO (4 centres) dataset with risk factors using strategies which had a higher probability of being cost effective as observed in the smaller simulation.

9.2.3.6 HAPO (4 centres) screening with NICE risk factors

9.2.3.6.1 *2000 simulations*

Table 120 and Figure 13 summarise the results of running 100 simulations with the HAPO (4 centres) dataset with NICE risk factors included.

Table 120: **HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=2000)**

Threshold	Mean net benefit[a]	Probability cost effective (£20,000 per QALY)	Probability cost effective (£30,000 per QALY)
No treatment	£278	82.5%	40.1%
WHO 1999	−£137,589	8.1%	41.0%
IADPSG 1.50	−£376,008	0.0%	2.5%
IADPSG 1.75	−£258,705	0.0%	0.0%
IADPSG 2.00	−£146,610	0.0%	0.0%
Fasting 5.3, 2 hour 7.8	−£223,919	0.0%	4.0%
Fasting 5.4, 2 hour 7.8	−£192,959	0.0%	0.0%
Fasting 5.5, 2 hour 7.8	−£179,485	0.0%	3.8%
Fasting 5.6, 2 hour 7.8	−£166,643	0.1%	2.6%
Fasting 5.3, 2 hour 8.5	−£163,324	0.0%	0.0%
Fasting 5.4, 2 hour 8.5	−£130,084	0.0%	0.0%
Fasting 5.5, 2 hour 8.5	−£113,933	0.0%	0.0%
Fasting 5.6, 2 hour 8.5	−£99,222	9.4%	6.2%
IADPSG 1.75 (incl 1 hour)	−£315,991	0.0%	0.0%

IADPSG International Association of the Diabetes and Pregnancy Study Groups, QALY quality adjusted life year, WHO World Health Organization
a. Mean Net Benefit based on £20,000 per QALY willingness to pay threshold

Figure 13: Cost effectiveness acceptability curve HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=2000)
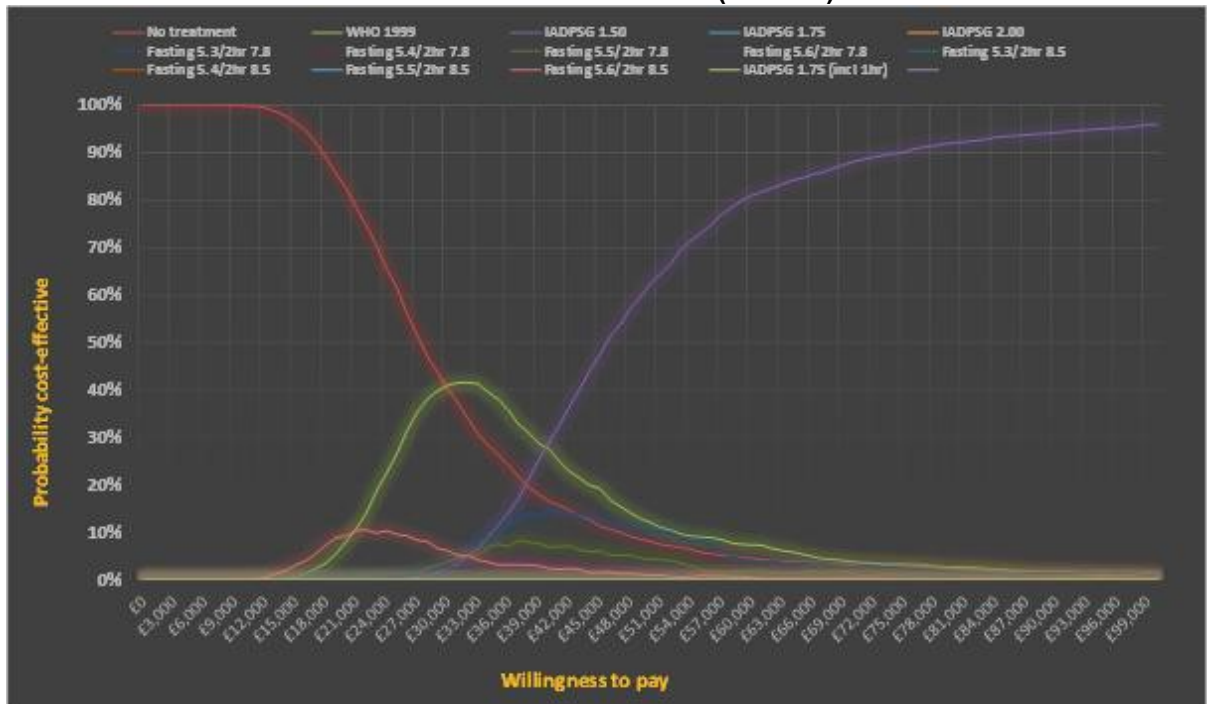
9.2.3.6.2   *20,000 simulations*

Table 121 and Figures 14 and 15 summarise the results of running 20,000 simulations with the HAPO (4 centres) dataset with NICE risk factors included

Table 121:   HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=20,000) HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=20,000)

Threshold	Mean net benefit	Probability cost effective (£20,000 per QALY)	Probability cost effective (£30,000 per QALY)
No treatment	£180	82.8%	42.3%
WHO 1999	−£133,378	17.2%	57.8%

QALY quality adjusted life year, WHO World Health Organization
Mean net benefit based on £20,000 per QALY willingness to pay threshold

Figure 14: Cost effectiveness acceptability curve HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=20,000)
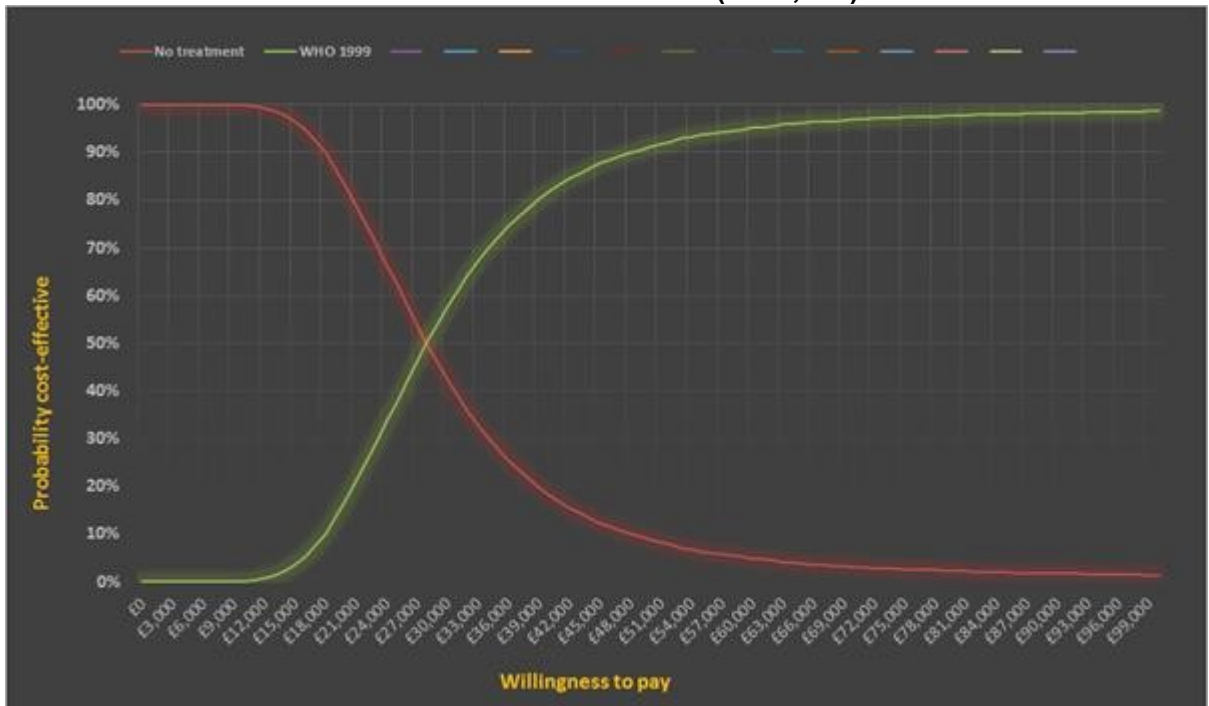
Figure 15:   Cost effectiveness plane HAPO (4 centres) screening with NICE risk factors Monte Carlo simulation (n=20,000)
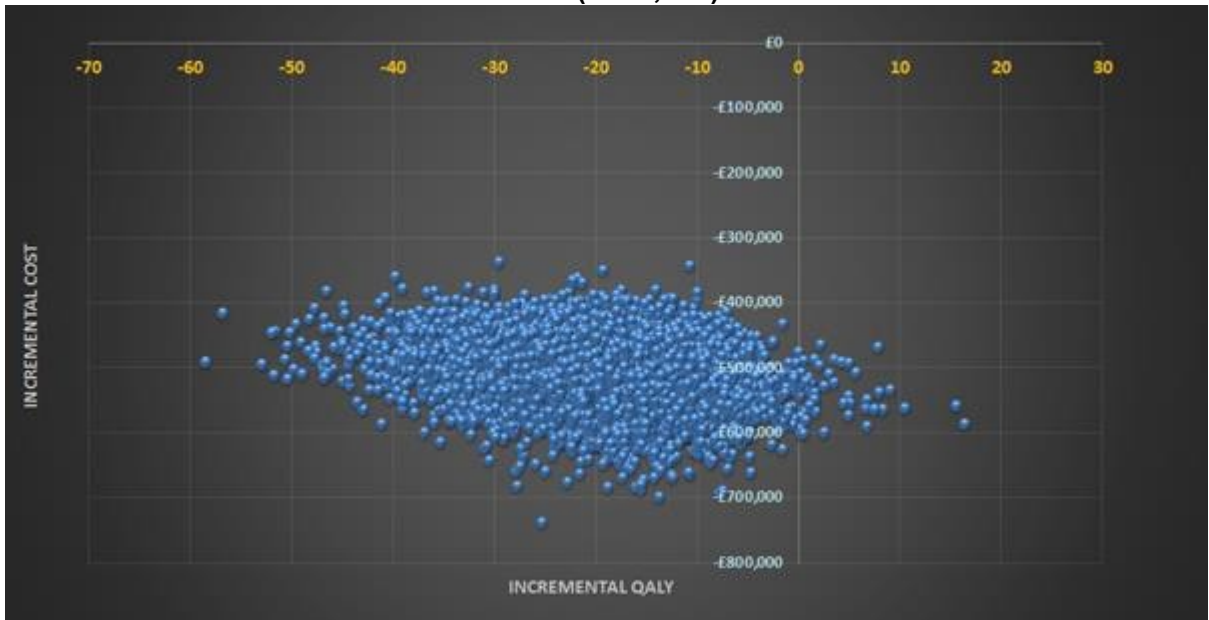
9.2.3.7   HAPO (4 centres) screening with no NICE risk factors (2000 simulations)

Table 122 and Figure 16 summarise the results of running 2000 simulations with the HAPO (4 centres) dataset without NICE risk factors included.

