

# Diabetes in pregnancy

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

**Clinical Guideline**

**March 2008**

Funded to produce guidelines for the NHS by NICE



# Diabetes in pregnancy

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

National Collaborating Centre for Women's  
and Children's Health

Commissioned by the National Institute for  
Health and Clinical Excellence

**Evidence tables**

March 2008



RCOG Press

Evidence tables should be read in conjunction with the main guideline.

Published by the **RCOG Press** at the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG

[www.rcog.org.uk](http://www.rcog.org.uk)

Registered charity no. 213280

First published 2008

© 2008 National Collaborating Centre for Women's and Children's Health

No part of this publication may be reproduced, stored or transmitted in any form or by any means, without the prior written permission of the publisher or, in the case of reprographic reproduction, in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK [[www.cla.co.uk](http://www.cla.co.uk)]. Enquiries concerning reproduction outside the terms stated here should be sent to the publisher at the UK address printed on this page.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore for general use.

While every effort has been made to ensure the accuracy of the information contained within this publication, the publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check current indications and accuracy by consulting other pharmaceutical literature and following the guidelines laid down by the manufacturers of specific products and the relevant authorities in the country in which they are practising.

ISBN 978-1-904752-47-9

RCOG Editor: Andrew Welsh  
Original design of main guideline by FiSH Books, London  
Typesetting of main guideline by Andrew Welsh

# Contents

---

<b>Abbreviations</b>	<b>6</b>
<b>3 Preconception care</b>	<b>8</b>
3.1 Outcomes and risks for the woman and baby	8
3.2 The importance of planning pregnancy and the role of contraception	9
3.3 Diet, dietary supplements, body weight and exercise	10
3.4 Target ranges for blood glucose in the preconception period	17
3.5 Monitoring blood glucose and ketones in the preconception period	36
3.6 The safety of medications for diabetes before and during pregnancy	38
3.7 The safety of medications for diabetic complications before and during pregnancy	56
3.8 Removing barriers to the uptake of preconception care and when to offer information	62
3.9 Cost-effectiveness of self-management programmes	70
<b>4 Gestational diabetes</b>	<b>71</b>
4.1 Risk factors for gestational diabetes	71
4.2 Diagnosis of gestational diabetes	76
4.3 Screening and treatment for gestational diabetes	76
4.3 Screening and treatment for gestational diabetes	115
<b>5 Antenatal care</b>	<b>116</b>
5.1 Target ranges for blood glucose during pregnancy	116
5.2 Monitoring blood glucose and ketones during pregnancy	126
5.3 Management of diabetes during pregnancy	134
5.4 Retinal assessment during pregnancy	144
5.5 Renal assessment during pregnancy	154
5.6 Screening for congenital malformations	156
5.7 Monitoring fetal growth and wellbeing	164
5.8 Timetable of antenatal appointments	182
5.9 Preterm labour in women with diabetes	183
<b>6 Intrapartum care</b>	<b>185</b>
6.1 Timing and mode of birth	185
6.2 Analgesia and anaesthesia	199
6.3 Glycaemic control during labour and birth	204
<b>7 Neonatal care</b>	<b>211</b>
7.1 Initial assessment and criteria for admission to intensive or special care	211
7.2 Prevention and assessment of neonatal hypoglycaemia	219
<b>8 Postnatal care</b>	<b>228</b>
8.1 Breastfeeding and effects on glycaemic control	228
8.2 Information and follow-up after birth	235
<b>References</b>	<b>241</b>

# Abbreviations

---

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	angiotensin-II receptor blocker (also known as angiotensin-II receptor antagonist)
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
HbA <sub>1c</sub>	glycosylated haemoglobin
hCG	human chorionic gonadotropin
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
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
TA	technology appraisal
TGA	transposition of the great arteries
uE3	unconjugated estriol
VBAC	vaginal birth after previous caesarean section
WHO	World Health Organization

# 3 Preconception care

---

## 3.1 Outcomes and risks for the woman and baby

### Q.1 What information should be offered in relation to outcomes and risks for the mother and the baby?

No specific searches were conducted for this clinical question and so there are no evidence tables.

### **3.2 The importance of planning pregnancy and the role of contraception**

#### **Q.2 What information should be offered in relation to the importance of planning a pregnancy and the role of contraception?**

No specific searches were conducted for this clinical question and so there are no evidence tables.

### 3.3 Diet, dietary supplements, body weight and exercise

#### Q.3 What information should be offered in relation to diet, dietary supplements, body weight and exercise?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Kaplan JS;Iqbal S;England BG;Zawacki CM;Herman WH;  1999 Jul  39	Study Type: Case-control  Evidence level: 2+	31 pregnant women with diabetes  54 nondiabetic pregnant women	Country:	Intervention: Folate metabolism in pregnant women with diabetes  Comparison: Nondiabetic pregnant women	Follow-up period:  Outcome Measures: Measures of folate metabolism: Dietary folic intake serum folate red blood cell folate urinary folate homocysteine	Results for unsupplemented participants (15 diabetic, 34 control)  Dietary folate Diabetic: 294±154 Control:455±334, P = 0.03  Serum folate (ng/ml) Diabetic: 17.6±10.3 Control:14.1±5.7, NS  Red blood cell folate (ng/ml) Diabetic: 385±73 Control:353±184, NS  Urinary folate (ng/ml) Diabetic: 8.8±5.2 Control:8.8±4.3  Urinary folate (ng/ml)/urinary creatine (mg/dl) Diabetic: 0.08±0.05 Control:0.07±0.03, NS  Homocysteine (umol/l) Diabetic: 8.0±8.1 Control:6.5±1.9, NS  Vitamin B12 (pg/ml) Diabetic: 493±275 Control:383±152, NS	There were no significant differences between the pregnant diabetic and nondiabetic pregnant women for any measures of folate metabolism after accounting for folate supplementation. In addition, among diabetic women, there were no associations among parameters of folate metabolism and glycaemic control.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Ray JG;Vermeulen MJ;Shapiro JL;Kenshole AB;  2001  41	Study Type: Cohort  Evidence level: 2++	428 women with gestational diabetes  196 women with pregestational diabetes	Country:	Intervention: Prepregnancy weight Weight gain during  Comparison:	Follow-up period:  Outcome Measures: Caesarean delivery Shoulder dystocia or cephalopelvic disproportion Gestational hypertension or toxemia Admission to neonatal intensive care unit (NICU) LGA Preterm birth (before 37 weeks)	Results are rate and adjusted OR (adjusted for type of diabetes, maternal age, parity, prepregnancy BMI, net weight gain during pregnancy and obstetric history)  Caesarean delivery Prepregnancy BMI <20: 30.2% (OR 1.0) 20.0–24.9: 39.0% (OR 1.2, 95%CI 0.5–2.8) 25.0–29.9: 43.4% (OR 1.3, 95% CI 0.6–3.3) ≥30: 55.3% (OR 3.5, 95% CI 1.4–8.6)  Weight gain (5 kg increments): OR 1.2, 95%CI 1.0 -1.4.  Shoulder dystocia or cephalopelvic disproportion Prepregnancy BMI <20: 14% (OR 1.0) 20.0–24.9: 21.1% (OR 1.5, 95%CI 0.6–3.8) 25.0–29.9: 16.4% (OR 1.3, 95%CI 0.5–3.5) ≥30: 15.4% (OR 1.2, 95%CI 0.4–3.4)  Weight gain (5 kg increments): OR 1.1 (0.9–1.3)  Hypertensive disorders of pregnancy Prepregnancy BMI <20: 4.6% (OR 1.0) 20.0–24.9: 10.6% (OR 1.8, 95%CI 0.4–8.1) 25.0–29.9: 13.2% (OR 2.6, 95% CI 0.6–11.8)	Maternal obesity and excessive weight gain were independent risk factors for Caesarean delivery, hypertensive disorders of pregnancy, admission to neonatal intensive care, LGA and preterm birth.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>≥30: 17.1% (OR 4.1, 95% CI 0.9–18.9)</p> <p>Weight gain (5 kg increments): OR 1.4 (95% CI 1.2–1.7)</p> <p>NICU admission:</p> <p>Prepregnancy BMI &lt;20: 39.5% (OR 1.0)</p> <p>20.0–24.9: 54.1% (OR 1.2, 95% CI 0.5–2.7)</p> <p>25.0–29.9: 61.8% (OR 1.9, 95% CI 0.8–4.4)</p> <p>≥30: 65.0% (OR 2.4, 95% CI 1.0–5.9)</p> <p>Weight gain (5 kg increments): OR 1.2 (1.0–1.4)</p> <p>LGA</p> <p>Prepregnancy BMI &lt;20: 9.3% (OR 1.0)</p> <p>20.0–24.9: 24.8% (OR 2.5, 95% CI 0.8–7.7)</p> <p>25.0–29.9: 24.3% (OR 2.6, 95% CI 0.8–8.2)</p> <p>≥30: 26% (OR 3.3, 95% CI 1.0–10.6)</p> <p>Weight gain (5 kg increments): 1.3 (1.1–1.6)</p> <p>Preterm birth &lt;37 weeks</p> <p>Prepregnancy BMI &lt;20: 7% (OR 1.0)</p> <p>20.0–24.9: 28.0% (OR 5.0, 95% 1.4–17.6)</p> <p>25.0–29.9: 28.3% (OR 5.5 (1.5–19.4)</p> <p>≥30: 27.6% (OR 5.1, 95% CI 1.4–18.6)</p> <p>Weight gain (5 kg increments): OR 1.0 (0.8–1.2).</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Moore, H; et al.  2005  46	Study Type: Systematic review - meta-analysis  Evidence level: 1++	6 studies compared dietary advice with dietary advice plus exercise ( <i>n</i> = 322)	Type 2 diabetes. Adults. Not pregnant.  Country:	Intervention: Dietary advice plus exercise  Comparison: Dietary advice	Follow-up period:  Outcome Measures: Weight loss HbA <sub>1c</sub>	The quality of the trials was assessed to be at high risk of bias  Weight change was reported in four trials. More weight was lost on average in the diet and exercise groups. HbA <sub>1c</sub> decreased more in the participants in the dietary advice and exercise groups than in those in the dietary advice group alone.  At six months, dietary advice plus exercise was associated with a statistically significant mean (pooled weighted mean difference) decrease in glycated haemoglobin of 0.9% (95% confidence interval 0.4 to 1.3). At 12 months dietary advice plus exercise was associated with a statistically significant mean decrease of 1% (95% CI 0.4 to 1.5).	The evidence suggests that dietary advice plus exercise has the potential to reduce weight and improve glycaemic control.	
Brand-Miller, J.  2003  38	Study Type: Systematic review - meta-analysis  Evidence level: 1++	14 studies comprising 356 subjects	203 participants had type 1 diabetes, 153 had type 2 diabetes.  Country:	Intervention: Low GI diets  Comparison: High GI diets	Follow-up period:  Outcome Measures: HbA <sub>1c</sub> Fructosamine	Low GI diets reduced HbA <sub>1c</sub> by 0.43% points (CI 0.72– 0.13) over and above that produced by high GI diets. Taking both HbA <sub>1c</sub> and fructosamine data together and adjusting for baseline differences, glycated proteins were reduced 7.4% (8.8–6.0) more on the low GI diet than on the high GI diet. Systematically taking out each study from the meta analysis did not change confidence intervals.	Choosing low GI foods in place of conventional or high GI foods has a clinically useful effect on medium-term glycaemic control in patients with diabetes	
Gillmer MD;Maresh M;Beard RW;Elkeles RS;Alderson C;Bloxham B;	Study Type: RCT  Evidence level: 1-	15	Women routinely screened at 28–30 weeks' gestation and revealed abnormal glucose	Intervention: A 24 h profile (hourly blood sampling during daytime and 2 hourly during night) performed	Follow-up period: Treatment continued until delivery  Outcome Measures:	Mean plasma glucose concentration of the diet- treated women significantly greater than those of the controls (pregnant women		Insulin therapy more likely achieved normoglycaemia in these women. (very small sample size)

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1986 40			tolerance test with a total area under the GTT curve between 42 and 65 mmol/l  Country: UK	during which a diet of 2800 kcal and 260 g carbohydrate provided. Patients then randomly allocated to treatment with diet alone or insulin and dietary advice.  Comparison: Controls were normal women and no intervention given.	Mean plasma glucose of women, Mean neonatal plasma glucose, Mean plasma 3-hydroxybutyrate concentrations of women.  Gestational age at delivery, Mean percentile infant birthweight.	with a normal glucose tolerance who ate according to appetite) at 10am, 2pm and 8pm as compared to significantly lower in the insulin-treated group at 6pm, 2am, 4am and 6am than the controls. Mean 2 h neonatal plasma glucose concentration of the diet-treated group was significantly higher than that of other groups. The neonatal skinfold thickness was similar in the groups. Diet therapy alone and insulin treatment lowered the plasma concentrations of 3-hydroxybutyrate.  No significant difference between the groups in terms of gestational age at delivery or mean percentile infant birthweight.		
Ceysens G, Rouiller D, Boulvian M  2006 47	Study Type: Systematic review - meta-analysis  Evidence level: 1+	114	Pregnant women with gestational diabetes  None included pregnant women with type 1 or type 2 diabetes.  Women were recruited during the third trimester and the intervention was performed for about six weeks.  Country:	Intervention: Studies (RCTs) comparing any type of exercise programme with no exercise programme or other therapy. Programmes generally consisted of exercising three times a week for 20 to 45 minutes.  Comparison:	Follow-up period:  Outcome Measures: Caesarean section, perinatal death (death occurring during pregnancy or the first six days of life), admission and length of stay in neonatal intensive care unit.	No significant difference between exercise and the other regimen in any of the outcomes evaluated.  The outcome 'use of insulin therapy' was only reported by Avery 1997 and Brankston 2004, where the difference between the two groups was not significant RR 0.98, 95% CI 0.51 to 1.87). No woman required insulin therapy in the study by Jovanovic 1989. In Bung 1991, exercise was compared to insulin treatment; therefore, this study was included in a separate analysis (diet + exercise versus diet + insulin).  The occurrence of macrosomia was defined in two of the trials as	There is insufficient evidence to recommend, or advise against, diabetic pregnant women enrolling in exercise programmes. Trials, with larger sample size, involving women with gestational diabetes, and possibly type 1 and 2 diabetes, are needed to evaluate this intervention.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>birthweight &gt; 4000 g (Avery 1997; Bung 1991). No information was given in the third trial (Jovanovic 1989).</p> <p>No significant difference between exercise and no exercise and between exercise and insulin in all the outcomes evaluated.</p>		
<p>Kieffer EC;Tabaei BP;Carman WJ;Nolan GH;Guzman JR;Herman WH;</p> <p>2006 Dec</p> <p>43</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2+</p>	1041 mother-infant pairs	<p>Exclusion criteria: Twin pregnancies, miscarriages, stillbirths, missing records, women who entered care in the final weeks of pregnancy and women who had participated during their previous pregnancy</p> <p>Country: USA</p>	<p>Intervention: Maternal sociodemographic, prenatal care, anthropometric, and metabolic characteristics</p> <p>Comparison:</p>	<p>Follow-up period:</p> <p>Outcome Measures: Infant birthweight</p>	<p>42% of women in this study entered pregnancy overweight or obese; at least 36% exceeded weight-gain recommendations. Twenty-seven percent of the women had at least some degree of glucose abnormality, including 6.8% who had gestational diabetes. Maternal multiparity, height, weight, weight gain, and 1-hour screening glucose levels were significant independent predictors of infant birthweight after adjustment for gestational age.</p>	<p>There is an increased risk of adverse maternal and infant outcomes associated with excessive maternal weight, weight gain, and glucose intolerance among Latinas. This gives public health professionals a unique opportunity for prevention through prenatal and postpartum interventions</p>	
<p>Stotland NE;Cheng YW;Hopkins LM;Caughey AB;</p> <p>2006 Sep</p> <p>44</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2-</p>	20,465	<p>Women without diabetes, term, singleton births</p> <p>Country: USA</p>	<p>Intervention: Associations between gestational weight gain and neonatal outcomes. Gestational weight gain categorised by the Institute of Medicine guidelines as well as extremes of gestational weight gain (less than 7 kg and more than 18 kg)</p> <p>Comparison:</p>	<p>Follow-up period:</p> <p>Outcome Measures: Neonatal outcomes: birth trauma, 5-min Apgar score &lt; 7, assisted ventilation, SGA, LGA, cord arterial pH &lt; 7.1, NICU admission, SCN admission, neonatal infection, seizure, hypoglycaemia, polycythemia, Meconium aspiration syndrome, Respiratory distress syndrome, hospital</p>	<p>Gestational weight gain above the Institute of Medicine guidelines was 43.3% vs 20.1% in gestational weight gain below. Gestational weight gain above guidelines was associated with a low 5-minute Apgar score (AOR 1.33, 95% CI 1.01–1.76), seizure (AOR 6.50, 95% CI 1.43–29.65), hypoglycemia (AOR 1.52, 95% CI 1.06–2.16), polycythemia (AOR 1.44, 95% CI 1.06–1.94), meconium aspiration syndrome (AOR 1.79, 95% CI 1.12–2.86), and large for gestational age (AOR 1.98, 95% CI 1.74–2.25)</p>	<p>Gestational weight gain above guidelines was common and associated with multiple adverse neonatal outcomes, whereas gestational weight gain below guidelines was only associated with SGA status.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					stay > 5 days and hospital stay > 10 days.	compared with women within weight gain guidelines. Gestational weight gain below guidelines was associated with decreased odds of neonatal intensive care unit admission (AOR 0.66, 95% CI 0.46–0.96) and increased odds of small for gestational age (SGA; AOR 1.66, 95% CI 1.44–1.92). Gestational weight gain less than 7 kg was associated with increased risk of seizure, hospital stay more than 5 days, and SGA. Gestational weight gain more than 18 kg was associated with assisted ventilation, seizure, hypoglycemia, polycythemia, meconium aspiration syndrome, and large for gestational age.		
Ricart W;Lopez J;Mozas J;Pericot A;Sancho MA;Gonzalez N;Balsells M;Luna R;Cortazar A;Navarro P;Ramirez O;Flandez B;Pallardo LF;Hernandez-Mijas A;Ampudia J;Fernandez-Real JM;Corcoy R;Spanish Group for the Study of the Impact of Carpenter and Coustan GDM Thresholds.;	Study Type: Cohort  Evidence level: 2++	9,270	Inclusion criteria: Spanish pregnant women with singleton pregnancies and without a former diagnosis of diabetes  Exclusion criteria: Pregnancies with preterm delivery (at less than 28 weeks) and the second pregnancy of women with two pregnancies in the same year.	Intervention: Prepregnancy BMI and glucose tolerance status  Comparison:	Follow-up period:  Outcome Measures: Primary outcome: fetal macrosomia, Caesarean section Secondary outcome: diabetes-related pregnancy outcomes.	Both prepregnancy BMI and abnormal glucose tolerance categories were independent predictors of pregnancy outcomes.  The upper quartile of BMI accounted for 23% of macrosomia, 9.4% of Caesarean section, 50% of pregnancy-induced hypertension and 17.6% of large-for-gestational-age newborns. In contrast, NDDG GDM accounted for 3.8% of macrosomia, 9.1% of pregnancy-induced hypertension and 3.4% of preterm births.	In terms of population impact, prepregnancy maternal BMI exhibits a much stronger influence than abnormal blood glucose tolerance on macrosomia, Caesarean section, pregnancy-induced hypertension and large-for-gestational-age newborns.	
2005 Sep								
45			Country: Spain					

### 3.4 Target ranges for blood glucose in the preconception period

#### Q.4 What are the target ranges for blood glucose in the preconception period?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Diabetes and Pregnancy Group F; 2003 54	Study Type: Cohort Evidence level: 2++	435 pregnancies, 289 in women with type 1 diabetes and 146 from women with type 2 diabetes.	Preconception care was provided in 48.5% women with type 1 diabetes and 24% of women with type 2 diabetes. Preconception capillary blood glucose targets were <5.3 mmol/l before meals and <6.7 mmol/l 2 h postprandial	Intervention: Prepregnancy glycaemic control  Comparison:	Follow-up period:  Outcome Measures: Perinatal mortality (Fetal death + Neonatal death) Major congenital malformations Preterm delivery Macrosomia Mode of delivery Neonatal complications  HbA <sub>1c</sub> (normal 4.9±0.6%) obtained during the first trimester. Actual values were not available as only values >8% were recorded. Therefore values < 8% was considered as a surrogate marker for effective prepregnancy control.	166 infants were delivered before 37 weeks. Multivariate analysis found first trimester HbA <sub>1c</sub> >8% to be associated with preterm delivery (OR 2.2; 95%CI 1.4–3.7; <i>P</i> = 0.002).  First trimester HbA <sub>1c</sub> was >8% in 120 women (27.6%). Women whose HbA <sub>1c</sub> was >8% had higher rates of perinatal mortality (9.2 vs 2.5%; OR 3.9; 95% CI 1.5–9.7; <i>P</i> < 0.005) major congenital malformations (8.3 vs. 2.5%; OR 3.5; 95% CI 1.3–8.9; <i>P</i> < 0.01) and preterm delivery (57.6% vs 24.8%; OR 1.4; 1.1–1.7; <i>P</i> < 0.005).  First trimester HbA <sub>1c</sub> was more frequently >8% in women who did not receive preconception care than in those who did (43.5 vs 4.0%; OR 18.5; 8.3–40.9; <i>P</i> < 0.001).	Participating centres are tertiary units recruiting high risk pregnancies.	
Dicker D;Feldberg D;Samuel N;Yeshaya A;Karp M;Goldman JA; 1988 May 63	Study Type: Cohort Evidence level: 2++	94 women. 59 attending preconception clinic, 35 nonattenders.	Type 1 diabetes  Pregnancies resulting in congenital malformation were excluded from the study population.	Intervention: Preconception care. Glycaemic control was obtained by intensified insulin therapy and monitored by blood glucose self monitoring.  Comparison: 35 pregnant women who did not receive preconception glycaemic control	Follow-up period:  Outcome Measures: Miscarriages (losses that occurred before 22 weeks)  HbA <sub>1c</sub> (normal range 6.0% to 7.5%)	Preconception group: Normoglycaemia and normal HbA <sub>1c</sub> levels were achieved in this group before conception and were maintained throughout pregnancy.  Miscarriage occurred in 5/59 women attending preconception care and in 10/35 not attending. ( <i>P</i> < 0.001)  HbA <sub>1c</sub> Initial visit:	Miscarriage rates among patients with wit diabetes not seen before pregnancy were significantly higher when compared with women who attended the clinic, whose rates represented the normal frequencies in the general population.  Poor metabolic control around conception and in the early weeks of pregnancy may be the	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>Preconception group: Pregnancy&gt;22 weeks: 10.70 ± 0.49 Miscarriage: 10.68 ± 0.49</p> <p>HbA<sub>1c</sub> at conception Preconception group: Pregnancy&gt;22 week: 7.54 ± 0.34 Miscarriage: 7.5 ± 0.34</p> <p>First trimester HbA<sub>1c</sub>: Preconception group: Pregnancy&gt;22 weeks: 7.4 ± 0.34 Miscarriage: 7.39 ± 0.34 Later group: Pregnancy &gt;22 weeks 10.42 ± 0.47 Miscarriage: 10.68 ± 0.49, <i>P</i> &lt; 0.001.</p> <p>Second trimester HbA<sub>1c</sub> Preconception group: Pregnancy&gt;22 weeks: 7.20 ± 0.33 Miscarriage: 7.21 ± 0.33 Later group: Pregnancy&gt;22 weeks: 8.14 ± 0.37 Miscarriage: 8.20 ± 0.38. <i>P</i> &lt; 0.50 Blood glucose level (mmol/l) initial visit: Preconception group: Pregnancy&gt;22 weeks: 9.7 ± 0.6 Miscarriage: 9.6 ± 0.4</p> <p>Blood glucose level at conception: Preconception group: Pregnancy&gt;22 weeks: 6.4 ± 0.4 Miscarriage: 6.5 ± 0.4</p> <p>First trimester blood glucose</p>	determining factor favouring abortion.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						control: Preconception group: Pregnancy>22 weeks: 6.05 ± 0.4 Miscarriage: 6.05 ± 0.4 Later group: Pregnancy>22 weeks: 9.02 ± 0.4 Miscarriage: 9.57 ± 0.6. P<0.001		
						Second trimester blood glucose control Preconception group: Pregnancy>22 weeks: 6.05 ± 0.4 Miscarriage: 6.05 ± 0.4 Later group: Pregnancy>22 weeks: 7.7 ± 0.5 Miscarriage: 8.14 ± 0.5. P<0.50		
Fuhrmann K;Reiher H;Semmler K;Glockner E;  1984 Apr  52	Study Type: Cohort  Evidence level: 2++	200 pregnant women, 56 received preconception care,144 referred after 8 weeks gestation	Pregnant women with type 1 diabetes In all patients the aim was to keep blood glucose levels between 3.3 and 6.6 mmol/l	Intervention: Pre-conception care  Comparison:	Follow-up period:  Outcome Measures: Glycaemic control: based on 24 hr capillary blood glucose profiles derived from 9 samples which were taken 1 to 3 times a week. The therapeutic goals was to keep values between 2.3 and 7.7 mmol/l. Values in this range, but below or above normal, were only considered for correction if repeatedly determined at the same time of day. Deviations outside the range were corrected immediately by changing insulin dose and/or diet	39/56 women in preconception group had 87% of readings between 2.3 and 7.7 mmol/l, 9 patients had 77% of readings in this range, 8 patients failed to achieve sufficient metabolic control.  1/56 (1.8%) of infants of women in preconception group had a congenital malformation. This occurred in one of the eight mothers who failed to achieve sufficient metabolic control. 9/136 (6.6%) infants in the late treatment group had congenital malformations.  When data pooled with earlier findings (from 1977–1981) 2/185 (1.1%) infants had malformations in preconception care group compared to 31/473 (6.6%) in late treatment group $P < 0.01$ .	The findings stress the importance of a reasonably strict metabolic control, started well before conception, to prevent excess rates of congenital malformation.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Fuhrmann K; 1986 53	Study Type: Cohort Evidence level: 2++	620 women with type 1 diabetes receiving education and intensive treatment. 184 recruited prior to conception 436 recruited 8 weeks after conception.	In all patients the aim was to achieve a blood glucose concentration comparable to that found in non diabetic pregnant women	Intervention: Preconception metabolic control Comparison: Metabolic control optimised after 8th week gestation.	Congenital malformation Follow-up period: Outcome Measures: Congenital malformations Normal blood glucose readings (2.5–7.8 mmol/l)	In the preconception group mean daily blood glucose was <6.1 mmol/l in 88.3% of subjects compared with only 20.7% of the later registrants ( $\chi^2 = 110.6$ ; $P < 0.001$ ). Among the 622 infants born to 620 diabetic patients 33 had malformations (5.3%). 31/437 women who began intensive metabolic control after the 8th week of gestation gave birth to an infant with a malformation (7.1%) compared to 2/185 (1.1%) infants born to mothers who optimised metabolic control prior to conception, $P < 0.01$ .	Strict metabolic control established before conception can reduce the rate of malformations in infants of diabetic mothers. Normal blood glucose levels can be achieved in about 85% of all diabetic women if they attend a preconception programme.	
Gold AE;Reilly R;Little J;Walker JD; 1998 67	Study Type: Cohort Evidence level: 2+	57 deliveries	Type 1 diabetes Only viable pregnancies were included as major outcome variable of interest was birth weight	Intervention: Glycaemic control preconception and in early pregnancy Comparison:	Follow-up period: Outcome Measures: Birth weight HbA1 (In Edinburgh the nondiabetic nonpregnant normal range is 5.2–6.8% and the normal range for pregnancy is 4.8 to 6.4%)	Two groups of approximately equal size: Group 1: Birth weight z score < 1 SD above nondiabetic mean Group 2: Birth weight z score >1 SD above nondiabetic mean The study had a >80% chance of detecting a large difference (0.8 SD) between the groups ( $P = 0.05$ ) HbA1 6–12 mths prepregnancy: Group 1 ( $n = 21$ ): $8.6 \pm 1.4$ Group 2 ( $n = 25$ ): $10.0 \pm 2.3$ , $P = 0.02$ HbA1 0–6 mths prepregnancy: Group 1 ( $n = 23$ ): $8.7 \pm 2.0$ Group 2 ( $n = 26$ ): $10.2 \pm 2.4$ , $P = 0.03$ HbA1 at booking: Group 1 ( $n = 25$ ): $8.4 \pm 1.6$ Group 2 ( $n = 26$ ): $9.5 \pm 2.2$ , $P = 0.04$	Glycaemic control assessed by glycosylated haemoglobin at the time of conception and in the early weeks of pregnancy is a more powerful predictor of birth weight than is glycaemic control measured during the later weeks of pregnancy. A multiple r value of 0.48 suggests that glycaemic control as measured by HbA1 only contributes 23% of the variance in birth weight.	A failure to find an association between third trimester glycaemic control and birthweight may be due to the fact that all of the women achieved glycaemic control between a narrow range Glycaemic control during different periods are interrelated

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>HbA1 0–12 weeks: Group 1 (<math>n = 26</math>): <math>8.0 \pm 1.3</math> Group 2 (<math>n = 31</math>): <math>9.5 \pm 2.2</math>, <math>P = 0.04</math></p> <p>Hb1 12–24 weeks: Group 1 (<math>n = 26</math>): <math>7.1 \pm 1.0</math>, Group 2 (<math>n = 31</math>): <math>7.4 \pm 0.9</math> (NS)</p> <p>HbA1 24 weeks-term Group 1 (<math>n = 26</math>): <math>7.4 \pm 0.8</math> Group 2 (<math>n = 31</math>): <math>7.2 \pm 1.1</math> (NS)</p> <p>Significant correlation between HbA<sub>1c</sub> during 6 mths before pregnancy (<math>r = 0.44</math>, <math>P = 0.002</math>) at booking (<math>r = 0.43</math>, <math>P = 0.001</math>), the first 12 weeks of pregnancy (<math>r = 0.48</math>, <math>P = 0.001</math>) weeks 12–4 of pregnancy (<math>r = 0.45</math>, <math>P = 0.001</math>) and weeks 24 to term (<math>r = 0.34</math>, <math>P = 0.009</math>) and z score of the birth weight.</p> <p>Regression analysis only HbA1 at 0–12 weeks entered in the equation (multiple <math>r = 0.48</math>, sig <math>F = 0.0005</math>).</p>		
Goldman JA;Dicker D;Feldberg D;Yeshaya A;Samuel N;Karp M;  1986 Aug  50	Study Type: Cohort  Evidence level: 2++	75 pregnant women with type 1 diabetes. 44 women attending preconception clinic, 31 nonattenders of the preconception clinic	Type1 diabetes	Intervention: Preconception care  Comparison: 31 Nonattenders of the preconception clinic	Follow-up period:  Outcome Measures: HbA <sub>1c</sub> (normal mean (SD) 6.6 (0.3))  Malformation	<p>The mean HbA<sub>1c</sub> was <math>10.68\% \pm 0.49\%</math> and the mean blood glucose level was <math>174 \pm 10.8</math> mg/100 ml in patients attending the preconception clinic.</p> <p>Women attending preconception clinic: HbA<sub>1c</sub>: Initial visit: <math>10.68 \pm 0.49</math> At conception: <math>7.56 \pm 0.34</math> First trimester: <math>7.39 \pm 0.34</math> Second trimester <math>7.21 \pm 0.33</math> Third trimester <math>7.14 \pm 0.32</math> Blood glucose level (mmol/l): Initial visit: <math>9.6 \pm 0.6</math></p>	<p>We confirm the evidence accumulated in the recent literature that congenital malformations in pregnancy complicated by diabetes may be linked to disturbances in maternal metabolism during the period of embryogenesis. Consequently we concur with the recommendation that tight diabetic control is required before the patient attempts to conceive.</p> <p>Our study reveals a relation between preconception blood</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>At conception: <math>6.4 \pm 0.4</math>            First trimester: <math>6 \pm 0.4</math>            Second trimester: <math>6 \pm 0.4</math>            Third trimester: <math>5.3 \pm 0.3</math>            Insulin dose:            Initial visit: <math>0.60 \pm 0.03</math>            At conception: <math>0.62 \pm 0.03</math>            First trimester: <math>0.71 \pm 0.04</math>            Second trimester: <math>0.80 \pm 0.04</math>            Third trimester: <math>0.95 \pm 0.05</math></p> <p>Nonattenders:            HbA<sub>1c</sub>:            First trimester: <math>10.42 \pm 0.47, P &lt; 0.001</math>            Second trimester: <math>8.13 \pm 0.37, P &lt; 0.05</math>            Third trimester: <math>7.44 \pm 0.3, NS</math>            Blood glucose level (mmol/l):            First trimester: <math>163 \pm 10.2, P &lt; 0.001</math>            Second trimester: <math>148 \pm 9.2, P &lt; 0.05</math>            Third trimester: <math>124 \pm 7.8, NS</math>            Insulin dose:            First trimester: <math>0.83 \pm 0.04, P &lt; 0.001</math>            Second trimester: <math>0.92 \pm 0.05, P &lt; 0.001</math>            Third trimester: <math>0.96 \pm 0.05, NS</math></p> <p>3 congenital malformations occurred, all in the nonattending group (incidence in this group 9.6%, <math>P &lt; 0.07</math>).            First trimester HbA<sub>1c</sub> values of mothers were 8.8%, 9.2% and 10.2%.</p> <p>Other outcomes            Preconception group:            CS: 22.7%            Preeclampsia: 9.1%            Gestational age (mean<math>\pm</math>SD) (wk): <math>39.3 \pm 0.5</math>            Birthweight (mean <math>\pm</math>SD) (gm): <math>3296.2 \pm 234.1</math></p>	glucose regulation and the degree of improved diabetic control.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>1 minute Apgar score (mean ± SD): 8.1±0.7</p> <p>Hypoglycaemia: (&lt;1.65 mmol/l) (%) 11.4</p> <p>Hypocalcemia (&lt;0.44 mmol/l) (%) 9.6</p> <p>Hyperbilirubinemia (&gt;0.825 mmol/l) (%) 22.7</p> <p>Respiratory distress syndrome (%): 2.3</p> <p>Nonattending group</p> <p>CS (%): 41.9 (SS not reported)</p> <p>Preeclampsia (%): 22.5 (SS not reported)</p> <p>Gestational age (mean±SD) (wk): 36.9 ± 0.5, <i>P</i> &lt; 0.05</p> <p>Birthweight (mean ±SD) (gm): 3681.4 ± 261.5, <i>P</i> &lt; 0.05</p> <p>1 minute Apgar score (mean ± SD): <i>P</i> &lt; 0.001</p> <p>Hypoglycaemia: (&lt;1.65 mmol/l) (%)25.8, NS</p> <p>Hypocalcemia (&lt;0.44 mmol/l) (%): 9.6, NS</p> <p>Hyperbilirubinemia (&gt;0.825 mmol/l) (%): 32.2, NS</p> <p>Respiratory distress syndrome (%): 12.9, NS</p>		
Greene MF;Hare JW;Cloherty JP;Benacerraf BR;Soeldner JS;	Study Type: Cohort Evidence level: 2++	303 pregnant women	Type 1 diabetes. All patients presenting at 12 weeks gestation or less	Intervention: First trimester glycaemic control  Comparison:	Follow-up period:  Outcome Measures: First trimester HbA1 (In nondiabetic population mean (SD) is 5.9% (0.57)).  Miscarriage  Congenital malformations	<p>35% of women had first trimester HbA1 &gt;9SD above the mean (&gt;11.0%)</p> <p>There were 20 major malformations.</p> <p>Miscarriages are significantly increased at &gt;9SD above the mean (HbA1 &gt;11.0%) the risk of major malformations is significantly elevated at &gt;12 SD above the mean (HbA1 &gt;12.7%)</p> <p>Miscarriage by first trimester HbA1: ≤9.3%: 14/113 (12.4%) RR=1</p>	<p>Although the risks for both adverse outcomes were markedly elevated following a first trimester in very poor metabolic control, there was a broad range of control over which the risks were not substantially elevated. To keep malformations and Miscarriages to a minimum among diabetic women does not require 'excellent' control; there seems to be a fairly broad range of 'acceptable' control.</p>	<p>Ten patients lost to follow up (mean HbA1 12.0%).</p> <p>Rate of Miscarriages may be higher</p>
1989 Mar								