Table 122:   HAPO (4 centres) screening with no NICE risk factors Monte Carlo simulation (n=2000)

Threshold	Mean net benefit	Probability cost-effective (£20,000 per QALY)	Probability cost-effective (£30,000 per QALY)
No treatment	£49	99.8%	82.7%
WHO 1999	−£107,898	0.2%	15.1%
IADPSG 1.50	−£179,773	0.0%	0.9%
IADPSG 1.75	−£116,409	0.0%	0.0%
IADPSG 2.00	−£75,187	0.0%	0.0%
Fasting 5.3, 2 hour 7.8	−£121,173	0.0%	0.3%
Fasting 5.4, 2 hour 7.8	−£117,043	0.0%	1.1%
Fasting 5.5, 2 hour 7.8	−£114,383	0.0%	0.0%
Fasting 5.6, 2 hour 7.8	−£113,348	0.0%	0.0%
Fasting 5.3, 2 hour 8.5	-−£83,846	0.0%	0.0%
Fasting 5.4, 2 hour 8.5	−£79,198	0.0%	0.0%
Fasting 5.5, 2 hour 8.5	−£75,939	0.0%	0.0%
Fasting 5.6, 2 hour 8.5	−£74,904	0.0%	0.0%
IADPSG 1.75 (incl 1 hour)	−£148,658	0.0%	0.0%

IADPSG International Association of the Diabetes and Pregnancy Study Groups, QALY quality adjusted life year, WHO World Health Organization
Mean net benefit based on £20,000 per QALY willingness to pay threshold

Figure 16:   Cost effectiveness acceptability curve HAPO (4 centres) screening with no NICE risk factors Monte Carlo simulation (n=2000)

9.2.3.8 Norwich dataset (1000 simulations)

Table 123 and Figure 17 summarise the results of running 1000 simulations with the Norwich dataset.

Table 123: **Norwich dataset Monte Carlo simulation (n=1000)**

Threshold	Mean net benefit	Probability cost-effective (£20,000 per QALY)	Probability cost-effective (£30,000 per QALY)
No treatment	£544	97.5%	71.0%
WHO 1999	−£363,811	2.5%	25.3%
IADPSG 1.50	−£820,086	0.0%	0.2%
IADPSG 1.75	−£624,484	0.0%	0.0%
IADPSG 2.00	−£442,254	0.0%	0.0%
Fasting 5.3, 2 hour 7.8	−£561,660	0.0%	0.6%
Fasting 5.4, 2 hour 7.8	−£510,463	0.0%	0.1%
Fasting 5.5, 2 hour 7.8	−£465,474	0.0%	0.5%
Fasting 5.6, 2 hour 7.8	−£438,816	0.0%	2.1%
Fasting 5.3, 2 hour 8.5	−£465,352	0.0%	0.0%
Fasting 5.4, 2 hour 8.5	−£410,716	0.0%	0.0%
Fasting 5.5, 2 hour 8.5	−£363,543	0.0%	0.0%
Fasting 5.6, 2 hour 8.5	−£334,953	0.0%	0.0%
IADPSG 1.75 (incl 1 hr)	−£919,085	0.0%	0.2%

IADPSG International Association of the Diabetes and Pregnancy Study Groups, QALY quality adjusted life year, WHO World Health Organization
Mean net benefit based on £20,000 per QALY willingness to pay threshold

Figure 17: **Cost effectiveness acceptability curve Norwich dataset Monte Carlo simulation (n=1000)**
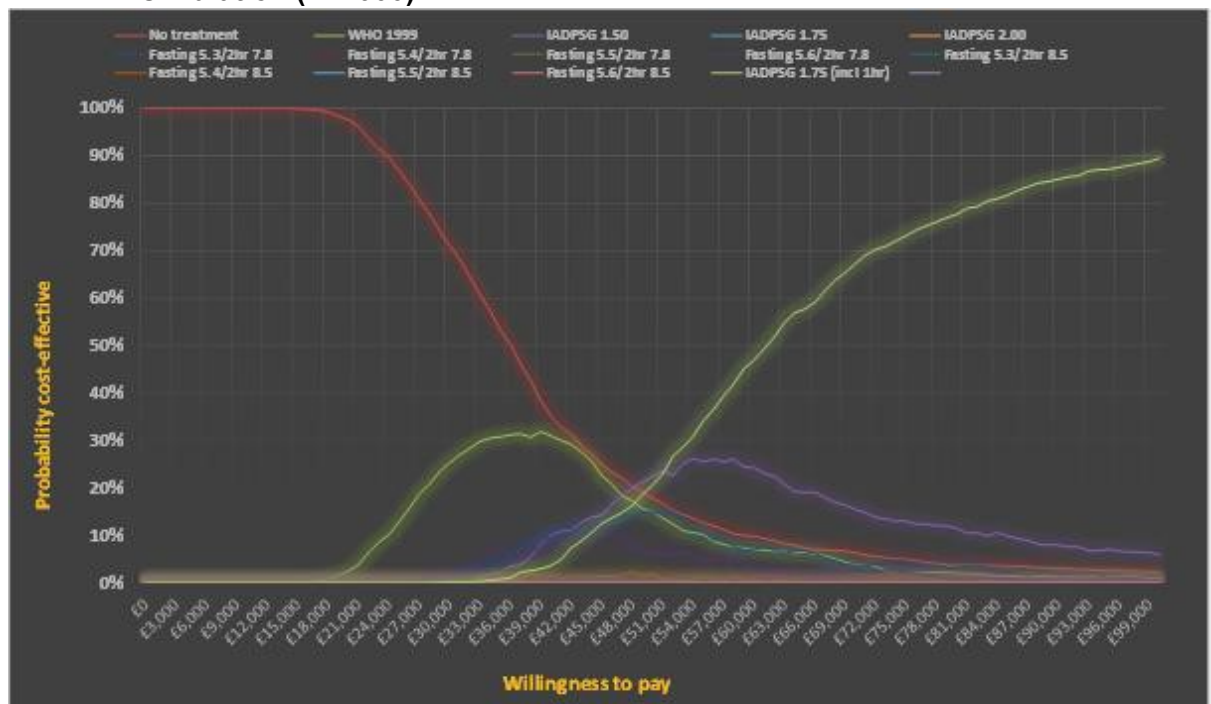
9.2.3.9 One-way sensitivity analysis

9.2.3.9.1 *Varying the cost of nurse*

Some uncertainty exists as to the exact opportunity cost of nurse time. Apart from the fact that the grade of the nurse may vary by setting, there is some uncertainty about the hourly rate. If the model timings captured all of a nurse's activity associated with delivering treatment for gestational diabetes then it would be appropriate to use the lower cost per hour of a nurse's time throughout rather than the £139 cost per patient hour, which allows for the fact that nurses have other tasks associated with their jobs that do not involve direct contact with patients.

In this sensitivity analysis we assumed a band 6 nurse delivers SMBG instruction and insulin instruction and that a nurse's time was valued at £49 per hour. Table 124 summarises the ICERs for the Norwich, HAPO (4 centres) complete dataset and HAPO (4 centres) subset selected using NICE risk factors with this opportunity cost.

Table 124:   ICERs for different datasets assuming that the opportunity cost of nurse time is valued at £49 per hour

	Norwich	HAPO (all)	HAPO (risk factors)
No treatment	-	-	-
Fasting 5.6, 2 hour 8.5	Extended dominance	£25,116	£21,089
Fasting 5.5, 2 hour 8.5	Extended dominance	£27,519	Extended dominance
Fasting 5.4, 2 hour 8.5	Extended dominance	Extended dominance	Extended dominance
Fasting 5.3, 2 hour 8.5	Dominated	Extended dominance	Dominated
WHO 1999	£31,759	£27,966	£24,084
IADPSG 2.00	Dominated	Dominated	Dominated
Fasting 5.6, 2 hour 7.8	£37,322	Extended dominance	£28,267
Fasting 5.5, 2 hour 7.8	£39,936	£30,659	£28,965
Fasting 5.4, 2 hour 7.8	£40,368	£34,483	£31,674
Fasting 5.3, 2 hour 7.8	£40,822	£36,831	£34,733
IADPSG 1.75	Dominated	Dominated	Dominated
IADPSG 1.75 (incl 1 hr)	£52,693	Extended dominance	Extended dominance
IADPSG 1.50	£44,543	£38,809	£34,938

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectiveness ratio, QALY quality adjusted life year, WHO World Health Organization

This sensitivity analysis would suggest that the model's conclusions are sensitive to a fairly small degree to changes in this parameter, noting that the change made was a large one (from £139 per hour to £49 per hour). No treatment remains the cost-effective option in the Norwich dataset, although WHO 1999 is closer to being cost effective using a £30,000 per QALY willingness to pay threshold.

In the complete HAPO dataset, which approximates to universal screening, WHO 1999 criteria is now the cost-effective strategy at a £30,000 per QALY willingness to pay threshold. In the HAPO subset selected by risk factors, it becomes cost effective to use a fasting threshold of 5.5 mmol/litre and a 2 hour post glucose threshold of 7.8 mmol/litre.

9.2.3.9.2 *Varying the cost of pre-clampsia*

The base case analysis used the NICE guideline on hypertension in pregnancy as the source of the cost of pre-eclampsia; however, included in the guideline was a reference to a UK Health Technology Assessment (Meads et al., 2008) which used a pre-eclampsia cost that was almost double. The guideline development group expressed considerable uncertainty as to likely cost of pre-eclampsia in this patient population. It is possible, for example, that

pre-eclampsia is less expensive in this group because many of the potentially large costs in women with pre-eclampsia are associated with prematurity. Conversely, in women with gestational diabetes, the onset of pre-eclampsia would be likely to be later in the pregnancy and less severe.

Therefore, as a sensitivity analysis we used the cost of pre-eclampsia cited in the Health Technology Assessment (HTA) (Meads et al., 2008). The cost cited was £9009 which was based on a 2004/05 price year. We therefore used the Hospital & Community Health Services (HCHS) index to convert this figure to £11,212 for a 2012/13 price year[ccc], using a multiplier of 1.245. The impact of changing this parameter is shown in Table 125.

Table 125: ICERs for different datasets assuming that the cost of pre-eclampsia is £11,212

	Norwich	HAPO (all)	HAPO (risk factors)
No treatment	-	-	-
Fasting 5.6, 2 hour 8.5	Extended dominance	£21,970	£17,540
Fasting 5.5, 2 hour 8.5	Extended dominance	£25,201	Extended dominance
Fasting 5.4, 2 hour 8.5	Extended dominance	Extended dominance	Extended dominance
Fasting 5.3, 2 hour 8.5	Dominated	Extended dominance	Dominated
WHO 1999	£28,607	£26,097	£21,109
IADPSG 2.00	Dominated	Dominated	Dominated
Fasting 5.6, 2 hour 7.8	£33,437	£26,500	£23,325
Fasting 5.5, 2 hour 7.8	£37,636	£28,790	Extended dominance
Fasting 5.4, 2 hour 7.8	£38,415	£30,022	£27,016
Fasting 5.3, 2 hour 7.8	£39,198	£35,158	£32,718
IADPSG 1.75	Dominated	Dominated	Dominated
IADPSG 1.75 (incl 1 hour)	£55,308	Extended dominance	Extended dominance
IADPSG 1.50	£43,610	£37,545	£32,882

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectiveness ratio, WHO World Health Organization

There are small changes to the model's outputs resulting from a more than doubling of the pre-eclampsia cost. In the Norwich dataset, WHO 1999 criteria would be the cost-effective diagnostic threshold if decision makers were using a willingness to pay threshold of £30,000 per QALY. In the unselected HAPO (4 centres) dataset a fasting blood glucose of 5.5 mmol/litre and a 2 hour blood glucose of 7.8 mmol/litre would be cost effective at £30,000 per QALY whereas a fasting blood glucose of 5.4 mmol/litre and a 2 hour blood glucose of 7.8 mmol/litre would be cost effective in the HAPO (4 centres) dataset with risk factors. Even if the more stringent £20,000 cost per QALY was being used then a fasting blood glucose of 5.6 mmol/litre and 2 hour blood glucose of 8.5 mmol/litre would be cost effective in these patients.