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						9.4–11.0%: 7/85 (8.3%) RR=0.7 (95% CI =0.3–1.6)		
						11.1–12.7%: 15/61 (24.6%) RR=1.98 (95% CI = 1.03–3.38)		
						12.8–14.4%: 10/28 (35.7%) RR=2.9 (1.4–5.8)		
						>14.4: 6/16 (37.5%) RR=3 (95% CI=1.3–7.0)		
						Major malformations by first trimester HbA1: ≤9.3% 3/99 (3%) RR=1		
						9.4–11.0%: 4/77 (5.2%) RR=1.7 (95% CI=0.4–1.7)		
						11.1–12.7%: 2/46 (4.3%) RR=1.4 (95% CI 0.3–8.3)		
						12.8–14.4%: 7/18 (38.9%) RR 12.8 (95% CI 4.7–35.0)		
						>14.4 %: 4/10 (40%) RR 13.2 (95% CI 4.3–40.4)		
						First trimester HbA1: Miscarriage ( <i>n</i> = 52): 11.6 ± 2.5 Major malformation ( <i>n</i> = 20): 12.4±2.9 No malformation ( <i>n</i> = 230): 9.9±1.9, <i>P</i> < 0.005.		
						Gestational age (wk) at first visit Miscarriage: 8.2±2.0 Major malformation: 8.6±2.1 No malformation: 7.5±1.9, <i>P</i> = 0.01		
						Years of diabetes prior to pregnancy: Miscarriage: 12.0±7.7 Major malformation: 8.9 ± 5.1 No malformation: 13.4 ± 7.0,		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Jensen DM;Damm P;Moelsted-Pedersen L;Ovesen P;Westergaard JG;Moeller M;Beck-Nielsen H;  2004  66	Study Type: Cohort  Evidence level: 2++	1218 pregnancies in 990 women	Type 1 diabetes	Intervention: Preconception HbA <sub>1c</sub>  Comparison:	Follow-up period:  Outcome Measures: Serious adverse outcome (perinatal death and/or congenital malformation)	$P = 0.025$  HbA <sub>1c</sub> 0–3 mths prior to conception (median and interquartile range): Adverse outcome: 8.0 (7.3–9.1) Others: 7.6 (6.8–8.5), $P = 0.005$ .  First trimester HbA <sub>1c</sub> : Adverse outcome: 7.6 (6.6–8.6) Others 7.3 (6.6–8.1), $P = 0.037$  Second trimester HbA <sub>1c</sub> : Adverse outcome: 6.9 (6.2–8.0) Others: 6.6 (6.0–7.3), $P = 0.012$  Third trimester HbA <sub>1c</sub> : Adverse outcome: 7.1 (6.5–7.9) Others: 6.7 (6.2–7.4) $P < 0.001$  Preconception guidance: Adverse outcome: 38 (42%) Others: 631 (59.2%) $P = 0.002$  Daily glucose monitoring at conception Adverse outcomes: 18 (22.5%) Others: 363 (34.6%) $P = 0.019$	Poor glucose control before and during pregnancy is associated with perinatal mortality and congenital malformations	
Key TC;Giuffrida R;Moore TR;  1987 May  59	Study Type: Cohort  Evidence level: 2++	83 pregnant women	Women with diabetes (63 types I and 20 type II) who came for care before the 15th week of gestation	Intervention: HbA <sub>1c</sub> (normal nondiabetic mean 5.1 (1.1)  Comparison:	Follow-up period:  Outcome Measures: Congenital malformations Miscarriages	Pregnancy outcomes in type I and type II diabetes were similar ( $\chi^2=2.8$ , $P > 0.05$ ). 25/63 (39%) of women with type 1 diabetes had an abnormal outcome and 6/20 (30%) of women with type II diabetes had an abnormal outcome.  There were 31/83 (37%) abnormal outcomes. 22 pregnancies terminated as miscarriages and there were 9 congenital malformations. The congenital malformation rate in	Abnormal glucose control during early pregnancy, as reflected by abnormal HbA <sub>1c</sub> , is associated with an increased incidence of congenital malformations and Miscarriage. The type of diabetes does not appear to be important in that type 1 and type 2 had similar pregnancy outcomes.  The present study establishes that fair to good diabetic control (HbA <sub>1c</sub> <9.5%) during early gestation is highly predictive of normal pregnancy outcome.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>continuing pregnancies was 15%; the overall Miscarriage rate was 26.5%.</p> <p>Malformations: 82% of patients in the study has HbA<sub>1c</sub> levels <math>\geq</math>9.5%, 42% had values <math>\geq</math>11.5%. All anomalies were seen in patients whose initial HbA<sub>1c</sub> was <math>&gt;</math>9.5%. 7/9 were seen in mothers whose HbA<sub>1c</sub> was <math>&gt;</math>11.5% and 6/9 in the 20% of the study population whose HbA<sub>1c</sub> was <math>&gt;</math>13.5%.</p> <p>Miscarriages: No Miscarriages occurred in mothers with HbA<sub>1c</sub> <math>&lt;</math>7.5%, 1/22 occurred in mothers whose HbA<sub>1c</sub> was 7.5%-9.4%. 21/22 (95%) occurred in mothers whose HbA<sub>1c</sub> was <math>&gt;</math>11.5%, 19/22 (86%) occurred in mothers whose HbA<sub>1c</sub> <math>&gt;</math>13.5%.</p> <p>Higher HbA<sub>1c</sub> levels predict abnormal outcomes and low HbA<sub>1c</sub> values predict normal outcomes (<math>P &lt; 0.005</math>). Predictive values: <math>&gt;</math>7.5%: Sensitivity 100%, Specificity 14%, PPV 0.41, NPV 1 <math>&gt;</math>9.5%: Sensitivity 97%, Specificity 42%, PPV 0.50, NPV 0.96 <math>&gt;</math>11.5%: Sensitivity 84%, Specificity 82%, PPV 0.74, NPV 0.89 <math>&gt;</math>13.5%: Sensitivity 55%, Specificity 94%, PPV 0.85, NPV 0.77.</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Kitzmilller JL;Gavin LA;Gin GD;Jovanovic-Peterson L;Main EK;Zigrang WD;  1991 Feb 13  36	Study Type: Cohort  Evidence level: 2++	84 women recruited prior to conception, 110 women referred at 6 to 8 weeks gestation	Women with diabetes undergoing education and intensive management. Type 1 diabetes present in 68% of women in preconception group and 60% in postconception group.	Intervention: Recruitment prior to conception  Comparison: Recruitment at 6 to 8 weeks conception	Follow-up period:  Outcome Measures: Congenital malformations  HbA <sub>1c</sub> (normalnondiabetic mean (SD) 6.3 (0.7)	When HbA <sub>1c</sub> exceeded 15.5% ( <i>n</i> = 6) all pregnancies resulted in an abnormal outcome, a predictive value of 1.00  One major congenital malformation occurred in 84 infants (1.2%) of women treated before conception compared with 12 anomalies in 110 infants (10.9%) of mothers in the post conception group. ( <i>P</i> =0.01). $\chi^2=40.9$ , <i>P</i> < 0.0001 for elevated initial HbA <sub>1c</sub> levels in the postconception compared with the preconception group $\chi^2=10.1$ , <i>P</i> = 0.04 for association of congenital anomalies with elevated HbA <sub>1c</sub> level in the postconception group only $\chi^2=19.5$ , <i>P</i> = 0.001 for association of congenital anomalies with elevated HbA <sub>1c</sub> level in both groups  Of the 12 mothers who had infants with congenital malformations 7 had HbA <sub>1c</sub> >10.5% at first prenatal visit and 4 had levels >9.2%.  Frequency of hypoglycemia in preconception group (No of episodes per week): 0, 42% 1-2, 35% 3-4, 14% 5-7, 6% ≥8, 3% Requiring third party intervention <i>n</i> = 2	Education and intensive management for glycaemic control of diabetic women before and during early pregnancy will prevent excess ratesof congenital malformations.	
Miodovnik M;Skillman C;Holroyde JC;Butler JB;Wendel JS;Siddiqi TA;  1985 Oct 15	Study Type: Cohort  Evidence level: 2++	116 pregnancies in 75 women	Type 1 diabetes.  Goal of glycaemic control were a fasting blood glucose <5.5 mmol/l and a 90	Intervention: First trimester HbA <sub>1</sub>  Comparison:	Follow-up period:  Outcome Measures: Miscarriage (between 5 and 15 weeks)	Two groups based on method of HbA <sub>1</sub> assessment. Group 1 (1981-1984) <i>n</i> = 79: Miscarriages: HbA <sub>1</sub> <12%: 11/68 (16%) HbA <sub>1</sub> ≥ 12%: 5/11 (45%)	Women with type 1 diabetes who experienced Miscarriages had significantly higher levels of HbA <sub>1</sub> in the first trimester than did women whose pregnancies progressed beyond 20 weeks.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
65			minute postprandial glucose of less than 7.7 mmol/l  Pregnancies that resulted in congenital malformations were excluded from the study			$P < 0.05$  Group 2 (1978–1980) $n = 37$ : Miscarriages: HbA1 <12%: 3/21 (14%) HbA1 $\geq$ 12%: 7/9 (44%)	This indicates an increased risk of fetal loss in insulin diabetic mothers with poor control of glycaemia in the first trimester. To reduce the frequency of Miscarriages in women with type 1 diabetes good metabolic control is essential prior to conception and in the early weeks of pregnancy.	
Miodovnik M;Mimouni F;Tsang RC;Ammar E;Kaplan L;Siddiqi TA;  1986 Sep  64	Study Type: Cohort  Evidence level: 2++	84 pregnancies in 68 women	Type 1 diabetes  Goal of glycaemic control were a fasting blood glucose <5.5 mmol/l and a 90 minute postprandial glucose of less than 7.7 mmol/l  Pregnancies that resulted in congenital malformations were excluded from the study	Intervention: Glycaemic control in early pregnancy  Comparison:	Follow-up period:  Outcome Measures: HbA1 at 8–9 weeks gestation (normal range 5.5–8.5%)  Glycosated proteins (at 9 weeks).  Glycosated albumin (9 weeks)  Miscarriage	Initial HbA1: Miscarriage ( $n = 18$ ): $12.0 \pm 0.6$ Pregnancy >20 weeks ( $n = 66$ ): $10.7 \pm 0.3$ ( $P < 0.05$ )  Mean initial glycosated proteins (%): Miscarriage: $22.7 \pm 2.0$ Pregnancy >20 weeks: $22.2 \pm 0.7$ (NS)  Mean initial glycosated albumin (%): Miscarriage: $14.2 \pm 1.1$ Pregnancy >20 weeks $15.1 \pm 0.6$ (NS)	HbA1 is higher in diabetic pregnancies leading to a spontaneous abortion compared with those progressing to viability. However glycosated proteins and glycosated albumin were not significantly different in abortion and control groups. Because the half life of albumin approximates 14 days, the percentage of glycosylated albumin reflects the metabolic control during the 2 to 4 weeks before measurement. Similarly, glycosylated total proteins reflect control during the previous one to two weeks before measurement. It appears therefore that poor metabolic control around conception and/or in the early weeks of pregnancy, but not in the few weeks preceding the abortive event, is the determining factor favouring abortion.  The authors speculated that an improved metabolic control at the time of conception and in the early pregnancy will will minimise the risk of both major malformations and Miscarriages.	Only pregnant women were enrolled which may underestimate abortion rate
Suhonen L;Hillesmaa V;Teramo K;  2000 Jan	Study Type: Cohort  Evidence level: 2++	691 pregnancies and 709 infants of 488 women with type 1 diabetes. 729 non-selected	Type 1 diabetes. 98% Finnish caucasians.	Intervention: Glycaemic control in early pregnancy  Comparison:	Follow-up period:  Outcome Measures: Congenital malformations	There were 30 (4.2%) malformations in patients with type I diabetes and 10 (1.2%) in controls (RR 3.1; 95% CI 1.6–6.2).	Even a slightly raised HbA <sub>1c</sub> during early pregnancy in women with Type 1 diabetes carries an increased risk for fetal malformations. Therefore	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
35		control pregnancies in women without diabetes.			HbA <sub>1c</sub> (mean normal nondiabetic 4.93 (0.32))	HbA <sub>1c</sub> (%): <5.6, RR=1.6 (0.3–9.5) 5.6–6.8, RR=3.0 (1.2–7.5) 6.9–8.0, RR=2.3 (1.0–5.7) 8.1–9.3, RR=3.3 (1.3–8.6) ≥9.4, RR=4.8 (1.6–13.9)  Regression: HbA <sub>1c</sub> associated with occurrence of malformations after adjusting for White's class, age at onset of diabetes, duration of diabetes, parity, smoking, and participation in prepregnancy counselling. ( $P = 0.02$ ).	normoglycaemia should be strived for during early pregnancy	
Miller E;Hare JW;Cloherty JP;Dunn PJ;Gleason RE;Soeldner JS;Kitzmler JL;  1981 May 28  57	Study Type: Cohort  Evidence level: 2++	116	women with type 1 diabetes	Intervention: HbA <sub>1c</sub>  Comparison:	Follow-up period:  Outcome Measures: A major congenital malformation was defined as one causing death or serious handicap or one requiring surgery.	15/116 (13%) had infant with major congenital malformation. The mean initial HbA <sub>1c</sub> was significantly higher in women with infants with major congenital malformations than those without ( $8.4 \pm 1.6$ vs $9.5 \pm 1.0$ , $P < 0.01$ ).  Congenital malformations by first trimester HbA <sub>1c</sub> ≤6.9%: 0/19 7.0–8.5%: 2/37(5.1%) 8.6–9.9%: 8/35 (22.9%) ≥ 10.0%: 5/23 (21.7%)  Group 1 (≤8.5%) 2/57 (3.4%) Group 2 (>8.5%) 13/58 (22.4%) $P < 0.01$ .	Our results revealed a significantly higher incidence of major congenital anomalies in the offspring of women with elevated HbA <sub>1c</sub> values, and we conclude that poorly controlled diabetes is associated with an increased risk of such anomalies.	
Mills JL;Simpson JL;Driscoll SG;Jovanovic-Peterson L;Van AM;Aarons JH;Metzger B;Bieber FR;Knopp RH;Holmes LB;  1988 Dec 22  61	Study Type: Cohort  Evidence level: 2++	386 type 1 diabetes, 432 control women	75.9% enrolled before conception, 24.1% enrolled before 21 days after conception.	Intervention: Glycaemic control  Comparison:	Follow-up period:  Outcome Measures: Glycosylated hemoglobin (Nanomoles of fructose/10 g of hemoglobin)	There were 62/386(16.1%) Miscarriages among women with diabetes and 70/432 (16.2%) in the control group.  Within the normal range there was no relation between the level of glycosylated hemoglobin and the rate of pregnancy loss. In diabetic or control subjects. Above the normal range loss rates in the	Diabetic women with good metabolic control are no more likely than nondiabetic women to lose a pregnancy but diabetic women with elevated blood glucose and glycosylated hemoglobin levels in the first trimester have a significantly increased risk of having a Miscarriage.	Diabetes in early pregnancy (DIEP) study  Because in the majority of women with diabetes blood glucose levels were well controlled the effect of poor diabetic control was not apparent in the overall loss rates.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>diabetic group increased in an approximately linear fashion with increasing levels of glycosylated hemoglobin (<math>y=0.7x - 19.1</math>; <math>P = 0.015</math>).</p> <p>Although the numbers are small they suggest an increase in the risk of abortion of 3.1% (95% CI 0.6–5.6) for each increase of 1 SD above the mean.</p> <p>Fasting (<math>P = 0.01</math>) and postprandial (<math>P = 0.004</math>) blood glucose levels were significantly higher in women who aborted and were significant predictors of loss when analysed by logistic regression.</p> <p>No relationship with hypoglycaemia</p>		
Rosenn B;Miodovnik M;Combs CA;Khoury J;Siddiqi TA;  1994 Oct  60	Study Type: Cohort  Evidence level: 2++	215	Type 1 diabetes. Glycaemic control achieved with dietary regimen and split, mixed dosage regimens of short and intermediate-acting insulin. Goals of glycaemic control were a fasting blood glucose < 5.6 mmol/l, and a 90 min postprandial glucose < 7.8 mmol/l. When necessary women were hospitalised to maintain these goals.	Intervention: HbA1 (normal range 5.5–8.5)  Comparison:	Follow-up period:  Outcome Measures: Miscarriage defined at miscarriages before 20 weeks gestation.  Major congenital malformations were defined as gross physical or anatomical developmental anomalies resulting in death, requiring major surgery or substantial medical treatment, or causing a substantial physical or psychological handicap.  HbA1 normal range 5.5–8.5%	52/215 women who enrolled before 9 weeks gestation (24%) had Miscarriages. The threshold for increase risk of abortion was a preprandial glucose concentration of 7.15 mmol/l or an initial HbA1 of 12% (6.2 SD above the normal mean) $P < 0.05$ .  55/284 women who enrolled before 14 weeks gestation had Miscarriages and were excluded from analysis. 14 of the remaining 229 (6.1%) infants were born with congenital malformations (including 3 stillborn and one neonatal death). The threshold for increased risk of malformations was a preprandial glucose concentration of 6.6 mmol/l or an initial HbA1 of 13% (6.2 SD above the normal mean)	Women with type 1 diabetes with initial HbA1 >12% or median first trimester preprandial glucose concentrations >6.6 mmol/l have an increased risk of abortion and malformations. Below these glycaemic thresholds the risks are comparable to those in nondiabetic women.	The study uses HbA1 with a normal range 5.5–8.5% which is higher than the normal range for HbA <sub>1c</sub>

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Ylinen K;Aula P;Stenman UH;Kesaniemi-Kuokkanen T;Teramo K;  1984 Aug 11  56	Study Type: Cohort  Evidence level: 2++	146 fetuses in 142 women	Women with type 1 diabetes	Intervention: HbA <sub>1c</sub> (mean nondiabetic HbA <sub>1c</sub> 5% (SD 0.5))  Comparison:	Follow-up period:  Outcome Measures: Malformation defined as major if fatal or likely to cause serious handicap to the child. Other malformations classified as minor.	$P < 0.05$ .  17/142 pregnancies complicated by malformation - 6 minor and 11 major. The mean initial HbA <sub>1c</sub> was significantly higher in the group with minor malformations (9.3, SD 1.9, $P < 0.05$ ) and the group with major malformations (9.6, SD 1.8, $P < 0.001$ ) than in the group without malformations (8.0, SD 1.4%)  Congenital malformations by initial HbA <sub>1c</sub> : <8.0%: 3/63 (4.8%) 8.0–9.9%: 8/62 (12.9%) ≥ 10.0%: 6/17(35.3%)	Increased incidence of fetal malformations is associated with maternal hyperglycaemia during organogenesis. Hence diabetic women who are planning to have a child - especially those with a high HbA <sub>1c</sub> value - should receive intensified metabolic control.	
Lucas MJ;Leveno KJ;Williams ML;Raskin P;Whalley PJ;  1989 Aug  58	Study Type: Cohort  Evidence level: 2++	105 women with diabetes 14 women without diabetes	GDM=23, White Class A= 4, B=27, C=25, D=18, F, H and R =8.	Intervention: Glycaemic control  Comparison:	Follow-up period:  Outcome Measures: congenital malformations Miscarriages  Total glycosylated haemoglobin (HbA <sub>1a+b+c</sub> ). Mean in nondiabetic women was 6.0% (range 5.0% - 6.9%).	The mean HbA <sub>1a+b+c</sub> of the 105 study patients was 9.2% (range 5.2% to 14.2%).  The mean ± SD HbA <sub>1a+b+c</sub> levels of the 73 mothers of infants with no malformations was 8.9%±2.3% compared with 10.3%±1.9% for mothers of infants with major or minor malformations ( $P = 0.05$ ).  In pregnancies that progressed beyond abortion there was a statistically significant ( $P = 0.05$ ) distribution of malformation above the HbA <sub>1a+b+c</sub> of 9.2%: 10/14 malformations occurred in 42 women whose levels exceeded this value, compared with four malformations in the 45 women with levels below this value.		
Rosenn B;Miodovnik M;Combs CA;Khoury J;Siddiqi TA;  1991 Jun	Study Type: Cohort  Evidence level: 2++	99 pregnant women with Type 1 diabetes. 28 had attended a preconception clinic and 71 had enrolled	Significantly more patients in the study group had advanced disease compared with the control group ( $P = 0.04$ )	Intervention: Preconception care  Comparison: Women enrolled after conception	Follow-up period:  Outcome Measures: Pregnancy loss  Glycohemoglobin	HbA <sub>1c</sub> were significantly lower in the preconception group at the first prenatal visit and at 9 and 14 weeks gestation $P = 0.0008$ , $P = 0.002$ , $P = 0.02$ ). There was no	Women in the pre-conception program achieved good glycaemic control before conceiving; this was associated with a significantly lower rate of Miscarriages.	High drop-out rate in preconception clinic

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
62		after conception.			(normal range 5.5–5.8)	<p>significant difference at 26 weeks or delivery. The rate of Miscarriage was significantly lower in the preconception group (7% compared to 24%, <math>P = 0.04</math>). One major malformation (microcephaly) was diagnosed in the preconception group and none in the postconception group.</p> <p>HbA<sub>1c</sub> at the first prenatal visit and at 9 and 14 weeks gestation were significantly higher among those who had Miscarriages (<math>P = 0.005</math>, <math>P = 0.02</math>, <math>P = 0.02</math>).</p> <p>Rate of Miscarriages according to HbA<sub>1c</sub> at 9 weeks gestation: HbA<sub>1c</sub> (SD above nondiabetic mean):</p> <ul style="list-style-type: none"> <li>&lt;1, 0.08</li> <li>1–3, 0.05</li> <li>3–5, 0.11</li> <li>5–9, 0.57</li> <li>&gt;9, 0.5</li> </ul>		
Schaefer-Graf UM; Buchanan TA; Xiang A; Songster G; Montoro M; Kjos SL; 2000 Feb 421	Study Type: Cohort Evidence level: 2++	4180 pregnancies (3764 complicated by gestational diabetes, 416 complicated by type 2 diabetes)		Intervention: glycaemic control Comparison:	Follow-up period: Outcome Measures: congenital malformations	<p>The initial fasting serum glucose, highest fasting serum glucose and HbA<sub>1c</sub> levels were significantly higher in pregnancies with major (143) and minor (<math>n = 112</math>) anomalies (<math>P &lt; 0.0001</math> for all glycemic parameters).</p> <p>Malformation rate by initial fasting serum glucose level</p> <ul style="list-style-type: none"> <li>≤6.6 mmol/l, 64/3060 (2.1%)</li> <li>6.65–11 mmol/l, 53/905 (5.9%)*</li> <li>&gt;11 mmol/l 26/185 (12.9%)*†</li> </ul> <p>* <math>P &lt; 0.0001</math>, compared with initial fasting serum glucose level of ≤6.6 mmol/l † <math>P &lt; 0.0001</math> when compared with initial fasting serum glucose level of 6.65–</p>	<p>Congenital malformations in offspring of women with gestational and type 2 diabetes affect the same organ systems that have previously been described in pregnancies complicated by type 1 diabetes .Increasing hyperglycaemia at diagnosis or presentation for care was associated with an increasing risk of malformations.</p>	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Steel JM;Johnstone FD;Hepburn DA;Smith AF; 1990 Nov 10 51	Study Type: Cohort Evidence level: 2++	143 women attending a prepregnancy clinic and 96 women managed over the same period who had not received specific prepregnancy care	type1 diabetes	Intervention: Prepregnancy care Comparison:	Follow-up period: Outcome Measures: Congenital malformations Maternal hypoglycaemia HbA1 (normal range 5.9–8.0%)	11 mmol/l Mean HbA1 during the first trimester was significantly lower among attenders at the prepregnancy clinic (8.4%) than among the non attenders (10.5%, $P < 0.0001$ ) Hypoglycaemia was significantly more common in all patients who had attended the prepregnancy clinic than non attenders (38/143 women v 8/96; $\chi^2=11.1$ , $P < 0.001$ ). One out of 12 mothers who had an infant with malformation had experienced hypoglycaemia in the first 9 weeks. The other 45 patients who had severe hypoglycaemia had no abnormal neonatal outcomes.  There were 12 infants with major congenital malformations. The malformations were significantly more common in babies born to patients who had not attended the prepregnancy clinic (10/96; 10.4%) than in babies of mothers who had attended (2/143; 1.4%, $\chi^2=8.0$ , $P < 0.005$ ; RR 7.4 95% CI 1.7–33.2). Median HbA1 in first 9 weeks of mothers of infants with malformations 12.5% (range 8.8–14.9).	Tight control of the maternal blood glucose concentration in the early weeks of pregnancy can be achieved by the prepregnancy clinic approach and is associated with a highly significant reduction in the risk of serious congenital abnormalities in the offspring. Hypoglycaemic episodes do not seem to lead to fetal malformation even when they occur during the period of organogenesis.	
Rosenn BM;Miodovnik M;Holcberg G;Khoury JC;Siddiqi TA; 1995 Mar 68	Study Type: Cohort Evidence level: 2++	84 women	Type 1 diabetes. Recruited before 9 weeks gestation and received intensive insulin therapy throughout pregnancy. Patients monitored glucose concentrations with	Intervention: Intensive insulin therapy throughout pregnancy Comparison:	Follow-up period: Outcome Measures: Hypoglycaemia Biochemical hypoglycaemia determined from glucometer data	71% of patients had at least one moderate symptomatic episode and 34% had at least one severe symptomatic episode.  19 patients had a total of 54 episodes of loss of consciousness and 12 patients	Hypoglycaemia is a frequent complication that significantly affects the majority of women who receive intensive insulin therapy during pregnancy.  This may be related to the institution of intensive therapy which diminishes	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			memory glucometers and insulin doses were adjusted weekly accordingly.		<p>Symptomatic hypoglycaemic episodes recorded weekly on standardised forms</p> <p>Moderate symptomatic hypoglycaemia: Any episode that could not be resolved by the patient herself and required active assistance from another person</p> <p>Severe symptomatic hypoglycaemia: an episode resulting in seizures, loss of consciousness, injury, IV glucose treatment or emergency glucagon administration.</p>	<p>had a total of 15 seizures.</p> <p>Most symptomatic episodes occurred during the first half of pregnancy. The peak incidence of severe or moderate symptomatic hypoglycaemia was between 10 and 15 weeks.</p> <p>There was no association between hypoglycaemia during early pregnancy and adverse pregnancy outcome.</p> <p>When hypoglycaemic and nonhypoglycaemic groups were compared there were no differences in any of the commonly used indices of glycaemic control, including preprandial glucose, postprandial glucose and glycohaemoglobin concentrations.</p>	<p>counterregulatory responses to hypoglycaemia and increases hypoglycaemic unawareness. Alternatively it may be that pregnancy independently increases the risk of hypoglycaemia, possibly due to hormonal changes, diminished counterregulatory responses to hypoglycaemia or the nausea and vomiting of pregnancy.</p> <p>At present, a measure of caution should be exercised for the occasional patient who demonstrates a tendency to have recurrent episodes of severe hypoglycaemia that cannot be resolved with the usual tactics of modifying insulin regimens, caloric intake, and physical activity.</p>	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
<p>The Diabetes Control and Complications Trial Research Group;</p> <p>1996 Apr</p> <p>49</p>	<p>Study Type: OtherNon randomised controlled trial</p> <p>Evidence Level: 2++</p>	<p>Intervention: Women originally assigned to intensive treatment</p> <p>Comparison: Women originally assigned to conventional treatment</p>	<p>180 women completed 270 pregnancies. 94 women originally assigned to intensive treatment. 86 women originally assigned to conventional treatment (26 changed to intensive treatment before conception, 60 after conception).</p>	<p>13–39 years, type1 diabetes, in good health.</p> <p>Goals for all pregnant women fasting level 3.85–5.5, 1 hour postprandial level 7.7 mmol/l</p>	<p>Miscarriage congenital malformation</p> <p>HbA<sub>1c</sub></p>	<p>Intensive treatment group mean HbA<sub>1c</sub> at conception 7.4%±1.3%. Conventional treatment group mean HbA<sub>1c</sub> at conception 8.1%±1.7%, <i>P</i> = 0.0001.</p> <p>Nine congenital malformations were identified, 8 in the conventional treatment group (<i>P</i> = 0.06).</p> <p>There were 18 (13.3%) Miscarriages in the intensive group and 14 (10.4%) in the conventional group (NS).</p> <p>Overall the median HbA<sub>1c</sub> level was higher in those women who had abnormal outcomes (ectopic pregnancy, Miscarriage, induced abortion for medical reasons, congenital</p>	<p>Timely institution of intensive therapy is associated with rates of miscarriage and congenital malformations similar to those in the nondiabetic population.</p>	

---

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						malformations, intrauterine death, neonatal death) than in those women with normal outcomes ( $P = 0.05$ ). At the 3 months prior to conception $P = 0.018$ and at 5 months $P = 0.019$ .		

---

### 3.5 Monitoring blood glucose and ketones in the preconception period

#### Q.5 How should blood glucose and ketones be monitored in the preconception period?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
The Diabetes Control and Complications Research Group 1993 70	Study Type: RCT Evidence level: 1++	711 intensive therapy 730 conventional therapy	Type 1 diabetes aged 13–39 years. Absence of hypertension, hypercholesterolemia and severe diabetic complications or medical conditions.  Country: US and Canada	Intervention: Intensive therapy (IT): Aimed at achieving preprandial blood glucose concentrations between 3.9 and 6.7 mmol/l, postprandial concentrations of <10 mmol/l, a weekly 3am measurement >3.6 mmol/l and HbA <sub>1c</sub> measured monthly within the normal range (<6.05%). Intensive therapy included the administration of insulin 3 or more times a day by injection or external pump. The dosage was adjusted according to the results of self monitoring of blood glucose performed at least four times per day, dietary intake and anticipated exercise.  Comparison: Conventional therapy (CT). CT consisted of 1 or 2 daily injections of insulin, daily self-monitoring of urine or blood glucose, and education about diet or exercise.	Follow-up period: mean 6.5 years  Outcome Measures: HbA <sub>1c</sub> Progression of retinopathy: change of at least three steps from baseline that was sustained for at least six months (early treatment diabetic retinopathy Study scale). Proliferative retinopathy Severe nonproliferative retinopathy  Secondary outcomes Nephropathic Neuropathic Neuropsychological Macrovascular Quality of life outcomes	A statistically significant difference in the average HbA <sub>1c</sub> was maintained after baseline between the IT and CT groups ( $P < 0.001$ ). The mean (SD) value for all glucose profiles in the IT group was $8.6 \pm 1.7$ mmol/l vs. $12.8 \pm 3.1$ mmol/l in the CT group ( $P < 0.0001$ ).  Primary prevention cohort (i.e. no retinopathy at baseline, $n = 348$ IT, 378 CT): Intensive therapy reduced the adjusted mean risk for developing retinopathy by 76% (95% CI 62–85%) as compared with conventional therapy. Secondary intervention cohort: Intensive therapy slowed the progression of retinopathy by 54% (95% CI 14–67%)  Intensive therapy reduced the occurrence of microalbuminuria by 39%, albuminuria by 54% and clinical neuropathy by 60%.  In the IT group there were 62 hypoglycaemic episodes requiring assistance per 100 patient years vs. 19 episodes per 100 patient years in the CT group ( $P < 0.001$ ). There were two fatal motor vehicle accidents (1 from each group).  There was no difference in QOL between the two groups.  Early worsening: There was a transient worsening of	Intensive therapy with the goal of achieving blood glucose concentrations as close as possible to the nondiabetic range delays onset and slows the progression of long-term diabetic complications.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>retinopathy with intensive therapy (22% in IT vs. 13% in CT). The abnormalities often disappeared by 18 months. Patients with early worsening who underwent intensive therapy had a 74% (95% CI 46–88%) reduction in the risk of subsequent progression as compared with patients with early worsening who received conventional therapy (<math>P &lt; 0.001</math>).</p> <p>Secondary analysis: There was a continuously increasing risk of sustained progression by three steps with increasing mean HbA<sub>1c</sub>.</p>		
<p>The Diabetes Control and Complications Trial Research Group;</p> <p>1996 Apr</p> <p>49</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2++</p>	<p>180 women completed 270 pregnancies. 94 women originally assigned to intensive treatment. 86 women originally assigned to conventional treatment (26 changed to intensive treatment before conception, 60 after conception).</p>	<p>Type 1 diabetes, in good health.</p> <p>Country: US and Canada</p>	<p>Intervention: Women originally assigned to intensive treatment</p> <p>Goals for all pregnant women fasting level 3.85–5.5 mmol/l, 1 hour postprandial level 7.7 mmol/l</p> <p>Comparison: Women originally assigned to conventional treatment</p>	<p>Follow-up period: 9 months</p> <p>Outcome Measures: Spontaneous abortion congenital malformation</p> <p>HbA<sub>1c</sub></p>	<p>Intensive treatment group mean HbA<sub>1c</sub> at conception 7.4%±1.3%. Conventional treatment group mean HbA<sub>1c</sub> at conception 8.1%±1.7%, <math>P = 0.0001</math>.</p> <p>Nine congenital malformations were identified, 8 in the conventional treatment group (<math>P = 0.06</math>).</p> <p>There were 18 (13.3%) spontaneous abortions in the intensive group and 14 (10.4%) in the conventional group (NS).</p> <p>Overall the median HbA<sub>1c</sub> level was higher in those women who had abnormal outcomes (ectopic pregnancy, spontaneous abortion, induced abortion for medical reasons, congenital malformations, intrauterine death, neonatal death) than in those women with normal outcomes (<math>P = 0.05</math>). At the 3 months prior to conception <math>P = 0.018</math> and at 5 months <math>P = 0.019</math>.</p>	<p>Timely institution of intensive therapy is associated with rates of spontaneous abortion and congenital malformations similar to those in the nondiabetic population.</p>	

### 3.6 The safety of medications for diabetes before and during pregnancy

#### Q.7 Which medications for diabetes are suitable for use during pregnancy and which should be discontinued?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Langer O;Conway DL;Berkus MD;Xenakis EM;Gonzales O;  2000 Oct 19  74	Study Type: RCT  Evidence level: 1++	404 women with gestational diabetes  201 assigned to receive glibenclamide and 203 to receive insulin.	Women were screened for diabetes with a one-hour, 50 g oral glucose challenge. The women ranged in age from 18 to 40 and were all medicaid recipients. 83% Hispanic, 12% non Hispanic white, 5 % black.  Country: USA	Intervention: Glibenclamide  Comparison: Insulin	Follow-up period:  Outcome Measures: Blood glucose Fasting (mmol/l) Preprandial (mmol/l) Postprandial (mmol/l) Mean (mmol/l) Glycosated haemoglobin (%)  Neonatal outcomes: Birth weight (g) LGA (no, %) Macrosomia (no, %) Cord-serum insulin Intravenous glucose therapy (no, %) Hypoglycaemia Hypocalcaemia Hyperbilirubinemia Polycythemia Lung complications (no, %) Respiratory support (no, %) Admission to neonatal intensive care Congenital anomaly Stillbirth Neonatal death	Blood glucose (mmol/l): Fasting Glibenclamide: 5.7±1.4 Insulin:5.9±1.4 (P = 0.12) Preprandial: Glibenclamide: 5.7± 1.1 Insulin:5.9±1.3 (P = 0.16) Postprandial: Glibenclamide: 7.2±1.4 Insulin:7.1±1.5 (P = 0.69) Mean: Glibenclamide: 6.3±1.05 Insulin: 6.4±0.12 (P = 0.33) Glycosated haemoglobin (%): Glibenclamide: 5.7±1.3 Insulin: 5.6±1.2 (P = 0.42)  Birth weight (g) Glibenclamide: 3256±543 Insulin: 3194±598 (P = 0.28) LGA (no,%) Glibenclamide: 25 (12) Insulin: 26 (13) P = 0.76 Macrosomia (no,%) Glibenclamide:14 (7) Insulin: 9 (4) P = 0.26 Cord-serum insulin Glibenclamide:15±13 Insulin:15±21 (P = 0.84) Intravenous glucose therapy (no, %) Glibenclamide:28 (14) Insulin: 22 (11)P = 0.36 Hypoglycaemia Glibenclamide:18 (9) Insulin:12 (6) P = 0.25 Hypocalcaemia Glibenclamide: 2 (1) Insulin: 2 (1) P = 0.99 Hyperbilirubinemia	We found that among women with gestational diabetes, the degree of glycaemic control and perinatal outcomes were essentially the same for those treated with glibenclamide and those treated with insulin.  Glibenclamide is an effective alternative to insulin in women with gestational diabetes.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Glibenclamide:12 (6) Insulin: 8 (4) $P = 0.36$ Polycythemia Glibenclamide: 4 (2) Insulin: 6 (3) $P = 0.52$ Lung complications (no, %) Glibenclamide: 16 (8) Insulin: 12 (6) $P = 0.43$ Respiratory support (no, %) Glibenclamide: 4 (2) Insulin: 6 (3) $P = 0.52$ Admission to neonatal intensive care Glibenclamide:12 (6) Insulin:14 (7) $P = 0.68$ Congenital anomaly: Glibenclamide: 5 (2) Insulin: 4 (2) $P = 0.74$ Stillbirth Glibenclamide: 1 (0.5) Insulin: 1 (0.5) $P = 0.99$ Neonatal death Glibenclamide:1 (0.05) Insulin: 1 (0.05) $P = 0.99$		
Hague, W., Davoren, P., Oliver, J., Rowan, J. 2003 75	Study Type: RCT Evidence level: 1-	14 Insulin 16 Metformin	Women with gestational diabetes diagnosed according to criteria of the Australasian Diabetes in Pregnancy Society (ADIPS) Country:	Intervention: Metformin Comparison: Insulin	Follow-up period: Outcome Measures: Mode of birth Birth weight (g) No birth weight >4000 g Median cord C-peptide Cord glucose Cord glucose/C-peptide No of neonates with IV dextrose Median time in special care nursery No of neonates with jaundice	Glibenclamide was not detected in the cord serum of any infant. Mode of birth No (%) Insulin: Vaginal delivery 11 (79) Induction of labour 9 (64) Elective caesarean 2 (14) Emergency caesarean 1 (7) Metformin Vaginal delivery 5 (31) Induction of labour 5(31) Elective caesarean 8 (50) Emergency caesarean 2 (13) Birth weight (g) Mean (SD) Insulin:3450 (510) Metformin: 3560 (50) No birth weight >4000 g	The outcome measure of fetal $\beta$ cell activity, assessed by cord C-peptide concentration was not different in the two groups ( $P = 0.31$ ). Perinatal outcomes were not different but numbers are too small to comment further.	Pilot study. A larger trial is underway (MiG study).

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Insulin: 2 Metformin:2  Median cord C-peptide (pmol/ml) (range) (No) Insulin: 0.66 (0.45–1.71) (7) Metformin:0.53 (0.35–2.86) (10)  Cord glucose (mmol/l) Mean (SD) (No) Insulin:4.2 (1.1) (11) Metformin:4.2 (1.9) (14)  Cord glucose/ C-peptide Insulin:5.7 (2.67) Metformin:7.4 (1.69)  No of neonates with IV dextrose Insulin: 1 Metformin:4  Median time in special care nursery Insulin:24 (0–102) Metformin:48 (0–360)  No of neonates with jaundice Insulin: 6 Metformin: 3		
Hawthorne, G. 2006  72	Study Type: Systematic review - meta-analysis  Evidence level: 2+	11 small, non-randomised, non-controlled studies, 5 in women with type 2 diabetes and 6 in women with polycystic ovary syndrome (PCOS).	Country:	Intervention: Metformin  Comparison:	Follow-up period:  Outcome Measures: Congenital malformations	No congenital malformations were reported. In one study metformin was associated with an increased incidence of perinatal mortality and preeclampsia. However this study was poorly controlled and outcomes could not be attributed to the use of metformin.  The use of metformin during pregnancy in women with PCOS is associated with a reduction in miscarriage in early pregnancy, weight loss, a reduction in fasting serum	metformin appears to be safe and non-teratogenic during pregnancy	No evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						insulin levels and in the incidence of gestational diabetes.		
Checa MA;Requena A;Salvador C;Tur R;Callejo J;Espinosa JJ;Fabregues F;Herrero J; 2005 422	Study Type: Systematic review - meta-analysis Evidence level: 2+		Type 2 diabetes, gestational diabetes or PCOS Country:	Intervention: Comparison:	Follow-up period: Outcome Measures:	2 small RCTs of metformin in gestational diabetes.  12 cohort studies undertaken between 1979 and 2004 in women with type 2 diabetes, gestational diabetes or PCOS.  No association with adverse maternal or neonatal outcomes.  One prospective study in 72 women with PCOS who conceived on metformin found treatment with metformin was safely associated with reduction in spontaneous abortion and in gestational diabetes, was not teratogenic and did not adversely affect birth length and weight, growth or motor-social development in the first 18 months of life.  Metformin treatment of pregnant women with PCOS may reduce pregnancy complications.	The safety profile of metformin has been sufficiently established for the use of this drug during gestation. In women currently treated with metformin who become pregnant, the administration of metformin should be maintained during the whole pregnancy to prevent the risk of abortion during the first trimester and the development of gestational diabetes.	Systematic review does not provide evidence tables or give details for the majority of studies included in the review.
Gutzin SJ;Kozar E;Magee LA;Feig DS;Koren G; 2003 71	Study Type: Systematic review - meta-analysis Evidence level: 2++	471 women exposed to oral hypoglycaemic agents (OHAs) 1344 women not exposed.	Most women in the studies had type II diabetes. Women with type I diabetes and gestational diabetes were also present in some studies. Country:	Intervention: oral hypoglycaemic agents Comparison: No exposure	Follow-up period: Outcome Measures:	There were 3 prospective cohort studies, 3 retrospective cohort studies, 3 case series and 1 case-control study. The oral hypoglycaemics used in the studies included chlorpropamide (8) tolbutamide (6) glibenclamide (4) metformin (5) and phenformin (3). 6 studies were rated 'poor' quality, 2 were 'fair' and 2 were 'good'.  There was no significant difference in the rate of major malformations between those	There was no significant difference in the rate of major malformations or neonatal death among women with first-trimester exposure to OHAs when compared to non-exposed women.  Because of the weakness of the available data this systematic review cannot be relied upon for clinical decision making.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					hyperglycaemia Preeclampsia labour and delivery complications	exposed to OHA and those not exposed ( $n = 10$ studies, OR 1.05, 95% CI 0.65–1.70).  The test for heterogeneity was significant ( $P = 0.05$ )  The rates of neonatal death did not differ significantly between the two groups ( $n = 6$ studies, OR 1.16, 95% CI 0.67–2.00).		
Simmons, D. 2002  87	Study Type: Systematic review - meta-analysis  Evidence level: 1+	12 observational studies (294 women with T1 diabetes and 9 women with T2 diabetes received insulin lispro during embryogenesis) 1 RCT of 42 women with GDM (19 insulin lispro, 23 regular insulin)	Country:	Intervention: Insulin lispro  Comparison: Insulin	Follow-up period:  Outcome Measures: Congenital malformations HbA <sub>1c</sub> Maternal hypoglycaemia Patient satisfaction	Congenital malformations: 12 observational studies involved 294 women with T1 diabetes, 9 women with T2 diabetes. Among 170 women treated with insulin lispro there were 7 (4.1%) congenital malformations. Among 133 women treated with regular soluble insulin there were 14 (10.5%) congenital malformations.  Other outcomes: An RCT compared 19 women with GDM receiving insulin lispro with 23 women with GDM receiving regular insulin. No insulin lispro was detected in the umbilical cord blood. Antibodies to regular and insulin lispro were within the reference range (with one exception). 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. Obstetric and fetal outcomes were similar. Data from observational studies also suggests improved glycaemic control (3	There is no suggestion of any risk to the fetus from antenatal use of insulin lispro.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						studies), fewer maternal hypoglycaemic episodes (2 studies) and greater maternal satisfaction (1 study) with insulin lispro compared with regular insulin.		
Cypryk K;Sobczak M;Pertynska-Marczewska M;Zawodniak-Szalapska M;Szymczak W;Wilczynski J;Lewinski A; 2004 Feb 92	Study Type: Cohort Evidence level: 2++	25 pregnant women with type 1 diabetes taking insulin lispro (Humalog) 46 pregnant women with type 1 diabetes taking regular insulin ( $n = 46$ )	All patients were treated with the same type of insulin as before conception. NPH or ultralente was used in both groups as long acting insulin. Country: Poland	Intervention: Insulin lispro Comparison: Human insulin	Follow-up period: Outcome Measures: HbA <sub>1c</sub> Pregnancy duration Caesarean section Birthweight Neonatal hypoglycaemia Hypertension Urinary tract infections	There were no significant differences in outcomes between the two groups. HbA <sub>1c</sub> First trimester: Lispro: 7.8±1.4% Regular human:7.5±1.5% Second trimester: lispro: 6.4±0.8% Regular human: 6.5±1.6% Third trimester Lispro: 6.7±0.7% Regular human: 6.3±1.2%  One malformation in the human insulin group	The course of pregnancy and pregnancy outcome is comparable in intensively treated diabetic women regardless of the short-acting insulin used. Humalog appears to be a safe alternative to human insulin in the treatment of diabetes during pregnancy.	
Jovanovic, L., Howard, C., Pettitt, D. 2005 80	Study Type: RCT Evidence level: 1+	27 women with GDM	Age 29.7±6.9 years, HbA <sub>1c</sub> <7% at diagnosis. Country: USA	Intervention: Insulin Aspart Comparison: Human Insulin	Follow-up period: From the diagnosis of GDM (18–28 weeks) to 6 weeks postpartum Outcome Measures: Mean reductions in HbA <sub>1c</sub> Hypoglycaemic events Insulin specific antibodies Birthweight	Mean reductions in HbA <sub>1c</sub> : Insulin aspart; 0.3±0.5% Human insulin:0.1±0.4%, NS Upper respiratory tract infection: Insulin aspart: 14% Human insulin:23% Hypoglycaemic events: Insulin aspart: 0 Human insulin: 0 Average insulin-specific antibodies Insulin aspart:0.97% Human insulin: 0.07% Average percentile birthweights: Insulin aspart:40% Human insulin:44% Overall safety profiles were similar for Insulin aspart and Human insulin treatment groups.	The safety and effectiveness of Insulin Aspart was comparable to Human Insulin in pregnant women. The ease of use of Insulin Aspart injected just before meals rather than 30 minutes prior to meals may offer a more convenient therapy for management of diabetes for patients with GDM.	
Kinsley, B., et al 2005	Study Type: Cohort Evidence level: 2+	20 women with t1 diabetes (10 insulin aspart, 10 human insulin)	Insulin regimens were 4 times daily basal NPH and 3 times daily short acting bolus	Intervention: Insulin aspart Comparison: Human	Follow-up period: Outcome Measures: Glycaemic control	HbA <sub>1c</sub> at booking Insulin aspart:7.0±1.0% Human insulin:8.6±1.0%, $P < 0.05$	Glycaemic control was better in the insulin aspart group at booking and through pregnancy. FPG and pre-lunch capillary	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
81			insulins  Country: Ireland	insulin		HbA <sub>1c</sub> at delivery Insulin Aspart: 5.8±0.8% Human Insulin 6.7±0.7%, <i>P</i> < 0.05  Postprandial glucose levels No difference  Fasting blood glucose Insulin Aspart: 4.3±1.4 Human Insulin: 5.4±2.0, <i>P</i> < 0.01  Pre-lunch blood glucose Insulin Aspart: 4.5±1.7 Human Insulin: 5.1±2.3 mmol/l, <i>P</i> < 0.01  Birthweight Insulin aspart: 3.4±0.5 kg Human insulin: 3.89±0.7 kg, <i>P</i> = 0.13	glucose reading were lower in the ASP group. These data suggest that the use of insulin aspart as part of a basal bolus regimen is as effective as short acting human insulin in pregnancy in T1 diabetes.	
Mathiesen et al 2006 79 See also Hodd et al 2006 (33656)	Study Type: RCT  Evidence level: 1++	157 women treated with Insulin aspart 165 treated with human insulin	Type 1 diabetes, age 19–34 years, HbA <sub>1c</sub> ≤ 8% at confirmation of pregnancy. Meal time insulin in a basal bolus regimen with NPH.  Country: Ireland, Spain, United Kingdom, Denmark	Intervention: Insulin aspart  Comparison: Human insulin	Follow-up period:  Outcome Measures: Severe hypoglycaemia (requiring assistance)	Severe night-time hypoglycaemia RR 0.48, 95% CI 0.2–1.14), <i>P</i> = 0.10.  Observed rates of severe hypoglycaemia (per yr) Insulin aspart: 1.4 Human insulin: 2.1 RR 0.72, 95% CI 0.36–1.46) <i>P</i> = 0.36  Prandial increments (mean: breakfast, lunch and dinner) 1st trimester: Insulin aspart: 0.73 Human insulin: 1.49 mM, <i>P</i> < 0.05 3rd trimester: Insulin aspart: 1.10 Human insulin: 1.50 mM, <i>P</i> < 0.05  24 hour mean PG No difference	The risk of hypoglycaemia tended to be lower in the insulin aspart group with a strong trend towards fewer nocturnal events.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						HbA <sub>1c</sub> 2nd trimester: Insulin aspart:6.0% Human insulin:6.04% 3rd trimester: Insulin aspart:6.18% Human insulin:6.26%		
BALAJI, V. et al. 2005 82	Study Type: RCT Evidence level: 1+	5 women with GDM given insulin aspart 5 women with GDM given human insulin.	Country: India	Intervention: Insulin aspart Comparison: Human insulin	Follow-up period: Outcome Measures: FPG 2 hr PG Insulin dose Fetal and maternal adverse outcomes Birthweight	There was no statistically significant difference between the two groups in the mean plasma glucose level or insulin dose at entry or before confinement. No adverse event in the maternal and fetal outcome of these two groups. No statistical difference in mean birthweight between the two groups.	Both insulin aspart and human insulin achieved satisfactory glycaemic control and good fetal outcome. Insulin aspart is safe during pregnancy. Pregnant women were comfortable with insulin aspart as it is being administered just before a meal. Insulin aspart can be safely tried out in a larger trial.	
Hod, M. et al 2006 423	Study Type: RCT Evidence level: 1++	322 women with type 1 diabetes Insulin aspart: 157 Human insulin: 165	Age 19–43 years. HbA <sub>1c</sub> <8% at confirmation of pregnancy. Meal rime basal-bolus regimen with NPH. Country: Israel, Netherlands, Finland, Ireland, Denmark	Intervention: Insulin aspart Comparison: Human insulin	Follow-up period: Outcome Measures:	The risk of major hypoglycaemia was 28% lower for insulin aspart than human insulin and even lower at night, with similar HbA <sub>1c</sub> values. Overall 268 live births and 35 fetal losses: Insulin aspart: 14 Human insulin: 21 No difference in fetal mortality or major congenital malformations was reported between the two groups. Neonatal hypoglycaemia leading to treatment was reported in 98 of the live births: Insulin aspart: 46 Human insulin: 52	Treatment with insulin aspart was at least as safe as Human Insulin regarding perinatal outcomes	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>Mean birth weight (g) corrected for gestational age:                      Insulin aspart: 3438±72                      Human insulin: 3555±73</p> <p>Median gestational age:                      Insulin aspart: 37.9                      Human insulin: 37.7</p> <p>Emergency caesarean                      Insulin aspart: 15.9%                      Human insulin: 12.7%</p> <p>Preeclampsia                      Insulin aspart: 8.3%                      Human insulin: 6.7%</p> <p>Imminent premature labour:                      Insulin aspart: 3.8%                      Human insulin: 4.2%</p> <p>Premature delivery:                      Insulin aspart: 20%                      Human insulin: 30%</p>		
Poyhonen-alho, M. et al  2006  93	Study Type: Cohort  Evidence level: 2++	47 pregnant women with t1 diabetes using glargine 50 pregnant women with t1 diabetes using Human long acting insulin (Protaphan)	Women in the intervention and control group were matched for age, parity, duration of diabetes and diabetes complications. All women injected short-acting insulin analogues before meals.  Country: Finland	Intervention: Insulin glargine  Comparison: Human long acting insulin	Follow-up period:  Outcome Measures: Gestational age at delivery pregnancy complications, birthweight shoulder dystocia respiratory distress infections first plasma glucose after birth	There was no difference for gestational age at delivery, pregnancy complications and perinatal outcomes  One newborn (Glargine group) had congenital malformations (anencephaly)  None of the women experienced significant progression of retinopathy or nephropathy  Although HbA <sub>1c</sub> was similar at first trimester of pregnancy (6.9% in protaphan group, 7.4% in Glargine group) the decrease from first trimester to third trimester was greater in the glargine group ( $P = 0.04$ ).  There was a tendency towards lower number of	Treatment with glargine insulin during pregnancy seems to be as safe and efficient as with conventional protaphan insulin.  There is a tendency towards better diabetic control during pregnancy with glargine insulin treatment without risk for hypoglycaemic events. Larger RCTs are needed to confirm these results.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Mecacci, F., et al 2003 85	Study Type: RCT Evidence level: 1++	25 women with GDM received insulin lispro 24 women with GDM received normal insulin 50 non GDM controls	Diagnosed according to C&C criteria. Three main meals at 8.00am, 12.00, 8.00pm. Insulin given before each meal. No NPH insulin.  Country: Italy	Intervention: Insulin lispro Comparison: Regular insulin	Follow-up period:  Outcome Measures: Blood glucose profiles performed using a reflectance meter and consisted of 9 determinations: fasting/preprandial, 1 and 2 hour post-prandial. HbA <sub>1c</sub> Birthweight Ponderal index Cranio-thoracic circumference	hypoglycaemic episodes in the glargine group (11/47) than in the protophan group (21/50, $P = 0.07$ ).  1 hr postprandial blood glucose values (Total) Insulin lispro: 108.4±10.7 Regular insulin: 121.0±13.2 Controls: 105.6±4.7, $P < 0.01$  Cranial-thoracic circumference (CC/CT) ratio (percentile rank, n, %) <10 Lispro: 1(4) Regular: 2(8.3) Control: 1(2) 10–25 Lispro: 3 (12) Regular: 9 (37.5) Control: 7 (14), L,C vs R <0.05 26–50 Lispro: 9 (36) Regular: 6 (25) Control: 19 (38) 51–75 Lispro: 8 (32) Regular: 4 (16.7) Control: 17 (34) 76–90 Lispro: 4 (16) Regular: 3 (12.5) Control: 5 (10) >90 Lispro:- Regular:- Control: 1 (2)	In women with GDM the use of insulin lispro enabled the attainment of near-normal glucose levels at the 1 hour postprandial time point and was associated with normal anthropometric characteristics; the use of regular insulin was not able to blunt the 1 hr postprandial response to a near-normal extent and resulted in infants with a tendency toward disproportionate growth. Insulin lispro can be considered as a valuable option for the treatment of gestational diabetes.	
						No other significant differences between groups in neonatal outcome.		
Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Gilbert C;Valois M;Koren G; 2006 73	Study Type: Systematic review - meta-analysis  Evidence level: 2+	Eight studies were included in the meta-analysis	Pregnant women with diabetes or polycystic ovary syndrome treated with metformin.  Country:	Intervention: Exposure to metformin in the first trimester of pregnancy.  Comparison: Pregnant women not receiving metformin.	Follow-up period:  Outcome Measures: Protective effect against malformation.	Eight studies were included in the meta-analysis.  Metformin treatment in the first trimester was associated with a protective effect of 57%.	There is no evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy.	
Plank J;Siebenhofer A;Berghold A;Jeitler K;Horvath K;Mrak P;Pieber TR; 2005 84	Study Type: Systematic review - meta-analysis  Evidence level: 1++	7933	People with diabetes who were treated with the currently available short acting insulin analogues lispro or aspart vs human regular insulin regardless of dose or schedule and whether insulin was injected subcutaneously via syringe, pen, or pump.  Country:	Intervention: Short-acting insulin analogues (lispro and aspart).  Comparison: Regular insulin.	Follow-up period:  Outcome Measures: 1. Glycaemic control 2. Hypoglycaemic episodes 3. Quality of life 4. Diabetes-specific complications	The weighted mean difference between HbA <sub>1c</sub> values obtained using short-acting insulin analogues and regular insulin was -0.12% (95% CI -0.17% to -0.07%) for adults with type 1 diabetes and -0.02% (95% CI -0.10% to 0.07%) for patients with type 2 diabetes mellitus.  The standardised mean difference for overall hypoglycaemia (episodes per person per month) was -0.05 (95% CI -0.22 to 0.11) and -0.04 (95% CI -0.12 to 0.04) comparing short-acting insulin analogues to regular insulin in adults with type 1 and type 2 diabetes, respectively.  No differences between treatments were observed in children with type 1 diabetes, pregnant women with type 1 diabetes, and women with gestational diabetes.	The systematic review suggests that only a minor benefit to HbA <sub>1c</sub> values in adults with type 1 diabetes but no benefit in the remaining population with type 2 or gestational diabetes from short-acting insulin analogue treatment.	
Persson B;Swahn ML;Hjertberg R;Hanson U;Nord E;Nordlander E;Hansson LO; 2002 Nov 86	Study Type: RCT  Evidence level: 1+	33 pregnant women with type 1 diabetes.  1. lispro insulin (n = 16) 2. regular insulin (n = 17)	33 pregnant women with type 1 diabetes.  Country: Sweden	Intervention: Short-acting insulin (lispro)  Comparison: Regular insulin	Follow-up period:  Outcome Measures: 1. Glycaemic control 2. Hypoglycaemia 3. Perinatal mortality	Blood glucose was significantly lower ( $P < 0.01$ ) after breakfast in the lispro group, but there were no significant group differences in glycaemic control during the rest of the day.  HbA <sub>1c</sub> values at inclusion were 6.5% and 6.6% in the lispro and regular insulin groups, respectively. HbA <sub>1c</sub> values declined during the study	The results suggest that it is possible to achieve at least as adequate glycaemic control with lispro as with regular insulin therapy in type 1 diabetic pregnancies.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						period and were similar in both groups.  There was no perinatal mortality or complications during pregnancy, route of delivery and fetal outcome did not differ between the groups.  Retinopathy progression was similar in both groups.		
Masson, J., Patmore, P., Brash, P. et al.  2003  90	Study Type: Other case series  Evidence Level: 3	Intervention: Insulin lispro  Comparison:	76 women with type 1 diabetes	Country: UK	Miscarriage Congenital malformation Perinatal mortality	There were 6/76 first trimester miscarriages. All 71 babies were born live. There were 4 (5.6%) congenital malformations (2 in mothers exposed to insulin lispro after the period of embryogenesis). No women developed retinopathy de novo during pregnancy.	This is the largest case series of pregnancies treated with insulin lispro. An excellent perinatal outcome has been documented.	
Garg, S., Frias, J., Anil, S., et al  89	Study Type: Other case series  Evidence Level: 3	Intervention: Insulin lispro  Comparison:	62 women with type 1 diabetes	Country: USA	HbA <sub>1c</sub> Progression of retinopathy Albumin excretion rate Congenital malformations	Mean HbA <sub>1c</sub> was reduced from 7.2±0.2% at the time of conception to 5.8±0.1% at the time of delivery.  Congenital malformations (cleft lip and palate, sensorineural hearing loss) occurred in 2/62 infants (3.2%).  No significant change was found in mean eye grade score for retinopathy or albumin excretion rate.	Insulin lispro therapy during pregnancy resulted in normalisation of glycaemic control and had no adverse effects on maternal or fetal outcomes	
Al-Shaikh AA;  2006 Apr  99	Study Type: Other  Evidence Level: 3	Intervention: Insulin glargine  Comparison:	11 women with type 1 diabetes	Aim was to lower fasting BG <5.5 mmol and postprandial <7.15 mmol/l.  Country:		There were no fetal anomalies. Mean birthweight 3.26 kg (range 2.8–4.3 kg). All except one patient were discharged within 24 hours.  The dose of glargine insulin ranged between 30–80 units per day. Mean first trimester HbA <sub>1c</sub> was 9.93% (range 7.8–12.4%). Mean third trimester HbA <sub>1c</sub> was 6.54% (range 5.9–7.4%).	We conclude from these cases that glargine insulin is safe and effective during pregnancy but more studies are needed.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Caronna S;Cioni F;Dall'Aglio E;Arsenio L; 2006 101	Study Type: Other Evidence Level: 3	Intervention: Insulin glargine  Comparison:	A pregnant woman with type 1 diabetes	Obesity, hypertension and 16 years duration of diabetes. Regimen of 3 meal time injections and 1 injection of glargine at bedtime continued throughout pregnancy and after childbirth.  Country: Italy		Normal spontaneous delivery in 7 patients, 3 caesarean section due to poor progression and fetal distress. A healthy baby was born by caesarean weighing 3.54 kg with an APGAR score of 9.	Both the mother and newborn resulted in perfect health conditions confirming the possibility of using glargine insulin profiles during pregnancy in selected cases with close monitoring may exist.	
Di CG;Volpe L;Lencioni C;Chatzianagnostou K;Cuccuru I;Ghio A;Benzi L;Del PS; 2005 Apr 96	Study Type: Other Evidence Level: 3	Intervention: Insulin glargine (Used from preconception to 6–12 weeks postconception).  Comparison:	5 women with type 1 diabetes	Country: Italy	Major and minor malformations Gestational age Mode of birth Birthweight Neonatal complications	Babies were delivered at mean gestational age of 36.6±1.1 weeks by caesarean section in 4/5 women. Mean weight was 3066±898 g with one baby >4 kg. There were no malformations and no neonatal complications.	Insulin glargine does not seem to affect embryo-fetal development. However the small number of women and the discontinuation of therapy does not allow firm conclusions to be drawn. This observation as well as other anecdotal observations emphasizes the need for properly planned investigations.	
Graves DE;White JC;Kirk JK; 2006 98	Study Type: Other Evidence Level: 3	Intervention:  Comparison:	4 women with gestational diabetes	Country:		All four women reported successful pregnancy outcomes.  Morning dosing of insulin glargine contributed to target postprandial readings throughout the day with no nocturnal hypoglycaemia reported. Higher than recommended starting doses were required to achieve blood glucose goals during pregnancy, especially in obese women.	Insulin glargine offers an alternative in GDM	
Woolderink JM;van Loon AJ;Storms F;de HL;Hoogenberg K; 2005 Oct 97	Study Type: Other Evidence Level: 3	Intervention:  Comparison:	7 women with type 1 diabetes	Mean age 34 (29–39) and a diabetes duration of 12 years (5–8). Five patients continued their preconception use of glargine for the entire pregnancy. Two		Glycaemic control was excellent in 6 patients (HbA <sub>1c</sub> 5.2–6.9%) and suboptimal in one (6.4–8.1%). Mean HbA <sub>1c</sub> was 6.4%. The occurrence of hypoglycaemia reduced in the two patients who converted to	The present observational study puts forward the possibility that insulin glargine is safe in pregnancy.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				converted to glargine during pregnancy because of recurrent nocturnal hypoglycaemia.  Country: Netherlands		glargine. All women delivered at term, three vaginally and four by caesarean section. Mean birthweight 4180 g. There were no malformations and no neonatal complications.		
Wyatt JW;Frias JL;Hoyme HE;Jovanovic L;Kaaja R;Brown F;Garg S;Lee-Parritz A;Seely EW;Kerr L;Mattoo V;Tan M;IONS study group.;  2005 Jun  91	Study Type: Other  Evidence Level: 3	Intervention: Insulin lispro  Comparison: Published rates of major anomalies in infants born to women with diabetes	533 pregnancies in 496 women (481 T1, 15 T2)	Age 29.9±5.2 years  Country:	Major congenital malformations (according to definitions of Spranger et al 1982).	HbA <sub>1c</sub> at first prenatal visit was 8.9%±4.2% and decreased to 6.2±2.4% in the third trimester ( <i>P</i> < 0.001).  There were 27 major and 2 minor malformations	The rate of major congenital malformations was 5.4% (95% CI 3.45%-7.44%). The current published rates of major anomalies in infants born to mothers with diabetes treated with insulin are between 2.1 and 10.9%. This suggests that the anomalies rate with insulin lispro treatment does not differ from the published major congenital malformation rates for other insulin treatments.	
Gallen, I., JAAP, I.  2006  94	Study Type: Other  Evidence Level: 3	Intervention: Insulin Glargine  Comparison:	115 women T1 diabetes 5 T2 diabetes 7 gestational diabetes	Mean maternal age 30.5±0.5. Insulin glargine was used prior to pregnancy in 82 (65%) women, started in 44 (35%) and stopped at booking in 1. Insulin aspart was the bolus insulin in 58 (46%) lispro in 48 (38%) and human soluble in 9 (7%) of women.  Country:		HbA <sub>1c</sub> fell from 8.1%±0.2% at booking to 6.7%±0.1% during the third trimester.  Background retinopathy developed in 1, progressed in 3 and laser photocoagulation was required in 7 women.  Hypoglycaemia requiring assistance occurred in 9 (7%) with 16 (12%) having ≥2 episodes.  Pre-eclampsia occurred in 16 (12.5%) cases.  There were 7 (6%) early miscarriages.  All 122 babies were live born, with a mean gestational age of 37.5 weeks, and a median birthweight of 3500 g.  24 (20%) babies weighed ≥4 kg	The use of glargine in Type 1 diabetes during pregnancy results in outcomes comparable to recently published studies with no evidence of increased congenital malformations or adverse maternal or fetal outcomes.	

## Diabetes in pregnancy: evidence tables

---

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>There were 3 congenital malformations (positional talipes, ventricular septal defect and transposition of the great arteries) 2 occurring in women taking glargine before pregnancy, giving a malformation rate of 2.5%.</p> <p>There were no neonatal deaths.</p> <p>5 babies had Apgar scores (1 minute) of &lt;5. Neonatal hypoglycaemia was seen in 51 (42%) and hyperbilirubinaemia in 28 (23%) babies. Other neonatal complications were seen in &lt;5% of babies.</p>		

---

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Price,N.; Bartlett,C.; Gillmer,M.D.	Study Type: Case-control  Evidence level: 2+	64 pregnant women.	64 pregnant women with diabetes  Country: UK	Intervention: Insulin glargine during their pregnancy (glargine group)  Comparison: Intermediate-acting human insulin (isophane or insulin zinc suspension)	Follow-up period: Not stated  Outcome Measures: 1. Birthweight 2. Centile birthweight 3. Gestation at delivery 4. Mode of delivery. 5. Apgar score at least 1 and 5 minutes 6. Congenital anomalies 7. Neonatal hypoglycaemia 8. Admission to special care baby unit	There was no significant difference between the birthweight or centile birthweight of babies born to the women treated with insulin glargine during pregnancy and those born to the control group treated with intermediate-acting human insulin.  The overall incidence of fetal macrosomia was 12/32 (37.5%) in the insulin glargine group and 13/32 (40.6%) in the control group.  There was no significant difference in neonatal morbidity between the groups.  For type 1 diabetes, there was no significant difference in the mean maternal weight gain during pregnancy between the insulin glargine and control groups.  For women with gestational diabetes the mean maternal weight gain during pregnancy was higher for those on insulin glargine than control.  There was no significant difference in the incidence of daytime or nocturnal hypoglycaemia in cases and controls.  No woman in the insulin glargine or control groups experienced hypoglycaemia following birth.  Gestational age at delivery, birthweight, centile birthweight or Apgar score in neonates of	Insulin glargine treatment during pregnancy does not appear to be associated with increased fetal macrosomia or neonatal morbidity.	

95

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						women on insulin glargine or intermediate insulin group did not differ significantly.		
						There was no difference in the mode of birth between intervention and control groups.		
Ekpebegh,C.O.; Coetzee,E.J.; van der,Merwe L.; Levitt,N.S.  2007  76	Study Type: Cohort  Evidence level: 2+	379 singleton pregnancies (between 1991–2000)	Type 2 diabetic singleton pregnant women of gestation $\geq$ 24 weeks. The women were mainly of mixed ancestry or black Africans aged 32.5–35 years and delivered at Grootte Shuur Tertiary Hospital.  Country: South Africa	Intervention: 1. Oral hypoglycaemic agents (OHAs) 2. Converted from OHAs to insulin 3. Insulin alone or converted from diet alone to insulin  The oral hypoglycaemic agents used were metformin and glybenclamide  Comparison: 1. Oral hypoglycaemic agents <i>versus</i> Oral hypoglycaemic agents converted to insulin 2. Oral hypoglycaemic agents <i>versus</i> insulin alone or diet-insulin 3. Oral hypoglycaemic agents then converted to insulin <i>versus</i> insulin alone or diet-insulin	Follow-up period: Approximately 16 weeks  Maternal outcomes: 1. Glycaemic control measured by mean fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glycosylated haemoglobin (HbA <sub>1c</sub> ). These were calculated for each trimester.  Fetal outcomes measured: 1. Fetal growth 2. Fetal anomaly rates 3. Perinatal mortality rates 4. Hypoglycaemia 5. Polycythaemia 6. Hyperbilirubinaemia 7. Respiratory distress	HbA <sub>1c</sub> was similar at booking and throughout pregnancy in all the study groups.  In oral hypoglycaemic agents alone, converted from oral hypoglycaemic agents to insulin and insulin alone/converted from diet alone to insulin groups, fetal anomaly rates were similar: 5.7%, 2.0% and 0.0%, respectively, $P = 0.2$ ; whereas perinatal mortality rates (per 1000 births) were higher for oral hypoglycaemic agents alone: 125, 28, 33, respectively, $P = 0.003$ .  Booking HbA <sub>1c</sub> was independently associated with fetal anomaly (OR 1.48, 95% CI 1.11 to 1.97, $P = 0.006$ ).  The specific oral hypoglycaemic agent used in the first trimester (metformin or glybenclamide) was not associated with the occurrence of fetal anomaly.  Last HbA <sub>1c</sub> was independently associated with perinatal mortality and fetal anomaly (OR 1.65, 95% CI 1.16 to 2.42, $P = 0.005$ ) and (OR 15.18, 95% CI 2.43 to 93.37, $P = 0.005$ ), respectively.  Conversion from OHA to	The two types of oral hypoglycaemic agents used (metformin and glibenclamide) are not teratogenic.  However, it is advisable to replace oral hypoglycaemic agents, in particular glibenclamide, with insulin when women book for pregnancy care to reduce perinatal mortality.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						insulin was protective for perinatal mortality compared to oral hypoglycaemic agents alone (OR 0.220, 95% CI 0.061 to 0.756, $P = 0.024$ ).		
						No perinatal mortality was observed in women on metformin alone.		
Lapolla A;Dalfra MG;Masin M;Bruttomesso D;Piva I;Crepaldi C;Tortul C;Dalla BB;Fedele D;  2003  228	Study Type: Cohort  Evidence level: 2++	93 women  1. Treated with continuous subcutaneous insulin infusion (n = 25).  2. Treated with conventional insulin therapy (n = 68).	Women with type 1 diabetes who underwent insulin treatment during pregnancy in northeast Italy.  68 were treated with conventional insulin therapy (multiple daily injections), and 25 with insulin pump infusion (i.e continuous subcutaneous insulin infusion).  Country: Italy	Intervention: Continuous subcutaneous insulin infusion.  Comparison: Conventional intensive insulin therapy.	Follow-up period: Not reported  Outcomes:  Metabolic: 1. Fasting and 1-hour post-prandial plasma glucose 2. HbA <sub>1c</sub> levels 3. Spontaneous or induced abortions 4. Time and mode of delivery  Maternal: 1. Pregnancy-induced hypertension 2. Pre-eclampsia 3. Placental insufficiency 4. Hydramnios 5. Hypoglycaemic coma 6. Ketoacidosis  Fetal: 1. Fetal weight 2. Hypoglycaemia 3. Hypocalcaemia 4. Hyperbilirubinemia 5. Fetal distress 6. Asphyxia 7. Hyaline membrane disease 8. Polycythaemia 9. Shoulder dystocia 10. Malformations	Women treated with insulin pump more frequently had background retinopathy and clinical neuropathy.  No significant differences were observed between the two groups in metabolic control and maternal outcome.  Progressive reduction in HbA <sub>1c</sub> levels: indicates glycaemic control was not optimal in the pre-pregnancy state, but improved significantly during pregnancy.  In terms of fetal outcome, no differences were observed between the two groups in morbidity and especially in malformation rate.  Women with malformed babies did not have optimal metabolic control at conception. Thus, maternal and perinatal outcomes were similar in patients treated with insulin pump and continuous subcutaneous insulin therapy, and depended on metabolic control.	Insulin pump therapy is useful in problematic, complicated cases of diabetes during pregnancy.	