9.2.3.9.3 *Including a maternal health state utility*

The inclusion of health state utility tended to make identification and treatment of gestational diabetes more cost effective but the overall effect was small and did little to reflect the ordinal performance of different thresholds. The results are shown in Table 126.

[ccc] The value of the index was 232.3 in 2004/05 and 289.1 in 2012/13. Therefore, the multiplier is calculated as 289.1÷232.3

Table 126: ICERs for different datasets including maternal utility

	Norwich	HAPO (all)	HAPO (risk factors)
No treatment	-	-	-
Fasting 5.6, 2 hour 8.5	Extended dominance	£26,327	£22,475
Fasting 5.5, 2 hour 8.5	Extended dominance	£28,976	Extended dominance
Fasting 5.4, 2 hour 8.5	Extended dominance	Extended dominance	Extended dominance
Fasting 5.3, 2 hour 8.5	Extended dominance	Extended dominance	Dominated
WHO 1999	£32,632	£29,403	£25,697
IADPSG 2.00	Dominated	Dominated	Dominated
Fasting 5.6, 2 hour 7.8	£38,122	Extended dominance	£29,797
Fasting 5.5, 2 hour 7.8	£40,451	£31,997	£30,334
Fasting 5.4, 2 hour 7.8	£40,834	£35,560	£32,986
Fasting 5.3, 2 hour 7.8	£41,235	£37,651	£35,741
IADPSG 1.75	Dominated	Dominated	Dominated
IADPSG 1.75 (incl 1 hour)	£51,491	Extended dominance	Extended dominance
IADPSG 1.50	£44,510	£39,430	£35,926

IADPSG International Association of the Diabetes and Pregnancy Study Groups, WHO World Health Organization

9.2.4 Discussion

Models are a simplification of the real world and have their limitations. However, this does not mean that they are not an appropriate tool to aid and improve decision-making. Any decision-making process involves assumptions, but at least those assumptions are more likely to be made explicit within a modelling framework which provides a transparent basis for decision-making. A key limitation in economic models is often the limitations in the evidence base that informs them. However, this is symptomatic of the real-life difficulties in arriving at optimal decisions and is better than making decisions with complete disregard to the evidence.

9.2.4.1 Patient datasets

Two datasets were analysed as scenarios as part of this economic analysis. The extent to which the results can be generalised to other settings in England and Wales may depend to some extent on how representative those datasets are of English and Welsh populations.

Patients in the Norwich dataset were selected for an OGTT on the basis of risk factors which broadly approximate to those recommended by NICE in previous guidance. Despite this the number of cases of gestational diabetes was relatively low. This may just reflect the fact that Norwich is a relatively low prevalence area, although other low prevalence areas (for example Southampton) had a higher percentage of cases in their risk selected population.

It should also be noted that the Norwich dataset was collected as part of clinical practice and may be 'contaminated' to some extent, especially compared with data collected as part of a study with its associated protocols. The results were obtained from a laboratory record and not collected with any patient data. Furthermore, in Norwich, in addition to screening women with NICE risk factors, the screening policy includes women with polycystic ovary syndrome and previous stillbirth, and those whose grandparents had diabetes.

It may be the case that if the risks are diluted in the Norwich dataset for these reasons, as seems possible given the low number of cases, then the cost effectiveness of treating gestational diabetes in low prevalence populations screened with NICE risk factors may be underestimated.

If Norwich represents a low prevalence scenario then the HAPO (4 centres) dataset would seem to represent a relatively high prevalence setting. Even using WHO 1999 criteria, more than 10% of the 6000 patients would be classified as having gestational diabetes.

Although it is important and instructive to examine analyses in both settings, the HAPO (4 centre) dataset can probably be considered superior in terms of being generalisable to other settings. There are a number of reasons for this. First, the data was collected as part of a research study and therefore is likely to be less prone to bias and contamination. Second, it was possible to develop regression models which used explanatory variables other than blood glucose results from the OGTT. Third, the model predictors of baseline risk with and without covariates were based on outcomes in this population. It has not been possible to validate the accuracy of the regression models applied to other settings and that is another reason why the analysis of the Norwich data should be interpreted with extra caution. Finally, it was possible to very closely replicate NICE recommended risk factor screening which arguably gives the most informative analysis.

9.2.4.2 Comparison of cost effectiveness results with previous guidelines

There are considerable differences of approach to the modelling in this guideline compared with the modelling that was undertaken for the 2008 guideline. This largely reflects the fact that the focus of the decision problem was different, and in particular this model addressed the cost effectiveness of different diagnostic criteria whereas the modelling in the previous guideline aimed to assess the cost effectiveness of different screening strategies for a given diagnostic criteria.

Clearly, the use of individual patient level data is beneficial in directly gauging the impact of different diagnostic thresholds and using patient level data represents a more sophisticated approach. The patient level data, at least in the HAPO dataset, also allows a more realistic analysis of the interaction of different risk factors.

However, there is considerable overlap with the modelling undertaken in the previous guideline, especially with respect to universal and risk factor screening strategies, although biochemical tests, other than OGTT, were not formally covered in this analysis. It is noticeable that treating gestational diabetes appears less cost effective in the model produced for this guideline than it did in the model produced for the guideline in 2008. The ICERs in this model are generally much higher and indeed are in a region that would be considered only borderline cost effective. However, the guideline development group felt that the costings used in the current model were more realistic and comprehensive.

Specifically, the group considered that far more healthcare resource use was triggered as a result of a diagnosis of gestational diabetes than was considered to be the case last time. In this model, for example, treatment additionally consisted of 3 ultrasounds and 3 antenatal appointments. This was done to reflect current practice and reflected recommendations in NICE guidance. It isn't clear to what extent this mirrors the treatment protocols in the intervention studies and illustrates a tension in economic evaluation in NICE guidelines. Although ideally costs that reflect current practice in the NHS should be used, at the same time calculations have to reflect the costs in the intervention study as it was that resource use which generated the treatment effect.

If there are aspects of current practice that are not necessary to generate the treatment effect then they are perhaps best considered as part of a different decision problem. Including such costs may cause the cost effectiveness to be underestimated.

9.2.4.3 Key model assumptions

The model assumes a single treatment effect size irrespective of the baseline risk or severity of disease. Some of the diagnostic thresholds are below that used in intervention studies and technically there is no evidence that there would be any treatment benefit in such patients, let

alone an equivalent relative effect. However, the importance of this should not be over-stated. As disease becomes less severe, the baseline risk becomes smaller. Thus, even if the relative treatment effect is assumed to be the same in these patients, they will derive less absolute benefit and therefore are less likely to be considered cost effective to treat. Admittedly, cost effectiveness will still be overestimated if it is subsequently shown that such patients experience either no treatment effect or a reduced effect.

The model is highly sensitive to the QALYs averted from a serious perinatal complication. An important driver of this QALY are the neonatal deaths and stillbirths reported in the ACHOIS study, which all occurred in the control group, and the weight they are given within serious complications. However, it is possible that chance in the ACHOIS study led the impact of mortality to be overestimated in serious perinatal complications. No deaths were reported in the Landon study (Landon et al., 2009) in either arm of the trial and HAPO does not report an association between blood glucose levels and neonatal death or stillbirth. On the other hand, the intervention studies excluded those with higher levels of blood glucose and therefore it was perhaps less likely that research studies would detect a reduction in mortality benefit even if one would exist in clinical practice.

9.2.4.4 Insulin treatment

In the model the first line pharmacological treatment is insulin if diet is judged to have insufficiently lowered blood glucose levels. This reflects the treatment protocols on which the treatment effectiveness parameters were based.

However, current practice would generally now favour using metformin as the first line pharmacological treatment which has a cheaper acquisition cost and requires no instruction. However, trials of metformin versus insulin, notably the MiG Trial (Rowan et al., 2008), are in populations in whom a diet and lifestyle intervention has been unsuccessful. Therefore, it would be difficult to base treatment effectiveness for our model population on such data.

Treatment costs may, therefore, be slightly overestimated in this model, although many patients starting on metformin ultimately receive insulin therapy and therefore the cost savings may be quite small. In addition, the pharmacological cost of treatment is a relatively small component of total treatment cost.

Also, any over-estimation will be reflected most in the ICER against 'No treatment'. The ICERs between alternative diagnostic strategies will be less affected as the treatment costs would be reduced by a similar amount.

The model does not account for differences in the requirement for insulin across different diagnostic categories, primarily because we were not aware of data linking OGTT blood glucose values at diagnosis to the proportion who subsequently achieve adequate control on diet. Diagnostic strategies which identify women with lower blood glucose values would be expected to have a higher proportion achieving satisfactory blood glucose levels on diet alone. However, where there is a trade-off between a higher 2 hour OGTT blood glucose value and lower faster blood glucose value (as is the case when IADPSG diagnostic criteria are compared with WHO 1999 diagnostic criteria, for example) then even the direction of the effect is difficult to predict.

The model's results are not particularly sensitive to the proportion of women who require insulin as this only constitutes a relatively small part of the treatment cost (approximately 12%). The total cost of treatment in the model including the cost of hypoglycaemia is £1,026 based on 36% of women achieving satisfactory blood glucose levels on diet alone. If the proportion achieving satisfactory blood glucose on diet alone is increased to 50% then the treatment cost would fall by just £35 to £991.

9.2.4.5 Model framework

The model framework, and in particular the approach to modelling treatment outcomes, was outlined in Section 9.2.2. However, there are alternative approaches that could have been undertaken which may have yielded different results. It is also possible that there is some double counting of costs among the 6 outcomes explicitly modelled.

The model does not consider a lifetime horizon from the maternal perspective and therefore does not capture any benefits that may arise in terms of delaying or even avoiding future diabetes (Ratner, 2007). In this respect it may underestimate the cost effectiveness of treating gestational diabetes.

9.2.4.6 Fasting plasma glucose as an independent predictor of outcomes

One of the facets of the logistic regression was that fasting plasma glucose did not often appear to be an important independent determinant of the adverse outcomes included in the model. Of course, it is correlated with other blood glucose values and therefore would show similar associations with adverse pregnancy outcomes when considered in isolation. A distinguishing feature of the IADPSG criteria is the relatively low fasting blood glucose threshold, which may explain the lack of cost effectiveness for any form of IADPSG in this model.

Nevertheless, other studies have suggested that fasting plasma glucose may have a more important independent impact on adverse pregnancy outcomes than suggested by this model. A retrospective analysis of clinic data (Black et al., 2010) suggested that women with elevated fasting plasma glucose on OGTT and a normal post-load OGTT had a greater risk of babies who were large for gestational age than women without gestational diabetes.