### 3.7 The safety of medications for diabetic complications before and during pregnancy

#### Q.8 Which medications for diabetic complications are suitable for use during pregnancy and which should be discontinued?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Cooper, W., Hernandez-Diaz, M., Arbogast, P. et al.  2006  105	Study Type: cohort  Evidence level: 2+	209 infants with exposure to ACE inhibitors in first trimester alone, 202 infants with exposure to other antihypertensive medications in the first trimester alone, 29096 infants with no exposure to antihypertensive drugs at any time during gestation.	Infants enrolled in Tennessee Medicaid and born between 1985 and 2000.  Exclusions: Maternal diabetes, exposure to angiotensin -reception antagonists, exposure to hypertensive beyond first trimester, exposure to other potential teratogens.	Intervention: Exposure to ACE inhibitor in first trimester alone  (Determined by Medicaid pharmacy files, which included the date the prescription was filled and the number of days for which the medicine was supplied)  Comparison: Exposure to other hypertensive in first trimester alone No exposure to hypertensive at any time during gestation	Follow-up period: 1 year old  Outcome Measures: Presence of a major congenital malformation not related to a chromosomal defect or a clinical genetic syndrome.	Infants with only first trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (RR 2.71; 95% CI 1.72–4.27)  Fetal exposure to any hypertensive medications during the first trimester did not confer an increased risk (RR 0.66, 95% CI 0.25–1.75)  Infants exposed to ACE inhibitors were at an increased risk for malformations of the cardiovascular system (RR 3.72; 95% CI 1.89–7.30) and the central nervous system (RR 4.39; 95% CI 1.37–14.02).	Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided	High quality study RR was adjusted for all known confounders. The robustness of study definitions was tested by secondary analysis: 1) restricting the group exposed to ACE inhibitors to infants whose mothers filled a prescription for ACE inhibitors 14 or more days after the last menstrual period (thus excluding women who were likely to have stopped use of ACE inhibitors before conception) 2) Using a broader definition of diabetes (further excluding women with a single prescription for a hypoglycaemic agent or one outpatient visit with a diabetes diagnosis through the first trimester) 3) Excluding patent ductus arteriosus as a major congenital malformation (since this condition infrequently persists)

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Feldkamp, M. 1997 <sup>108</sup>	Study Type: Other Evidence Level: 3	Intervention: First trimester only exposure to ACE inhibitors  Comparison:	66 women with ACE inhibitors limited to the first trimester of pregnancy	Women who self reported to ACE inhibitor registry.	Live birth  Miscarriage  Congenital malformations	Among the 48 live births, there were 3 cases of intrauterine growth restriction (IUGR). One infant with IUGR was from twins delivered at 36 weeks gestation; the other two were full-term. Another child had patent ductus arteriosus (PDA) that required surgical ligation at 18 months. That infant was born at 40 weeks gestation to a woman who discontinued therapy with an ACE inhibitor at 7 1/2 weeks gestation. The mother was also treated with digoxin throughout her pregnancy and with warfarin sodium for the first 5 weeks followed by heparin throughout the remainder of her pregnancy.	The number of exposures reported so far to the registry is too small to determine conclusively that exposure to an ACE inhibitor exclusively during the first trimester is not associated with the features of fetopathy.  Whenever possible pregnant women should be changed to another hypertensive medication to maintain normal blood pressure	It is unknown whether first trimester exposure to ACE inhibitors was associated with the development of IUGR in the three infants in this study because other known risk factors were present. Because there were no controls the rate of IUGR could not be compared with that in the unexposed group. Register is voluntary which may cause selection bias.
Bar J;Hod M;Merlob P; 1997 <sup>109</sup>	Study Type: Other Evidence Level: 3	Intervention: First trimester exposure to ACE inhibitors  Comparison:	8 women treated with ACE inhibitors	3 women treated for chronic hypertension, 2 women treated by diabetic nephropathy, 2 for cardiomyopathy and one treated for systemic lupus erythematosus. All women were taking one, two or three additional antihypertensive agents.	Preterm delivery  Low birth weight  IUGR  fetal/neonatal renal failure  skull ossification abnormalities  Major congenital malformations	There were 8 live births (one set of twins). Mean length of gestation was 34.5 ( $\pm 1.6$ ) weeks and average weight was 2288 ( $\pm 991$ ) g, which may be explained by the twin pregnancy and the severe disease in two patients (one with diabetic nephropathy and renal deterioration, one with severe preeclampsia and systemic lupus erythematosus) which resulted in preterm deliveries, IUGR and low birth weight.  Exposure to ACE inhibitors ranged from 2 and 12 embryonic weeks (mean 7.2 weeks).  No major malformations were detected in the 9 newborns. Two cases of intra-uterine growth restriction (IUGR) were observed, one of them ended in intra-uterine death, which may be attributed to maternal illness and not to drug effect (renal function deterioration with massive proteinuria in a diabetic nephropathy patient).	No major malformations were detected. Two newborns were growth retarded and four were born prematurely, mainly because of maternal disease.  The results are reassuring for women who inadvertently become pregnant whilst on this drug.	Prospective case series with definitive timing of exposure.
Bar J;Chen	Study Type: Other	Intervention: ACE inhibitor	24 women with type 1	Maternal age at	Maternal renal function	The six months of captopril treatment	The administration	The stillbirth was an

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
R;Schoenfeld A;Orvieto R;Yahav J;Ben-Rafael Z;Hod M; 1999 Sep 104	Evidence Level: 3	(captopril) for a minimum of 6 months prior to conception. Treatment was discontinued immediately after a missed period and a positive pregnancy test.  Comparison:	diabetes and diabetic nephropathy	conception ranged from 21 to 30 years. The nullparity rate was 71% and the duration of diabetes was 10 to 23 years. 9 patients were categorised as RF (retinopathy and nephropathy) and 15 as class F (nephropathy only). Renal function was normal to mildly impaired in all the patients. 11 patients (46%) had hypertension.	Short and long-term (2 year) pregnancy outcome	<p>combined with an intensive insulin regimen led to significantly decreased mean proteinuria at conception (<math>202 \pm 141</math> mg/day vs. <math>1292 \pm 656</math> mg/day, <math>P = 0.001</math>).</p> <p>HbA<sub>1c</sub> decreased from 9.8% before treatment to 7.9% at conception (<math>P = 0.01</math>).</p> <p>Renal function during pregnancy: mean serum creatine and uric acid levels increased significantly in the 3rd trimester from the 1st and 2nd trimesters (<math>0.82 \pm 0.12</math> to <math>0.94 \pm 0.13</math> mg/dl, <math>P = 0.02</math> and <math>3.8 \pm 0.7</math> to <math>5.4 \pm 0.7</math> mg/dl, <math>P = 0.0001</math>). No significant changes were noted in the grade of proteinuria from conception. Creatine clearance and potassium levels remained stable throughout pregnancy.</p> <p>All patients maintained close to normal glycaemic control throughout pregnancy.</p> <p>Pregnancy outcome: Superimposed preeclampsia 11(46%) Preterm delivery 4(17%) IUGR 5(21%) Caesarean delivery 15 (62.5%) Hospitalisation in NICU 1 (4.2%) Stillbirth 1 (4.2%)</p> <p>2 year outcomes: Significant increase in serum creatine (&gt;1 mg/dl) 0 End stage renal disease 0 Severe disability or late infant death 2(8.4%)</p> <p>Prediction of outcome: Only preexisting hypertension was a significant factor in worse pregnancy outcome (superimposed preeclampsia, preterm delivery and IUGR, <math>P = 0.0004</math>). No other factors were significant (serum creatine, uric acid, urinary creatine clearance, grade of proteinuria).</p>	<p>of captopril for at least 6 months prior to pregnancy led to a significant decrease in proteinuria at conception. There was a concomitant improvement in blood glucose control. Moderately good outcomes. Poor pregnancy outcomes attributed to pre-existing hypertension. No apparent decline in renal function at 2 year follow up however all patients had preserved or only mildly decreased renal function at conception. .</p>	<p>intrauterine death at 24 weeks secondary to early IUGR</p> <p>Two infants had cerebral palsy owing to birth trauma secondary to LGA</p>
Hod M;van Dijk DJ;Karp M;Weintraub	Study Type: Other	Intervention: ACE inhibitor (captopril). Treatment was	Eight women with diabetic nephropathy	Maternal age at conception ranged from	Renal function	Duration of treatment was >12 mths in 5 patients and 8, 9 and 11 mths in the	Prepregnancy captopril treatment	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
N;Rabinerson D;Bar J;Peled Y;Erman A;Boner G;Ovadia J; 1995 Dec 103	Evidence Level: 3	discontinued immediately following a missed period and a positive pregnancy test.  Comparison:	planning pregnancy	23 to 29 years and the duration of diabetes between 11 and 21 years. Three patients were diagnosed as class RF (retinopathy and nephropathy) and 5 patients as class F (nephropathy only).	Glycaemic control  Pregnancy outcome	<p>remaining three patients. At conception the level of proteinuria was &lt;500 mg/day which was significantly lower than at the beginning of captopril therapy (range 760–3000, mean 1633± 666 mg/day, <math>P &lt; 0.001</math>).</p> <p>Blood sugar levels were significantly lower at conception than at entry to the intensified programme (mean HbA<sub>1c</sub> 9.3% vs. 7.9%)</p> <p>At conception all patients were normotensive.</p> <p>All patients experienced a gradual increase in the amount of protein excreted during pregnancy (first trimester mean: 593±515 mg/day, second trimester mean: 783±813 mg/day, third trimester mean: 1000±1185 mg/day). In only two patients did the amount of excreted protein exceed 1000 mg/day.</p> <p>Serum creatine, creatine clearance serum, uric acid and K<sup>+</sup> remained stable throughout the study.</p> <p>BP remained normal throughout the study except for an abrupt onset of preeclampsia toxemia (PET) just prior to delivery in three patients.</p> <p>All patients had good glycaemic control.</p> <p>Outcomes of pregnancy: 1 patient delivered preterm at 35 weeks due to PET. There were three cases of PET just prior to delivery that resolved immediately postpartum. 6 patients were delivered by caesarean. There was one SGA infant and one LGA infant delivered without complications.</p>	that is discontinued at conception and is combined with strict glycaemic control in preparation for a planned pregnancy protects against acceleration of diabetic nephropathy during pregnancy and results in a favourable maternal and fetal outcome.  ACE inhibitor treatment should be used in patients with diabetic nephropathy attempting to become pregnant and discontinued at conception, concomitantly with intensive insulin management.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Lip,G.Y.; Churchill,D.; Beevers,M.; Auckett,A.; Beevers,D.G.  1999  106	Study Type: Cohort  Evidence level: 2++	18 women (19 pregnancies)	Pregnant women who conceived while taking angiotensin-converting enzyme (ACE) inhibitors and who were seen at the antenatal hypertension clinic between 1980 and 1997.  Country: UK	Intervention: Angiotensin-converting enzyme (ACE) inhibitor. Treatment with ACE inhibitor was stopped at either before or at a mean gestation of 10.3 weeks (range 6–25 weeks).  Comparison: No angiotensin-converting enzyme (ACE) inhibitor.	Follow-up period:  Outcome Measures: 1. Gestational age at delivery 2. Birthweight 3. Apgar score	Two women, one with type 1 diabetes and the other mitral valve replacement, had a miscarriage (at 7 and 8 weeks, respectively).  17 pregnancies proceeded to live birth with a mean gestational age at birth of 34.1 weeks (range 28–41 weeks).  No congenital abnormalities were reported with no evident neonatal renal dysfunction.  The mean birthweight was 2.58 kg (range 1.26- 3.82 kg); mean Apgar scores were initially 5.9 (range 2–10) and subsequently 8.6.  Even in the six pregnancies in which ACE inhibitors were continued to more than 12 weeks (including one who continued therapy until 25 weeks) there were no congenital abnormalities or neonatal problems.	ACE inhibitors taken at the time of conception or in early pregnancy do not lead to adverse outcomes as long as these drugs are discontinued as soon as pregnancy is confirmed.	
Steffensen,F.H.; Nielsen,G.L.; Sorensen,H.T.; Olesen,C.; Olsen,J.  1998  107	Study Type: Cohort  Evidence level: 2++	21 pregnant women	Pregnant women who had a prescription for ACE inhibitors during their first trimester between 1991 and 1996.  Country: Denmark	Intervention: angiotensin-converting enzyme (ACE) inhibitors. The drug was prescribed at 5–15 gestational weeks (median 8 weeks).  Comparison:	Follow-up period:  Outcome Measures: 1. Preterm delivery 2. Still birth 3. Gestational age at delivery 4. Birthweight 5. Congenital malformation	None of the 21 infants were stillborn.  One preterm infant born at 27 weeks' gestation to a mother with diabetes died later.  There were no congenital malformations.  Mean gestational age was 38.6 weeks (range 36–41)	Given the results, there is no reason to deny women of childbearing age these effective drugs, especially in countries where most pregnancies are planned and contraception methods make it possible to stop treatment when pregnancy is confirmed.	
Belfort,M.A.; Anthony,J.; Buccimazza,A.; Davey,D.A.  1990	Study Type: Cohort  Evidence level: 2+	9 women	Women with severe gestational proteinuric hypertension.  Country: South Africa	Intervention: Calcium antagonist verapamil intravenously infused after plasma volume expansion with dextran-70.	Follow-up period:  Outcome Measures: 1. Haemodynamic response 2. Adverse fetal effects	Verapamil produced a statistically significant reduction in mean arterial pressure and systemic vascular resistance without adversely affecting the cardiac	Verapamil is efficacious and justifies further investigation.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
111				Comparison:		output.  The decrease in blood pressure was smooth and controlled and was associated with an insignificant increase in heart rate.  There were no adverse fetal effects as evidenced by cardiotocographic monitoring.		
Magee,L.A.; Schick,B.; Donnenfeld,A.E.; Sage,S.R.; Conover,B.; Cook,L.; McElhatton,P.R.; Schmidt,M.A.; Koren,G.	Study Type: Cohort  Evidence level: 2++	78 women with first-trimester exposure to calcium channel blockers.	Women with first-trimester exposure to calcium channel blockers.  Country:	Intervention: First-trimester exposure to calcium channel blockers.  Comparison: No first-trimester exposure to calcium channel blockers.	Follow-up period:  Outcome Measures: 1. Major malformation 2. Preterm delivery	There was no increase in major malformation (2/66=3.0% [calcium channel blockers] vs 0% [nonteratogenic controls], $P = 0.27$ ); a fivefold increase was ruled out (baseline 2%, $\alpha = 0.05$ , $\beta = 0.20$ ).	Calcium channel blockers do not represent a major teratogenic risk.	
1996						The defects reported were attributable to maternal diabetes or coingestion of teratogens.  The increase in preterm delivery 28% [calcium channel blockers] vs 9% [nonteratogenic controls], $P = 0.003$ , attributed to maternal disease by stepwise regression, was the most important factor responsible for the observed decrease in birth weight (mean -334 gm vs nonteratogenic controls, $P = 0.08$ ).		
110								

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

#### Q.9 What are the barriers to uptake of preconception care?

#### Q.10 When should information be offered to i) women of reproductive age with diabetes? ii) women with diabetes who are planning a pregnancy?

These two clinical questions were addressed together.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Casele HL; Laifer SA; 1998 Jun 22 115	Study Type: Other  Evidence Level: 2+	What factors influence preconception control of glycaemia in women with diabetes?	55 women with pre-existing diabetes		HbA <sub>1c</sub> - determined before conception or in the first trimester. Optimal glycaemic control defined as within the normal range at the institution (4% to 6%) Adequate control defined as between 6% and 8% Suboptimal control >8%	33/55 (60%) of women had suboptimal control at conception. 6/55 (11%) had HbA <sub>1c</sub> within the normal range. Women with prior poor outcome of pregnancy were significantly more likely to enter pregnancy with poor glycaemic control ( $P = 0.02$ ). There was no difference with regard to other variables (payer status, age, race, weight, parity, vascular complications, and duration of diabetes).  Logistic regression found not being advised to achieve target glucose values (from questionnaire responses) was significantly associated with entering pregnancy with poor glycaemic control ( $P=0.02$ ). There was no difference with regard to other questionnaire responses ( Did not see diabetes physician before conception, did not plan pregnancy, did not make changes in glycaemic control to prepare for pregnancy, did not monitor blood glucose, did not follow diet, was not aware of complications of diabetes in pregnancy, was not advised to plan pregnancy, was not advised to see a physician prior to pregnancy, was not advised to change glycaemic	Patients may not be sufficiently educated about the target glucose levels recommended for preconception control.  Recommendations: Propose that the implementation of an intensive effort to control blood glucose levels in all women with diabetes of childbearing age, based on the findings of the DCCT, would obviate the need for preconception regimen changes and would result in patients entering pregnancy with better glycaemic control.	Limitations: Small sample size underpowered to detect difference. Unvalidated questionnaire.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						control to prepare for pregnancy).		
Holing EV;Beyer CS;Brown ZA;Connell FA; 1998 Jun 112	Study Type: Other Evidence Level: 2+	Why don't women with diabetes plan their pregnancies?	85 women with pre-existing diabetes	85/122 women with pre-existing diabetes who gave birth at 15 centres in Washington State. Nonparticipants included 13 women who were excluded because of an adverse pregnancy outcome.	Planned pregnancy (defined as a pregnancy that was desired before conception and in which conception was stopped or avoided for the purpose of becoming pregnant and in which the woman stated that she attempted to achieve optimal blood glucose control before becoming pregnant.)  Medical record review - HbA <sub>1c</sub>  Self administered questionnaire - information on demographics, health insurance and access to health care. Includes marital satisfaction scale.  Interview - open ended questions to elicit responses on a range of topics potentially related to pregnancy planning behaviour.	35/85 (41%) of pregnancies were planned The average SD above the laboratory mean for glycohaemoglobin at the first prenatal visit was significantly lower in planned than unplanned pregnancies (3.1 vs. 5.8, $P = 0.004$ ). Age: Planned:31.5 Unplanned:28.3, $P = 0.003$ Married: Planned: 35(100%) Unplanned: 24(48%), $P = 0.001$ Annual income: >\$20,000 Planned: 32(94%) Unplanned: 17(40%), $P < 0.0001$ > 12 years education Planned: 29(83%) Unplanned: 31(63%), $P = 0.05$ Race: White Planned: 32(91%) Unplanned: 33(66%), $P = 0.007$ Medical coverage: None Planned: 0(0) Unplanned: 14(28%), $P < 0.001$ Provider seen within 6 months before contraception for diabetes care: Planned: 33(94%) Unplanned: 31(67%), $P = 0.003$ Prior pregnancy with diabetes: Unplanned: 17(49%) Planned: 28(56%)  Unplanned pregnancy: 35/50(70%) used contraception less than half the time (included 5 women who though diabetes made it more difficult to get pregnant).	Recommendations: Pregnancy counselling should involve the women's partner.  Data suggests degrees of pregnancy planning rather than a dichotomous variable. Some unplanned pregnancies may not be unexpected. Therefore pregnancy issues should be discussed with all women of childbearing age.  Couples should be reassured that with preconception glucose control women with diabetes can have healthy babies.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						<p>35/50 (70%) said they were very happy to be pregnant.</p> <p>Partner relationship: Women with planned pregnancies were more satisfied with their partner relationship (OR 3.86, <math>P = 0.0002</math>).</p> <p>Planned pregnancy: 28 (80%) believed their partner was well informed about diabetes and pregnancy issues before the pregnancy. Many couples had attended counselling together. In almost all cases women expressed a feeling of being supported.</p> <p>Unplanned pregnancies: 8(16%) felt their partners were well informed about diabetes and pregnancy before the pregnancy. Most felt that their partners did not understand the risks or the enormity of effort required to achieve good diabetes control.</p> <p>Locus of control: Women unplanned pregnancies more likely to have external locus of control (OR 2.28, <math>P &lt; 0.004</math>). No association between pregnancy planning and 'internal' or 'chance' locus of control.</p> <p>Knowledge: Aware that should be in good diabetes control before pregnancy: Planned: 33(94%) Unplanned: 34(68%) No knowledge about diabetes and pregnancy: Planned: 0(0) Unplanned: 8(16)</p> <p>Advice from health care provider Positive, encouraging: planned: 26(75%) unplanned: 7(14%) Negative/advised not to get</p>		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						<p>pregnant: Planned: 4(11) Unplanned: 19(38)</p> <p>Relationship with hc provider Positive: Planned: 25(71%) Unplanned: 14(29%) Negative felt judged or disliked: Planned: 2(6%) Unplanned: 17(35%)</p>		
<p>Janz NK;Herman WH;Becker MP;Charron-Prochownik D;Shayna VL;Lesnick TG;Jacobson S;Fachnie JD;Kruger DF;Sanfield JA;</p> <p>1995 Feb</p> <p>113</p>	<p>Study Type: Other Evidence Level: 2+</p>	<p>What factors are associated with seeking pre-conception care?</p>	<p>57 women who sought preconception care, 97 women who did not seek pre-conception care.</p>	<p>Preconception care (PC) group: 53 Type 1 diabetes, 4 type 2 diabetes Antenatal care (AC) group: 79 type 1 diabetes, 18 type 2 diabetes</p>	<p>sociodemographic characteristics, medical factors, knowledge, attitudes and health-related behaviours</p>	<p>Race: PC: White 100% AC: White 63.9%, African-American 35.1%, Other 1.0%, <math>P &lt; 0.001</math>. Living with partner: PC: 96.2% AC: 59.8%, <math>P &lt; 0.001</math> Not high school graduate PC: 3.6% AC: 22.7% <math>P &lt; 0.001</math> Employed: PC: 78.2% AC: 41.2%, <math>P &lt; 0.001</math> Income &lt;\$6000: PC: 2% AC: 12.5%, <math>P &lt; 0.01</math></p> <p>Note: As there were only 4 women in the preconception care group with type 2 diabetes these were excluded from the following analysis: Discussed PC with health care provider: PC (Type 1, <math>n = 53</math>): 97.6% AC (type 1, <math>n = 79</math>): 51.4% AC (Type 2, <math>n = 18</math>): 35.7%, <math>P &lt; 0.05</math> Health provider encouraged preconception care: PC: 77.4% AC (Type 1): 43.0% AC (type 2): 5.9%, <math>P &lt; 0.05</math> Patient perceived very good diabetes control in past 6 months: PC: 26.9% AC (Type 1): 8.9%</p>	<p>Providers must treat every visit with a diabetic woman as a preconception visit. In counselling the benefits of preconception care should be stressed and the support of families and friends should be elicited.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
St James PJ;Younger	Study Type: Other	What factors relate to the	66 women with type 1		Use of birth control	<p>AC (Type 2): 11.8%, <math>P &lt; 0.05</math></p> <p>Prior pregnancy with diabetes:            PC: 52.8%            AC (Type 1): 57.7%            AC (Type 2): 70.6%            Prior neonatal death:            PC: 0.0            AC (Type 1): 4.6%            AC (Type 2): 7.7%</p> <p>Knowledge, attitudes, beliefs and behaviours questionnaire:            Awareness of preconception care:            PC: n/a            AC (Type 1): 72.7%            AC (Type 2): 58.8%            Knowledge of benefits to mother (% high):            PC: 94.3%, <math>P &lt; 0.05</math>            AC (Type 1): 76.6%            AC (Type 2): 70.6%            Knowledge of benefits to baby:            PC: 94.3%, <math>P &lt; 0.05</math>            AC (Type 1): 73.1%            AC (Type 2): 82.4%            Instrumental social support score (1–5):            PC: 1.3 (<math>P &lt; 0.05</math>)            AC (type 1): 1.6            AC (type 2): 1.7            Adherence with clinic visits (% all/most)            PC: 93.9 (<math>P &lt; 0.05</math>)            AC (type 1): 80.5%            AC (type 2): 92.3%</p> <p>Significant variables after logistic regression (adjusted odds ratios):            Education: 4.81, <math>P = 0.01</math>            Living with partner: 11.25, <math>P = 0.01</math>            Diabetes clinic visit in last year: 8.25, <math>P = 0.01</math>            Provider encouraged preconception care: 3.39, <math>P = 0.02</math>            Adherence with diabetes regimen: 3.03, <math>P = 0.01</math></p>	Some women may have	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
MD;Hamilton BD;Waisbren SE; 1993 Dec 114	Evidence Level: 2+	family planning behaviour of diabetic women?	diabetes  Comparison: 207 non diabetic women		Knowledge about fertility and contraception tested by a questionnaire adapted from Kempton and Foreman.  Knowledge about diabetes tested by a questionnaire developed for the study.  Locus of control measured by the Adult Nowicki-Strickland Internal-External Locus of Control Scale.  Attitudes and beliefs regarding contraception, sex, and childbearing were measured by subject ratings on a 7-point scale of statements adapted from Geis and Gerrard and Nathanson and Becker.  Scores for social support and attitudes toward birth control were also calculated.	Diabetes group: 82% Nondiabetic group: 88% Diabetic women were more likely to use condoms ( $P=0.05$ ). Interview themes: Belief that oral contraceptives were unsafe for diabetic women Belief that diabetes made it difficult to conceive  Pregnancies: Women with diabetes: 17/23 (78%) were unplanned Nondiabetic: 16/33 (48%) were unplanned.  Factors associated with consistent use of birth control Social support for birth control (mean score/SD) Always used birth control: $6.51 \pm 0.95$ Others: $5.39 \pm 1.77$ , $P < 0.05$  Attitudes about birth control: Always use: $19.65 \pm 2.45$ Others: $17.03 \pm 3.26$ , $P < 0.05$  (No significant differences between groups in scores for knowledge of family planning, knowledge of diabetes, locus of control, self esteem).	misconceptions about fertility and contraception.  Recommendations: Because social support for birth control is important clinicians should emphasize to parents of young diabetic women the importance of birth control. Educational programs for diabetic women should engender positive attitudes towards birth control use. Family and friends should be involved in this process as much as possible because their attitudes are important to the young woman's behaviour.	
Harris, K., Campbell, E. 1999 116	Study Type: Other  Evidence Level: 2+	Qualitative study exploring hypothesis that women with unplanned pregnancies are more likely to have secondary gain particularly in the domain of partnership.	45 women with planned pregnancies 43 women with unplanned pregnancies 40 non pregnant women	Non diabetic. No differences in social class between groups.	Secondary gain (benefit or advantage from becoming pregnant) rated on a scale (high/some/little or none).  Quality of sexual partnership (measured by the self esteem and social support schedule).  Interview data	Women with unplanned pregnancies were significantly more likely to be rated as having a 'high' chance of secondary gain than women with planned pregnancies ( $\chi^2 = 29.41$ , $P < 0.0001$ ). Examples of secondary gain included autonomy from parents, solidification of a shaky relationship, an excuse to leave a boring job and begin a new and important phase in their lives.  Women with planned pregnancies were significantly more likely to have a partnership rated high in	Some 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.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Confidential Enquiry into Maternal and Child Health 2004 32	Study Type: Other Evidence Level: 2+	To assess the quality of maternity services for women with diabetes in 2002  Comparison: Data from 1994	213/222 maternity units in England, Wales and Northern Ireland		Standards set out in the National Services Framework for Diabetes	overall quality (x2 = 7.10, <i>P</i> < 0.05). NSF criteria: A preconception clinic should be run jointly by the adult diabetes service and the maternity service for women wishing to become pregnant Units meeting criteria: 2002: 17% 1994: 16%		
Barrett, G., Wellings, K., 2002 117	Study Type: Other Evidence Level: 2+	Do women use particular concepts or terms when discussing pregnancy?  How do women understand the terms planned/unplanned/intended/unintended/wanted/unwanted?	47 nondiabetic women	6 in the first trimester, 13 in the 2nd trimester, 10 in the 3rd trimester. Ages 15–43. 15 married, 1 separated, 1 divorced, 9 co-habiting, 21 single. 13 already had children. 21 had been or were about to be in higher education, 14 had been in full time education to the age of 18, 4 were studying for GNVQs, 8 had left school at 16 or under and 1 was still at school.	Interview topic guide: 1) Background information 2) current pregnancy situation 3) earliest awareness of pregnancy 4) confirming pregnancy 5) contraception around the time of pregnancy 6) feelings about being pregnant 7) decision about pregnancy 8) orientation to motherhood 9) timing of childbearing 10) nature of partnership 11) understanding of terms planned/unplanned/intended/unintended/wanted/unwanted.	When discussing the circumstances of their pregnancies, women tended not to use the terms planned/unplanned/intended/unintended/wanted/unwanted spontaneously. When asked to explain the terms there was considerable variation in understanding. Women applied the term 'planned' only if they had met four key criteria. Intending to become pregnant and stopping contraception were not sufficient criteria, in themselves, to apply the term; Agreement from their partner and reaching the right time in terms of lifestyle/life stage were also necessary. In contrast 'unplanned' was a widely applied term and covered a variety of circumstances of pregnancy.	Survey questions eliciting information on women's circumstances of pregnancy do not rely on the above terms in isolation. A more circumspect use of the term in policy and clinical settings is required.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Charron-Prochownik D;Sereika SM;Falsetti D;Wang SL;Becker D;Jacobson S;Mansfield J;White NH; 2006 Oct 118	Study Type: Case-control Evidence level: 2-	80 cases 37 controls	Young women (aged 16–23 years) with type 1 diabetes of ≥ 1 yr duration, no other chronic illness, not pregnant, English speaking  Country: USA	Intervention: Theory (Expanded Health belief model) based structured telephone interview conducted for 80 cases with type 1 diabetes  Comparison: 37 matched controls without diabetes	Follow-up period:  Outcome Measures: Knowledge, attitudes, intentions, and behaviours regarding diabetes and reproductive issues, sexuality, and contraception	Cases appeared to lack an understanding of critical information that could prevent unplanned pregnancies and pregnancy-related complications. Although they scored significantly higher than the controls on diabetes-related information, the cases had their lowest mean average of 59% for the diabetes and pregnancy score. They did not appear to have greater protective attitudes regarding reproductive health issues than the control group. The cases group felt that they were only moderately susceptible to becoming	Having diabetes did not appear to significantly decrease the risk-taking behaviour of young women. Early sexual activity and some unsafe sexual practices may increase their risk for an unplanned pregnancy that could result in	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						pregnant and that severe complications would not happen to them. The cases group perceived greater severity to sex-related outcomes ( $P = 0.001$ ). The cases group did not report safer and more effective family-planning behaviours (mean age at first coitus = 15.7 yr), which for them could be more detrimental. Similar trends were noted between groups regarding contraceptive methods; only a single method (e.g., pill only) rather than a dual method (e.g., pill and condom) was most frequently used.	pregnancy-related complications.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Charron-Prochownik D;Sereika SM;Wang SL;Hannan MF;Fischl AR;Stewart SH;an-McElhinny T;  2006 Mar  {Charron-Prochownik, 2006 36577 /id}	Study Type: Qualitative Descriptive  Evidence Level: 3	Intervention: A multisite, structured 1 hr telephone interview with an open-ended section.  Comparison:	80	16–23 yr old women with type 1 diabetes for at least 1 yr, no other chronic illnesses or mental retardation, not pregnant, English speaking  Country: USA	Knowledge, attitudes, intentions, and behaviours. Awareness of issues related to diabetes and pregnancy, preconception counselling (PC), and contraception.	The response "don't know" or "never heard about it" was most frequently given. Most young women in this sample were unaware of the term preconception counselling  65% (n = 52) indicated they knew nothing about PC.  Many were not aware of the risks of pregnancy-related complications in women with diabetes.  25% were aware of preplanning a pregnancy and the importance of good metabolic control.  Many knew where to seek information about diabetes and pregnancy, and birth control	The study sample lacked awareness of pregnancy-related complications with diabetes, knowledge of the term and role of PC in preventing these complications, and the importance for women with diabetes to use a highly effective birth control method for preventing unplanned pregnancy.	

### 3.9 Cost-effectiveness of self-management programmes

#### Q.6 How cost effective are self management programmes for women with diabetes who are planning a pregnancy?

No specific searches were conducted for this clinical question (this is a health economics question), however, the following study was identified in searches for other questions.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Feig DS;Cleave B;Tomlinson G;  2006  120	Study Type: Other Retrospective  Evidence Level: 2-	Intervention: Retrospective chart review done to obtain information on self-management behaviours at entry to the programme and at delivery and compared with the present.  Comparison:	64	Inclusion criteria: Women with type 1 or type 2 diabetes, who were at least 1 year postpartum Exclusion criteria: if women gave birth before 20 weeks' gestation  Country: Canada	Diabetes self-management behaviours: frequency of self-monitoring of blood glucose, frequency of insulin injections and frequency and complexity of insulin dose adjustments) HbA <sub>1c</sub>	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 delivery. Significant improvement in the HbA <sub>1c</sub> from entry to delivery. While comparing entry to the present, a significant improvement in frequency of insulin injections, frequency and complexity of insulin dose adjustment. No significant change in frequency of self-monitoring of blood glucose from before pregnancy to the present, and a significant decrease in HbA <sub>1c</sub> by 0.015 ( $P < 0.0001$ , 95% CI 0.009–0.021) from entry to the programme to the present.	Women participating in an intensive diabetes management programme during pregnancy improve significantly from entry to delivery in diabetes self-management behaviours and glycaemic control and in the long term retention of some of the behaviours and knowledge. No improvement in HbA <sub>1c</sub> level	Decrease in HbA <sub>1c</sub> may be explained by the loss of contact with the diabetes care team and/or the discontinuation of frequent self-monitoring of blood glucose that necessary for achieving optimal glycaemic control.

# 4 Gestational diabetes

---

## 4.1 Risk factors for gestational diabetes

### Q.11 Which women are at high risk of gestational diabetes?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Scott, D., Loveman, E., McIntyre, L., Waugh, N. 2002 {Scott, 2002 12764 /id}	Study Type: Systematic review - meta-analysis  Evidence level: 2++		Pregnant women	Intervention: Screening for gestational diabetes  Comparison:	Follow-up period:  Outcome Measures: GTT (gold standard for diagnosis of gestational diabetes)	135 studies included in the review. In 16 studies all women were given a diagnostic test regardless of screening result.  Risk factors for gestational diabetes are obesity, advanced maternal age, family history of diabetes, non-white ethnic origin, obesity, increased weight gain in early adulthood and current smoker.  Using risk factors alone as a screening test produces low sensitivities (50–69%) (8 studies).  One study found that four risk factors (age, BMI, ethnic group and family history) gave most of the information and that adding other items added little.	The principal risk factors for gestational diabetes are overweight, age and ethnicity.  The author concludes that the use of risk factors as a screening test for gestational diabetes has led to high proportions (up to 50%) of women with gestational diabetes being missed.	

---

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Ostlund, I., Hanson, U  2003  {Ostlund, 2003 29266 /id}	Study Type: Other  Evidence Level: 2+	Intervention: Age  Weight  BMI  NonNordic origin  Heredity  Prior infant  Prior GDM  Prior macrosomic infant  Comparison:	4918 pregnant nondiabetic women	All pregnant nondiabetic women in a defined geographic area in Sweden	Gestational diabetes Diagnosis made using 75 g OGTT according to WHO. Test offered between weeks 28–32. Gestational diabetes diagnosed as fasting blood glucose $\geq 6.7$ mmol/l or 2 hour blood glucose $\geq 9.0$ mmol/l.	3616/4918 (73.5%) had an OGTT performed. Women who did not have an OGTT were more likely to have had previous births, be of nonNordic origin and have a lower rate of traditional risk factors.  Of the 3616 women who had an OGTT, 61 (1.7%) were diagnosed with GDM.(47 IGT, 14 DM)  Risk factors: i. Weight $\geq 80$ kg: 11.1%, OR 1.98 (1.05–3.77) $\geq 90$ kg: 4.5%, OR 3.33 (1.56–7.13) $\geq 100$ kg: 1.8%, OR 4.09 (1.44–11.6) ii. BMI $\geq 25$ : 28.3%, OR 2.05 (1.23–3.41) $\geq 28$ : 12.3%, OR 1.66 (0.88–3.15) $\geq 30$ : 7.9%, OR 2.65 (1.36–5.14) iii. Age (years) $< 25$ : 26.4%, OR 0.30 (0.13–0.70) $\geq 25$ : 73.6%, OR 3.37 (1.45–7.85) $\geq 30$ : 33.3%, OR 2.40 (1.45–4.00) $\geq 35$ : 10%, OR 3.03 (1.68–5.49) iv. Heredity: 9.4%, OR 2.74 (1.47–5.11) v. Nonnordic origin: 11.2%, OR 2.19 (1.18–4.08) vi. Prior macrosomia: 3.2%, OR 5.59 (2.68–11.7) vii. Prior GDM: 1.3%, OR 23.6 (11.6–48.0)  Screening model using traditional risk factors (family history of diabetes, obesity $\geq 90$ kg, prior macrosomic infant or GDM): Occurrence: 15.8% Sensitivity: 47.5% (29/61) Specificity: 84.7% PPV: 5.1% OR: 5.02 (3.01–8.36) Traditional risk factors+nonNordic origin: Occurrence: 25.2% Sensitivity: 60.7% (37/61) Specificity: 75.4% PPV: 4.1% OR 4.74 (2.82–7.96) Traditional risk factors+nonNordic origin+age $\geq 25$ years	Prior GDM and macrosomic infant had the highest association with GDM. Women below age 25 have a low risk of GDM.  Using traditional risk factors such as heredity diabetes, obesity, prior macrosomic infant or GDM to perform a OGTT will identify less than half of women with GDM. Introducing ethnicity improves sensitivity but will markedly increase the number of women who have to perform an OGTT. A prior macrosomic infant or GDM are of significant predictors of GDM but are restricted to multiparas women. Especially for primiparas there is a lack of good risk indicators for detecting GDM.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						Occurrence: 79.7% Sensitivity: 57/61 (93.4%)		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Doherty DA;Magann EF;Francis J;Morrison JC;Newnham JP;  2006  {Doherty, 2006 36659 /id}	Study Type: Cohort  Evidence level: 2+	2827	Recruited pregnancies between 16 and 18 weeks' gestation. Inclusion criteria: singleton pregnancies, pre pregnancy BMI available for analysis.  Country: USA	Intervention: BMI evaluated underweight, BMI<18.5, normal, BMI 18.5–25, overweight BMI 25–30, and obese BMI>30 women  Comparison:	Follow-up period:  Outcome Measures: Antenatal and intrapartum outcomes: Gestational diabetes, hypertension, preeclampsia, antenatal admissions, induction of labour, caesarean section, caesarean section for fetal distress. Postpartum and neonatal outcomes: postpartum hemorrhage, any perineal trauma, maternal infection, retained placenta, intrauterine growth retardation, time to spontaneous respiration > 1 min, any resuscitation and hypoglycaemia.	Pre-pregnancy BMI classified 331 women as underweight (11.7%), 1982 normal (69.9%), 326 overweight (11.5%), and 188 as obese (6.6%). Obese women were more likely to develop gestational diabetes ( $P < 0.001$ ), hypertension ( $P < 0.001$ ), preeclampsia ( $P < 0.001$ ), need labour induction ( $P < 0.001$ ), caesarean section for fetal distress ( $P < 0.001$ ), postpartum hemorrhage ( $P = 0.003$ ), need neonatal resuscitation ( $P = 0.001$ ) and deliver hypoglycemic infants ( $P = 0.007$ ). Being underweight is correlated with fetal growth restriction ( $P = 0.001$ ).	Pre-pregnancy obesity is a risk factor for gestational diabetes, preeclampsia, labour induction, caesarean section for fetal distress, postpartum hemorrhage and neonatal hypoglycaemic and need for resuscitation.	
Keshavarz M;Cheung NW;Babaee GR;Moghadam HK;Ajami ME;Shariati M;  2005  131	Study Type: Cohort  Evidence level: 2+	1310	Exclusion criteria: twin pregnancies, miscarriages, terminations and women with pre-existing diabetes  Country: Iran	Intervention: At first antenatal visit urine tested for glycosuria. If this was positive or women had risk factors (age >30 yrs, obesity, BMI $\geq 30$ kg/m <sup>2</sup> , family history of diabetes, previous macrosomia, unexplained recurrent miscarriages, previous congenital malformations, previous stillbirth, unexplained neonatal death, previous	Follow-up period:  Outcome Measures: Fetal, maternal and neonatal outcomes Macrosomia, gestational hypertension, hydramnios, stillbirth, congenital malformation, pre-eclampsia, pylonephritis, pre-term delivery, low birth weight, intrauterine	Incidence of GDM was 4.8%. There were statistically significant ( $P < 0.001$ ) differences in risk factors: age >30 years, family history of diabetes, obesity, previous macrosomia, glycosuria between the two groups. Women with GDM had a significantly higher rate of stillbirth ( $P < 0.001$ ; OR 17.1, 95% CI 4.5–65.5), hydramnios ( $P < 0.001$ ; OR 15.5, 95% CI 4.8–50.5), gestational hypertension ( $P < 0.001$ ; OR 6,	Screening for GDM is recommended in Iran	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				<p>gestational hypertension and preeclampsia, previous hydramnios and glycosuria on 2 successive occasions in the current pregnancy) early screening with 50 g oral glucose challenge test was done. If initial screening test was negative, and for all women without risk factors, another screening test was done at 24–28 weeks' gestation. A positive screen if 1 h serum glucose value of <math>\geq 130</math> mg/dl on glucose challenge test. Women with positive screen underwent a 100 g 3 h OGTT and the diagnosis of GDM was made with the Carpenter and Coustan criteria. Group 1 women with normal glucose tolerance</p> <p>Comparison: Group 2 women with gestational diabetes</p>	growth retardation	95% CI 2.3–15.3), macrosomia ( $P < 0.05$ ; OR 3.2, 95% CI 1.2–8.6) and caesarean section ( $P < 0.001$ ).		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
<p>Counstan D; Nelson C; Carpenter M; Carr S; Rontondo L; Widness J</p> <p>1989</p> <p>135</p>	<p>Study Type: Other</p> <p>Evidence Level: 2+</p>	<p>Intervention: To evaluate the sensitivity and cost-effectiveness of various screening schemes for GDM.</p> <p>Testing at 24–28 weeks 1 hour 59 g GCT without regard to last meal. Threshold of <math>\geq 130</math> mg/dL had 3 hour 100 g GTT NDDG criteria for diagnosis. Women asked</p>	<p>6214 pregnancies among 6034 women provided information.</p>	<p>Unselected women aged &lt;20 to &gt;40 years (no mean given).</p> <p>Population characteristics, calculated from the proportion of each clinic participating in study as 87.9% white, 8.1% black, 1.2% Asian, 0.5% Indian, 0.1% Chinese. 2.0% unknown.</p>	<p>Incidence GDM Maternal age</p> <p>Risk factors defined as: previous GDM, previous macrosomic infant, obesity, previous stillborn or neonatal death or family history of diabetes.</p>	<p>2.0% of pregnancies (n = 125) were complicated by GDM.</p> <p>GDM increased with maternal age (<math>P &lt; 0.001</math>)</p> <p>Of women with GDM 70 (56%) were &lt; 30 years, of these 58% had one or more RFs.</p> <p>If a threshold of <math>\geq 140</math> mg/dL had been used, 10% or women with GDM, who</p>	<p>GDM increases with maternal age.</p> <p>Increasing the threshold to <math>\geq 140</math> mg/dL may have missed 10% of women with GDM.</p>	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
		for age and RFs.		Country: USA		had screening values of 130–139 mg/dL, would have been missed.		
Solomon CG; Willett W; Carey VJ; Rich-Edwards J; Hunter D; Colditz GA; Stampfer M; Speizer FE; Spiegelman DJ; Manson JE.	Study Type: OtherPart of larger cohort study of health outcomes for 116 678 female registered nurses.	Intervention: To determine if risk factors for NIDDM are markers for GDM  Comparison:	14613 women without previous GDM or other known diabetes who reported singleton pregnancy between 1990–1994.	Age at study entry 25–42 years.  Place of residence at study inception was 1 of 14 US states.  Country: USA	Maternal age Obesity Family history of DM Ethnicity Pregravid weight gain Smoking Physical activity level	Maternal age >40 years had two fold increased risk of GDM compared with women aged 25–29 years. Crude RR for GDM increased 4% (95%CI 2% to 6%) with each year over 25.  GDM risk increased with weight gain between age 18 and 1989 RR (for weight gain 5–9.9 kgs) 1.67 95% CI 1.37 to 2.05 compared to stable weight.  Risk for GDM increased directly with greater weight gain RR 3.56 (95% CI 2.70 to 4.69) for weight gain of 20 kgs or more since age 18 years.  Family history of DM in a first degree relative (multivariate 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 GDM compared to white women.  Higher pregravid (1989) BMI, higher BMI at age 18 years and weight gain between 18 years and 1989 all significantly increased the risk for GDM.  Current smoking increased the RR for GDM 1.43 (95% CI 1.14 to 1.80) when compared with never smokers. Past smokers had no increased risk.  Pre gravid physical activity was not associated with risk for GDM.	Age 30 years, white ethnicity, pregravid BMI <20.0 kg/m2, no family history of DM, weight gain from age 18 years of less than 5 kg and non-smoker at the time of pregravid assessment had significantly reduced risk for GDM compared to women who did not share all of the above.	
1997	Evidence Level: 2+							