The HAPO study itself (HAPO Study Cooperative Research Group, 2008), perhaps reflecting its bigger sample size, reported "The individual measures from the oral glucose tolerance tests were not highly correlated, and no single measure was clearly superior in predicting the primary outcomes. When adjusted for potential confounders, relative increases in each glucose measure were similarly predictive of birth weight above the 90th percentile. When the glucose measures were analysed as continuous variables, each was a significant predictor of primary caesarean delivery, with a one standard deviation increase in glucose level being associated with an increase of 8 to 11% in the odds of delivery by caesarean section. Clinical neonatal hypoglycaemia was infrequent (overall incidence, 2.1%), and when adjusted for confounders, only the 1-hour plasma glucose level remained a significant predictor of this outcome. All three measures of plasma glucose were highly predictive of cord-blood serum C-peptide values, with the fasting plasma glucose level being the strongest predictor."

9.2.5 Conclusion

The IADPSG criteria would lead to a substantial increase in women in England and Wales being identified with gestational diabetes. Although IADPSG generally led to increased benefit when compared with WHO 1999 diagnostic criteria, this analysis suggests that this would be only achieved at unacceptably high incremental costs. No analyses were produced which supported the use of IADPSG diagnostic criteria using either a 2-sample or 3-sample OGTT.

WHO 1999 criteria, which were used in previous NICE guidance, came out as one of the most cost-effective criteria, but the guideline development group did not feel able to continue to recommend this as an appropriate threshold for gestational diabetes. In particular, they considered that the fasting threshold of 7.0 mmol/litre was too high and that this was also an overwhelming consensus view of specialists in the field. They noted that the intervention studies used a lower fasting threshold for inclusion and therefore those studies made a case for intervention at a lower fasting levels. They were also concerned that the model results

were driven by a regression analysis that down-played the role of fasting blood glucose levels in the outcomes included in the model. They were of the view that a relationship between fasting blood glucose had been well established with biochemical markers of disease. As a result they decided that a fasting blood glucose of 5.6 mmol/litre and a 2 hour blood glucose of 7.8 mmol/litre was reasonable, especially as this criteria had some evidence of cost effectiveness to support it.

The guideline development group was aware that these diagnostic criteria are different from recently recommended WHO diagnostic thresholds for gestational diabetes (WHO, 2013), which are the same as the IADPSG recommended thresholds. The group also recognised that it would be desirable to have internationally agreed diagnostic thresholds. However, the group noted that the strength of the WHO recommendation was weak and that the WHO guideline suggested that these thresholds could be rapidly revised in the event of newly published evidence on cost effectiveness: "It is likely that a substantial body of new data will emerge in the near future, providing currently scarce health and economic evaluation of the recommended criteria applied to various populations and with different approaches (universal screening, screening only women at high risk, diagnostic testing only). The guideline will be updated in 3–5 years, or earlier if new evidence becomes available which could substantially impact the recommendations."

9.3 Cost effectiveness of screening for gestational diabetes

9.3.1 Introduction

Screening for gestational diabetes was considered in the previous NICE guideline on diabetes in pregnancy and a wide variety of risk factor and biochemical screening strategies were assessed, including sequential screening strategies. The final recommendations drew on the health economic model produced for that guideline but also took into account a number of practical considerations before reaching a recommendation for a particular form of risk factor screening, hereafter referred to as 'NICE risk factor screening'.

However, this recommendation has been controversial (Simmons et al., 2010) and has probably not been followed everywhere in the NHS. In particular, there have been a number of papers putting the case for universal screening (Avalos et al., 2013; Moses et al., 2009)

The evidence was such for the previous guideline that it was difficult to model the continuous and multiplicative relationship of risk factor combinations. However, the HAPO (4 centres) dataset allows the assessment of the interactions between risk factor combinations, albeit in a sample that is not necessarily representative of all populations in England and Wales. Therefore, we addressed the cost effectiveness of screening for gestational diabetes using this patient level data.

9.3.2 Methods

In this analysis the following screening strategies for gestational diabetes were evaluated.
- risk factor screening
- universal screening
- 50 g glucose challenge test
- fasting plasma glucose (FPG).

Unlike the 2008 NICE guideline, a single model was not developed to assess screening, diagnosis and treatment.

Recommended practice based on the NICE 2008 guideline is to screen for gestational diabetes using risk factors. Women who have 1 or more of the listed risk factors should be offered an OGTT. This analysis takes a pragmatic approach, comparing 3 screening

strategies as alternatives to risk factor based screening to assess whether a cost effectiveness case can be made which would warrant changing current practice.

9.3.2.1 NICE risk factor screening versus universal screening

With a risk factor screening strategy pregnant women are only offered an OGTT if they have at least 1 of a pre-specified list of risk factors. In universal screening, all pregnant women are offered an OGTT, which is the gold-standard test to diagnose gestational diabetes.

In Section 9.2.2.1, we described a number of patient datasets that were received in order to develop a model to compare alternative diagnostic thresholds. The HAPO dataset approximates to an unselected population and, therefore, the analyses run on this population for different diagnostic thresholds were essentially based on a universal screening strategy. In Section 9.2.3.4, we also ran the diagnostic threshold in a subset of the HAPO population who had NICE risk factors and therefore these analyses reflect the cost effectiveness of different diagnostic thresholds using a NICE risk factor approach to screening.

Therefore, we used the models developed in Section 9.2.3.3 to compare the cost effectiveness of NICE risk factor screening versus universal screening. Additionally, we ran the model for the subset of the HAPO dataset that did not have risk factors. This can be considered to be the incremental cost effectiveness of universal screening compared with NICE risk factor screening.

9.3.2.2 NICE risk factor screening versus 1 hour 50 g glucose challenge test

We developed a tool in Microsoft Excel™ to assess the diagnostic accuracy of NICE risk factor screening for different diagnostic thresholds using the HAPO (4 centres) dataset (see Section 9.2.2.1). The sensitivity of NICE risk factors at all diagnostic thresholds was generally comparable or better than reported sensitivities of the 50 g glucose challenge test. For example, a systematic review reported a pooled sensitivity of 74% from 26 studies for the 50 g glucose challenge test (van Leeuwen et al., 2012). Therefore, we made the assumption that the detection rates of the 50 g glucose challenge test and NICE risk factor screening would be the same. Furthermore, we assumed that disease severity would not differ in a cohort selected by NICE risk factor screening and a cohort selected by the 50 g glucose challenge test. If detection rates and severity were the same, then there would be no difference in QALYs between the alternatives or 'downstream' costs. Thus, a cost analysis restricted to screening and diagnostic tests was used to compare NICE risk factor screening with the 50 g glucose challenge test.

The costs of the OGTT were those reported in Section 9.2.2.4. For the 50 g glucose challenge test we used a cost of £16. This is based on the 2-sample OGTT cost but assuming that there would be 1 less sample to process at £4 per sample and that there would be 5 minutes less of healthcare assistant time as only 1 blood sample would be required. The value is not dissimilar to the £13 value used for a 50 g glucose challenge test used in a published cost effectiveness study (Round et al., 2011).

A threshold analysis was performed to see what the cost differential would have to be in order to achieve cost neutrality between NICE risk factor based screening and screening using the 50 g glucose challenge test.

9.3.2.3 NICE risk factor screening versus fasting plasma glucose

In this analysis we derived receiver operating characteristic (ROC) curves for fasting plasma glucose in the HAPO (4 centres) dataset. This was then contrasted with the detection features of NICE risk factor screening in the same dataset in order to assess the likely cost effectiveness of fasting plasma glucose relative to NICE risk factor screening.

9.3.3 Results

9.3.3.1 NICE risk factor screening versus universal screening

The cost effectiveness of different diagnostic thresholds using a de facto universal screening approach (that is, a population that is made up of those with NICE risk factors and those without NICE risk factors) is given in Section 9.2.3.3. The cost effectiveness of the different diagnostic thresholds in a HAPO dataset is described in Section 9.2.3.4.

In considering whether universal screening is cost effective relative to NICE risk factor screening the critical issue is whether the additional or incremental benefits of universal screening are worth the additional costs. By definition those incremental benefits and costs are incurred in a population without risk factors. Therefore, we used the model developed to address the cost-effectiveness of different diagnostic thresholds for gestational diabetes in a subset of the HAPO (4 centre) population without NICE risk factors. The results of this analysis are shown in Table 127 and Figure 18.

Table 127:   Incremental cost effectiveness of alternative diagnostic thresholds (HAPO without risk factors)

Threshold	Cost	QALY	ICER
No treatment	£0	0.00	-
IADPSG 2.00	£123,262	1.68	Extended dominance
Fasting 5.6, 2 hour 8.5	£136,478	2.43	Extended dominance
Fasting 5.5, 2 hour 8.5	£138,381	2.45	Extended dominance
Fasting 5.4, 2 hour 8.5	£145,539	2.61	Extended dominance
Fasting 5.3, 2 hour 8.5	£154,822	2.72	Extended dominance
IADPSG 1.75	£218,522	3.84	Extended dominance
WHO 1999	£229,270	4.76	£48,141
Fasting 5.6, 2 hour 7.8	£239,387	4.91	Extended dominance
Fasting 5.5, 2 hour 7.8	£241,290	4.93	Extended dominance
Fasting 5.4, 2 hour 7.8	£246,656	5.02	Extended dominance
Fasting 5.3, 2 hour 7.8	£254,120	5.12	Extended dominance
IADPSG 1.75 (incl 1 hour)	£284,084	4.99	Dominated
IADPSG 1.50	£355,068	6.80	£62,718

IADPSG International Association of the Diabetes and Pregnancy Study Groups, ICER incremental cost effectiveness ratio, QALY quality adjusted life year, WHO World Health Organization

Figure 18: Graph to illustrate cost and QALYs of the different diagnostic thresholds in a HAPO subset selected without NICE risk factors
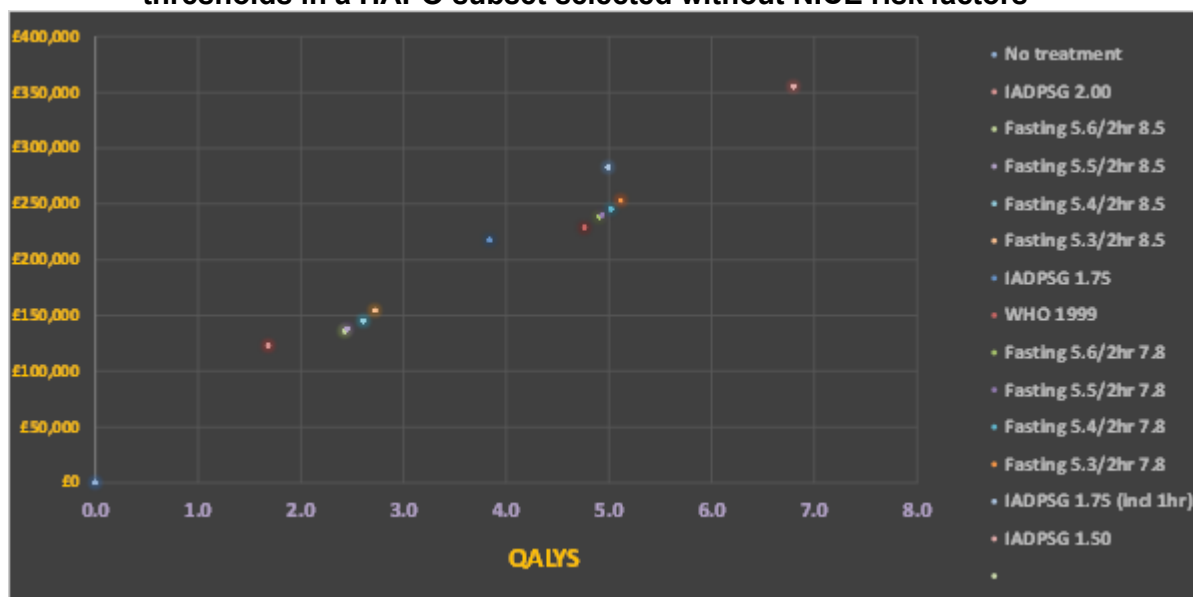
Source: Health economic model produced for this guideline

The sizes of the HAPO populations with and without risk factors were of a similar magnitude. However, it is apparent from Table 118 and Table 127 that the QALY gain in the population without risk factors was much less than in the population with risk factors. This was then reflected in the incremental cost effectiveness ratios which strongly suggest that no treatment or testing is the cost-effective strategy in this subset without risk factors.

Unsurprisingly, the ICERs for the complete dataset fall in between the 2 subsets, with and without risk factors, but it would be a mistake to base a universal screening strategy on that analysis as that essentially gives an average QALY gain of those with and without risk factors. As always in the economic evaluation of healthcare, the correct comparison is to look at the incremental costs and effects of an alternative course of action against the next best alternative. The relevant incremental analysis in this case should be made on the analysis undertaken in those without risk factors.

9.3.3.2 NICE risk factor screening versus glucose challenge test

Table 128 shows the measures of diagnostic accuracy for NICE risk factor screening in the HAPO (4 centres) population for each of the diagnostic thresholds used in the model.

Table 128: Diagnostic accuracy statistics for NICE risk factor screening in the HAPO (4 centres) population for different diagnostic thresholds

Threshold	Prevalence	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Fasting 5.6, 2 hour 8.5	8.1%	81.9%	45.1%	11.6%	96.6%	1.49	0.4
Fasting 5.5, 2 hour 8.5	8.7%	82.9%	45.4%	12.7%	96.5%	1.52	0.38
Fasting 5.4, 2 hour 8.5	9.5%	82.9%	45.7%	13.7%	96.2%	1.53	0.38
Fasting 5.3, 2 hour 8.5	10.8%	83.6%	46.3%	15.9%	95.9%	1.56	0.35
Fasting 5.6, 2 hour 7.8	13.3%	75.1%	46.4%	17.7%	92.4%	1.40	0.54

Threshold	Prevalence	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Fasting 5.5, 2 hour 7.8	13.8%	75.8%	46.7%	18.6%	92.3%	1.42	0.52
Fasting 5.4, 2 hour 7.8	14.4%	76.1%	46.9%	19.4%	92.1%	1.43	0.51
Fasting 5.3, 2 hour 7.8	15.6%	77.2%	47.5%	21.3%	91.8%	1.47	0.48
WHO 1999	12.0%	73.9%	45.9%	15.7%	92.8%	1.37	0.57
IADPSG 2.00	8.8%	87.1%	45.7%	13.5%	97.3%	1.60	0.28
IADPSG 1.75	15.2%	81.0%	47.7%	21.8%	93.3%	1.55	0.40
IADPSG 1.75 (incl 1hr)	18.4%	78.3%	48.8%	25.7%	90.9%	1.53	0.45
IADPSG 2.00	22.0%	76.0%	49.9%	29.9%	88.0%	1.52	0.48

IADPSG International Association of the Diabetes and Pregnancy Study Groups, LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value, WHO World Health Organization

A systematic review (van Leeuwen et al., 2012) of the 50 g glucose challenge test gave a pooled sensitivity of 74% and a pooled specificity of 77% from 26 studies which included women with risk factors and a pooled sensitivity of 74% and a pooled specificity of 85% in studies with consecutive recruitment.

This cost analysis compared NICE risk factor screening with the 50 g glucose challenge test, assuming that both detect the same number of cases. In order to subject the current practice of NICE risk factor screening to the most rigorous scrutiny we assumed a best case scenario for the 50 g glucose challenge test and use a specificity of 85%.

We used a fasting blood glucose threshold of 5.6 mmol/litre and a 2 hour post glucose challenge of 7.8 mmol/litre for the OGTT diagnostic threshold, as that is the threshold recommended for diagnosis of gestational diabetes in this guideline.

> HAPO population = 6221

Cost of NICE risk factor screening:

> Women with risk factors = 3550

> Cost of OGTT is 3550×£22 = £78,100

Cost of 50 g glucose challenge test:

> Women with a positive 50 g GCT = (0.74×0.133×6221)+(0.15×0.867×6221)=1421

> Cost of 50 g GCT = 6221×£16 = £99,536

> Cost of OGTT = 1421×£22 = £31,262

> Total cost = £130,798

Although there is some uncertainty with respect to the cost differential between an OGTT and a 50 g glucose challenge test, the differential would have to increase from £6 to over £14 before cost neutrality would be achieved.

This analysis suggests that screening with the 50 g glucose challenge test would be considerably more expensive than using NICE risk factor screening. To justify this additional screening and testing expense, there would have to be considerable benefit in terms of improved detection of gestational diabetes and a consequent improvement in health outcomes arising from more appropriate treatment. However, using the HAPO (4 centres) dataset there is no evidence to support 50 g glucose challenge test having any superiority over NICE risk factor screening in identifying patients with gestational diabetes.

9.3.3.3 NICE risk factor screening versus fasting plasma glucose

Figure 19 shows the ROC curve for fasting plasma glucose for detecting gestational diabetes defined, in this example, using an OGTT threshold of 5.6 mmol/litre for fasting blood glucose and 7.8 mmol/litre for the 2 hour blood glucose.

Figure 19: **Fasting plasma glucose ROC curve for diagnosing gestational diabetes in HAPO (4 centres) dataset**
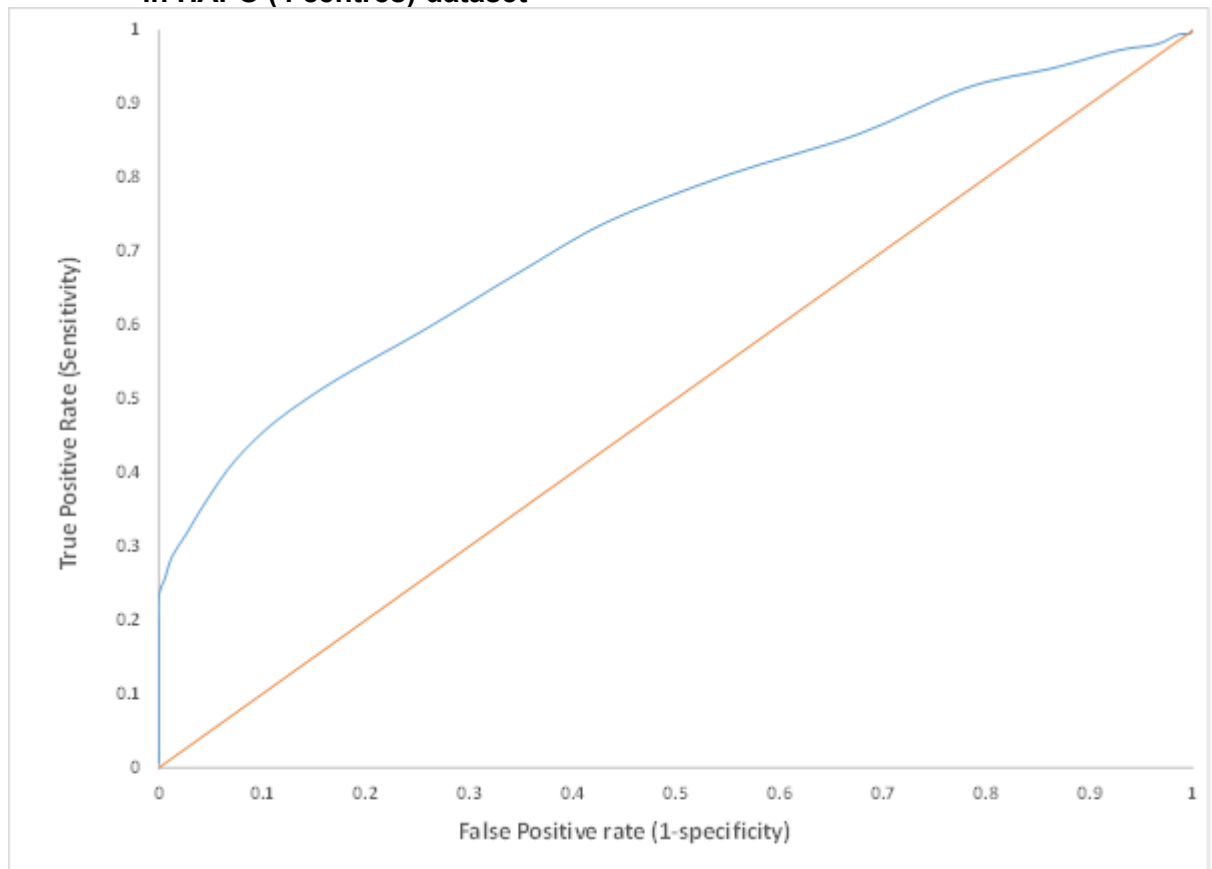
Source: Generated for this guideline from HAPO (4 centres) dataset

This curve shows the trade-off between true positives and false positives. As the fasting plasma glucose screening threshold is increased the true positive rate falls and the false positive rate rises. When the fasting plasma glucose threshold is set to equal or above the fasting threshold used in the OGTT then there can be, by definition, no false positives as those women who meet or exceed the fasting threshold meet the diagnostic criteria set by the OGTT for gestational diabetes.

In many ways, the logical threshold to set for fasting plasma glucose as a screening test would be the same as the fasting blood glucose threshold used for diagnosis. The measures of diagnostic accuracy for fasting plasma glucose taking this approach and using a diagnostic threshold of 5.6 mmol/litre for fasting blood glucose and 7.8 mmol/litre for 2 hour blood glucose are shown in Table 129.

Table 129: **Diagnostic accuracy of fasting plasma glucose as a screening test for gestational diabetes in the HAPO (4 centres) dataset [a, b]**

Measure	Value
Sensitivity	23.3%
Specificity	100%
PPV	100%
NPV	89.2%
LR+	Infinity
LR-	0.77

LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value
a. Screening threshold set at 5.6 mmol/litre

b. Diagnostic threshold set at 5.6 mmol/litre fasting and 7.8 mmol/litre 2 hour

The fasting plasma glucose test has the potential advantage that it would avoid a lot of unnecessary OGTTs and as a result may be a cheaper screening test in this scenario, as long as the costs of testing all women with an FPG are more than offset by savings on OGTT. However, the downside is that only 195 of the 837 women with gestational diabetes would be detected, which would be expected to lead to markedly lower improvement in health related quality of life as many women who had potential to benefit from treatment would not receive it.

At least as judged by average 2 hour values, it does not appear as though the cases missed by a fasting plasma glucose screen would have markedly less severe disease, as illustrated in Table 130.