136

## 4.2 Diagnosis of gestational diabetes

## 4.3 Screening and treatment for gestational diabetes

### Q.12 How should gestational diabetes be diagnosed?

### Q.13 Does diagnosis, monitoring and intervention for gestational diabetes improve outcomes in mothers and babies?

The evidence tables for these clinical questions have been combined.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Crowther CA;Hiller JE;Moss JR;McPhee AJ;Jeffries WS;Robinson JS;Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group.;	Study Type: RCT Evidence level: 1++	490 women with IGT in intervention group 510 women in routine care group	Women between 16–30 weeks gestation. One or more risk factors for gestational diabetes on selective screening or a +ve 50 g GCT and had a 75 g OGTT at 24–34 weeks gestation in which venous plasma glucose <7.8 mmol/l after an overnight fast and 7.8–11.0 mmol/l at 2 hours. Exclusions: Women previously treated for gestational diabetes or active chronic systemic disease (except essential hypertension).	Intervention: Treatment (institution's clinical practice for gestational diabetes) including individualised dietary advice, instructions on self-monitoring (4xday), target levels for blood glucose of between 3.5 and 5.5 (fasting) <5.5 (preprandial) and <7.0 (postprandial) and insulin therapy. Comparison: Routine care	Outcome Measures: A composite measure of serious perinatal complications (death, shoulder dystocia, bone fracture, nerve palsy) Admission to neonatal nursery Jaundice requiring phototherapy Induction of labour Caesarian section Maternal health (SF-36) Anxiety (Spielberger State-Trait Anxiety Inventory) Depression (Edinburgh Postnatal Depression Scale)	The rate of serious perinatal outcomes among infants was significantly lower in the intervention group than the routine care group (1% vs. 4%; $P = 0.01$ , adjusted for maternal age, ethnic group and parity). The number needed to treat to prevent a serious outcome in an infant was 34 (95% CI 20–103). Admission to neonatal nursery Intervention: 71% Routine care: 61%, adjusted $P = 0.01$ Jaundice requiring phototherapy: No significant difference Induction of labour: Intervention: 39% Routine care: 29%, adjusted $P < 0.001$ Caesarean: No significant difference All measures on the SF-36 showed trends in favour of the intervention group but not all were significant Depression At three months postpartum fewer women in the intervention group had a	Treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring and insulin therapy as required for glycaemic control reduces the rate of serious perinatal complications, without increasing the rate of caesarean delivery.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>score on the Edinburgh postnatal depression scale suggestive of depression 8% vs. 17%)</p> <p>Anxiety Similar in both groups.</p> <p>Birthweight - g Intervention: 335±551 Routine care: 3482±660, adjusted P&lt;0.001</p> <p>Secondary outcomes: Neonatal: LGA Intervention: 68 (13%) Routine care: 115 (22%), adjusted P&lt;0.001</p> <p>Macrosomia ≥4 kg Intervention:49 (10%) Routine care: 110 (21), adjusted P &lt; 0.001</p> <p>Neonatal Hypoglycaemia requiring IV therapy: No significant difference</p> <p>Respiratory distress syndrome: No significant difference Maternal: Antenatal preeclampsia: No significant difference</p> <p>Any perineal trauma: No significant difference</p> <p>Length of postnatal stay Intervention:4 (3–5) Routine care:4 (3.5)</p>		
Jensen DM;Damm P;Sorensen B;Molsted-Pedersen L;Westergaard JG;Korsholm L;Ovesen P;Beck-Nielsen H;	Study Type: Cohort Evidence level: 2++	3260	Pregnant women who underwent OGTT at 31.3 weeks.	Diagnostic thresholds based on a 75 g 2 hour OGTT. Group 1: 2 hour value <7.8 mmol/l (n = 2596) not treated	Outcome Measures: Pregnancy induced hypertension (PIH)/preeclampsia Shoulder dystocia	Results from multivariate logistic regression: Odds Ratio (OR) vs. group 1 i.e.: 2 hour blood glucose <7.8 mmol/l Preeclampsia/PIH: Group 2: OR 0.9 (0.5–1.8)	The frequency of macrosomia showed >50% increase in women with 2 hour OGTT 7.8 mmol/l - 8.9 mmol/l compared with women with 2 hour OGTT <7.8 mmol.	IGT not treated Multivariate logistic regression controlled for maternal prepregnancy BMI, maternal age, parity, smoking, weight gain during pregnancy,

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
2003 Jan 149				Group 2: 2 hour value 7.8–8.9 mmol/l ( <i>n</i> = 289) not treated  Group 3: 2 hour value 9.0–11.0 mmol/l ( <i>n</i> = 278) treated  Group 4: 2 hour value ≥11.1 mmol/l ( <i>n</i> = 97) treated	Spontaneous preterm birth  Caesarean section  LGA  Macrosomia (birthweight ≥4000 g)  Hypoglycaemia (IV glucose during the first 48 hours of life)  Jaundice (treated with phototherapy)  Respiratory distress	Group 3: OR 1.6 (0.9–2.7) Group 4: 2.9 (1.3–6.2)  Spontaneous preterm delivery Group 2: OR 1.3 (0.4–3.9) Group 3: OR 2.0 (1.0–3.6) Group 4: OR 5.1 (2.4–11.0) <i>P</i> < 0.001  LGA Group 2: OR 1.7 (1.1–2.4) Group 3: OR 2.0 (1.4–2.8) Group 4: 3.0 (1.8–5.1) <i>P</i> < 0.001  Birthweight ≥4000 g Group 2: 1.5 (1.1–2.2) Group 3: 1.2 (0.8–1.7) Group 4: 2.1 (1.1–3.8)  Hypoglycaemia Group 2: 0.7 (0.2–2.2) Group 3: 3.4 (2.0–5.9) Group 4: 8.1 (3.9–16.7) <i>P</i> < 0.001  Shoulder dystocia was significantly increased in univariate analysis (group 1: 1.5%; group 2: 3.4%; group 3: 4.4%; group 4: 5.1%; <i>P</i> = 0.004).		gestational age, anamnestic risk indicators for GDM, ethnic background and clinical centre
Langer O;Brustman L;Anyaeqbunam A;Mazze R; 1987 148	Study Type: Case-control  Evidence level: 2++	126 GDM 126 one abnormal value 126 normal values	All women referred for an OGTT	Intervention: GDM by NDDG criteria vs. 1 abnormal value on OGTT  Comparison: Normal values on OGTT	Outcome Measures: LGA (≥90%)  Macrosomia (≥4000 g)  Neonatal hypoglycaemia (blood glucose <2.2 mmol/l at birth reconfirmed by laboratory analysis)  Hyperbilirubinemia (blood level >12 m/dl)  Polycythemia (central venous hematocrit >65%)	No significant difference in blood glucose value (mean and SD) between GDM group before treatment and the group with 1 abnormal OGTT value. Significant difference between GDM group after treatment and the group with one abnormal OGTT value: Fasting: <i>P</i> < 0.002 After breakfast: <i>P</i> < 0.0001 Before lunch: <i>P</i> < 0.0001 After lunch: <i>P</i> < 0.0001 Before dinner: <i>P</i> < 0.01 After dinner: <i>P</i> < 0.001 Bedtime: <i>P</i> < 0.0001  Ambulatory glucose profile: The profiles of the GDM group before treatment were indistinguishable from the profiles of the group with 1 abnormal value. The profiles of the GDM group and the group with 1 abnormal value	The incidence of adverse neonatal outcome among the one abnormal value group was significantly higher than for other groups.  If treated the patients with one abnormal value would have most probably experienced a significantly lower incidence of adverse perinatal outcome consistent with that found among individuals treated for GDM.	IGT untreated  Matched by age, weight, parity and race

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>were significantly different from those of the normal group. After treatment the profiles of the GDM group were significantly different from the group with one abnormal value. There was no significant difference between the GDM group after treatment and the normal group.</p> <p>Neonatal outcomes: A significant difference in the incidence of LGA and macrosomic infants between the group with 1 abnormal value and the normal group (34% vs. 9%; <math>P &lt; 0.01</math>) and the GDM group (34% vs. 12%, <math>P &lt; 0.01</math>). No significant difference in LGA and macrosomic infants was found between the GDM group and the normal group. Neonatal metabolic disorders were significantly higher in the group with 1 abnormal value (15%) when compared with group the GDM and normal groups (3%, <math>P &lt; 0.01</math>).</p>		
<p>Mello G;Parretti E;Cioni R;Lucchetti R;Carignani L;Martini E;Mecacci F;Lagazio C;Pratesi M;</p> <p>2003 Apr</p> <p>146</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2++</p>	<p>829 women who did not have GDM according to Carpenter and Coustan criteria</p>	<p>No history of pregestational diabetes or GDM.</p>	<p>Glucose levels</p>	<p>Outcome Measures:</p> <p>Neonatal:</p> <p>Cranial/thoracic circumference (CC/TC) ratio <math>\leq</math> 10th percentile</p> <p>Ponderal index (birthweight/length<sup>3</sup> x 100)</p> <p>Macrosomia (<math>\geq</math> 90th percentile for gestational age)</p>	<p>Logistic regression</p> <p>Early period (16–20 weeks)</p> <p>1. Neonatal CC/TC ratio <math>\leq</math> 10th percentile: Fasting 75 g glucose load values; adjusted OR 1.05 (95% CI 1.02–1.07)</p> <p>1 hour 75 g glucose load value: adjusted OR 1.81 (95% CI 1.15–2.83)</p> <p>2 hour 75 g glucose load: adjusted OR 1.03 (1.02–1.04)</p> <p>2.Neonatal ponderal index <math>\geq</math> 90th percentile for gestational age: Fasting 75 g glucose load value: adjusted OR 1.02 (0.99–1.05)</p> <p>1 hour 75 g glucose load value: adjusted OR 1.03 (1.02–1.03)</p> <p>2 hour 75 g glucose load value: adjusted OR 1.03 (1.02–1.04)</p> <p>3. Macrosomia Fasting 75 g glucose load value: adjusted OR 1.03 (1.00–1.06)</p> <p>1 hour 75 g glucose load value: adjusted</p>	<p>There is a significant association between 75 g load values and abnormal neonatal anthropometric features.</p> <p>The results suggest the possibility of using 1 hour 75 g glucose load as a single test for the diagnosis of GDM adopting a threshold value of 8.3 mmol/l at 16–20 weeks and 8.8 mmol/l at 26–30 weeks.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>OR 1.02 (1.02–1.03)            2 hour 75 g glucose load value: adjusted            OR 1.02 (1.00–1.03)</p> <p>Late period (26–30 weeks)            1. Neonatal CC/TC ratio ≤10th percentile            Fasting 75 g glucose load values:            adjusted OR 1.07 (1.05–1.10)            1 hour 75 g glucose load value: adjusted            OR 1.86 (1.19–2.91)            2 hour 75 g glucose load adjusted OR:            1.04 (1.03–1.05)</p> <p>2. Neonatal ponderal index ≥90th percentile for gestational age            Fasting 75 g glucose load value:            adjusted OR 1.04 (1.01–1.06)            1 hour 75 g glucose load value: adjusted            OR 1.03 (1.02–1.03)            2 hour 75 g glucose load value: adjusted            OR            1.03 (1.02–1.04)</p> <p>3. Macrosomia            Fasting 75 g glucose load value:            adjusted OR 1.03 (1.00–1.06)            1 hour 75 g glucose load value: adjusted            OR 1.02 (1.01–1.03)            2 hour 75 g glucose load value: adjusted            OR 1.02 (1.00–1.03)</p> <p>There were significant differences between pregnancies with a neonatal CC/TC ratio ≤10th percentile or &gt;10th percentile in rates of caesarean section (38/112 (33.9%) vs. 119/717 (16.6%); <math>P &lt; 0.001</math>; OR 3.93, 95% CI 2.6–5.9) and shoulder dystocia (6/112 (5.4%) v. 1/717 (0.1%); <math>P &lt; 0.0003</math>; OR 6.65, 95% CI 4.6–9.4)</p> <p>ROC curves for the prediction of neonatal CC/TC ratio ≤10th percentile in both early and late periods were constructed for 1 hour 75 g glucose load values. Inflection points were identified for a threshold value of 8.3 mmol/l in the early period and 8.8 mmol/l in the late</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Ostlund I;Hanson U;Bjorklund A;Hjertberg R;Eva N;Nordlander E;Swahn ML;Wager J; 2003 Jul 150	Study Type: Case-control Evidence level: 2++	213 women with undiagnosed and untreated IGT during pregnancy		GDM defined as fasting blood glucose $\geq$ 6.7 mmol/l and/or 2 hour blood glucose $\geq$ 11.1 mmol/l  IGT fasting blood glucose <6.7 mmol/l and 2 hour level 9.0–11.0 mmol/  Comparison: 815 controls	Outcome Measures: Caesarean section  Prematurity (<37 weeks)  Birthweight  Macrosomia ( $\geq$ 4000 g, $\geq$ 5000 g)  LGA  SGA  Hypoglycaemia  Hyperbilirubinemia requiring treatment  Admission to NICU 2 days or longer	period. Caesarean section adjusted OR (adjusted for parity, LGA infant, PIH/preeclampsia, ethnicity, BMI) 1.9 (1.2–2.9). Emergency caesarean section adjusted OR 2.1 (1.3–3.5 mmol/l)  Prematurity adjusted OR 2.0 (95% CI 1.0–3.9)  LGA adjusted OR 7.3 (95% CI 4.1–12.7).  Admission to NICU adjusted OR 2.3 (95% CI 1.3–4.0)  71.3% of infants in the IGT group had no neonatal complications compared with 87.3% of the control group.	IGT is independently and significantly associated with an increased incidence of caesarean section and prematurity and a markedly increased proportion of LGA and macrosomic infants and admission to NICU for 2 days or longer	Higher caesarean rate not linked to diagnosis of GDM
Sermer M;Naylor CD;Farine D;Kenshole AB;Ritchie JW;Gare DJ;Cohen HR;McArthur K;Holzapfel S;Biringer A; 1998 Aug 147	Study Type: Cohort Evidence level: 2++	3637 nondiabetic patients (by NDDG criteria)	Women who were 24 years or over at time of delivery.	Plasma glucose values following OGTT	Outcome Measures: Preeclampsia  Macrosomia (birthweight $\geq$ 4000 g)  Caesarean section  Phototherapy  Maternal length of stay (LOS)  Neonatal nursery LOS  Fetal trauma	Macrosomia: Increased with each quartile of OGTT fasting level ( $P < 0.001$ ) 1 hour level ( $P = 0.004$ ) 2 hour level ( $P < 0.001$ ) and with each quartile of GCT ( $=0.001$ ).  Preeclampsia: Increased with each quartile of OGTT 1 hour level, ( $P = 0.004$ ) 2 hour level ( $P = 0.001$ ) and GCT ( $P = 0.001$ ).  Caesarean section: Increased with each quartile of OGTT 1 hour level ( $P = 0.005$ ) 2 hour level ( $P = 0.003$ ) 3 hour level ( $P = 0.001$ ) and each quartile of GCT ( $P = 0.001$ ).  The need for phototherapy, maternal LOS and neonatal nursery LOS all significantly increased with worsening carbohydrate intolerance. There was no relationship between OGTT and GCT values and congenital malformations, IV therapy for hypoglycaemia and RDS.	Progressively increasing plasma glucose was associated with an increased incidence of a variety of adverse outcomes  However after adjusting for other risk factors the independent incidence of glucose values on maternal and fetal outcomes was modest.  The usual treatment of GDM lowers macrosomia but the rate of caesarean delivery remains inexplicably high	Untreated and undiagnosed IGT. Physicians and researchers blinded to GCT and OGTT results.  Multivariate analysis controlled for obesity

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>For fetal trauma the higher quartiles are associated with the highest percentage of fetal trauma (NS).</p> <p>Multivariate analysis: Caesarean section: BMI (OR 1.10, 95% CI 1.07–1.16, <math>P &lt; 0.05</math>) OGTT 1 hour (OR 1.10, 95% CI 1.01–1.22) OGTT 3 hour (OR 1.10, 95% CI 1.06–1.22, <math>P &lt; 0.05</math>)</p> <p>Birthweight &gt; 4500: BMI (OR 1.2, 95% CI 1.06–1.25, <math>P &lt; 0.05</math>) OGTT Fasting level (OR 2.6, 95% CI 1.69–4.11, <math>P &lt; 0.05</math>)</p> <p>Preeclampsia: BMI (OR 1.30, 95% CI 1.19–1.32, <math>P &lt; 0.05</math>) OGTT 2 hour (OR 1.10, 95% CI 1.00–1.27).</p> <p>Pregnancy outcomes based on glucose test results: Macrosomia (&gt;4000 g) Negative screenees: 13.7% Untreated GDM by C&amp;C criteria: 28.7% Treated GDM by NDDG criteria: 10.5% (<math>P &lt; 0.001</math>)</p> <p>Caesarean delivery: Negative screenees: 20.2% Untreated GDM by C&amp;C criteria: 29.6% Treated GDM by NDDG criteria: 33.6% <math>P &lt; 0.001</math></p>		
Weiss PAM; Haeusler M; Tamussino K; Haas J; 2000 144	Study Type: Case-control Evidence level: 2++	220	OGTT at 28 weeks and elevated amniotic fluid insulin levels at 31 weeks ( $\geq 42$ pmol/l). Excluded: Women with factors other than GDM that could influence amniotic fluid insulin levels such as	Capillary blood glucose levels at 0, 1 and 2 hour following glucose load of 1 g/kg ( $n = 161$ ) or 75 g ( $n = 59$ ) Comparison: 220 nondiabetic (i.e. with normal OGTT) pregnant women with amniotic	Sensitivity for the diagnosis of fetal hyperinsulinism	<p>Sensitivity and specificity of fasting and postload glucose values for the diagnosis of elevated amniotic fluid insulin concentration</p> <p>Fasting <math>\geq 5.0</math> mmol/l Sensitivity: 58% Specificity: 97%</p> <p>1 hour <math>\geq 8.9</math> mmol/l</p>	<p>In women with elevated amniotic fluid insulin concentration 97% had 1 hour postload glucose levels <math>&gt; 8.9</math> mmol/l.</p> <p>The 1 hour value had the highest sensitivity for measuring fetal hyperinsulinism.</p>	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			type 1 diabetes, insulin treatment, rhesus disease and fetal malformation.	insulin fluid levels <42 pmol/l.		Sensitivity: 97% Specificity: 99%  2 hour $\geq 7.8$ mmol/l Sensitivity: 54% Specificity: 97%		
Tallarigo, L., Giampietro, O., Penno, G., et al 1986 143	Study Type: Cohort Evidence level: 2++	249	Normal results on the 100 g OGTT using O'Sullivan's criteria (0=5.8, 1-h=10.5, 2-h=9.2, 3-h=8.0 mmol/l.) No history of diabetes.	Group A ( <i>n</i> = 151) women with 2 hour plasma glucose levels <5.6 mmol/l.  Group B ( <i>n</i> = 58) women with 2 hour levels of 5.6–6.6 mmol/l  Group C ( <i>n</i> = 40) women with 2 hour values 6.6–9.1 mmol/l (IGT according to NDDG).	Outcome Measures: Macrosomia ( $\geq 4000$ g)  Congenital abnormalities  Toxaemia (presence of convulsive seizures or any two of the following signs: proteinuria, hypertension, and edema).  Caesarean section	Macrosomia Group A: 15/151 (9.9%) Group B: 9/58 (15.5%) Group C: 11/40 (27.5%) P<0.01 (test for linear trend)  Maternal complications (toxemia/cesarean) Group A: 30/151 (19.9%) Group B: 15/58 (25.9%) Group C: 16/40 (40%) P<0.01 (test for linear trend)  No correlation was found between the two-hour plasma glucose level and maternal age or maternal weight.  A significant association between 2 hour plasma glucose level and both macrosomia and complications persisted after controlling for maternal age and weight.	There is a positive correlation between the 2 hour plasma glucose level and the incidence of complications of pregnancy even though all values were in the accepted normal range (<9.1 mmol/l). In addition there is a correlation between frequency of macrosomia, toxemia, caesarean section or both and the 2 hour plasma glucose level in nonobese women	
Sacks, D., et al 1995 145	Study Type: Cohort Evidence level: 2++	3352 women	Fasting blood glucose <5.8 mmol/l and 2 hour values <11 mmol/l. Untreated.	2 hour post 75 g plasma glucose levels	Birthweight  Macrosomia ( $\geq 90$ th percentile for gestational age)  Ponderal index	Multivariate analysis adjusted for maternal age, ethnicity, parity, BMI, mean weight gain, family history of diabetes and obstetric history.  A significant positive relationship was found between fasting, 1 and 2 hour values and percentiles of birthweight.  Only the fasting and 2 hour levels were found to be significantly and independently associated with macrosomia.  ROC curves were constructed for fasting and 2 values for the prediction of macrosomia. No clear inflection point was identified for any threshold value.	Although there was an overall progressive increase in the prevalence of macrosomia with incremental GTT threshold values no isolated infection point for fasting or 2 hour values could be identified.	
Saldana, T. et al	Study Type: Cohort	1190 white women 865 Black women	Women between 24 and 29 weeks	GDM defined as two abnormal values on 100 g	Birthweight	The overall prevalence of GDM was 5.0% and IGT was 2.6%.		Small numbers of women with IGT

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
2003 151	Evidence level: 2+		pregnancy	OGTT (Carpenter and Coustan criteria)- treated with diet/insulin IGT defined as one abnormal value on 100 g OGTT - not treated NGT no high values on OGTT	Macrosomia ( $\geq 4000$ g) LGA	Among white women 70 had GDM, 40 had IGT and 1,080 had NGT. Among black women 32 had GDM, 13 had IGT and 820 had NGT.  Among Black women logistic regression adjusted for pre-pregnancy BMI, maternal age and height and gestational age continued to show a significant increase in birthweight compared with women with NGT.  In contrast among white women there was no significant increase in birthweight associated with IGT compared with NGT.		
Kremer CJ;Duff P; 2004 185	Study Type: Cohort Evidence level: 3	197 women with gestational diabetes	Average age 28 (range 18–40). The mean gestational age at diagnosis was 24 weeks and the mean gestational age at start of glyburide treatment was 30 weeks  82% had BMI>30 33% had BMI>40  (cf Langer)  Country: Florida	Intervention: Treatment with glyburide.  The starting dose was 2.5 mg, administered in the morning before breakfast. The daily dose was increased in increments as needed to a maximum of 20 mg.  The goal was to maintain fasting glucose $\leq 5$ mmol/l and 1-hour value $\leq 7.4$ mmol/l  Patients were prescribed an American Diabetes Association Diet, calculated as 30 kcal/kg of ideal body weight, and were asked to monitor their blood sugar 4 times per day (before breakfast and 1 hour after each meal) 4 to 7 days per week.  The dose was adjusted if weekly mean blood	Follow-up period:  Outcome Measures: Achievement of satisfactory glucose control (mean plasma fasting glucose $\leq 5$ mmol/l, mean 1-hour value $\leq 7.4$ mmol/l)	124 women (63%) achieved satisfactory blood glucose control with diet alone; 73 (37%) required glyburide. Women in the glyburide group were significantly more likely to be morbidly obese than the group controlled by diet ( $P < 0.05$ ).  Of the 73 patients treated with glyburide, 59 (81%; 95% CI 76.4–86.6) had acceptable glucose control on medical therapy. 23 patients required a dose of only 2.5 mg, 20 responded to 5 mg, 8 to 7.5 mg and 8 required doses greater than 7.5 mg. 21 women required morning and evening doses of glyburide.  9 women experienced side effects (4 malaise and weakness, 2 nausea, 1 light headed, 2 symptoms of hypoglycaemia). Only 1 patient discontinued due to side effects.  In the 59 women controlled with glyburide, 11 (19%) had infants who weighed $>4000$ g. Overall 36/59 (49%) required caesarean delivery. 11 (19%) had caesarean deliveries because of labour abnormalities or suspected macrosomia. (Cf 14–17% primary CS	Approximately 80% of patients who fail to respond to diet can be treated effectively with glyburide.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				glucose values exceeded the threshold or if 20% of values exceeded the threshold.  Patients who failed to achieve satisfactory control were treated with twice daily dose of insulin.  Comparison:		rate in general obstetric population).  No fetal abnormalities		
Langer O;Conway DL;Berkus MD;Xenakis EM;Gonzales O;  2000 Oct 19  424	Study Type: RCT  Evidence level: 1++	404 women with gestational diabetes 201 assigned to receive glyburide and 203 to receive insulin.	Women were screened for diabetes with a one-hour, 50 g oral glucose challenge. The women ranged in age from 18 to 40 and were all medicaid recipients. 83% Hispanic, 12% non Hispanic white, 5 % black.  Country: USA	Intervention: Glyburide  Comparison: Insulin	Follow-up period:  Outcome Measures: Blood glucose Fasting (mmol/l) Preprandial (mmol/l) Postprandial (mmol/l) Mean (mmol/l) Glycosated haemoglobin (%)  Neonatal outcomes: Birth weight (g) LGA (no, %) Macrosomia (no, %) Cord-serum insulin Intravenous glucose therapy (no, %) Hypoglycaemia Hypocalcaemia Hyperbilirubinemia Polycythemia Lung complications (no, %) Respiratory support (no, %) Admission to neonatal intensive care Congenital anomaly Stillbirth Neonatal death	Blood glucose (mmol/l): Fasting Glyburide: 5.7±1.4 Insulin: 5.9±1.4 ( <i>P</i> = 0.12)  Preprandial: Glyburide: 5.7± 1.1 Insulin: 5.9±1.3 ( <i>P</i> = 0.16)  Postprandial: Glyburide: 7.2±1.4 Insulin: 7.1±1.5 ( <i>P</i> = 0.69) Mean: Glyburide: 6.3±1.05 Insulin: 6.4±0.1.2 ( <i>P</i> = 0.33)  Glycosated haemoglobin (%): Glyburide: 5.7±1.3 Insulin: 5.6±1.2 ( <i>P</i> = 0.42)  Birth weight (g) Glyburide: 3256±543 Insulin: 3194±598 ( <i>P</i> = 0.28)  LGA (no, %) Glyburide: 25 (12) Insulin: 26 (13) <i>P</i> = 0.76  Macrosomia (no, %) Glyburide: 14 (7) Insulin: 9 (4) <i>P</i> = 0.26  Cord-serum insulin Glyburide: 15±13 Insulin: 15±21 ( <i>P</i> = 0.84)  Intravenous glucose therapy (no, %)	We found that among women with gestational diabetes, the degree of glycemic control and perinatal outcomes were essentially the same for those treated with glyburide and those treated with insulin.  Glyburide is an effective alternative to insulin in women with gestational diabetes.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>Glyburide: 28 (14) Insulin: 22 (11) <math>P = 0.36</math></p> <p>Neonatal hypoglycaemia Glyburide: 18 (9) Insulin: 12 (6) <math>P = 0.25</math></p> <p>Hypocalcaemia Glyburide: 2 (1) Insulin: 2 (1) <math>P = 0.99</math></p> <p>Hyperbilirubinemia Glyburide: 12 (6) Insulin: 8 (4) <math>P = 0.36</math></p> <p>Polycythemia Glyburide: 4 (2) Insulin: 6 (3) <math>P = 0.52</math></p> <p>Lung complications (no, %) Glyburide: 16 (8) Insulin: 12 (6) <math>P = 0.43</math></p> <p>Respiratory support (no, %) Glyburide: 4 (2) Insulin: 6 (3) <math>P = 0.52</math></p> <p>Admission to neonatal intensive care Glyburide: 12 (6) Insulin: 14 (7) <math>P = 0.68</math></p> <p>Congenital anomaly: Glyburide: 5 (2) Insulin: 4 (2) <math>P = 0.74</math></p> <p>Stillbirth Glyburide: 1 (0.5) Insulin: 1 (0.5) <math>P = 0.99</math></p> <p>Neonatal death Glyburide: 1 (0.05) Insulin: 1 (0.05) <math>P = 0.99</math></p> <p>Glyburide was not detected in the cord serum of any infant.</p>		
Bertini AM;Silva JC;Taborda W;Becker F;Lemos Beber	Study Type: RCT Evidence level: 1+	27 women assigned insulin therapy 24 women assigned	Women with GDM (WHO criteria) who needed therapy in	Intervention: OHA (glibenclamide acarbose)	Follow-up period: Outcome Measures:	Glucose control was not achieved in 5 patients in the Glibenclamide group (20.8%) and 8 patients in the acarbose	Glibenclamide controlled blood glucose levels in 79% of patients	Not blinded

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
FR;Zucco Viesi JM;Aquim G;Engel RT; 2005 182		glibenclamide therapy 19 assigned to acarbose therapy	addition to diet and exercise. Brazil. Patients exclusively from the public health system. Patients with concomitant pathologies that could affect therapy or perinatal results were excluded.  Country: Brazil	Whenever maximum dose was reached without reaching glucose control this therapy was replaced by insulin therapy.  Comparison: Insulin	Birth weight Macrosomia (>4000 g) LGA (>90th percentile) Neonatal hypoglycaemia (glucose level <40 mg/dl)	group (42.1%). No maternal hypoglycaemia requiring hospital admission was reported.  GA at birth: mean (SD) Insulin: 38.5 (1.2) Glibenclamide: 38.1 (1.2) Acarbose:38.2 (1.2) P=0.42  Apgar 1: mean (SD) Insulin: 8.1 (0.97) Glibenclamide:8 (0.7) Acarbose 8.4 (0.9) P=0.19  Apgar 5: mean (SD) Insulin: 9.4 (0.7) Glibenclamide: 9.0 (0.6) Acarbose: 9.3 (.4) P=0.10  Birth weight Insulin: 3151.2 (407.2) Glibenclamide: 3395.6 (524.4) Acarbose: 3242.6 (400.6) P=0.15  LGA Insulin: 1 (3.7%) Glibenclamide: 6 (25%) Acarbose: 2 (10.5%) P=0.073  SGA Insulin: 2 (7.4%) Glibenclamide: 0 Acarbose: 0  >4000 g Insulin: 0 Glibenclamide: 4 (16%) Acarbose: 0  Neonatal hypoglycaemia: Insulin: 1 (3.7%) Glibenclamide: 8 (33.3%) Acarbose: 1 (5.3%)		

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>P=0.006</p> <p>1 infant from Glibenclamide group (born at 36 weeks) required special care for 2 days. The other cases were of mild hypoglycaemia and managed with maternal milk.</p> <p>There were 2 SGA infants in the insulin group (7.4%).</p> <p>C section                      Insulin:44.4%                      Gylburide:50%                      Acarbose: 52.2%</p> <p>There were no perinatal deaths</p>		
<p>Glueck CJ;Goldenberg N;Wang P;Loftspring M;Sherman A;</p> <p>2004</p> <p>425</p>	<p>Study Type: Cohort</p> <p>Evidence level:</p>	<p>42 pregnancies in 39 women with PCOS</p>	<p>Country:</p>	<p>Intervention: Metformin</p> <p>Comparison:</p>	<p>Follow-up period:</p> <p>Outcome Measures:</p>	<p>Of the 42 pregnancies, gestational diabetes was diagnosed in three (7.1%)</p> <p>Weight                      The median percentage reduction in weight was 5.8% (<math>P &lt; 0.0001</math>).</p> <p>Insulin                      The median reduction in insulin from pre-treatment baseline to the last preconception visit was 40% (<math>P &lt; 0.0001</math>). Insulin did not increase in the first or second trimester (<math>P &gt; 0.05</math>) and rose 10% in the third trimester.</p> <p>Insulin resistance                      The median percentage reduction in HOMA Insulin resistance from pre-treatment baseline to the last preconception visit was 46% (<math>P &lt; 0.0001</math>). Median insulin resistance at the last pre-conception visit did not differ from insulin resistance in the third trimester.</p> <p>Insulin secretion                      The median percentage reduction in insulin secretion from pre-treatment baseline to last preconception visit was 45% (<math>P = 0.0004</math>).</p>		
Jacobson GF;Ramos GA;Ching JY;Kirby	Study Type: Cohort	268 women with GDM treated with	Diagnosed with GDM (50 g GCT $\geq$ 7.7	Intervention: Glibenclamide	Follow-up period:	During 1999 through to 2000 268 women were diagnosed with GDM and	Our retrospective study suggests that glibenclamide can	Demographic changes in obstetric population

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
RS;Ferrara A;Field DR; 2005 183	Evidence level: 2+	insulin  236 women with GDM treated with glibenclamide	mmol/l) OGTT NDDG criteria). Between 12 and 34 weeks where diet therapy insufficient.  Exclusions fasting plasma glucose: >7.7 mmol/l  Population of managed care organisation (does not include extremes of socio-economic distribution).  Country: USA	Both groups: nutritional counselling on a diabetic diet for pregnancy with 3 meals and 3 snacks; and instructions on SBGM (4 times per day: fasting and either 1 or 2 hours postprandial). Targets for fasting, 1 hour and 2 hour postprandial were <5.5, <8.5 and <7 respectively.  Patients were expected to have BS evaluation for a minimum of 3 days on an appropriate diet before initiating glibenclamide.  Glibenclamide was begun with an initial daily dose of 2.5 mg with the morning meal. If targets were not met on a maximum dose of 20 mg insulin was initiated.  Comparison: Insulin	Outcome Measures: Preterm delivery (<37 weeks) LGA (above 90th percentile) Macrosomia (≥4000 g) Hyperbilirubinemia (total bilirubin 12 mg/dL or greater within the first 7 days of birth) Polycythemia (hematocrit >60%) Hypocalcaemia (calcium 7.0 mg/dL or less within 3 days of birth). NICU admission, length of stay, need for oxygen/assisted ventilation Maternal hypoglycaemia (<3.3 mmol/l)	treated with insulin  During 2001 through 2002, after the introduction of glibenclamide, 236 women were diagnosed with GDM and treated with glibenclamide.  Women in the insulin group had a higher mean BMI (31.9 vs 30.6, <i>P</i> = 0.04) a greater proportion identified themselves as white (43%, 28%, <i>P</i> < 0.001) and fewer as Asian (24%, 37%, <i>P</i> = 0.001) OGTT performed at a later gestational age (26.3±5.3 weeks vs 25.5±5.3weeks, <i>P</i> = 0.02) and a significantly higher fasting OGTT ( <i>P</i> = 0.005) compared with the glibenclamide group.  After logistic regression (BMI, ethnicity, gestational age at diagnosis, fasting plasma glucose on OGTT) glibenclamide treatment was significantly more likely to be associated with achieving mean glucose goals (adjusted OR 0.27, 95% CI 0.13–0.52).  Adjusted OR (insulin group s reference): Preeclampsia: 2.32 (95% CI 1.17–4.63) NICU admission: 0.7 (0.34–0.93). Phototherapy: 2.20 (0.99–4.87) No other differences in maternal or neonatal outcomes.  28 (12%) women failed glibenclamide and were switched to insulin: 8 for side effects primarily attributed to hypoglycaemia, 14 for poor control and for 6 the reason was not clear. For these women the mean BMI was 31.6, mean fasting level on OGTT 5.7 mmol/l and mean pregnancy weight gain 25.6 lb. Only 3 women who switched for poor control were on maximum dose of 20 mg/d. An additional 11 (5%) discontinued glibenclamide; most for side effects attributed to hypoglycaemia, and never	be effectively introduced for the treatment of women with GDM  Larger randomised trials are needed to investigate less frequent complications such as preeclampsia, NICU admission, need for phototherapy and birth injury.	overtime.  Dosing protocol varied between centres