Table 130:   Mean glucose values in women according to their diagnostic classification using fasting plasma glucose as a screening test [a, b]

Diagnostic classification	Mean fasting	Mean 2 hour
True positive	6.14	8.76
False positive	NA	NA
True negative	4.52	5.82
False negative	4.73	8.71

NA not applicable
a. Screening threshold set at 5.6mmol/litre
b. Diagnostic threshold set at 5.6mmol/litre fasting and 7.8mmol/litre two-hour

The threshold for fasting plasma glucose as a screening test would have to be lowered 4.6 mmol/litre to achieve a similar rate of detection as risk factor screening. However, this would then result in only 610 fewer OGTTs and the saving in fewer OGTTs would be unlikely to offset the costs of 6221 fasting plasma glucose tests. For a saving still to be achieved in this scenario, the fasting plasma glucose test would have to cost less than £2.15[ddd].

9.3.4   Discussion

There are some limitations with this analysis. It is based on patient data from 4 centres in Belfast and Manchester in the UK and Brisbane and Newcastle in Australia. It is reasonable to assume that these are likely to be representative of the population in England and Wales but they might not be completely representative given the wide regional variation that exists. Some of the demographic characteristics of this population are shown below in Figures 20 to 24.

[ddd] Saving from 610 fewer OGTT's: 610x£22=£13,420
But 6221 fasting plasma glucose tests: £13,410÷6221=£2.15

Figure 20:   Ethnicity of HAPO (4 centres) dataset
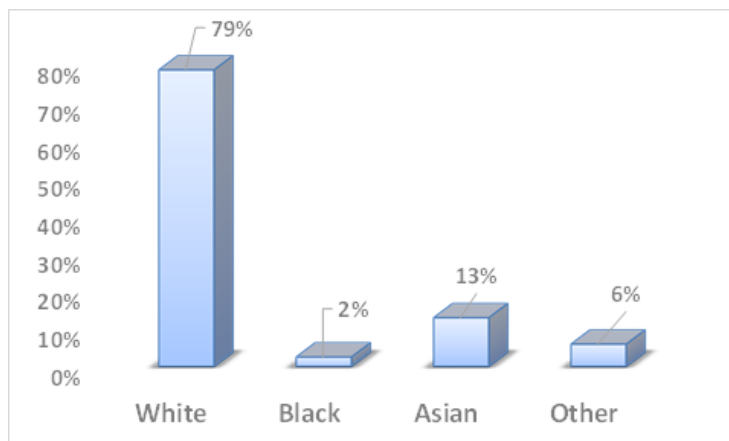
Source: Generated for this guideline from HAPO (4 centres) dataset

Figure 21:   Previous family history of diabetes in HAPO (4 centres) dataset
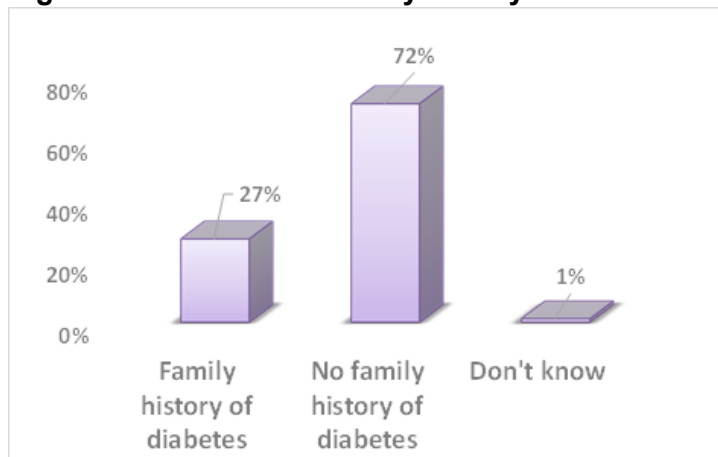
Source: Generated for this guideline from HAPO (4 centres) dataset

Figure 22: **Age distribution of HAPO (4 centres) dataset**
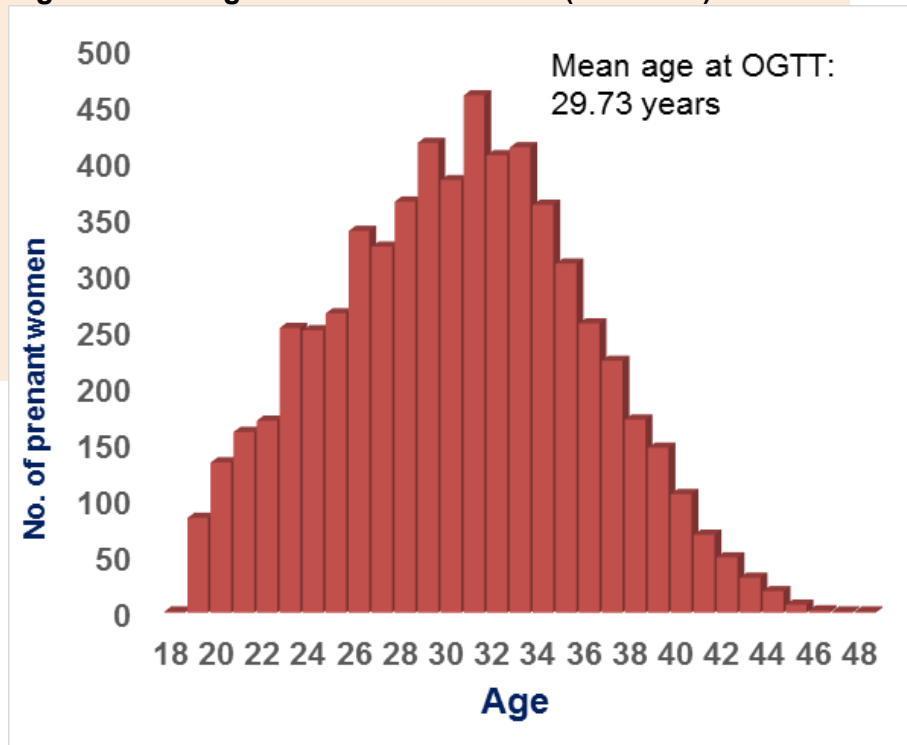
Source: Generated for this guideline from HAPO (4 centres) dataset

Figure 23: **BMI distribution of HAPO (4 centres) dataset**
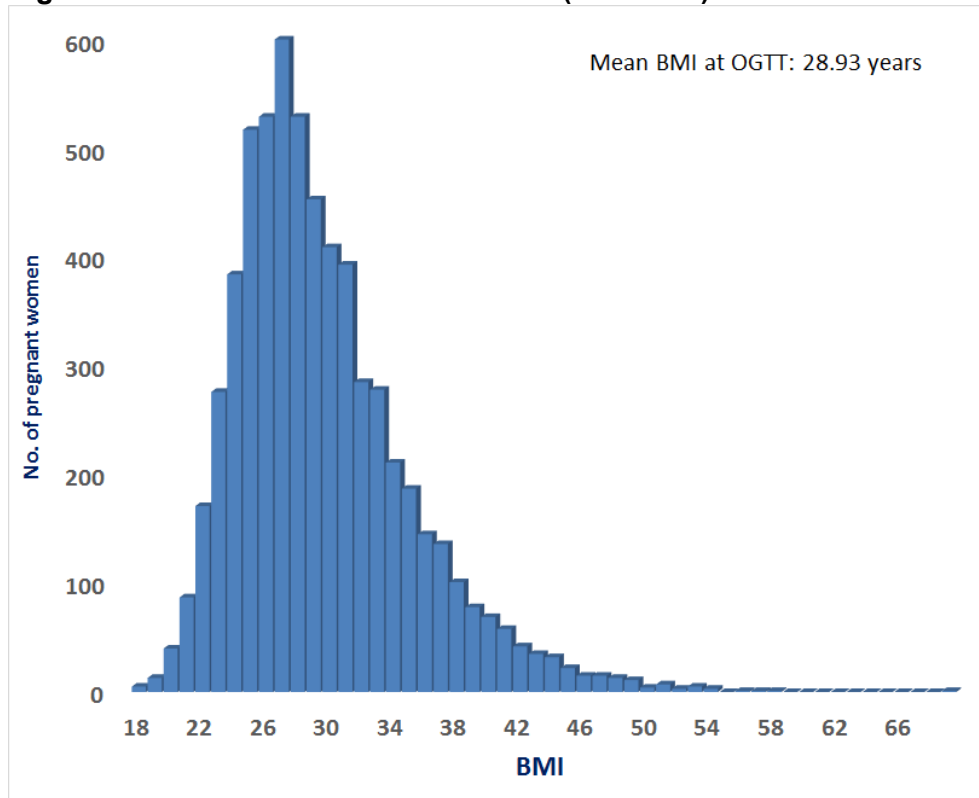
Source: Generated for this guideline from HAPO (4 centres) dataset

Figure 24:   Risk factor classification of HAPO (4 centres) dataset
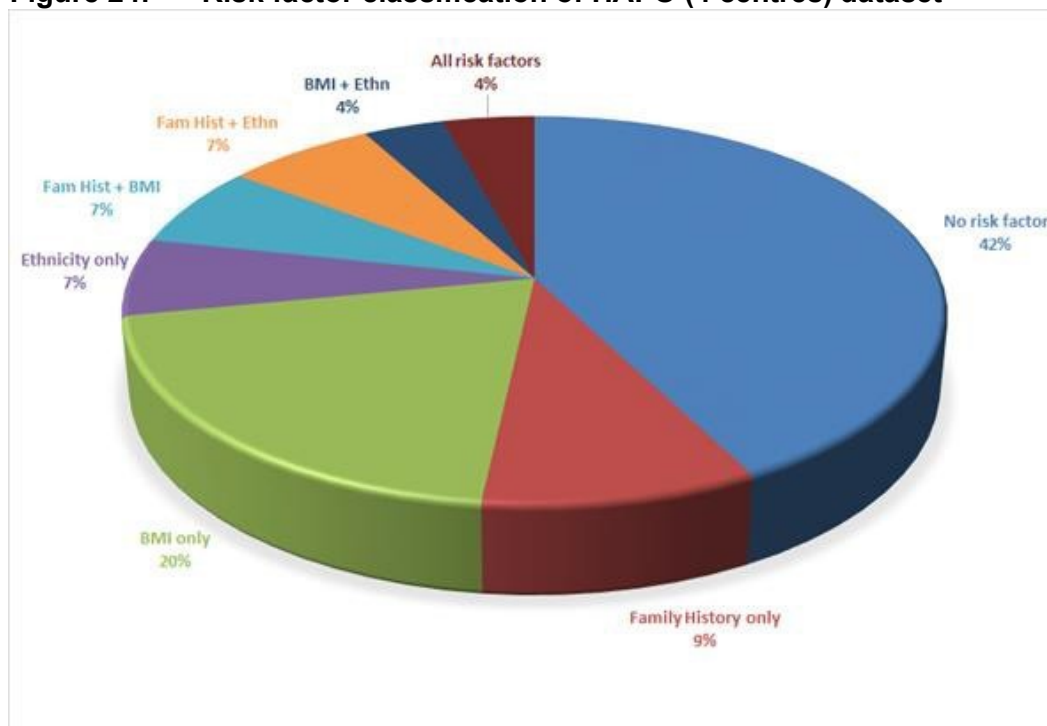
Source: HAPO (4 centres) dataset used in modelling in this guideline

Another study by Avalos et al. (2013) using the ATLANTIC DIP data, which came to a different conclusion with respect to universal screening, found that 54% of patients had at least 1 NICE risk factor and that 20% of cases of gestational diabetes would have been missed using NICE risk factor screening. This is very similar to the results in our HAPO (4 centres) dataset, where 56% of patients had at least 1 NICE risk factor and where 22% of cases would be missed using an IADPSG 1.75 diagnostic threshold. However, that paper treats all cases the same, whether they are missed or detected; in other words, it does not reflect that there may be systematic differences in disease severity between the detected and missed cases. The analysis described above shows that there are systematic differences between detected cases and missed cases (those detected having higher mean glucose values than those missed). This makes intuitive sense. Cases that are missed are not the same as detected cases and importantly are likely to have less severe disease. Table 131 illustrates this for our HAPO (4 centres) dataset using the 3-sample IADPSG 1.75 as the diagnostic criteria. Berger et al. (2009) also alluded to the possibility that missed cases in low risk populations might have less clinical significance.