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						started insulin.		
						3 infants in the insulin group had birth injuries (1 clavicle fracture, 1 brachial plexus injury, 1 bone injury). 8 infants in the glibenclamide group had birth injuries (4 clavicle fractures, 1 brachial plexus injury, 3 bone injuries)		
Ostlund I;Hanson U;Bjorklund A;Hjertberg R;Eva N;Nordlander E;Swahn ML;Wager J; 2003 Jul 150	Study Type: Case-control Evidence level: 2++	213 women with undiagnosed and untreated IGT during pregnancy	Country: Sweden	Intervention: Is increased maternal or neonatal morbidity in connection with Impaired glucose tolerance (IGT) during pregnancy when the condition is not treated.  GDM defined as fasting blood glucose $\geq$ 6.7 mmol/l and/or 2 hour blood glucose $\geq$ 11.1 mmol/l  IGT fasting blood glucose <6.7 mmol/l and 2 hour level 9.0–11.0 mmol/l  Comparison: 815 controls	Follow-up period:  Outcome Measures: Caesarean section Prematurity (<37 weeks) Birthweight Macrosomia ( $\geq$ 4000 g, $\geq$ 4500 g, $\geq$ 5000 g) LGA SGA Hypoglycaemia Hyperbilirubinemia requiring treatment Admission to NICU 2 days or longer	Caesarean section Adjusted OR (adjusted for parity, LGA infant, PIH/preeclampsia, ethnicity, BMI) 1.9 (1.2–2.9). Emergency caesarean section adjusted OR 2.1 (1.3–3.5 mmol/l)  Prematurity adjusted OR 2.0 (95% CI 1.0–3.9)  LGA adjusted OR 7.3 (95% CI 4.1–12.7).  Admission to NICU adjusted OR adjusted OR 2.3 (95% CI 1.3–4.0)  71.3% of infants in the IGT group had no neonatal complications compared with 87.3% of the control group.	IGT is independently and significantly associated with an increased incidence of caesarean section and prematurity and a markedly increased proportion of LGA and macrosomic infants and admission to NICU for 2 days or longer	Higher caesarean rate not linked to diagnosis of GDM
Langer, O., Yogev, Y., Most, O., Xenakis, E., 2005 426	Study Type: Case-control Evidence level: 2++	555 women with untreated gestational diabetes 1110 women treated for gestational diabetes 1110 nondiabetic women	Exclusion criteria included established pregestational diabetes, substance abuse, and multifetal gestation. GDM in untreated group diagnosed after week 37. Groups were matched on obesity, parity, gestational age at delivery, ethnicity and number of prenatal visits.  Country: USA	Intervention: Treatment for gestational diabetes (SMBG, diet alone or insulin +diet). Patients remained in diet group if OGTT at fasting <5.3 mmol/l, 2 hour postprandial levels <6.6 mmol/l and mean blood glucose levels <5.5 mmol/l. Diet involved caloric restriction using 25 (overweight/obese) to 35 (normal weight) kcal/kg for actual pregnancy weight with a recommended diet of 3 meals and 4 snacks. Patients who did not achieve established	Follow-up period:  Outcome Measures: Primary outcome: a composite variable composed of stillbirth, neonatal macrosomia/LGA, neonatal hypoglycaemia, erythrocytosis  Total pregnancy weight gain Fetal growth and wellbeing assessments LGA (>90th percentile) Macrosomia (birthweight>4000 g) Neonatal ponderal	Composite variable Untreated: 327/555 (59) Treated: 197/1110 (18) Nondiabetic: 126/1110 (11) OR untreated GDM vs nondiabetic 11.20 (8.71–14.39) OR treated GDM vs nondiabetic 1.69 (1.33–2.15)  Stratification by BMI: In the untreated group there was a significantly higher rate of adverse outcome in the overweight group compared to normal weight group. Comparable rates of adverse outcome were found between overweight and normal weight groups in the treated and nondiabetic groups.  Stratification by severity category: The untreated group had a higher level	Untreated gestational diabetes carries significant risks for perinatal morbidity in all disease severity levels.	The sample size was calculated to detect reductions of 30% in the primary outcome rate for the treated and nondiabetic control groups with a type 1 error of 5% (2-sided) and power of 80%.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				levels of glycaemic control after 2 weeks on diet therapy received insulin therapy (both intermediate and/or short-acting human insulin).  Comparison: No treatment for gestational diabetes	index >2.85 Respiratory distress Neonatal hypoglycaemia (2 consecutive values <2.2 mmol/l) Hyperbilirubinaemia Erythrocytosis Hypocalcaemia	of adverse outcomes in comparison with the treatment group in all severity categories.		
Jovanovic, L., Howard, C., Pettitt, D.  2005  80	Study Type: RCT  Evidence level: 1+	27 women with GDM	Age 29.7±6.9 years, HbA <sub>1c</sub> <7% at diagnosis.  Country: USA	Intervention: Insulin Aspart  5 minutes before meal using NovoPen-3  Both groups also received basal insulin (Novolin N)  Comparison: Human Insulin  30 minutes before meal	Follow-up period: From the diagnosis of GDM (18–28 weeks) to 6 weeks postpartum  Outcome Measures: Mean reductions in HbA <sub>1c</sub> Hypoglycaemic events Insulin specific antibodies Birthweight	Mean reductions in HbA <sub>1c</sub> : Insulin aspart; 0.3±0.5% Human insulin:0.1±0.4%, NS Upper respiratory tract infection: Insulin aspart: 14% Human insulin:23% Hypoglycaemic events: Insulin aspart: 0 Human insulin: 0 Average insulin-specific antibodies Insulin aspart:0.97% Human insulin: 0.07% Average percentile birthweights: Insulin aspart:40% Human insulin:44% Overall safety profiles were similar for Insulin aspart and Human insulin treatment groups	The safety and effectiveness of Insulin Aspart was comparable to Human Insulin in pregnant women. The ease of use of Insulin Aspart injected just before meals rather than 30 minutes prior to meals may offer a more convenient therapy for management of diabetes for patients with GDM	
Mecacci, F., et al  2003  85	Study Type: RCT  Evidence level: 1++	25 women with GDM received insulin lispro 24 women with GDM received normal insulin 50 non GDM controls	Diagnosed according to C&C criteria. Three main meals at 8.00am, 12.00, 8.00pm. Insulin given before each meal. No NPH insulin.  Country: Italy	Intervention: Insulin lispro  Comparison: Regular insulin	Follow-up period:  Outcome Measures: Blood glucose profiles performed using a reflectance meter and consisted of 9 determinations: fasting/preprandial, 1 and 2 hour post-prandial. HbA <sub>1c</sub> Birthweight Ponderal index Cranio-thoracic circumference	1 hr postprandial blood glucose values (Total) Insulin lispro:108.4±10.7 Regular insulin:121.0±13.2 Controls:105.6±4.7, <i>P</i> < 0.01  Cranial-thoracic circumference (CC/CT) ratio (percentile rank, n, %) <10 Lispro:1(4) Regular:2(8.3) Control:1(2) 10–25 Lispro:3 (12) Regular:9 (37.5) Control:7 (14), L,C vs R <0.05 26–50 Lispro:9 (36) Regular:6 (25) Control:19 (38)	In women with GDM the use of insulin lispro enabled the attainment of near-normal glucose levels at the 1 hour postprandial time point and was associated with normal anthropometric characteristics; the use of regular insulin was not able to blunt the 1 hr postprandial response to a near-normal extent and resulted in infants with a tendency toward disproportionate growth. Insulin lispro can be considered as a valuable option for the treatment of gestational diabetes.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						51–75 Lispro:8 (32) Regular:4 (16.7) Control:17 (34) 76–90 Lispro:4 (16) Regular:3 (12.5) Control:5 (10) >90 Lispro:- Regular:- Control:1 (2)		
Algert S;Shragg P;Hollingsworth DR;  1985 Apr  166	Study Type: Cohort  Evidence level: 2+	22 obese women with GDM 31 lean women with GDM (BMI<27) 10 nonobese normal glucose tolerant controls	GDM (O'Sullivan and Mahan criteria) Obese group were significantly older than other groups.  Country:	Intervention: Moderate calorie restriction  Obese women with GDM: 1700–1800 kcal/day (2 women received small amounts of regular insulin before each meal)  Lean women with GDM: 2000–3000 kcal/day  Comparison: Control group: recommended diet for pregnancy	Follow-up period:  Outcome Measures:	No other significant differences between groups in neonatal outcome.  Average calorie intake: Control: 2282±524 Lean women with GDM: 1822±224 Obese women with GDM: 1750±188 kcal/day  Mean weight gain during pregnancy: Control:13.4±3.5 kg Lean GDM:13.3±4.1 kg Obese GDM:10.6±7.7 kg, $P < 0.03$  Ketonuria was not observed in any patient even when reported caloric intakes were as low as 1500 to 1600 per day.  Mean birthweight was significantly higher in obese women with GDM than other two groups despite a lower caloric intake and a smaller weight gain during pregnancy.  Mean birthweight Control: 3448±303 g Lean GDM:3 544±598 g Obese GDM: 3922±662 g,, $P < 0.03$  All women had excellent glycaemic control (2 hour postbreakfast plasma glucose levels <7).	Modest calorie reduction to 25 kcal/kg per day (1700–1800 kal/day) is a reasonable and safe approach for obese women with GDM.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						HbA <sub>1c</sub> at 35 weeks Control: 6.4±1.2% Lean: 6.7±0.7% Obese: 6.8±0.4%		
Clapp III JE; 1998 158	Study Type: RCT Evidence level: 1+	A cross-over study of 14 nonpregnant nondiabetic women	Country:	Intervention: Low GI diet  After 7–10 days on the diet postprandial glucose was measured after a 540 kcal test meal. Each meal contained 17% protein, 28% fat and 55% carbohydrate but differed in the GI of the carbohydrates (54 s 92).  Comparison: Hi GI diet	Follow-up period:  Outcome Measures: Glycaemic response	The blood glucose values were significantly higher on the High GI diet at each time point through 120 minutes. As a result the average increase in blood sugar was significantly lower ( $P < 0.001$ ) on the low GI diet (0.33 mmol/min vs 0.72 mmol/min). The insulin response was also significantly lower ( $P < 0.001$ ) on the low GI diet (102 nmol/min vs 168 nmol/min)	The average increase in blood sugar was significantly lower on the low GI diet. Insulin response was also significantly lower.	
Dornhorst A; Nicholls JS; Probst F; Paterson CM; Hollier KL; Elkeles RS; Beard RW; 1991 Dec 164	Study Type: Cohort Evidence level: 2++	35 women with GDM 2337 nondiabetic women	GDM diagnosed after O'Sullivan screen with 3 hour OGTT. 2337 controls included two control groups of 35 women each matched for race, age, BMI, and parity - Group A (normal screen) and Group B (abnormal screen, normal OGTT).  Country:	Intervention: GDM women prescribed a calorie-restricted diet with complex carbohydrates replacing refined carbohydrates and fats. The total calorie intake was prescribed to be 30% less than consumed before pregnancy. The composition of the diet was 50% carbohydrate, 15% protein and 35% fat, with most carbohydrate taken as unrefined carbohydrate, protein as fish, white meat, beans and dairy products; and fat as polyunsaturated fat.  The criterion for remaining on dietary treatment alone was a diurnal glucose profile of averaged over six measurements of $\leq 6$ mM.  Comparison: Control group given no specific dietary advice.	Follow-up period:  Outcome Measures: Maternal weight gain Birth weight Birth weight percentile Macrosomia Admission to special care baby unit	8/43 (18%) women with GDM diagnosed during the study required insulin in addition to diet.  Weight gain Booking to delivery (kg): GDM: 4.6±4.9 General prenatal population: 9.3±5.3 Group A: 9.7±5.3 Group B: 9.7±5.4, $P < 0.005$ (GDM vs. controls groups). 28 week to delivery GDM: 1.7±1.6 Group A: 4.1±3.1 Group B: 4.6±2.9 $P < 0.005$ (GDM vs. controls groups).  Macrosomia ( $\geq 4000$ g) GDM: 2 (6%) General postnatal population: 178 (7.5%) Group A: 3 (9%) Group B: 8 (23%) $P < 0.005$ vs. general population  Birthweight, birth weight percentile, gestational age and admission to baby care unit were similar across all groups.	Calorie restriction reduced infant birth weights to levels comparable with the general prenatal population with no adverse maternal or neonatal outcomes.  Only 18% required insulin in addition to diet.	
Gillen L; Tapsell	Study Type: Case-	16 women with		Intervention: Diet in	Follow-up period:	The GDM group consumed significantly	Compared with glucose tolerant	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
LC;Martin GS;Daniells S;Knights S;Moses RG; 2002 160	control Evidence level: 2+	newly diagnosed GDM 24 healthy pregnant women	Country: Australia	women with newly diagnosed GDM  Comparison: Health pregnant women matched for age, prepregnancy weight at gestation age.	Outcome Measures:	less total energy and carbohydrate from low glycaemic index (GI) foods. ( $P = 0.01$ ).	women with GDM reported less carbohydrate rich foods with low GI values and a reduced spread of consumption of foods with higher GI values.	
Nolan CJ; 1984 Aug 161	Study Type: RCT Evidence level: 1+	5 women with gestational diabetes	mean gestation 33.4±1.4 weeks gestation  Country: NZ	Intervention: Low fat high unrefined carbohydrate diet  Comparison: Low carbohydrate diet	Follow-up period: 4 days  Outcome Measures: Fasting plasma glucose Urinary glucose output Fasting plasma triglyceride levels Fasting plasma cholesterol Concentrations Fasting plasma free fatty acid levels Glucose tolerance	A significant ( $P < 0.05$ ) improvement in glucose tolerance was observed in the high unrefined carbohydrate (HUC) diet compared to the low carbohydrate (LC) diet. Urinary glucose output was 50% lower during the HUC diet than during the LC diet. Fasting plasma triglyceride levels were generally lower. Fasting plasma cholesterol concentrations were 6% lower on the NUC diet ( $P < 0.01$ ) Fasting plasma free fatty acids were 14% lower ( $P < 0.02$ )	A diet rich in unrefined carbohydrate was associated with improvement in glucose tolerance, reductions in urinary glucose output, fasting FFA and cholesterol concentrations.	
Ostman EM;Frid AH;Groop LC;Bjorck IME; 2006 162	Study Type: RCT Evidence level: 1+	7 women with impaired glucose tolerance	Mean age 32 (range 27–41 years). Mean BMI 28.3±4.9. Previous diagnosis of gestational diabetes in last 3 years. Diagnosed with IGT at follow up (WHO criteria).  Country:	Intervention: Low GI/high dietary fibre bread Cross over design: 3 weeks each arm with 3 weeks washout period.  Comparison: High GI/low dietary fibre bread	Follow-up period:  Outcome Measures: Fasting blood glucose insulin serum lipids Intravenous glucose tolerance test followed by a euglycaemic-hyperinsulinaemic clamp was performed to assess potential effects of the two dietary regimens on insulin requirement and insulin resistance.	All women lowered their insulin response to the intravenous glucose challenge (mean 35%). No changes were found in fasting levels of glucose, insulin, HDL cholesterol or TG.	Replacing high GI/Low dietary fibre bread with low GI/high dietary fibre bread improved insulin economy in women with impaired glucose tolerance.	
Wang Y;Storlien LH;Jenkins AB;Tapsell LC;Jin Y;Pan JF;Shao YF;Calvert GD;Moses RG;Shi HL;Zhu XX; 2000 Apr 427	Study Type: Case-control Evidence level: 2+	56 women with GDM 38 women with glucose intolerance 77 women with normal glucose tolerance	Chinese GDM diagnosed using NDDG criteria for OGTT performed between 24 and 28 weeks of pregnancy.  Country:	Intervention: Diet (24 hour diet recall at time of screening).  Comparison: IGT (1 value met on OGTT by NDDG criteria) Normal glucose tolerance	Follow-up period:  Outcome Measures:	Weight GDM: 68.6±1.2 kg IGT: 66.1±1.4 kg Controls: 61.2±0.8 kg ( $P < 0.05$ GDM and IGT compared to controls). BMI GDM: 26.4±0.4 IGT: 25.7±0.5 Controls: 24.2 ±0.31 ( $P < 0.05$ GDM and IGT compared to controls).	Glucose intolerance and gestational diabetes were associated independently with a reduced intake of polyunsaturated fats.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Total energy (kcal) GDM:2134±61 IGT: 2223±75 Controls: 2133±42  Fat (%kcal) GDM:30.0±1.0 IGT: 30.6±1.0 Controls: 32.4±0.8  Protein (%kcal) GDM:16.2±0.4 IGT: 17.2±0.5 Controls:16.3±0.3  Carbohydrate (%kcal) GDM: 53.8±1.2 IGT: 52.3±1.3 Controls:51.7±0.9  Fat profile (%fat) Polyunsaturated: GDM:28.2±0.9 IGT: 29.5±1.0 Controls: 31.6±0.7, <i>P</i> < 0.05 Monosaturated GDM: 25.7±0.8 IGT: 28.8±1.0 Controls: 26.3±0.6 Saturated: GDM: 46.1±1.4 IGT: 41.8±1.6 Controls: 42.1±1.0, <i>P</i> < 0.05 P:S ratio GDM: 0.67±0.04 IGT: 0.77±0.05 Controls: 0.81±0.04 Fiber (g) GDM: 13.2±0.7 IGT: 14.4±1.3 Controls: 14.1±0.8		
Clapp, J. 2002 159	Study Type: RCT Evidence level: 1+	10 pregnant women on low glycaemic index diet 10 women on high glycaemic index diet	Country:	Intervention: Low glycaemic diet in pregnancy Comparison: High glycaemic diet	Follow-up period: Outcome Measures: Postprandial glucose response Postprandial insulin	Fasting glucose - Mean (SE) Mid pregnancy Low GI: 3.83 (0.11) High GI:4.00 (0.17) Late pregnancy Low GI: 3.78 (0.11)	Dietary carbohydrates which elevate postprandial glucose levels in mid and late pregnancy markedly increase fetoplacental growth rate. The type of carbohydrate eaten	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					response	High GI: 4.28 (0.22) $P < 0.05$	during pregnancy influences	
					Insulin resistance index	Fasting insulin	maternal fat deposition.	
					Insulin sensitivity index (after Matsuda and DeFronzo 1999)	Mid pregnancy Low GI: 67 (9) High GI: 83(11)		
					Maternal weight gain	Late pregnancy Low GI: 63 (9)		
					Birthweight	High GI: 131 (15), $P < 0.05$		
						Average postprandial glucose increase		
						Mid pregnancy Low GI: 0.61 (0.18) High GI: 1.44 (0.17), $P < 0.05$		
						Late pregnancy Low GI: 0.60 (0.23) High GI: 1.56 (0.22), $P < 0.05$		
						Average insulin increase		
						Mid pregnancy Low GI: 138 (300) High GI: 234 (36), $P < 0.05$		
						Late pregnancy Low GI: 186 (30) High GI: 324 (48) $P < 0.05$		
						Insulin resistance index		
						Mid pregnancy Low GI: 257 High GI: 336, $P < 0.05$		
						Late pregnancy Low GI: 238 High GI: 536, $P < 0.05$		
						Insulin sensitivity index		
						Mid pregnancy Low GI: 0.53 High GI: 0.40, $P < 0.05$		
						Late pregnancy Low GI: 0.54 High GI: 0.24, $P < 0.05$		
						Birthweight (kg) - Mean (SE)		
						Low GI:3.33 (0.11) High GI:4.17 (0.12), $P < 0.01$		
						Ponderal index:		
						Low GI:2.47 (0.08)		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						High GI:2.74 (0.04), $P < 0.01$  Fat mass (g) Low GI:266 (44) High GI:427 (61), $P < 0.01$  Maternal weight gain (kg) Low GI:10.4 (1.1) High GI:18.6 (1.1), $P < 0.01$		
Fraser, R., Ford, F., Lawrence, G.  1988  157	Study Type: RCT  Evidence level: 1++	15 non pregnant women  14 pregnant women	Country: UK	Intervention: Diet  Comparison: Diet 1: 40% energy as carbohydrate 10% as dietary fibre Diet 2: 40% energy as carbohydrate 52 g dietary fibre Diet 3: 60% energy as carbohydrate and 84 g dietary fibre	Follow-up period:  Outcome Measures: Insulin sensitivity	On diet 1 there was a loss of insulin sensitivity in pregnancy but not on diets 2 or 3.	The loss of insulin sensitivity which is typical of western women in the third trimester of pregnancy and which is considered to be physiological may be a diet induced artefact.	
Fraser, B.,  1981  156	Study Type: Cohort  Evidence level: 2++	64 nonpregnant women  27 women at 30 weeks gestation  31 women after 37 weeks gestation	African  Country: Kenya	Intervention: Glucose tolerance testing  Comparison:	Follow-up period:  Outcome Measures: Blood glucose levels	Mean (1 SD) blood glucose levels Fasting Non pregnant: 73.5 (13.1) Week 30: 67.0 (7.4) Week 37+:66.5 (9.6), $P = 0.05$  Peak value Non pregnant:137.4 (22.01) Week 30:123.6 (25.2) Week 37+:118.3 (23.3), $P = 0.05$  One hour: Non pregnant:129 (23.8) Week 30:109.7 (26.8) Week 37+:108.1 (25.0), $P = 0.05$  Mean +2SD (upper criteria for normality) Fasting Non pregnant:100 Week 30:82 Week 37+:86  Peak value Non pregnant:181 Week 30:174 Week 37+:165  One hour:	Normal pregnant women in Nairobi have a lower fasting level of blood glucose than non pregnant women. The diabetogenic influence of pregnancy is not demonstrated in this series; in fact the opposite is the case as pregnant women have improved homeostasis with advancing pregnancy.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Non pregnant:177 Week 30:163 Week 37+:158		
Bonomo, M., et al. 2004 180	Study Type: RCT Evidence level: 1+	151 women with GDM managed according to US assessment 78 GDM controls	Women diagnosed with GDM between 24 and 28 weeks gestation. Diagnosed using 50 g GCT screen followed by 100 g OGTT (C&C criteria). Exclusions: Other medical complications affecting fetal growth. All women on SMBG and diet or diet and insulin if bg exceeded target values.  Country: Italy	Intervention: US exams were scheduled every two weeks in the intervention group  BG targets for intervention group were 4.4 mmol/l fasting and 5.5 mmol/l postprandial if $\geq$ 75th abdominal circumference centile and 5.5 mmol/l fasting and 7.7 mmol/l postprandial if $<$ 75th abdominal circumference centile  Comparison: US exams were scheduled at 34 and 38 weeks in the control group.  BG targets for control group were 5 mmol/l fasting and 6.6 mmol/l postprandial.	Follow-up period:  Outcome Measures: Macrosomia (birthweight $\geq$ 4000 g LGA Neonatal hypoglycaemia Admission to neonatal intensive care unit	Insulin treatment was required in 16.7% of control group and 30.5% of intervention group ( $P = 0.024$ )  The intervention group had significantly lower incidence of LGA and macrosomia		
Brankston, G., Mitchell, B., Ryan, E. 2004 169	Study Type: RCT Evidence level: 1++	32 women with gestational diabetes	GDM diagnosed after 50 g screen (GDM diagnosed if $\geq$ 10.3 mmol/l) and 75 g OGTT (Canadian Diabetic Association Criteria). Gestational age between 26 and 32 weeks, BMI $<$ 4  Country: Canada	Intervention: Diet + Resistance exercise  Diet: 40% carbohydrate, 20% protein, 40% fat, calculated at 24 to 30 cal/kg per day on basis of subject's ideal prepregnant body weight, and divided into 3 meals and 3 snacks.  Circuit type resistance exercise 3xweek. Exercise intensity progressively increased.  Glucose monitoring in	Follow-up period:  Outcome Measures: Requirement for insulin Gestational age at delivery Birthweight	32 women completed the study  Required insulin Diet: 9/16 (56.3%) Diet +exercise: 7/16 (43.8%), $P = 0.48$  Amount of insulin required: Diet:0.48 $\pm$ 0.3 Diet+insulin: 0.22 $\pm$ 0.2, $P <$ 0.05  Latency to insulin requirement: Diet:1.11 $\pm$ 0.8 Diet+insulin:371 $\pm$ 3.1, $P <$ 0.05  Within the diet+exercise group 30% of the women who exercised 2 to 3 times per week were prescribed insulin	Resistance exercise may help to avoid insulin therapy for overweight women with gestational diabetes.	Diagnostic fasting and 1-hour values were significantly higher in the diet alone group  A larger sample size ( $n = 56$ ) would be needed to show that the effect that was shown (12.5%) was significant

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				<p>both groups included daily fasting and 1 or 2 hour postprandial measurements.</p> <p>Insulin therapy initiated if any of the following were exceeded consistently:                      Mean fasting <math>\geq 5.3</math> mmol/l                      Mean 1-hour postprandial <math>\geq 7.8</math>                      Mean 2-hour postprandial <math>\geq 6.7</math> mmol/l.                      These values were also goals for insulin therapy.</p> <p>Comparison: Diet</p>		<p>therapy compared to 67% of those who exercised 0 to 1.9 times.</p> <p>A subgroup analysis that looked only at women with a prepregnancy BMI <math>&gt;25</math> found that women in the diet+exercise group showed a significantly lower incidence of insulin use (3/10 vs 8/10, <math>P &lt; 0.05</math>).</p> <p>Home blood glucose levels (4 women did not record adequately)                      Fasting                      Diet (<math>n = 12</math>): <math>5.1 \pm 0.65</math>                      Diet+exercise (<math>n = 12</math>): <math>4.7 \pm 0.39</math>, <math>P = 0.07</math>                      Pooled 2-hour postprandial:                      Diet: <math>6.4 \pm 0.81</math>                      Diet+exercise: <math>6.0 \pm 0.29</math>, <math>P &lt; 0.05</math></p> <p>There were no significant differences in gestational age at delivery, rate of caesarean deliveries or birthweight.</p>		
Pettitt, D., 2003 189	Study Type: RCT Evidence level: 1+	15 women with gestational diabetes randomised to insulin aspart of regular human insulin	Women with GDM unable to control glucose concentrations with diet and exercise  Country: USA	<p>Intervention: Insulin Aspart (5 minutes before a meal)</p> <p>Randomised cross over study:                      Day 1: Test meal with no insulin                      Day 2: Test meal with either insulin or aspart                      Day 3: Test meal with the other insulin preparation                      Test meal consisted of yoghurt and banana (40% carbohydrate, 20% protein and 40% fat).</p> <p>Comparison: Regular insulin (30 minutes before a meal)</p>	<p>Follow-up period:</p> <p>Outcome Measures:                      Plasma glucose concentration area under the curve and Serum Insulin area under the curve calculated at 120, 180 and 240 minutes.</p>	<p>Glucose</p> <p>60 minutes:                      No exogenous insulin: <math>122.8 \pm 3.0</math>                      Regular insulin: <math>115.8 \pm 2.9</math>, <math>P &lt; 0.05</math>                      Insulin aspart: <math>111.6 \pm 3.9</math>, <math>P = 0.01</math></p> <p>90 minutes:                      No exogenous insulin: <math>112.8 \pm 2.8</math>                      Regular insulin: <math>108.4 \pm 2.6</math>, <math>P &lt; 0.05</math>                      Insulin aspart: <math>103.3 \pm 4.3</math>, <math>P &lt; 0.05</math></p> <p>120 minutes:                      No exogenous insulin: <math>102.5 \pm 2.5</math>                      Regular insulin: <math>100.6 \pm 2.5</math>                      Insulin aspart: <math>93.1 \pm 3.5</math>, <math>P = 0.01</math></p> <p>180 minutes:                      No exogenous insulin: <math>85.1 \pm 2.1</math>                      Regular insulin: <math>79.9 \pm 2.6</math>, <math>P &lt; 0.05</math>                      Insulin aspart: <math>72.5 \pm 3.4</math>, <math>P = 0.01</math>, (<math>P &lt; 0.05</math> apart vs regular insulin)</p> <p>240 minutes:                      No exogenous insulin: <math>74.7 \pm 1.7</math>                      Regular insulin: <math>66.7 \pm 2.0</math>, <math>P = 0.01</math>                      Insulin aspart: <math>65.5 \pm 2.0</math>, <math>P = 0.01</math></p> <p>Insulin:                      60 minutes:</p>	<p>Insulin aspart was effective in decreasing the postprandial glucose concentration when administered 5 minutes before a meal to women with GDM.</p> <p>Regular human insulin failed to make a significant impact in lowering the postprandial glucose concentration.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>No exogenous insulin:72.3±9.7            Regular insulin:84.7±10.8, <math>P &lt; 0.05</math>            Insulin aspart:95.9±10.9, <math>P = 0.01</math></p> <p>90 minutes:            No exogenous insulin:53.9±8.6            Regular insulin:68.2±10.4, <math>P &lt; 0.05</math>            Insulin aspart:77.4±8.8, <math>P = 0.01</math></p> <p>120 minutes:            No exogenous insulin:35.6±6.2            Regular insulin:55.2±9.4, <math>P = 0.01</math>            Insulin aspart:51.7±9.8, <math>P = 0.01</math></p> <p>180 minutes:            No exogenous insulin:20.0±4.1            Regular insulin:26.9±4.5, <math>P &lt; 0.05</math>            Insulin aspart:24.6±4.6</p> <p>240 minutes:            No exogenous insulin:11.2±3.0            Regular insulin:18.8±3.3, <math>P = 0.01</math>            Insulin aspart:15.4±1.9, <math>P &lt; 0.05</math></p> <p>C-peptide            60 minutes:            No exogenous insulin:6.8±0.7            Regular insulin:5.8±0.4            Insulin aspart:5.5±0.3, <math>P &lt; 0.05</math></p> <p>90 minutes:            No exogenous insulin:6.2±0.6            Regular insulin:5.8±0.5            Insulin aspart:5.4±0.5</p> <p>120 minutes:            No exogenous insulin:5.4±0.7            Regular insulin:5.4±0.6            Insulin aspart:4.8±0.7</p> <p>180 minutes:            No exogenous insulin:3.9±0.5            Regular insulin:3.1±0.4            Insulin aspart:2.7±0.4, <math>P = 0.01</math>            (<math>P &lt; 0.05</math> aspart vs regular insulin)</p> <p>240 minutes:            No exogenous insulin:2.6±0.5            Regular insulin:1.8±0.4, <math>P = 0.01</math>            Insulin aspart:1.5±0.2, <math>P = 0.01</math>            (<math>P &lt; 0.05</math> aspart vs regular human insulin)</p> <p>Glucose areas under the curve were significantly lower with insulin aspart but not with regular human insulin.</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Conway, D., Gonzales, O., Skiver, D. 2004 184	Study Type: Cohort Evidence level: 2+	75 women with GDM treated with glyburide (glibenclamide)	GDM (ADA criteria). All women on diet (40% carbohydrate, 35% protein, 25% fat) and SBGM 7x/day (before and 2 hour after each meal and before bed). Targets mean level $\leq 5.8$ , fasting $\leq 5.2$ , 2 hour postprandial $\leq 6.3$ . If good control was not achieved within 2 weeks of diet patients offered glyburide as alternative to insulin (if gestational ages 11–33 weeks and OGTT fasting level $< 7.7$ ).  Country:	Intervention: Glibenclamide  Patients started on 2.5 mg/day.  Comparison:	Follow-up period:  Outcome Measures:	63/75 women (84%) treated with glibenclamide were able to achieve good glycemic control. 12(16%) switched to insulin prior to delivery.  The two groups were similar in terms of baseline characteristics and diabetes risk factors but women who were successfully treated with glibenclamide were had significantly lower values on the OGTT.  Fasting on OGTT: Glibenclamide: $5.61 \pm 0.77$ Insulin: $6.3 \pm 1.32$ , $P = 0.02$ 1 hour value Glibenclamide: $11.28 \pm 1.27$ Insulin: $12.65 \pm 1.98$ , $P < 0.01$ 2 hour value Glibenclamide: $9.30 \pm 1.87$ Insulin: $11.22 \pm 3.63$ , $P < 0.01$ 3 hour value Glibenclamide: $7.32 \pm 1.82$ , $P < 0.01$ Insulin: $9.68 \pm 3.58$  Fasting levels of $\geq 5.2$ mmol/l detected 92% of women who converted to insulin but had a false positive rate of 70%.  Macrosomia Glibenclamide: 11.1% Insulin: 8.3% (NS)  Neonatal IV glucose infusion: Glibenclamide: 25% Insulin: 12.7% (NS)	It appears that women with GDM can be successfully treated with glibenclamide when diet therapy alone fails to reduce blood glucose values sufficiently.  Women who are farther along the continuum to type 2 diabetes, as evidenced by an accumulation of risk factors, or fasting hyperglycaemia, may be better served by treatment with insulin rather than glyburide.	
Schaefer-Graf, U., et al 2004 179	Study Type: RCT Evidence level: 1+	99 women with GDM managed according to Ultrasound assessment of abdominal circumference 100 controls (managed by glycaemic levels)	All women prescribed diet (30 kcal/kg/day) with caloric restriction for overweight women (25 kcal/kg/day). Women advised to exercise after meals and taught to self monitor blood glucose with a memory reflectance meter. After one week	Intervention: Insulin started when the abdominal circumference (AC) $> 75$ th percentile before 36 completed weeks. Glucose targets were not discussed with patients and glucose values were not used as a guide to management, unless any fasting value $> 6.6$ mmol/l or any 2 hour	Follow-up period:  Outcome Measures: SGA ( $\leq 10$ th percentile) LGA ( $\geq 90$ th percentile)	In the control group 30 women (30%) met the criteria for insulin. Of these 27 received insulin, 2 refused and 1 left care.  In the US group 40 women (40%) met the criteria for insulin, all with AC $> 75$ th percentile. Of these, 3 refused insulin and 1 did not receive therapy due to an erroneous AC calculation.  Neonatal outcomes (no significant	GDM management based on fetal growth combined with high glycemic criteria provides outcomes equivalent to management based on strict glycemic criteria alone.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			women assessed for eligibility to protocol. Criteria: GDM (2 abnormal values on 75 g OGTT). All capillary fasting values <6.6 and 2 hour <11.0 mmol/l. 16–34 weeks gestation. No drug abuse.	value greater than 11.0 mmol/l. Insulin was not prescribed, regardless of AC, when FCG <4.4 and 2 hour value was <5.5. US was performed at entry and then 4-week intervals at 20, 4, 28, 32 and 36 weeks.  Insulin was titrated to achieve FCG <4.4 mmol/l and 2 hour <6.05 mmol/l  Comparison: Insulin prescribed before 36 weeks if 2 glucose profiles had ≥2 elevated values (FCG>4.95 mmol/l, 2 hour >6.6 mmol/l) or 4 profiles had at least 1 elevated value during a 2 week period. Insulin was titrated to achieve FCG <4.95 & 2 hour pp <6.6 mmol/l		differences) C-section (%): US group: 18 Control group:19 Birth weight (g) US group:3306.1±558 Control group:3371.2±500 SGA (%) US group:12 Control group:13 LGA (%) US group: 12 Control group: 10 Hypoglycaemia US group: 17 Control group: 16 Transfer to NICU US group:14 Control group: 15		
Kjos, S.  2001  178	Study Type: RCT  Evidence level: 1+	48 women with GDM managed on relaxed glycaemic criteria and ultrasound measurement of fetal AC.  48 women with GDM managed on maternal glycaemic criteria	Inclusion criteria 1)GDM, 2) FPG concentrations >5.8 and <6.6 3)gestational age >14 and <34 weeks at time of entry to study 5) No drug abuse. All women received instruction in SBGM, diet and exercise.  Country: USA	Intervention: Intervention group: Prescribed insulin if fetal abdominal circumference (AC) was ≥70th percentile or FPG >6.6 mmol/l. Insulin was titrated to achieve preprandial capillary blood glucose ≤4.4 mmol/l and 2 hour postprandial values of ≤6.05 mmol/l.  After the baseline measurements, AC measurements made at 20, 24, 28, 32 and 36 weeks.  Comparison: Control group: Insulin prescribed	Follow-up period:  Outcome Measures: SGA (≤10th percentile) LGA (≥90th percentile)	Mean BMI significantly > in control group.  In the intervention group 22 women (45%) had a fetal AC of ≥70th percentile at enrolment. 21 of these women were immediately started on insulin. An additional 9 women in the intervention group began insulin subsequently because AC≥70th percentile ( <i>n</i> = 6) or FSG >6.6 mmol/l ( <i>n</i> = 2) or because of inadequate SBGM ( <i>n</i> = 1)  Neonatal outcomes: Birthweight: Intervention: 3369 (461) Control: 3271 (458)  Birthweight ≥4000 g Intervention: 3 (6.3%) Control: 2 (4.2%)	US measurement of fetal AC identified fetuses at low risk of neonatal macrosomia.  The difference in C-section rate was not explained by birthweights.	Control group: Insulin prescribed to all women immediately

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				to all women immediately. Insulin adjusted to achieve preprandial capillary blood glucose concentrations $\leq 4.95$ mmol/l and 2 hour postprandial values $\leq 6.6$ mmol/l			C-section rate was significantly lower in the control group (33.3% vs 14.6%, $P = 0.03$ ).	
Botta, R., et al  175	Study Type: Cohort  Evidence level: 2+	75 women with GDM  75 women with normal glucose tolerance	GDM according to NDDG & C&C criteria. All women instructed on SBGM and diet. Insulin started when fasting bg $>5.2$ mmol/l and 2 hour pp $> 6.9$ mmol/l  Country:	Intervention: What factors are predictive of insulin treatment in women with GDM?  Comparison:	Follow-up period:  Outcome Measures: Gestational week at diagnosis Pregpregnancy BMI Blood glucose levels during OGTT Area under the curve (AUC) Triglycerdie levels Weight gain	52 pateints were treated with diet alone and 23 with diet and insulin.  Week of diagnosis: Insulin group: $19.4 \pm 6.9$ weeks Diet group: $24.5 \pm 6.2$ weeks, $P < 0.003$  Pregestational BMI Insulin: $28.8 \pm 5.1$ Diet: $27.7 \pm 5.4$ Normal glucose tolerance (NGT): $25.7 \pm 4.5$ $P < 0.05$ insulin group vs NGT  Weight gain: Insulin: $5.3 \pm 4.7$ Diet: $8.0 \pm 5.6$ NGT: $5.8 \pm 5.4$ $P < 0.05$ diet vs insulin and NGT  Triglycerdie levels (mg/dl) Insulin: $232.2 \pm 110.7$ Diet: $185.9 \pm 81.8$ NGT: $147.4 \pm 70.1$ $P < 0.001$ insulin group vs NGT  3 hour bg levels on OGTT Insulin: $9.2 \pm 2.7$ mmol/l Diet: $7.04 \pm 2.2$ $P < 0.001$  AUC Insulin: $10.97 \pm 1,949$ Diet: $9,199 \pm 1,277$ , $P < 0.01$  Infant body weight index Insulin: $1.24 \pm 0.16$ Diet: $1.14 \pm 0.14$ NGT: $1.09 \pm 0.7$ $P < 0.001$ insulin group vs NGT and diet	Early diagnosis of GDM, early rise in triglyceride levels and elevated blood glucose levels 180 minutes after glucose load in women with gestational diabetes with a pregestational BMI $>28$ and normal weight gain can be predictive of insulin treatment.  In these women insulin treatment was initiated when blood glucose levels were higher than 5.2 (fasting) and 6.9 mmol/l (2 hour postprandial). This treatment strategy was insufficient to normalise birthweights.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						group LGA (>90th percentile) Insulin group: 39% Diet: 32% NGT: 21%		
Bochner, C., et al 1987 176	Study Type: Cohort Evidence level: 2+	201 women with GDM	GDM (according to O'Sullivan and Mahan) diagnosed before 34 weeks. Maintained weekly fasting glucose levels <5.5 mmol/l and 2 hour postprandial glucose levels <6.6 mmol/l with dietary management alone.  Country: USA	Intervention: 30–33 week Ultrasound (US)  Comparison:	Follow-up period:  Outcome Measures: Sensitivity to predict macrosomia or labour dystocia at term (cut off point 90th percentile) Labour dystocia (failure to progress in labour for >2 hours once the active phase of labour had begun) Shoulder dystocia	Infants with a birthweight of >90th percentile had significantly > incidence ( $P < 0.001$ ) of C-section for failure to progress in labour (41.7% vs 14.3%), shoulder dystocia (16.7% vs 0.7%) and birth trauma (3.6% vs 20.8%) compared with infants with a birth weight <90th percentile.  Predicting macrosomia at term: AC >90th percentile: 36/64 AC ≤ 90th percentile: 5/137 Sensitivity: 87.8 Specificity: 82.5 PPV : 56.3 NPV: 96.4	Patients with fetal abdominal circumference >90th percentile at 30 to 33 weeks had a significantly increased incidence of failure to progress, shoulder dystocia and birth trauma, whereas patients with AC measurement ≤90th percentile had no greater risk than general population.	
Catalano, P., et al 2003 428	Study Type: Cohort Evidence level: 2++	195 women with GDM 220 women with NGT	GDM diagnosed with 3 hour 100 g OGTT (NDDG). Exclusions: Birthweight <2000 g, multifetal gestations and neonates with abnormalities.  Country: USA	Intervention: Women with GDM performed home glucose monitoring (7 times/day). Targets <5.5 mmol/l (fasting) and <6.6 mmol/l (2 hour pp). All women encouraged to walk for 30 minutes after meals. Insulin initiated when women had persistent glucose concentrations >targets.  Comparison: 220 women with NGT	Follow-up period:  Outcome Measures:	67/195 women (34%) required insulin. Women treated with insulin had greater pregestational weight ( $87.9 \pm 25.5$ kg vs $77.4 \pm 21.1$ kg, $P < 0.0002$ ) and parity ( $49\% .1$ vs $32\% >1.0$ , $P = 0.02$ ) than diet group. There was no significant difference in birthweight between groups ( $3497 \pm 556$ vs $3346 \pm 542$ g, $P = 0.07$ ).  The skinfold thickness was significantly greater in the insulin group than in the NGT group. Subscapular: $5.9 \pm 1.6$ mm vs $5.1 \pm 1.2$ mm, $P = 0.0001$ Triceps: $5.0 \pm 1.1$ mm vs $4.5 \pm 1.0$ mm, $P < 0.003$ Flank: $4.5 \pm 1.2$ mm vs $4.0 \pm 1.1$ mm, $P = 0.01$ Thigh: $6.3 \pm 1.5$ mm vs $5.8 \pm 1.3$ mm, $P = 0.02$ Abdomin: $4.0 \pm 1.4$ mm vs $3.3 \pm 0.9$ mm, $P = 0.0001$  There was significantly greater fat mass ( $492 \pm 215$ g vs $407 \pm 196$ g, $P = 0.006$ )	Infants of women with GDM have increased body fat compared with women with NGT. This is independent of birth weight.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						and % body fat (13.6% $\pm$ 4.6% vs 11.7% $\pm$ 4.5%, $P = 0.007$ ) in the insulin group compared with the diet group.  Regression: In the GDM group gestational age had the strongest correlation with birthweight although fasting blood glucose had the strongest correlation with fat mass and percent body fat.		
Jovanovic, L. 1999 187	Study Type: RCT  Evidence level: 1+	23 women with GDM taking regular human insulin 19 women with GDM taking insulin lispro	>18 years of age, diagnosed with OGTT between 14 and 32 weeks.  Country: USA	Intervention: Insulin lispro  Comparison: Regular human insulin	Follow-up period:  Outcome Measures: Serum insulin Blood glucose C peptide concentrations  C-sections Gestational age at delivery Neonatal birthweight 1-min and 5-min apgar scores Fetal abnormality Neonatal hypoglycaemia Neonatal hypocalcaemia	Women randomised to the lispro group were older (34.2 years) than in the regular insulin group (29.8 years, $P < 0.01$ )  No insulin lispro was detected in umbilical cord blood.  The areas under the curve for glucose, insulin and C peptide were lower for insulin lispro group, a difference that remained significant after multiple regressions (age, BMI, fasting plasma glucose concentration).  HbA <sub>1c</sub> (%) Regular human insulin At enrollment: 5.24 $\pm$ 0.09 After 6 weeks: 5.16 $\pm$ 0.12 Difference from baseline: 0.07 (2.8%) Lispro At enrolment: 5.47 $\pm$ 0.09 After 6 weeks: 5.12 $\pm$ 0.11 Difference from baseline: 0.0018 (5.7%)	The postprandial glucose rise was significantly less after a standardized dose of insulin lispro than after regular human insulin. It was also effective in lowering overall glycaemia. The women in the lispro group had less hypoglycaemia.	Not blinded
Jovanovic-Peterson, M., et al	Study Type: RCT	9 women with GDM in diet group	GDM	Intervention: Diet plus cardiovascular	Follow-up period:	HbA <sub>1c</sub> : Diet: 4.7% $\pm$ 0.2%	Arm ergometer training is feasible n women with	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1989 168	Evidence level: 1++	10 women with GDM in diet plus exercise group	Country: USA	conditioning  Diet: 6 weeks, 24–30 kcal/kg/24 hours; 20% protein, 40% carbohydrate, 40% fat.  Diet plus exercise: As above + 20 minutes exercise 3 times/ week on arm ergometer.	Outcome Measures: HbA <sub>1c</sub> 50 g GCT Self monitoring (fasting and 1 hour after meals).	Diet + exercise: 4.2%±0.2%, <i>P</i> < 0.001  GCT: Fasting: Diet: 4.8±0.3 mmol/l Diet + exercise: 3.9±0.4 mmol/l, <i>P</i> < 0.001 1-hour value: Diet: 10.3±0.7 mmol/l Diet + exercise: 5.8±1.0, <0.001	gestational diabetes mellitus and results in lower HbA <sub>1c</sub> fasting and 1 hour plasma glucose concentrations than diet alone.	
Buchanan, et al 1994 177	Study Type: RCT  Evidence level: 1+	303 women with GDM	GDM (fasting <5.8 mmol/l). Hispanic women between 29 and 33 weeks gestation.  Country: USA	Intervention: 30 women with AC ≥75th percentile in diet (and SBGM) and insulin group. Insulin dose adjusted to maintain premeal glycaemia between 3.3 and 4.4 mmol/l and 2 hour postmeal glycaemia <6.1 mmol/l.  Comparison: 29 women with AC ≥75th percentile in diet (+ SBGM) group  205 women with AC <75th percentile prescribed diet. Insulin administered if fasting glucose ≥5.8 mmol/l.	Follow-up period:  Outcome Measures: Birthweight Body length Tricep thickness Subscapular thickness Iliac crest skin fold thickness Birth trauma	205/303 (68%) women with GDM had AC <75th percentile. Of these, 15 (7.3%) were placed on insulin therapy because of persistent fasting glycaemia ≥5.8 mmol/l. 11 women delivered before 36 weeks and 8 delivered at another location. Analysis was undertaken on data from remaining 171 women. Birthweight: 3,444±38 g LGA: 24/171 (14%)  Women with AC ≥75th percentile 1. Birthweight Diet+insulin: 3,647±67 g Diet: 3,878±84 g <i>P</i> < 0.02 2. LGA Diet+insulin: 4/30 (13%) Diet: 13/29 (45%) <i>P</i> < 0.02	Fetal ultrasound identified women with mild GDM at risk for fetal macrosomia. Insulin therapy reduced the macrosomia indicating that fetal ultrasound can be used to guide metabolic therapy in pregnancies complicated by mild GDM.	Rate of LGA infants in group <75th percentile does not include women removed from analysis due to initiation of insulin ( <i>n</i> = 15).  In total this strategy would give insulin to 37% of GDM population (98 women with AC ≥ 75th percentile + 15 women with persistent fasting glycaemia >5.8 mmol/l)
						Neonatal skinfold measurements at 3 sites were reduced in insulin treatment group ( <i>P</i> < 0.005)  The insulin treated group had much higher c-section rates (43%, <i>P</i> < 0.05 vs other groups)  No difference in rates of neonatal hypoglycaemia Glucose levels in both groups were lower at the follow-up breakfast test than at baseline ( <i>P</i> < 0.01 for diet only, <i>P</i> < 0.0001 for insulin group). Weekly		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>capillary blood glucose readings also reduced significantly in both treatment groups, although they were 0.3–0.6 mmol/l lower in the insulin group throughout the treatment period (<math>P &lt; 0.005</math>).</p> <p>The frequency of symptomatic hypoglycaemia (<math>&lt; 3.3</math> mmol/l) was 0.3 episodes per week. Half of the insulin treated women experienced no symptomatic hypoglycaemia. 5 women had <math>&gt; 5</math> episodes during 5–10 Weeks of treatment. There were no episodes requiring assistance.</p> <p>3/29 women in the diet treated group would have qualified for insulin based on glycaemic control (fasting <math>&lt; 5.5</math> and 1 hour pp <math>&lt; 7</math>). 1 of these women had a LGA infant. 26/29 women in diet treated group would not have qualified for insulin treatment on the basis of glycaemic control. 12 of these women had a LGA infant.</p>		
Simmons, D., 1997 429	Study Type: Cohort Evidence level: 2+	Infants of 20 mothers with gestational diabetes	GDM. Maori and pacific islander population. Exclusions: (Maternal) Smoked $\geq 10$ cigarettes/day, late booking, poor clinic attendance, antenatal or perinatal complications  Country: NZ	Intervention: Maternal insulin treatment  Comparison:	Follow-up period: Follow up (mean 2 years 8 months $\pm$ 1 month) of infants of mothers with GDM.  Outcome Measures: Crown-rump length Biceps skinfold thickness Triceps skinfold thickness: Subscapular skinfold thickness: Suprailiac skinfold thickness: Waist, hip and head circumference.	Follow-up data was obtained from 11/20 women treated with diet and 9/15 women treated with insulin. Women treated with insulin were older, had $> \text{BMI}$ and a greater proportion of pacific islanders.  Subscapular skinfold thickness (mm) median and interquartile range: Diet group: 7.9 (7.0–9.4) Insulin group: 5.9 (5.4–7.9) $P < 0.05$ Bicep skinfold thickness: Diet: 6.3 (6.0–9.0) Insulin: 5.1 (4.3–6.6) $P = 0.01$ Triceps skinfold thickness (mm) Diet: 10.8 (9.0–11.3) Insulin: 8.4 (7.1–10.7) $P = 0.06$ Sum (mm) Diet: 34.2 (29.9–36.1) Insulin: 26.2 (23.7–34.9)	A larger RCT is required to answer the question: Does insulin therapy reduce the risk of obesity in offspring of mothers with GDM?	
Drexel, H., 1988	Study Type: Cohort Evidence level: 2++	102 women with GDM 102 nondiabetic women	Country:	Intervention: GDM to maintain blood glucose concentration $< 7.15$ mmol/l 1 hour after	Follow-up period: Austria  Outcome Measures:	By the end of gestation 88/102 women received insulin at a mean dose of 18 U/day. Fasting blood glucose levels on OGTT	Excess mortality and morbidity can be prevented by early institution of tight metabolic control.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
430		25 untreated women due to late presentation		breakfast. Treatment consisted of a diet low in oligosaccharides and fat and, if necessary, once daily insulin.  Comparison: GDM (O'Sullivan criteria) Diet (low fat, low oligosaccharide )	Birthweight Macrosomia Dystrophia hypoglycaemia Hypocalcaemia Hyperbilirubinemia Fetal acidosis Apgar scores	did not predict insulin use.  LGA Control: 9/103 GDM:7/103 Untreated GDM:5/25  >4000 g Contol:9/103 GDM:6/103 Untreated GDM:4/25  >4500 g Contol:2/103 GDM:1/103 Untreated GDM:1/25		
Cheng YW;Esakoff TF;Block-Kurbisch I;Ustinov A;Shafer S;Caughey AB;  2006 Nov  152	Study Type: Cohort  Evidence level: 2-	14,771	Inclusion criteria: women had a 50-g glucose loading test during the study period (including the ones who underwent early screening for GDM and screened at 24–28 weeks' gestation and beyond).  Exclusion criteria: Intrauterine fetal demise, neonates with known lethal congenital anomalies, multiple gestations and maternal diabetes diagnosed before the study pregnancy	Intervention: 50 g glucose load test (GLT). Women with GLT results $\geq 200$ mg/dL  Comparison: GLT $< 200$ mg/dL stratified by GDM diagnosis.	Follow-up period:  Outcome Measures: Maternal outcomes: Mode of delivery (as well as indication for caesarean delivery), preeclampsia, third- or fourth degree perineal lacerations, postpartum hemorrhage and peripartum infections. Neonatal outcomes: Birth weight, preterm delivery, shoulder dystocia, 5-min Apgar score $< 7$ and birth trauma	Estimated risks in women with GLT $\geq 200$ mg/dL but no GDM: caesarean section OR 4.18 (95% CI 1.15–15.2); preterm delivery $< 32$ weeks' gestation OR 8.05 (95% CI 1.02–63.6), shoulder dystocia OR 15.14 (95% CI 64–140), 5-minute Apgar score $< 7$ for neonates OR 6.41 (95% CI 1.23–33.3).  Estimated risks in women with a GLT $\geq 200$ mg/dL and diagnosed with GDM: caesarean section OR was also elevated compared to those with a GLT $< 200$ mg/dL (OR 2.24, 95% CI 1.19–4.21).	Although a markedly elevated GLT may not be universally diagnostic for GDM, a GLT value of $\geq 200$ mg/dL is associated with unfavourable perinatal outcomes and may warrant further follow-up regardless of the subsequent GTT results.	
			Country: USA					

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Downs DS;Ulbrecht JS; 2006 Feb 171	Study Type: OtherRetrospective  Evidence Level: 2-	Intervention: A mail survey assessing their self-reported exercise beliefs (advantages, barriers, and important social influences) and behaviours. Leisure-Time Exercise Questionnaire (LTEQ), assessing mild, moderate, and strenuous exercise done for at least 15 min  Comparison:	28	Postpartum women with gestational diabetes  Country: USA	Behavioural (exercise advantages), normative (important others with a strong influence), and control (factors preventing exercise	-Strongest perceived advantage of exercise during pregnancy was controlling blood glucose and during postpartum it was controlling weight -Most common barrier to exercise during pregnancy was fatigue and postpartum it was lack of time -Women's husband/partner most strongly influenced their exercise during pregnancy and postpartum -Women exercised more during the postpartum period than before or during pregnancy -Number of exercise advantages was positively associated with women's pregnancy and postpartum exercise behavior.	To increase exercise behaviour and reduce the risk of type 2 diabetes in women with gestational diabetes, researchers and health care professionals are encouraged to use women's exercise beliefs, that is, advantages, social influences, and perceived barriers to exercise, as a framework for designing effective diabetes treatment and prevention programmes	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Lesser KB;Gruppuso PA;Terry RB;Carpenter MW;  1996 Jul  170	Study Type: RCT  Evidence level: 1+	5 normal and 6 women with gestational diabetes	Women with normal glucose levels (NL) and women with gestational diabetes (GDM)  Country: USA	Intervention: A mixed nutrient meal with exercise stress test. Exercise consisted of upright stationary cycling for 30 min at a heart rate consistent with 60% VO2 max  Comparison: A mixed nutrient meal without an exercise stress that took place 14 h earlier.	Follow-up period:  Outcome Measures: Fasting glucose and insulin levels, peak glucose and insulin levels and incremental area of the glycaemic and insulin curves	Mean values with vs without exercise did not differ for Fasting glucose (NL 78.9 +/- 2.6 vs. 80.0 +/- 2.6 mg/dl; GDM 86.4 +/- 2.0 vs. 82.1 +/- 3.5 mg/dl), Peak glucose (NL 132.3 +/- 10.4 vs. 139.1 +/- 15.6 mg/dl; GDM 165.8 +/- 5.5 vs. 160.3 +/- 7.8 mg/dl), Area under the glycaemic curve (NL 5758 +/- 1038 vs. 6393 +/- 1281 mg/dl.min; GDM 8,178 +/- 890 vs. 8,331 +/- 563 mg/dl.min). Plasma insulin levels did not differ between the two groups.	Study results indicate that a single bout of exercise did not blunt the glycaemic response observed following a mixed nutrient meal.	
Peterson CM;Jovanovic-Peterson L;  1995 Aug  167	Study Type: RCT  Evidence level: 1+	25	Women aged 21–50 yrs  Exclusion criteria: Any medical condition for which a calorie-restricted diet may be harmful including pregnancy or planned pregnancy during the trial, hypertension, diuretic use, thyroid disease, or frank diabetes by National Diabetes Data Group Criteria.  Group 1: obese women with previous gestational diabetes Group 2 : obese women who had not had gestational diabetes  Country: USA	Intervention: Each woman received nutritional supplement bars for breakfast, lunch, and snacks and a meal plan for dinner which comprised 1/3 of total calories. The nutritional supplement bars were identically wrapped, each containing 180 kcal with 20% protein. Group 1 received bar containing 40% carbohydrate  Comparison: Group 2 received bar containing 55% carbohydrate	Follow-up period: 1st follow up at week 6 and 2nd follow up at week 12  Outcome Measures: Women's adherence to the program, Body weight, triglyceride levels, cholesterol levels and fasting insulin levels.	(Group 1) Women with previous gestational diabetes mellitus were comparable to (Group 2) obese women without a history of previous gestational diabetes except that the former had higher maximum levels of glucose on a glucose tolerance test and higher fasting insulin levels consistent with greater insulin resistance. Weight loss was comparable for all groups during the first 6 weeks but attenuated in all groups during the second 6 weeks of the trial regardless of diabetes history or treatment group allocation. Women with or without a previous history of gestational diabetes had higher triglycerides while on a 55% carbohydrate diet than while on a 40% carbohydrate diet.	A weight loss regimen consisting of 40% carbohydrate results in lower triglyceride levels than those achieved with a 55% carbohydrate content diet in obese women.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Smits MW;Paulk TH;Kee CC; 1995 191	Study Type: Other Descriptive  Evidence Level: 3	Intervention: A hospital, outpatient-based, nursing intervention and the traditional, office-based care provided by obstetricians by using a research model. The research model used three types of variables as suggested by the literature: input variables (risk factors prior to gestation), moderating variables (conditions that occur during pregnancy), and outcome variables (normal vs abnormal outcomes for mother and infant).  Comparison:	263	Women diagnosed with gestational diabetes delivered at the hospital during the year following the initiation of the Nursing intervention  Country: USA	Outcomes in women: Polyhydramnios, preeclampsia, premature contractions, vaginal bleeding due to placenta praevia. Delivery at <37 weeks or > 42 weeks. Delivery complications such as induction, caesarean section, mid-forceps, mid cavity vacuum extraction. Postpartum length of stay 5 days or longer. Infant outcomes: APGAR 7 or less at 1 min and 5 min, SGA < 10th percentile or LGA > 90th percentile, postpartum length of stay ≥5 days, hypoglycaemia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, hypocalcemia, birth trauma.	Overall incidence of abnormal outcomes for women with gestational diabetes was 54.1% and 72.7% for their infants. Nurse-led intervention had 53.7% incidence of abnormal maternal outcomes and 68.3% incidence of abnormal infant outcomes versus an incidence of 50% and 75% respectively for obstetrician-led intervention.	No significant reduction in the risk of abnormal outcomes for woman or infant. A significantly greater risk of having an infant with one or more abnormal outcomes in first-time mothers, women with gestational diabetes on medications, and women with gestational diabetes experiencing complications.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Rossi G; Somigliana E; Moschetta M; Bottani B; Barbieri M; Vignali M; 2000 Aug 181	Study Type: RCT  Evidence level: 1++	141 women  1. Group A (n = 73)  2. Group B (n = 68)	Women with uncomplicated singleton pregnancies, who planned to deliver vaginally and whose diagnosis of gestational diabetes was established before 28 weeks' gestation.  In all cases gestational age had been determined previously	Intervention: Group A, fetal ultrasound was assessed at 28 weeks' and 32 weeks' gestation.  Comparison: Group B, fetal ultrasound was assessed at 32 weeks' gestation only.	Follow-up period: 41 months  Outcome Measures: 1. HbA <sub>1c</sub> values 2. Gestational age at delivery 3 Mode of delivery 4. Hypoglycaemia 5. Hypocalcemia 6. Hyperbilirubin	Twenty-nine women whose fetal abdominal circumference exceeded the 75th percentile were considered eligible for insulin therapy.  15 out of 20 macrosomic infants had an abdominal circumference ≥ 75th percentile at ultrasound assessment performed before 32 weeks' gestation.  There was a statistically	Early fetal ultrasound assessment at 28 weeks' gestation should be encouraged since insulin administration after 32 weeks' gestation is less effective in lowering the rate of macrosomic infants.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			and verified by the first-trimester ultrasound.  Insulin plus dietary therapy was initiated as soon as fetal abdominal circumference exceeded the 75th percentile. Women whose abdominal circumference was less than 75th percentile were maintained on diet only.  Country: Italy			significant increase in the percentage of macrosomic infants born to women whose ultrasound abdominal circumference assessment was performed only at 32 weeks' gestation (Group B) when compared to women evaluated at both 28 weeks' and 32 weeks' gestation (Group A) [71.43% vs 33.33%, $P < 0.05$ ].  The rate of macrosomia was reduced significantly to 11.1% in women in Group A where insulin was initiated at 28 weeks' gestation.		
Sacks DA;Chen W;Wolde-Tsadiq G;Buchanan TA; 1999 Oct 163	Study Type: Cohort  Evidence level: 2-	30	Inclusion criteria: -Pregnant women between 28–38 weeks' gestation -singleton pregnancies -gestational diabetes being managed by diet alone -fasting plasma glucose levels < 105 mg/dl and the 1 h postprandial glucose level <140 mg/dl Exclusion criteria: -cigarette smoking -recreational drug use -chronic hypertension -cardiac, pulmonary, gastrointestinal or renal disease (if they were on medication for any of these conditions)  Country: USA	Intervention: Compare glucose values for women with diet-controlled gestational diabetes during two 9 hour fasts, 1 during the day and 1 overnight  Analyses of hormones and metabolites involved in intermediary metabolism  Comparison:	Follow-up period:  Outcome Measures: Plasma glucose Insulin/glucose ratios Free fatty acid Serum cortisol $\beta$ -hydroxybutyrate	Glucose concentrations after morning meal vs evening meal were significantly greater at 1 hour, not different at 2 hours, and significantly lower from 3–9 hours postprandially. Plasma beta-hydroxybutyrate and free fatty acid concentrations higher 5–9 hours after morning meal vs evening meal. Total and free cortisol levels higher for the first 7 hours after the morning feeding. Overweight patients' glucose values significantly greater than those of lean subjects during the last 4 hours of the overnight fast.	Glucose concentrations were significantly higher 3–9 hours after an evening meal, whereas suppression of free fatty acids and beta-hydroxybutyrate was less sustained after a morning meal among women with gestational diabetes treated with diet alone  The mechanisms underlying these may involve diurnal influences of counter-regulatory hormones.	Very small sample size

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Sameshima H;Kamitomo M;Kajiya S;Kai M;Ikenoue T;  2001 Aug  190	Study Type: Other Paired Prospective study  Evidence Level: 2-	Intervention: 2 insulin-meal intervals 15 min 30 min  Both regimens examined in each patient in random order, 2 days apart  Comparison: 15 min vs 30 min	11	Inclusion criteria: Japanese women with gestational diabetes requiring insulin for good glycaemic control (fasting level <100 mg/dl and 2 h postprandial level of <120 mg/dl Exclusion criteria: toxemia chronic hypertension diabetic complications thyroid disease collagen disease multiple pregnancies cigarette smoking  Country: Japan	Blood glucose	Daily glucose profiles of the two groups showed that their glycaemic control on the days of observation was good and that the two glucose profile curves were superimposable.  A transient decrease in glucose (nadir 62 +/- 6 mg/dl) was observed at 6-10 min of meal ingestion in the 30-min regimen, which was significantly different from the glucose fluctuations during the 15-min regimen. 2 hour postprandial glucose levels were similar in both experiments.	In women with tightly controlled gestational diabetes during 3rd trimester, insulin-meal intervals of 15 min are beneficial when compared to 30-min intervals, because they avoid preprandial hypoglycemia without increasing 2 hour postprandial hyperglycaemia.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Poyhonen-Alho M; Teramo K; Kaaja R; 2002 Mar 188	Study Type: RCT Evidence level: 1+	23 consecutive women with insulin-requiring gestational diabetes.	Women with insulin-requiring gestational diabetes  Country: Finland	Intervention: Short-acting insulin  Comparison: Long-acting insulin	Follow-up period:  Outcome Measures: HbA <sub>1c</sub>	The two groups were similar in terms of age, BMI and parity.  Insulin dose was raised in 6 of the 11 pregnant women on short-acting insulin.  Birth weight was higher in the long-acting insulin group (3943 g ± 492 g and 3079 g ± 722 g, respectively; <i>P</i> = 0.005).  There were no differences in the mode of delivery, neonatal complications, malformations, number of infants with Apgar score less than 7 at 1 min of age, or maternal HbA <sub>1c</sub> between the groups.	The results suggest that gestational diabetes can be treated with short-acting insulin.	
Thompson DJ; Porter KB; Gunnells DJ; Wagner PC; Spinnato JA; 1990 Jun 173	Study Type: RCT Evidence level: 1+	108 women	68 women with gestational diabetes who received either diet alone or diet plus insulin (20 units NPH and 10 units regular) for glycaemic control were included in this study.  Country: USA	Intervention: Diet alone  Comparison: Diet plus insulin.	Follow-up period:  Outcome Measures: 1. Mean birth weight 2. Macrosomia rate	Among 68 women successfully treated for a minimum of 6 weeks, the mean birth weight and macrosomia rate were reduced significantly in the insulin-treated group.  Insulin reduced birth weights significantly. (4060 ± 342 versus 3397 ± 640 g).  No woman with good glucose control had a newborn over 4000 g. Women with poor glycaemic control were at greatest risk (30%) for fetal overgrowth whether initially receiving insulin or not.	Maternal obesity or failure to achieve glycaemic control should alert the clinician to a substantially increased risk of macrosomia.	

**Q.14**      **What is cost effective treatment for gestational diabetes?**

No specific searches were conducted for this clinical question and so there are no evidence tables (this is a health economics question)