Table 131:   Mean glucose values in women according to their diagnostic classification using NICE risk factors as a screening test

Diagnostic classification	Mean fasting	Mean 1 hour	Mean 2 hour
True positive[a]	5.24	9.90	7.89
False positive[b]	4.50	7.20	5.95
True negative[c]	4.44	6.95	5.78
False negative[d]	4.89	9.52	7.41

Screening threshold set at 5.6 mmol/litre
Diagnostic threshold set at 5.6 mmol/litre fasting, 10.0 mmol/litre 1 hour and 7.8 mmol/litre 2 hour
a. True positive – risk factor present and diagnosed with gestational diabetes
b. False positive – risk factor present but not diagnosed with gestational diabetes
c. True negative – no risk factor present and not diagnosed with gestational diabetes
d. False negative – no risk factor present but diagnosed with gestational diabetes

As a result there are likely to be diminishing returns to finding and treating missed cases. The missed cases have a lower baseline risk of adverse outcomes and therefore, although the women would still be able to benefit, their capacity to do so is less. Therefore, it is not surprising that the analysis in Section 9.3.3.1 finds that treatment following universal screening is less cost effective than treatment following risk factor screening. Using conventional decision rules on willingness to pay for a QALY, universal screening in this analysis falls well short of what is required to be considered cost effective in a UK context. This is without formally capturing in the analysis the inconvenience, discomfort and anxiety that would be entailed in almost doubling the number of pregnant women required to have an OGTT.

The result presented in this analysis is consistent with published work suggesting that the cost effectiveness of different screening strategies in any pregnant woman is likely to depend on her individual risk of disease (Round et al., 2011). That study suggested a strategy of using OGTT alone, as in the case of universal screening, would only be cost effective at relatively high levels of individual risk. Unless the NICE risk factors are inappropriate or could be improved upon, pregnant women lacking such risk factors are unlikely to have such a relatively high individual risk of disease.

The analysis of NICE risk factor based screening versus 50 g glucose challenge test relies on simplifying assumptions. Based on the evidence presented it seems reasonable to assume equivalence in detection, but in practice there are likely to be at least some small differences. Furthermore, any discrepancy is likely to be dependent on the actual diagnostic criteria used. Nevertheless, we used the diagnostic criteria which had the lowest NICE risk factor screening sensitivity and therefore, if anything, we attempted to bias the analysis against current practice. A further assumption was that disease severity would not differ between patients identified by NICE risk factor screening and patients identified by the 50 g glucose challenge test. This assumption was made so that the alternatives would differ only in screening and testing costs. It is possible that the 50 g glucose challenge test would identify patients with more severe disease on average and therefore having a greater capacity to benefit. However, to the extent that it was identifying different patients, they would have to be drawn from a cohort without risk factors who, as shown in Table 131. have less severe disease as defined by mean glucose values.

No formal economic evaluation has been used to assess the cost effectiveness of fasting plasma glucose screening when compared with NICE risk factor based screening. Again, the relative cost effectiveness of the different screening options may depend to some extent on the diagnostic threshold used to establish a diagnosis of gestational diabetes. However, using a fasting plasma glucose screening threshold in the range typically used for diagnosis results in very poor sensitivity, albeit that those identified are likely to be at the more severe end of the spectrum. Sensitivity can be improved by using a lower threshold, but then fasting plasma glucose as a screening tool rapidly loses the advantage it has as a screening test which avoids unnecessary testing and anxiety from false positives.

Finally, it should be noted that the sensitivity of NICE risk factors is underestimated in this HAPO (4 centres) dataset because it does not include data on previous gestational diabetes or previous macrosomic baby. However, the number of patients with these risk factors is likely to be small and they will often have 1 of the other risk factors. The corollary of sensitivity being underestimated is that specificity will be slightly overestimated.

9.3.5 Conclusion

These analyses do not demonstrate that alternative screening strategies are more cost effective than NICE risk factor screening as recommended in the previous NICE guidance.

10 References

10.1 2015 update

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11 Abbreviations

11.1 2008 guideline

AC	abdominal circumference
ACE	angiotensin-converting enzyme
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ADA	American Diabetes Association
AFP	alpha fetoprotein
AGA	appropriate for gestational age
ARB antagonist)	angiotensin-II receptor blocker (also known as angiotensin-II receptor
BMI	body mass index
BP	blood pressure
CBG	capillary blood glucose
CEMACH	Confidential Enquiry into Maternal and Child Health
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CSII	continuous subcutaneous insulin infusion
DAFNE	Dose Adjustment for Normal Eating
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes Education and Self Management for Ongoing and Newly Diagnosed
DKA	diabetic ketoacidosis
DPP	Diabetes Prevention Program
DVLA	Driver and Vehicle Licensing Agency
EFW	estimated fetal weight
eGFR	estimated glomerular filtration rate
EL	evidence level
EPO	erythropoietin
ETDRS	Early Treatment Diabetic Retinopathy Study
EUROCAT	European Surveillance of Congenital Anomalies
FBG	fasting blood glucose
FCG	fasting capillary glucose
FPG	fasting plasma glucose

GCT	glucose challenge test
GDG	guideline development group
GI	glycaemic index
GP	general practitioner
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HbA1c	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IGT	impaired glucose tolerance
IUGR	intrauterine growth restriction
LGA	large for gestational age
LR	likelihood ratio
MIG	Metformin in Gestational Diabetes
MDI	multiple daily injection
MODY	maturity-onset diabetes of the young
MoM	multiple-of-median
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NDDG	National Diabetes Data Group
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHSLA	National Health Service Litigation Authority
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NNH	number needed to harm
NNT	number needed to treat
NPDR	non-proliferative diabetic retinopathy
NPV	negative predictive value
NSF	National Service Framework
NT	nuchal translucency
OGTT	oral glucose tolerance test
ONS	Office for National Statistics

OR	odds ratio
PAPP-A	pregnancy-associated plasma protein-A
PDR	proliferative diabetic retinopathy
PPIP	Patient and Public Involvement Programme
PPV	positive predictive value
QALY	quality adjusted life year
RBG	random blood glucose
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
SD	standard deviation
SE	standard error
SGA	small for gestational age
SPC	summary of product characteristics
TA	technology appraisal
TGA `	transposition of the great arteries
uE3	unconjugated estriol
VBAC	vaginal birth after previous caesarean section
WHO	World Health Organization

11.2 Additional abbreviations – 2015 guideline

CEMACH	Confidential Enquiry into Maternal and Child Health
CGM	continuous glucose monitoring
DALY	disability-adjusted life year
GDM	gestations diabetes
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	heath technology assessment
HDL	high density lipoprotein
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IFG	impaired fasting glucose
IUD	intrauterine device
MD	mean difference
NC	not calculable
NPH insulin	neutral protamine hagedorn insulin
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
TTN	transient tachypnoea of the newborn
WTP	willingness to pay

12 Glossary of terms

Term	Description
ACE inhibitor	Angiotensin converting enzyme inhibitor; a class of medicines that reduce peripheral arterial resistance by inactivating an enzyme that converts angiotensin-I to the vasoconstrictor angiotensin-II.
Albuminuria	The presence of albumin in the urine, indicating renal dysfunction.
Antenatal	The period of time in pregnancy preceding birth
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria.
Best available evidence	The strongest research evidence available to support a particular guideline recommendation
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, publication bias.
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also double-blind study, single-blind study, triple-blind study
Body mass index (BMI)	The body's weight in kilograms divided by the square of the height in metres, used in the assessment of obesity.
Cardiomegaly	Enlargement of the heart.
Cardiotocograph	Graphical representation of electronic monitoring of the fetal heart rate and of uterine contractions. The fetal heart rate is recorded by means of either an external ultrasonic abdominal transducer or a fetal scalp electrode. Uterine contractions are recorded by means of an abdominal pressure transducer.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Case–control study	A study that compares exposure in subjects who have a particular outcome with those who do not. The study starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.
Causal relationship	Describes the relationship between two variables whenever it can be established that one causes the other. For example, there is a causal relationship between a treatment and a disease if it can be shown that the

Term	Description
	treatment changes the course or outcome of the disease. Usually randomised controlled trials are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness – unless all other possible causes (e.g. environmental factors) had been ruled out.
Centile	Any of the 99 numbered points that divide an ordered set of scores into 100 parts each of which contains one-hundredth of the total
Checklist	See study checklist
Clinical audit	A systematic process for setting and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a cycle or spiral. Within the cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as efficacy.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the target population.
Clinical importance	The importance of a particular guideline recommendation to the clinical management of the target population.
Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses controlled clinical trials and randomised controlled trials.
Clinician	A qualified healthcare professional providing patient care, e.g. doctor, nurse, physiotherapist.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called randomised controlled trials. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the Cochrane Library.
Cochrane Library	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). The Cochrane Library is available on CD-ROM and the internet.
Cohort	A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or

Term	Description
	interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Comorbidity	Coexistence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Confidence interval (CI)	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	A factor that can bring an alternative explanation to an association observed between an exposure and the outcome of interest. It influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Congenital anomaly	A physical or biochemical malformation which is present at birth
Consensus development conference	A technique used for the purpose of reaching an agreement on a particular issue. It involves bringing together a group of about ten people who are presented with evidence by various interest groups or experts who are not part of the decision-making group. The group then retires to consider the questions in the light of the evidence presented and attempts to reach a consensus. See also consensus methods.
Consensus methods	A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.
Consensus statement	A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.
Considered judgement	The application of the collective knowledge of a guideline development group to a body of evidence, to assess its applicability to the target population and the strength of any recommendation that it would support.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also homogeneity.

Term	Description
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect or a placebo (dummy treatment) in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost–benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-effectiveness	Value for money. A specific healthcare treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost-effectiveness analysis	A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.
Cost–utility analysis	A special form of cost-effectiveness analysis where health effects are measured in quality- adjusted life years. A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.
Crossover study design	A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.
Data set	A list of required information relating to a specific disease.
Decision analysis	The study of how people make decisions or how they should make decisions. There are several methods that decision analysts use to help people to make better decisions, including decision trees.
Decision tree	A method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of different actions can then be compared.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity, for example if their position or department is funded by a pharmaceutical company.
Delphi method	A technique used for the purpose of reaching an agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of postal questionnaires asking

Term	Description
	them to record their views. After the first questionnaire, participants are asked to give further views in the light of the group feedback. The judgements of the participants are statistically aggregated, sometimes after weighting for expertise. See also consensus methods.
Diabetic ketoacidosis (DKA)	A state of absolute or relative insulin deficiency characterised by hyperglycaemia, dehydration, acidosis and ketosis.
Diabetic nephropathy	Kidney dysfunction or disease occurring as a result of diabetes.
Diabetic retinopathy	A complication of diabetes affecting the blood vessels in the retina at the back of the eye, which can affect vision. There may be bleeding from retinal vessels (non-proliferative retinopathy) or the development of new abnormal vessels (proliferative retinopathy).
Diagnostic study	A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.
Dominance	A term used in health economics describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be 'dominated'.
Double-blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In health economic evaluations the consequences should include health outcomes.
Effectiveness	See clinical effectiveness.
Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (e.g. in a laboratory) has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care.
Elective	Clinical procedures that are regarded as advantageous to the patient but not urgent.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
Erb palsy	Injury to the nerve roots of the brachial plexus of an arm mainly related to birth trauma and leading to various degrees of weakness of the affected arm which may resolve during the first year of life.
Evidence based	The process of systematically finding, appraising and using research findings as the basis for clinical decisions.
Evidence level	A code (e.g. 1++, 1+) linked to an individual study, indicating where it fits into the hierarchy of evidence and how well it has adhered to recognised research principles. Also called level of evidence.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Evidence-based clinical practice	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
Exclusion criteria	See selection criteria.
Experimental study	A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease – where the conditions of testing are to some extent under the control of the

Term	Description
	investigator. Controlled clinical trial and randomised controlled trial are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see if it has an effect on the course or outcome of a condition or disease.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Fetal growth restriction	Evidence of abnormally slow growth of the fetus within the uterus; either estimated weight or abdominal circumference below the 10th percentile, or slowing growth velocity of the abdominal circumference as measured at a subsequent ultrasound scan.
Fetal surveillance	The process of performing fetal wellbeing tests. These may include ultrasound scans, fetal and placental Doppler ultrasounds, biophysical profiles and fetal heart monitoring.
Focused question	A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. For example, do insulin pumps (intervention) improve blood sugar control (outcome) in adolescents with type 1 diabetes (population) compared with multiple insulin injections (comparison)? See also clinical question.
Folic acid	A water-soluble vitamin in the B-complex group which helps to prevent fetal neural tube defect when commenced by the mother before conception.
Funnel plot	Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. Publication bias may lead to asymmetry in funnel plots.
Gestation	The time from conception to birth. The duration of gestation is measured from the first day of the last normal menstrual period.
Gestational diabetes	Carbohydrate intolerance of varying severity which is diagnosed in pregnancy and may or may not resolve after pregnancy.
Glucose electrode	Blood glucose measurement using electrochemical biosensors.
Glycaemic control targets	Recommended levels of blood glucose.
Glycosylated haemoglobin (HbA1c) test	Test which measures the amount of glucose-bound haemoglobin and reflects how well the blood glucose level has been controlled over the previous 2–3 months
A Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Grey literature	Reports that are unpublished or have limited distribution and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool that describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care based on the best research available, rather than opinion. It is used to assist clinician and patient decision-making about appropriate health care for specific clinical conditions.
Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Health economics	A branch of economics that studies decisions about the use and distribution of healthcare resources

Term	Description
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.
Heterogeneity, Or lack of homogeneity	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well-conducted study. Well- conducted randomised controlled trials (RCTs) are at the top of this hierarchy (for example, several large statistically significant RCTs which are in agreement represent stronger evidence than one small RCT). Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also consistency.
Hypertension	High blood pressure.
Hypoglycaemia	Low blood glucose level.
Inclusion criteria	See selection criteria.
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of blinding), response errors (e.g. lack of blinding if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).
Interquartile range (IQR)	The spread of a set of values between which 25% (25th centile) and 75% (75th centile) of these values lie.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.
Level of evidence	See evidence level.
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A study of the same group of people at more than one point in time. This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.
Ketonaemia	The presence of detectable concentrations of ketone molecules in the blood
Ketonuria	The presence of detectable concentrations of ketone molecules in the urine
Macrosomia	Oversized baby as seen, for example as a consequence of the effect of diabetes during pregnancy. Often defined as having a birthweight above the 90th centile for gestation or a birthweight of 4000 g or more.
Masking	See blinding.
Median	The value of the middle item of a series when the items are arranged in numerical order.
Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. because of differences in the study populations or in the

Term	Description
	outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also systematic review and heterogeneity.
Metformin	An oral antidiabetic agent that decreases glucose production by the liver and lowers plasma glucose levels.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Methodology	The overall approach of a research project; for example, that the study will be a randomised controlled trial of 200 people over 1 year.
Microalbuminuria	A very small increase in urinary albumin.
Miscarriage	Spontaneous ending of a pregnancy before viability (currently taken as 24 weeks of gestation).
Maturity-onset diabetes of the young (MODY)	A group of autosomal dominant disorders in young people each caused by a single gene defect, associated with decreased insulin production and varying degrees of clinical severity.
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a cooperative study between different hospitals or an international collaboration involving patients from more than one country.
Multidisciplinary clinic	A clinic with access to care from health professionals in more than one discipline. For diabetes, the disciplines recommended are obstetrics, diabetology, nursing, midwifery and dietetics.
Multiparous	A woman who has had at least one previous birth (from 24 weeks onwards).
Negative predictive value (NPV)	The proportion of people with a negative test result who do not have the disease (where not having the disease is indicated by the 'gold standard' test being negative).
Neonatal death	Death of a liveborn baby before 28 completed days after birth.
Neonatal unit	A unit which provides additional care for babies over and above that which can be offered on a postnatal ward or transitional care unit. There are different levels of complexity of care which can be offered by an individual neonatal unit.
Neural tube defect	A major birth defect caused by abnormal development of the neural tube, the structure present during embryonic life which later gives rise to the central nervous system (brain and spinal cord).
Nominal group technique	A technique used for the purpose of reaching an agreement on a particular issue. It uses a variety of postal and direct contact techniques, with individual judgements being aggregated statistically to derive the group judgement. See also consensus methods.
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias
Non-systematic review	See review.
Number needed to treat (NNT)	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur, e.g. if the NNT = 4, then four patients would have to be treated to prevent one bad outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the number needed to harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event, e.g. if the NNH = 4, then four patients would have to be treated for one bad outcome to occur.
Obesity	Increased body weight, defined as a body mass index of 30 kg/m² or greater.

Term	Description
Observation	A research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research
Observational study Odds ratio (OR)	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They are a measure of the excess risk or degree of protection given by exposure to a certain factor. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. An odds ratio of greater than 1 shows an increased risk and less than 1 shows a protective effect. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar. See also relative risk, risk ratio.
Outcome	The end result of care and treatment and/or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.
P value	If a study is done to compare two treatments then the P value is the probability of obtaining the results of that study or something more extreme if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the P value was P = 0.03. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the confidence interval.
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/or patient/carer representatives.
Performance bias	Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the control group they may be more likely to use other forms of care; people who know they are in the experimental group may experience placebo effects, and care providers may treat patients differently according to what group they are in. Masking (blinding) of both the recipients and providers of care is used to protect against performance bias.
Pilot study	A small scale 'test' of the research instrument, for example testing out (piloting) a new questionnaire with people who are similar to the population of the study in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.
Placebo	Fake or inactive treatments received by participants allocated to the control group in a clinical trial that are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any placebo effect due to receiving care or attention.

Term	Description
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Positive predictive value (PPV)	The proportion of people with a positive test result who have the disease (where having the disease is indicated by the 'gold standard' test being positive).
Postnatal	The period of time occurring after birth.
Power	See statistical power.
Preterm birth	Birth before 37 weeks and 0 days of gestation.
Prevalence	The proportion of individuals in a population having a disease.
Probability	How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Protocol	A plan or set of steps that defines appropriate action. A research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.
Publication bias	Studies with statistically significant results are more likely to get published than those with non-significant results. Meta-analyses that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a funnel plot.
Quality-adjusted life years (QALYs)	A measure of health outcome that looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to 1 year of life in perfect health or 2 years at 50% health, and so on.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census that counts people and households.
Quintile	The portion of a frequency distribution containing one-fifth of the total sample.
Random allocation or randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial (RCT)	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.
Range	The difference or interval between the smallest and largest values in a frequency distribution.
Relative risk (RR)	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients

Term	Description
	receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession and if their assessments tend to agree then the method of assessment is said to be reliable.
Retinal assessment	Examining the fundi through pupils which have been dilated with eye drops.
Retrospective study	A study that deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term relative risk is sometimes used as a synonym of risk ratio.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Sampling	The way participants are selected for inclusion in a study.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence- based clinical guidelines for the NHS in Scotland.
Selection bias	Selection bias has occurred if: the characteristics of the sample differ from those of the wider population from which the sample has been drawn, or there are systematic differences between comparison groups of patients in a study in terms of prognosis or responsiveness to treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Sensitivity	In diagnostic testing, sensitivity is the proportion of true positive results that are correctly identified as positive by the test. 100% sensitivity means that all those with a negative test result do not have the disease. Specificity should be considered alongside sensitivity to fully judge the accuracy of a test
Severe hypoglycaemia	Hypoglycaemia requiring help from another person.
Shoulder dystocia	Any documented evidence of difficulty with delivering the shoulders after delivery of the baby's head.
Single-blind study	A study in which either the subject (patient/participant) or the observer (clinician/ investigator) is not aware of which treatment or intervention the subject is receiving.
Singleton	One fetus or baby.

Term	Description
Sliding scale	Intravenous insulin and dextrose infusions with a set of instructions for adjusting the dose of insulin on the basis of blood glucose test results.
Specificity	In diagnostic testing, specificity is the proportion of true negative results that are correctly identified as negative by the test. 100% specificity means that all those with a positive test result have the disease. Sensitivity should be considered alongside specificity to fully judge the accuracy of a test.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also P value.
Stillbirth	Legal definition: a child that has issued forth from its mother after the 24th week of pregnancy and which did not at any time after being completely expelled from its mother breathe or show any other signs of life (Section 41 of the Births and Deaths Registration Act 1953 as amended by the Stillbirth Definition Act 1992).
Study checklist	A list of questions addressing the key aspects of the research methodology that must be in place if a study is to be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.
Study population	People who have been identified as the subjects of a study.
Study quality	See methodological quality.
Study type	The kind of design used for a study. Randomised controlled trials, case–control studies, and cohort studies are all examples of study types.
Subject	A person who takes part in an experiment or research study.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic	Methodical, according to plan; not random.
Systematic error	Refers to the various errors or biases inherent in a study. See also bias.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.
Target population	The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study, for example in terms of age, disease state, social background.
Technology appraisal (TA)	A technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost-effectiveness of a health technology. NICE technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.
Transitional care unit	A unit providing care of term or near-term babies not needing high-dependency or intensive care, which can be safely delivered without babies being separated from their mothers.

Term	Description
Trimester	One of the 3 month periods into which pregnancy is divided. The first trimester is 0– 13 weeks of gestation, the second trimester is 14–26 weeks of gestation, and the third trimester is 27 weeks of gestation until birth.
Triple-blind study	A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigators/clinicians being unaware which treatment patients were getting.
Type 1 diabetes	There is an absolute deficiency of insulin production, due to autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans in the pancreas. It accounts for 5–15% of all people with diabetes.
Type 2 diabetes	There is a relative deficiency of insulin production, and/or the insulin produced is not effective (insulin resistance). It accounts for 85–95% of all people with diabetes.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time with respect to any characteristic or feature that can be assessed or measured.

Appendices

The appendices are presented in separate documents; one for Appendix H (Evidence tables) and a second containing all the remaining appendices.