# 5 Antenatal care

## 5.1 Target ranges for blood glucose during pregnancy

### Q.15 What are the target ranges for blood glucose during pregnancy?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Jovanovic L;Druzin M;Peterson CM; 1981 Dec  198	Study Type: Cohort  Evidence level: 2+	52 women with type 1 diabetes 52 nondiabetic women	Mean age 28.6 years and had type 1 diabetes for mean duration of 7.1 years (range 1 to 23).	Intervention: Euglycaemia program instituted prior to the 12th week of pregnancy  Euglycemia in the diabetic group was documented by daily home-monitored glucose determinations and bimonthly HbA <sub>1c</sub> levels and 25 hr glucose profiles and urinary collections during periods of hospitalisation, at presentation, 20 or 26 weeks, and at term.  Therapy was initiated during a 5 to 7 day hospitalisation in which diet and insulin regulation were calculated according to body weight and adjusted to achieve 'normal' bloodglucose levels, defined as a fasting level of 3.0–3.6 mmol/l, a mean blood	Follow-up period:  Outcome Measures: Fetal loss Malformations Birthweight Hypoglycaemia Respiratory distress 1 and 5 min Apgar scores Hypocalcaemia	All 52 patients maintained glucose control within the desired range throughout gestation in the outpatient department, except for two patients who were hospitalised for 53 and 45 days respectively to ensure glucose control.  During gestation there was no deterioration in renal or ocular status  No fetal loss. Mean body weight 2910 g, no infants above 75th percentile or below 48th percentile. No major or minor malformations (compared to 2 minor and 2 major malformations in the nondiabetic group, $P < 0.03$ ). All infants maintained blood glucose levels between 3.0 and 4.4 mmol/l except for twin B who had asymptomatic blood glucose 2.2 mmol/l at 2 hours. No respiratory distress compared to 5 cases in nondiabetic group ( $P < 0.03$ ) No other morbidity.	Problems of morbidity and mortality may be eliminated if patients are maintained euglycemic from the 12th week.	The original study design was to randomise patients with insulin-dependent diabetes into two groups. Group 1 would receive standard care and group 2 would receive intensive care. However after 4 deliveries in the standard care group resulted in two infants with macrosomia, three infants with severe neonatal hypoglycaemia, one delivery complicated by shoulder dystocia, and one pregnancy with premature rupture of membranes and fetal death, it was decided that to continue with the original protocol would be unethical. Therefore all patients were offered the intensive program.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				glucose level of 4.4 to 4.8 mmol/l and a one-hour postprandial level not exceeding 7.7 mmol/l.  Comparison: 52 nondiabetic women matched for maternal age, mode of delivery, gestational age, and socioeconomic status and ethnic background.				
Wyse LJ; Jones M; Mandel F;  1994 Jul  196	Study Type: Cohort  Evidence level: 2+	66	22 type 1, 4 type 2, 41 gestational	Intervention: Glycaemic control  Comparison:	Follow-up period:  Outcome Measures: HbA <sub>1c</sub> (the one taken closest to the ultrasound)  Fetal complications based on ultrasound assessment: Macrosomia (estimated fetal weight >90th percentile for gestational age using the Williams growth curve; polyhydramnios (amniotic fluid index ≥25 cm or one fluid pocket ≥8 cm, or fat line (≥ 5 mm subcutaneous tissue near the level of the umbilical vein insertion).	19/66 (29%) had birthweight macrosomia.  13/66 (20%) had at least one marker. Of these 13, 10 had HbA <sub>1c</sub> >6.3% and also had birthweight macrosomia.  There was a significant difference in HbA <sub>1c</sub> between those with markers and those without (P<0.03)  To reduce the incidence of birthweight macrosomia glycaemic control needs to be geared to maintaining long term euglycaemia or a HbA <sub>1c</sub> value <6.3%		
Karlsson K; Kjellmer I;  1972 Jan 15  204	Study Type: Cohort  Evidence level: 2+	180 infants in 179 women, 20 with gestational diabetes, 160 with pre-existing type 1 diabetes.	Gestational diabetes 20, White class B 49, White Class C 60, White class D 42, White Class F+R 9.  84 patients treated between 1961 and 1965 95 mothers treated	Intervention: Maternal blood sugar  Blood sugar was routinely measured at least three times/ day. For each patient a mean blood sugar	Follow-up period:  Outcome Measures: Perinatal deaths  Hypoglycaemia  Jaundice	Perinatal deaths: <5.5 mmol/l: 2/52 (3.8%) 5.5–8.25 mmol/l: 12/77 (16%) >8.25 mmol/l 9/38: (24%)  Neonatal hypoglycaemia <5.5 mmol/l: 6/52 (12%) 5.5–8.25 mmol/l: 8/77 (10%)	There is a significant reduction of the perinatal mortality rate to about 4% when the maternal blood glucose level is reduced below 5.5 mmol/l.  The low frequency of	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			between 1966 and 1970 (more intensive therapy)	level was calculated for the time period between 30 and 32 weeks until delivery.  Women divided into three groups: <5.5 mmol/l 5.5–8.25 mmol/l >8.25 mmol/l  Comparison:	Respiratory distress  Malformations	>8.25 mmol/l: 4/38 (11%)  Jaundice <5.5 mmol/l: 0/52 (0%) 5.5–8.25 mmol/l: 6/77 (8%) >8.25 mmol/l: 3/38 (8%)  Respiratory distress <5.5 mmol/l: 9/52 (17%) 5.5–8.25 mmol/l: 24/77 (31%) >8.25 mmol/l: 9/38 (24%)  Malformations <5.5 mmol/l: 2/52 (3.8%) 5.5–8.25 mmol/l: 12/77 (16%) >8.25 mmol/l: 5/38 (13%)  There was a statistically significant difference ( $P < 0.05$ ) between women with blood glucose values <5.5 mmol/l and those above for perinatal death, respiratory distress, jaundice and malformations.  No association was found between maternal hyperglycaemia and overweight neonate at birth.	neonatal hypoglycaemia may be due to the earlier provision of fluid and nutrients compared to other studies	
Landon MB; Gabbe SG; Piana R; Mennuti MT; Main EK;  1987 May  195	Study Type: Cohort  Evidence level: 2++	75 women with type 1 diabetes	White class B through to D	Intervention: Maternal blood glucose levels  Optimal glucose control was considered present if fasting capillary glucose values were $\leq 5.5$ mmol/l and preprandial values were $\leq 6.6$ mmol/l.  Patients performed a daily fasting and three preprandial determinations throughout the second and third trimesters. These values were used to calculate mean capillary blood	Follow-up period:  Outcome Measures: Hypoglycaemia (<1.65 mmol/l)  Macrosomia  Respiratory distress  LGA (birth weight $\geq$ 90th percentile)  SGA ( $\leq$ 10th percentile)	Group 1 (<6.0 mmol/l): $n = 43$ Group 2 (>6.0 mmol/l): $n = 32$  Gestational age (wk) Group 1: $38.42 \pm 1.4$ Group 2: $38.15 \pm 2.2$ , NS  Morbidity Group 1: 14 (32%) Group 2: 17 (53.1%), NS  Nursery days Group 1: $4.72 \pm 1.4$ Group 2: $6.56 \pm 2.0$ , $P < 0.001$ .  Birth weight >4000 g Group 1: 7% Group 2: 28%, $P < 0.05$  LGA Group 1: 4 (9.3%)	These data suggest that maintaining mean capillary blood glucose values < 6.0 mmol/l may serve to reduce several major forms of morbidity in the infant of the diabetic mother. This information is helpful in establishing objectives for glycaemic control in pregnant women using self-monitoring techniques.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				glucose. Mean capillary blood glucose was calculated from a minimum of 16 weeks of determinations.  The study population was divided into two groups based on mean capillary blood glucose values. Optimal control was defined as a mean capillary blood glucose level <6.0 mmol/l  Comparison:		Group 2: 11 (34.3%), $P < 0.05$  Neonatal hypoglycaemia Group 1: 8 (18.6%) Group 2: 13 (40.6%), $P < 0.05$  Respiratory distress syndrome Group 1:1 (2.3%) Group 2: 7 (21.8%), $P < 0.01$  Hyperbilirubinemia Group 1:10 (23.2%) Group 2: 13 (40.6%), NS  Polycythemia Group 1:1(2.3%) Group 2: 3 (9.3%)  Hypocalcaemia Group1: 0 Group 2: 2 (6.2%)  There was only one perinatal death which occurred in an infant with a malformation whose mother presented at 12 weeks with a HbA <sub>1c</sub> of 10.2%		
Miodovnik M;  1987  205	Study Type: Cohort  Evidence level: 2++	145 women	Type 1 diabetes. Recruited during first trimester.	Intervention: Glucose control Goals of glucose control were fasting blood glucose <5.5 mmol/l and a 90 minute postprandial glucose level <7.7 mmol/l.  Glycaemic control was obtained with a split dosage regiment of insulin, using both short and long lasting insulin, and dietary regulation. Patients were hospitalised where necessary to maintain these goals.  Comparison: Control	Follow-up period:  Outcome Measures: HbA <sub>1c</sub> every four weeks (normal range 5.5–8.5%). Pre and postprandial capillary glucose were measured alternately at each weekly visit.  Premature labour: Gestational age 20–37 weeks with evidence of regular uterine contractions documented by tocodynametry, and cervical dilation of 3 cm or more and/or progressive effacement of the	Excluding 17 pregnancies with premature delivery due to fetal distress the premature labour rate was 51/164 (31.1%) vs 828/4109 (20.2%) in the control population.  HbA <sub>1</sub> at 26 weeks (%) No premature labour: 7.9 ± 1.5 Premature labour: 8.7 ± 1.8, $P < 0.01$  Previous premature delivery: No premature labour:31 (27.4) Premature labour: 20 (39.2), $P = 0.001$  Premature rupture of membranes: No premature labour: 2 (1.8) Premature labour: 14 (27.4), $P < 0.001$ Candida vaginitis: No premature labour: 28 (24.5) Premature labour:	History of premature labour in a previous pregnancy, premature rupture of membranes, poor second trimester glycaemic control, and urogenital infection was significantly associated with premature labour.  Polyhydramnios and hypomagnesemia, contrary to hypothesis, were not factors significantly associated with premature labour. (May reflect sample size and socio-economic profile of sample).  Improvement of glycaemic control and eradication of	Tocolytic agents (isoxsuprine hydrochloride until 1980, then ritrodine hydrochloride) were used in all cases except for patients with ruptured chorioamniotic membranes of cervical dilation of 4 cm or more.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				population 4109 nondiabetic pregnant women who received prenatal and delivery care from the same obstetricians.	cervix.	21 (41.2%), $P < 0.03$  Urogenital infection: No premature labour: 49 (43.4) Premature labour: 34 (66.7), $P < 0.005$  Logistic regression, once the contribution of pregnancy history and premature rupture of membranes were excluded, confirmed HbA <sub>1c</sub> (R <sup>2</sup> =0.105) and urogenital infection (R <sup>2</sup> =0.093) as significant covariates predicting the onset of premature labour.	urogenital infection will decrease the spontaneous premature labour rate in these patients.	
Rosenn B; 1990 206	Study Type: Cohort Evidence level: 2+	171	Women with type 1 diabetes. 86% had entered study by 13th week of gestation.  Goals of glycaemic control were a fasting blood glucose concentration of $\leq 5.5$ mmol/l and a 90-minute postprandial glucose concentration $< 7.7$ mmol/l.  Glycaemic control obtained with split dosage regimen of short and intermediate acting insulin + dietary control	Intervention: Glycaemic control  HbA <sub>1c</sub> measured every 4 weeks (normal range 5.5–8.5%). Pre or postprandial capillary glucose measured alternately at each weekly visit. After 1982 patients routinely recorded self-monitoring of glucose with reflectance meters.  Comparison:	Follow-up period:  Outcome Measures: Minor congenital malformations	39 minor congenital malformations diagnosed in 32 infants (18.7%)  HbA <sub>1c</sub> week 8 Malformation group ( $n = 32$ ): $10.6 \pm 1.7$ No malformation group ( $n = 139$ ): $9.8 \pm 2.2$ , NS  HbA <sub>1c</sub> week 12 Malformation group: $10.0 \pm 1.6$ No malformation: $9.0 \pm 1.8$ ( $P = 0.02$ )  HbA <sub>1c</sub> week 16 Malformation group: $9.1 \pm 1.5$ No malformation: $8.3 \pm 1.6$ , ( $P = 0.02$ )  HbA <sub>1c</sub> week 20 Malformation group: $8.9 \pm 1.3$ No malformation: $7.9 \pm 1.5$ , $P = 0.001$  HbA <sub>1c</sub> week 24 Malformation group: $8.1 \pm 0.9$ No malformation group: $7.8 \pm 1.5$ , NS  Multivariate analysis indicated that HbA <sub>1c</sub> at 20 weeks was the strongest independent variable correlated with the presence of minor malformations ( $P = 0.02$ ).	Poor glycaemic control during the latter part of the first trimester is associated with an increased risk of minor malformations. Improving glycaemic control during this period should decrease the risk.	
Jovanovic-Peterson L; Peterson CM; Reed GF; Metzger BE; Mills JL; Knopp RH; Aarons JH;	Study Type: Cohort Evidence level: 2++	323 women with diabetes, 361 control	Recruited before 21 days gestation	Intervention: Glycaemic control  No fixed goals for glycaemic control	Follow-up period:  Outcome Measures: Fasting and nonfasting venous plasma	LGA (>90th percentile) Diabetic: 92 (28.5%) Control: 47 (13.1%), $P < 0.001$  The relationship between metabolic parameters and birth weight when each	The data indicate that glycaemic control in late pregnancy is the strongest metabolic determinant of birth weight, but there is a	Elevated blood glucose variables in the first trimester correlated significantly with elevated variables in the third trimester.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1991 Jan 200				Comparison:	glucose were measured on alternate weeks in the first trimester and monthly thereafter.  HbA <sub>1c</sub> measured week; in the first trimester and monthly thereafter	trimester analyzed independently: (slope ± SE) Fasting glucose: First trimester: 0.002±0.002, <i>P</i> = 0.248 Second trimester: 0.006 ± 0.002, <i>P</i> = 0.024 Third trimester: 0.005 ± 0.003, <i>P</i> = 0.068  Nonfasting glucose: First trimester: 0.006 ± 0.002, <i>P</i> < 0.001 Second trimester: 0.006 ± 0.002, <i>P</i> = 0.02 Third trimester: 0.013 ± 0.004, <i>P</i> < 0.001 HbA <sub>1c</sub> First trimester: 0.25 ± 0.009, <i>P</i> = 0.008 Second trimester: 0.032 ± 0.012, <i>P</i> = 0.009 Third trimester: 0.047 ± 0.013, <i>P</i> < 0.001  After adjusting for variables in the prior trimester or trimesters, second trimester mean fasting plasma glucose ( <i>P</i> = 0.035), third trimester mean nonfasting plasma glucose ( <i>P</i> = 0.009) and third trimester HbA <sub>1c</sub> ( <i>P</i> = 0.018) correlated with infant birth weight.  After adjusting for maternal hypertension; renal dysfunction, smoking, ponderal index, and weight gain, the above relationships remained.	major contribution from the nonfasting and glycosated haemoglobin from both prior trimesters.  Our study shows that peak glucose levels during the day are more predictive of the infant birth weight than the lowest blood glucose level of the day (fasting).  Our data also indicate that monitoring only fasting and premeal glucose concentrations, which reflect the lowest glucose levels of the day, does not provide an adequate indication of overall metabolic control and risk of macrosomia. If women who are at risk of macrosomia are to be identified early and have their treatment altered to improve metabolic control, optimum surveillance should include measurements of HbA <sub>1c</sub> and nonfasting (postprandial) blood glucose concentrations.	
Evers IM;De Valk HW;Mol BWJ;Ter Braak EWMT;Visser GHA; 2002 199	Study Type: Cohort Evidence level: 2++	289	Women with type 1 diabetes	Intervention: HbA <sub>1c</sub> Comparison:	Follow-up period:  Outcome Measures: Macrosomia (birth weight >90th percentile)	Macrosomia: 49% when compared to growth charts based on data collected in 1998. 73/289 had a birth weight > 4000 gms.  Overall blood glucose control was good (mean HbA <sub>1c</sub> ≤ 7.0%) in 84% of mothers.  HbA <sub>1c</sub> first trimester Macrosomia: 6.7 ± 1.1 No Macrosomia: 6.4 ± 1.0, <i>P</i> = 0.07	Glucose variability and postprandial peaks, which are not reflected in the HbA <sub>1c</sub> value, may be involved  Future research should focus on new more detailed glucose monitoring (such as continuous glucose monitoring)	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>HbA<sub>1c</sub> second trimester            Macrosomia: 6.1 ± 1.0            No Macrosomia: 5.8 ± 0.8, <i>P</i> = 0.007</p>		
						<p>HbA<sub>1c</sub> third trimester            Macrosomia: 6.5 ± 1.1            No Macrosomia: 6.0 ± 1.1, <i>P</i> = 0.0001</p>		
						<p>Third trimester HbA<sub>1c</sub> &gt;6.5: RR 2.7 95%            CI 1.3–5.4</p>		
						<p>In logistic regression 3rd trimester HbA<sub>1c</sub> was the most powerful predictor for the occurrence of macrosomia but only explained 4.7% of variance in macrosomia.</p>		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Langer O;Rodriguez DA;Xenakis EM;McFarland MB;Berkus MD;Arrendondo F; 1994 Apr 194	Study Type: OtherNon randomised intervention study  Evidence Level: 2++	Intervention: Intensive management: patients assigned memory reflectance meters and instructed by nurse educators in self monitoring blood glucose technique (7 times/day: fasting, preprandial, 2 hour postprandial and at bedtime).  Treatment (diet or diet+insulin) for both groups the same.  Goals for both groups: Mean blood glucose (overall mean from diagnosis to delivery) between 4.95 and 5.5 mmol/l, fasting blood glucose between 3.3and 4.95 mmol/l and postprandial blood glucose <6.6 mmol/l.  Comparison: Conventional management: Patients instructed by a nurse educator and assessed weekly for fasting and 2-hour postprandial venous plasma glucose during clinic visits. 4 daily self-monitored blood glucose determinations with strips.	2461 women with gestational diabetes 1316 conventional management 1145 intensified management	Diagnosed with gestational diabetes (1 hour glucose challenge test (50 gm) followed by 100 gm OGTT if plasma glucose $\geq$ 7.2 mmol/l) between week 24 and week 28 of pregnancy. 83% Hispanic, 12% white, 5% black	Blood glucose (mean per day) Labour augmentation (%) Induction (%) No of days of hospital stay (mean $\pm$ SD) Primary caesarean section (%) LGA ( $\geq$ 90th percentile) Macrosomia (birth weight $\geq$ 4000 gm) Neonatal intensive care unit (% admission) Respiratory complications (%): Shoulder dystocia:	Blood glucose (mean per day) Intensified group: $5 \pm 2$  Labour augmentation (%) Conventional: 28 Intensified: 15, $P < 0.01$ Non diabetic control: 28, $P < 0.01$  Induction (%) Conventional:27 Intensified: 22, $P < 0.01$ Non diabetic control: 13  Failed induction (%) Conventional: 10 Intensified: 7, $P < 0.01$ Non diabetic control: 10  No of days of hospital stay (mean $\pm$ SD) Conventional 4.3 $\pm$ 4 Intensified 3.7 $\pm$ 4, $P < 0.01$ Non diabetic control:3.3 $\pm$ 3  Primary caesarean section (%) Conventional: 19 Intensified: 13.0, $P < 0.01$ Non diabetic control: 11  LGA (%) Conventional:20.1 Intensified: 13.1, $P < 0.0001$ Nondiabetic control: 11.9  Macrosomia Conventional: 13.6 Intensified: 7.1, $P < 0.0001$ RR 2.07, 95% CI 1.6–2.8  Neonatal intensive care unit (% admission) Conventional: 25.0 Intensified: 6.3, $P < 0.0001$ Non diabetic control: 4.7  Respiratory complications (%): Conventional: 6.2 Intensified: 2.3, $P < 0.0001$	Memory reflectance meters enabled us to demonstrate a significant correlation between rates of LGA and macrosomia and glycaemiccontrol. Verified self-monitored blood glucose measurement enhanced glycaemia control and significantly reduced macrosomia.	No differences between the groups with regard to parity, ethnicity, obesity, past obstetric history, family history, gestational age at entry, degree of abnormality of the screening or GTTs.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						<p>Non diabetic control: 2.1</p> <p>Shoulder dystocia: Conventional: 1.4 Intensified: 0.4, <math>P &lt; 0.0001</math> Nondiabetic control: 0.5</p> <p>Stillbirth: Conventional: 4/1000 Intensified: 1/1000, NS Nondiabetic control: 4/1000</p> <p>Neonatal death: Conventional: 2/1000 Intensified: 3/1000, NS Nondiabetic control: 4.7/1000</p> <p>Logistic regression: only overall mean blood glucose (seven determinations per day) previous LGA infants and gestational age at delivery predicted fetal macrosomia.</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Nielsen GL, Møller M, Sørensen HT. 2006 207	Study Type: Cohort Evidence level: 2++	573 pregnancies in women with type 1 diabetes	Women with type 1 diabetes residing in North Jutland County, Denmark whose pregnancies ended between 1985 and 2003.  Women with gestational or type 2 diabetes were not included in the study.  Country: Denmark	Intervention: Routine ultrasound scan (11, 14, 20, 21 and 24 gestational weeks) of women with type 1 diabetes.  Comparison: Routine ultrasound scan (11, 14, 20, 21 and 24 gestational weeks) of women without diabetes.	Follow-up period: First through third gestational week.  Outcome Measures: 1. Congenital anomalies 2. Morbidity of the infant diagnosed within the first month of life. 3. Mortality	Of 573 pregnancies, 165 (29%) terminated with adverse outcomes.  The prevalence of adverse outcomes varied six-fold from 12% (95% CI 7.2 to 17) in the lowest to 79% (95% CI 60% to 91%) in the highest quintile of HbA <sub>1c</sub> measurements.  From HbA <sub>1c</sub> levels >7%, there was almost linear association between with risk of adverse outcome: a 1% increase in HbA <sub>1c</sub> corresponded to 5.5% (95% CI 3.8% to 7.3%) increased risk of adverse outcome.	First-trimester HbA <sub>1c</sub> levels slightly >7% show a dose-dependent association with risk of adverse pregnancy outcome, but HbA <sub>1c</sub> levels have limited value in predicting outcome in individual pregnancies.	

## 5.2 Monitoring blood glucose and ketones during pregnancy

### Q.16 How should blood glucose and ketones be monitored during pregnancy?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Crowther CA;Hiller JE;Moss JR;McPhee AJ;Jeffries WS;Robinson JS;Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group.;  2005 Jun 16  153	Study Type: RCT  Evidence level: 1++	490 women in intervention group  510 women in routine care group	Women between 16–30 weeks gestation. One or more risk factors for gestational diabetes on selective screening or a +ve 50 g GCT and had a 75 g OGTT at 24–34 weeks gestation in which venous plasma glucose <7.8 mmol/l after an overnight fast and 7.8–11.0 mmol/l at 2 hours. Exclusions: Women previously treated for gestational diabetes or active chronic systemic disease (except essential hypertension).  Country: Multi-centre (Australia , UK)	Intervention: Treatment (institution's clinical practice for gestational diabetes) including individualised dietary advice, instructions on self-monitoring (4xday), target levels for blood glucose of between 3.5 and 5.5 mmol/l (fasting) and <7.0 mmol/l (postprandial) and insulin therapy.  Comparison: Routine care	Follow-up period:  Outcome Measures: A composite measure of serious perinatal complications (death, shoulder dystocia, bone fracture, nerve palsy) Admission to neonatal nursery Jaundice requiring phototherapy Induction of labour Caesarean section Maternal health (SF-36) Anxiety (Spielberger State-Trait Anxiety Inventory) Depression (Edinburgh Postnatal Depression Scale)	The rate of serious perinatal outcomes among infants was significantly lower in the intervention group than the routine care group (1% vs. 4%; $P = 0.01$ , adjusted for maternal age, ethnic group and parity).  The number needed to treat to prevent a serious outcome in an infant was 34 (95% CI 20–103).  Admission to neonatal nursery Intervention: 71% Routine care: 61%, adjusted $P = 0.01$  Jaundice requiring phototherapy: No significant difference (adjusted $P = 0.72$ )  Induction of labour: Intervention: 39% Routine care: 29%, adjusted $P < 0.001$  Caesarean section: No significant difference (adjusted $P = 0.73$ )  All measures on the SF-36 showed trends in favour of the intervention group but not all were significant  Depression At 3 months postpartum fewer women in the intervention	Treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring and insulin therapy as required for glycaemic control reduces the rate of serious perinatal complications without increasing the rate of cesarean section.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>group had a score on the Edinburgh postnatal depression scale suggestive of depression (8% vs 17%)</p> <p>Anxiety Similar in both groups.</p> <p>Birthweight (g) Intervention: 335±551 Routine care: 3482±660, adjusted <math>P &lt; 0.001</math></p> <p>Secondary outcomes: Neonatal: LGA Intervention: 68 (13%) Routine care: 115 (22%), adjusted <math>P &lt; 0.001</math></p> <p>Macrosomia <math>\geq 4</math> kg Intervention: 49 (10%) Routine care: 110 (21%), adjusted <math>P &lt; 0.001</math></p> <p>Neonatal Hypoglycaemia requiring IV therapy: No significant difference (adjusted <math>P = 0.16</math>)</p> <p>Respiratory distress syndrome: No significant difference (adjusted <math>P = 0.15</math>)</p> <p>Maternal: Antenatal preeclampsia: Intervention group: 58 (12) Routine care group: 93 (18) Adjusted <math>P = 0.02</math></p> <p>Any perineal trauma: No significant difference (adjusted <math>P = 0.42</math>)</p> <p>Length of postnatal stay (days) No significant difference</p>		

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Manderson, J., Patterson, C., Hadden, D. et al. 2003 202	Study Type: RCT Evidence level: 1++	31 women with type 1 diabetes assigned to preprandial monitoring, 30 assigned to postprandial monitoring.	Country: Northern Ireland	Intervention: Postprandial monitoring: Before breakfast and 1 hour after the commencement of each meal.  Insulin doses were adjusted to achieve fasting glucose levels between 3.3 and 5.0 mmol/l, preprandial values between 3.3 and 5.9 mmol/l and postprandial values less than 7.8 mmol/l  The glucose reflectance meters were downloaded every 2 weeks.  Comparison: Preprandial monitoring	Follow-up period:  Outcome Measures: Success in glycaemic control: the number of readings within target ranges/total number of readings taken Compliance with monitoring schedule: Number of readings taken/expected number of readings  Preeclampsia  Neonatal hypoglycaemia (blood glucose <1.7 mmol/l)  Hyperbilirubinemia	(adjusted $P = 0.80$ )  Preeclampsia Preprandial: 6/38 (21%) Postprandial: 1/30 (3%), $P = 0.048$  Triceps skinfold thickness (mm) mean (SD) Preprandial: 5.1 (1.3) Postprandial: 4.5 (0.9), $P = 0.05$  Respiratory problem Preprandial: 10/31 (32%) Postprandial: 5/30 (16%), $P = 0.07$  Birthweight >4000 g Preprandial: 9/31 (29%) Postprandial: 4/30 (3.3%), $P = 0.35$  Success in glycaemic control (%) trimester 2: Preprandial: 29.4 Postprandial: 51.6, $P < 0.001$ trimester 3: Preprandial: 30.3 Postprandial: 55.5, $P < 0.001$  Compliance with schedule: Trimester 2 Preprandial: 47.6 Postprandial: 39.7, $P = 0.13$ Trimester 3: Preprandial: 30.2 Postprandial: 35.7, $p=0.35$  One unexplained stillbirth occurred at 35 weeks in the preprandial group.	Postprandial capillary blood glucose monitoring during pregnancy in type 1 diabetes may lead to significant improvements in obstetric and neonatal outcomes.	
De Veciana, M., Major, C., Morgan, M. et al. 1995 155	Study Type: RCT Evidence level: 1++	33 preprandial monitoring 33 postprandial monitoring	85% Hispanic. BMI 29.0 $\pm$ 3.2 (preprandial group) 28.4 $\pm$ 3.8 (postprandial group). Age 31 $\pm$ 6 years (preprandial group)	Intervention: Postprandial monitoring: daily monitoring before breakfast (fasting) and one hour after each meal.	Follow-up period:  Outcome Measures: Glycosylated haemoglobin Mode of delivery	Glycosylated haemoglobin (%) Initial Preprandial: 8.6 $\pm$ 2.3 Postprandial: 8.9 $\pm$ 3.2 Final Preprandial: 8.1 $\pm$ 2.2	The results of this study support the hypothesis that postprandial glucose monitoring can significantly improve the outcomes of pregnancy in women with gestational	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			29±5 years (postprandial group) Country: USA	Insulin dose was adjusted to achieve a fasting blood glucose value of 3.3–5.0 mmol/l, preprandial values of 3.3–5.9 mmol/l or postprandial values <7.7 mmol/l  Comparison: Preprandial monitoring: Daily monitoring of fasting, preprandial and bedtime capillary-blood glucose concentrations.	Preterm labour Preeclampsia Birth weight Neonatal hypoglycaemia (blood glucose <1.7 mmol/l). Hyperbilirubinemia Respiratory complications	Postprandial: 6.5±1.4, $P = 0.006$ Change Preprandial: -0.6±1.6 Postprandial: -3.0±2.2, $P < 0.001$  Caesarean sections performed for cephalopelvic disproportion (%) Preprandial: 36 Postprandial: 12 RR 3.0 (1.1–8.3) $P = 0.04$  LGA Preprandial: 14 (42) Postprandial: 4(12) RR 3.5 (1.3–9.5) $P = 0.01$  Birthweight >4000 g Preprandial: 12(36) Postprandial: 3 (9) RR 4.1 (1.3–13.2) $P = 0.01$  Shoulder dystocia Preprandial: 6(18) Postprandial: 1(3) RR 6.0 (0.8–47.1) $P = 0.10$  Neonatal hypoglycaemia preprandial: 7(21) postprandial: 1(3) RR7.0 (0.9–53.8) $P = 0.05$  Stillbirth preprandial: 1(3) Postprandial: 0	diabetes who require insulin therapy.	
Kerssen, A., de Valk, H., Visser, G.  2005  210	Study Type: Cohort  Evidence level: 2+	43	Pregnant women with type 1 diabetes  Country: The Netherlands	Intervention: Continuous glucose monitoring  Comparison: HbA <sub>1c</sub> Self blood glucose monitoring	Follow-up period:  Outcome Measures: Mean glucose level Glucose range Hyperglycaemic episodes Hypoglycaemic episodes	Self blood glucose monitoring Detection of hyperglycaemic episodes 4–5 times/day:35% 6–9 times/day: 59% 10 or more times per day: 100% ( $P < 0.05$ )  Detection of hypoglycaemic episodes: 4–5 times/day:26%	Hyperglycaemia and hypoglycaemia detection rates increase when patients measure their blood glucose levels 10 or more times a day.	Does not look at pregnancy outcome

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Yogev, Y., Chen, R., Ben-Haroush, A. et al 2003 209	Study Type: Cohort Evidence level: 2+	34	Pregnant women with type 1 diabetes. Gestational age ranged from 16–32 weeks. Mean HbA <sub>1c</sub> 6.1±1.2% (normal range 4.5–5.7%)  Country: Israel	Intervention: Continuous glucose monitoring  Comparison: Self-blood glucose monitoring	Follow-up period: 3 days  Outcome Measures:	6–9 times/day: 48% 10 or more times per day:73% (P<0.05)  All patients had hyperglycaemia undetected by self blood glucose monitoring. The mean total time of hyperglycaemia (>7.7 mmol/l) undetected by self-blood glucose measurements was 192±28 minutes/day.  Nocturnal hypoglycaemic events were recorded in 26 patients; in all cases there was an interval of 1–4 hours before clinical manifestations appeared or the event was revealed by random blood glucose examination.  In 24 of 34 patients (70%) the physician recommended that the insulin regimen be changed. The most common change was a decrease in the long-acting or intermediate-acting insulin dosage at night (mean reduction 25% in insulin dosage).  The correlation coefficient between the glucose measurements by the sensor and meter were 0.93±0.04, and between the plasma glucose, meter monitoring and sensor recording 0.91±0.02. The reliability coefficient was 0.88.  High patient satisfaction using CGM device	Glucose levels were above the upper normal threshold for many hours during the day. These events were related to unscheduled meals and between-meal snacks and were not detected by conventional self-blood glucose monitoring protocols.  Continuous monitoring profiles allow the physician to identify glucose patterns and to better target insulin treatment.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Jovanovic, M. 2000 {Jovanovic, 2000 28822 /id}	Study Type: Othercase series  Evidence Level: 3	Intervention: Continuous blood glucose monitoring	10	Women with gestational diabetes. mean HbA <sub>1c</sub> 5.2±0.5%  Country: USA		Women spent a mean of 5.5 hours/day in previously unrecognised hyperglycaemia (>6.6 mmol/l). For a mean of 1 hour/day blood glucose exceeded 7.7 mmol/l.  Examining the 72 hour profiles with each patient revealed important information about eating habits. For example, one patient was measuring blood glucose glucose as instructed after a low carbohydrate meal, and then eating a high-carbohydrate 'snack'.	CGM profiles demonstrated graphically to patients the damaging effect of high carbohydrate between-meal snacks and improved patient adherence to diet.  Instructions for SBGM were clarified so that patients were directed to check their blood glucose levels after each time they ate, rather than just after 'formal' meals.	
Feig DS;Cleave B;Tomlinson G; 2006 120	Study Type: Other Retrospective  Evidence Level: 2-	Intervention: Retrospective chart review done to obtain information on self-management behaviours at entry to the programme and at delivery and compared with the present.  Comparison:	64	Inclusion criteria: Women with type 1 or type 2 diabetes, who were at least 1 year postpartum Exclusion criteria: if women gave birth before 20 weeks' gestation  Country: Canada	Diabetes self-management behaviours: frequency of self-monitoring of blood glucose, frequency of insulin injections and frequency and complexity of insulin dose adjustments) HbA <sub>1c</sub>	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 delivery. Significant improvement in the HbA <sub>1c</sub> from entry to delivery. While comparing entry to the present, a significant improvement in frequency of insulin injections, frequency and complexity of insulin dose adjustment No significant change in frequency of self-monitoring of blood glucose from before pregnancy to the present, and a significant decrease in HbA <sub>1c</sub> by 0.015 ( $P < 0.0001$ , 95% CI 0.009–0.021) from entry to the programme to the present.	Women participating in an intensive diabetes management programme during pregnancy improve significantly from entry to delivery in diabetes self-management behaviours and glycaemic control and in the long term retention of some of the behaviours and knowledge. No improvement in HbA <sub>1c</sub> level	Decrease in HbA <sub>1c</sub> may be explained by the loss of contact with the diabetes care team and/or the discontinuation of frequent self-monitoring of blood glucose that necessary for achieving optimal glycaemic control.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
di BN;Napoli A;Sabbatini A;Borrello E;Buongiorno AM;Fallucca F;  1997  212	Study Type: RCT  Evidence level: 1+	10 in experimental group (telemedicine DIANET) 10 in control group	Women with type 1 diabetes All women used intensified protocols of insulin administration  Country: Italy	Intervention: A completely automatic DIANET (telephone modems for the transmission of self-monitored blood glucose data) system for glycaemic control  Comparison: Conventional system for glycaemic control	Follow-up period: "Entry" 9.5 weeks "Basal" 9.5–16.8 weeks "1st month" of investigation "end" near delivery  Outcome Measures: Blood glucose absolute values	Treatment with DIANET vs conventional system before breakfast: 87 ± 6 mg vs 104 ± 4 mg lunch: 85 ± 5 mg vs 104 ± 4 mg after dinner: 102 ± 5 mg vs 124 ± 6 mg Higher insulin doses in the DIANET vs conventional group. Significant reduction of hypoglycaemic reaction in both groups.	Telemedicine-DIANET is a practical way of providing specialist care in pregnancy area	
Inkster ME;Fahey TP;Donnan PT;Leese GP;Mires GJ;Murphy DJ;  2006  213	Study Type: Systematic review - meta-analysis  Evidence level: 3	13 studies which compared poor versus optimal glycaemic control in relation to maternal, fetal and neonatal outcomes	Inclusion criteria: -published observational studies -studies that examined pregnancy outcomes in women with type 1 and type 2 diabetes -studies that reported a measure of glycated haemoglobin and had clearly categorised pregnancy outcomes according to poor and optimal glycaemic control using a cut-off point Exclusion criteria: women with gestational diabetes  Country:	Intervention: To investigate and quantify the risk of adverse pregnancy outcomes in women with diabetes in relation to glycaemic control (whether poor or optimal)  Comparison:	Follow-up period:  Outcome Measures: Congenital malformations Miscarriage Perinatal mortality (including stillbirths and neonatal deaths)	12 studies reported the outcome of congenital malformations and showed an increased risk with poor glycaemic control (pooled OR 3.44, 95% CI 2.30 to 5.15). For 4 of 12 studies, it was also possible to calculate a relative risk reduction of congenital malformation for each 1-percent decrease in HbA <sub>1c</sub> ; these varied from 0.39 to 0.59. 4 studies reported risk of miscarriage and this was associated with poor glycaemic control (pooled OR 3.23, 95% CI 1.64 to 6.36). 4 studies showed increased perinatal mortality was also associated with poor glycaemic control (pooled OR 3.03, 95% CI 1.87 to 4.92).	There was an increase in adverse pregnancy outcomes in women with diabetes who had poor glycaemic control. Relating percentage risk reduction in HbA <sub>1c</sub> to relative risk of adverse pregnancy events may be useful in motivating women to achieve optimal control prior to conception.	
Stainton MC;Lohan M;Fethney J;Woodhart L;Islam S;  2006  431	Study Type: Cohort  Evidence level: 2++	61 women assigned to high-risk antenatal care.  1. Traditional Hospital Bed Rest (n = 29).  2. Pregnancy Day Stay Unit (n = 32)	Women admitted into the high-risk antenatal care were included in this study. Women with a known fetal anomaly were not considered. One group was assigned to the antenatal hospital unit another group to the pregnancy day	Intervention: Pregnancy Day Stay Unit  Comparison: Traditional Antenatal Hospital Unit.	Follow-up period: From time of admission to 3–6-weeks postpartum.  Outcome Measures: 1. Antenatal stressors 2. Anxiety 3. Sensation seeking (sensory deprivation) 4. Family relationships	Stress from emotions was the highest antenatal stressor for both groups and highest for the hospital rest group.  Stress about health increased over time for those in the Pregnancy Day Stay Unit and varied for those in Antenatal Hospital Unit.	Managing high-risk pregnancies by Antenatal Hospital Unit is less satisfactory compared to managing by Pregnancy Day Stay Unit.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			<p>stay unit.</p> <p>The vast majority of women were admitted on the basis of having pre-eclampsia, a few though on account of pre-existing diabetes or gestational diabetes.</p> <p>Country: Australia</p>			<p>Anxiety was significantly different between the groups over time (<math>P &lt; 0.01</math>), being highest for the Antenatal Hospital Unit group and decreasing from admission to 6-weeks postnatal for both groups.</p> <p>Sensation Seeking (sensory deprivation) showed significant differences (<math>P &lt; 0.05</math>) with the highest scores in the Antenatal Hospital Unit group and increasing over time for both groups.</p> <p>Family relationships were most disrupted for those in Antenatal Hospital Unit.</p> <p>The two groups were both satisfied with support from spouse, family and friends.</p>		

### 5.3 Management of diabetes during pregnancy

#### Q.17 What special considerations apply to the management of diabetes during pregnancy?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Laatikainen L;Teramo K;Hieta-Heikurainen H; 1987 226	Study Type: RCT Evidence level: 1+	13 women using continuous subcutaneous insulin infusion (CSII) 18 using conventional insulin treatment (CT)	Pregnant women with Type 1 diabetes. Country: Helsinki	Intervention: CSII Comparison: CT	Follow-up period: Outcome Measures: Retinopathy	9/22 patents randomised to CSII group declined pump treatment. Mean HbA <sub>1c</sub> decreased ( $P < 0.001$ ) in both groups with no difference between groups. Daily dose of insulin increased by 13.3 UI (32%) in the CT group and 5.7 UI (13%) in the CSII group. The difference between groups in number of patients with progressing retinopathy was not significant. Two patients (both CSII) progressed from background retinopathy to preproliferative retinopathy and then to proliferative retinopathy, in spite of laser treatment, following fast and significant decrease in HbA <sub>1c</sub> . Both patients were hypertensive at the beginning of pregnancy.	A rapid near normalisation of glycaemic control by CSII during pregnancy can accelerate the progress of retinopathy in poorly controlled diabetic patients.	
Rosenn BM;Miodovnik M;Holcberg G;Khoury JC;Siddiqi TA; 1995 Mar 68	Study Type: Cohort Evidence level: 2++	84 women	Type 1 diabetes. Recruited before 9 weeks gestation and received intensive insulin therapy throughout pregnancy. Patients monitored glucose concentrations with memory glucometers and insulin doses were adjusted weekly accordingly. Country:	Intervention: Intensive insulin therapy throughout pregnancy Comparison:	Follow-up period: Outcome Measures: Hypoglycaemia Biochemical hypoglycaemia determined from glucometer data Symptomatic hypoglycaemic episodes recorded weekly on standardised forms Moderate symptomatic hypoglycaemia: Any	71% of patients had at least one moderate symptomatic episode and 34% had at least one severe symptomatic episode. 19 patients had a total of 54 episodes of loss of consciousness and 12 patients had a total of 15 seizures. Most symptomatic episodes occurred during the first half of pregnancy. The peak incidence of severe or moderate symptomatic hypoglycaemia was between 10 and 15 weeks. There was no association between hypoglycaemia during early pregnancy	Hypoglycaemia is a frequent complication that significantly affects the majority of women who receive intensive insulin therapy during pregnancy. This may be related to the institution of intensive therapy which diminishes counterregulatory responses to hypoglycaemia and increases hypoglycaemic unawareness. Alternatively it may be that pregnancy independently increases the risk of hypoglycaemia, possibly due to hormonal changes, diminished	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					episode that could not be resolved by the patient herself and required active assistance from another person  Severe symptomatic hypoglycaemia: an episode resulting in seizures, loss of consciousness, injury, IV glucose treatment or emergency glucagon administration.	and adverse pregnancy outcome.  When hypoglycaemic and nonhypoglycaemic groups were compared there were no differences in any of the commonly used indices of glycaemic control, including preprandial glucose, postprandial glucose and glycohaemoglobin concentrations.	counterregulatory responses to hypoglycaemia or the nausea and vomiting of pregnancy.  At present, a measure of caution should be exercised for the occasional patient who demonstrates a tendency to have recurrent episodes of severe hypoglycaemia that cannot be resolved with the usual tactics of modifying insulin regimens, caloric intake, and physical activity.	
Lapolla A;Dalfra MG;Masin M;Bruttomesso D;Piva I;Crepaldi C;Tortul C;Dalla BB;Fedele D;  2003  228	Study Type: Cohort  Evidence level: 2+	68 women treated with conventional insulin therapy 25 women treated with continuous subcutaneous insulin infusion. Pump therapy suggested because of difficulties with metabolic control.	Type 1 diabetes 20/25 patients on pumps were switched from conventional therapy 1 year becoming pregnant. 21 used regular insulin and 4 used lispro.  Pump therapy suggested because of difficulties with metabolic control. Pump group had greater severity of diabetes.  Country:	Intervention: Insulin pump  Comparison: conventional therapy	Follow-up period:  Outcome Measures: Fasting blood glucose 1 hour post prandial HbA <sub>1c</sub> Spontaneous or induced abortion Time and mode of delivery Maternal outcomes: Pregnancy induced hypertension Preeclampsia Placental insufficiency Hydramnios Hypoglycaemic coma Ketoacidosis Fetal outcomes: Weight Hypoglycaemia Hypocalcaemia Hyperbilirubinemia Fetal distress Asphyxia Hyaline membrane disease Polycythemia Shoulder dystocia Malformations	There was no difference in outcomes between the two groups.	Insulin pump therapy is useful in problematic, complicated cases.	Groups differed with regard to White class and severity of retinopathy and neuropathy.
Burkart W;Hanker JP;Schneider HP;	Study Type: RCT	48 women using continuous	Pregnant women with Type 1 diabetes.	Intervention: CSII	Follow-up period:	There was no difference between CSII and ICT groups in the rate of pregnancy	CSII is indicated if intensified conventional treatment does not	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1988 227	Evidence level: 1++	subcutaneous insulin infusion (CSII) 41 women using intensified conventional treatment (ICT) 28 women with conventional diabetes treatment (CT)	Country: Germany	Comparison: ICT CT	Outcome Measures: HbA <sub>1c</sub> Mode of delivery Birthweight >95th percentile <10th percentile Gestational age at delivery Perinatal mortality Malformations	complications or fetal outcome. Both CSII and ICT groups had significantly better outcomes when compared with CT group.  >95th percentile: CSII: 5/48 ICT: 6/41 CT: 8/28, $P < 0.05$  <10th percentile CSII: 3/48 ICT: 1/41 CT: 5/28, $P < 0.05$  Healthy newborns: CSII: 40/48 ICT: 34/41 CT: 5/28, $P < 0.05$  Minor symptoms: CSII: 8/48 ICT: 2/41 CT: 5/28  Major symptoms CSII: 0 ICT: 2/41 CT: 22/28, $P > 0.05$	lead to normoglycaemia	
Carta Q;Meriggi E;Trossarelli GF;Catella G;Dal M;Menato G;Gagliardi L;Massobrio M;Vitelli A; 1986 Jun 432	Study Type: RCT Evidence level: 1++	8 women with T1 diabetes in pump group 7 women with T1 diabetes in conventional treatment group 6 women with T2 diabetes in pump group 8 women with T2 diabetes in conventional treatment group 10 nondiabetic controls	15 Type 1 diabetes 14 type 2 diabetes  Country: Italy	Intervention: Continuous Subcutaneous Insulin Infusion (CSII)  Comparison: Intensive conventional treatment (ICT)	Follow-up period:  Outcome Measures: Glycaemic control Insulin requirement Perinatal outcome	LGA (>90th percentile) Type 1: CSII: 2 ICT: 0 Type 2: CSII: 1 ICT: 0  No significant differences in any outcome measures	CSII is a practical, safe and effective method of maintaining glycaemic control	
Coustan DR;Reece EA;Sherwin RS;Rudolf MC;Bates SE;Sockin	Study Type: RCT Evidence level: 1++	11 women randomised to intensive	Pregnant women with type 1 diabetes	Intervention: Insulin pump therapy (Autosyringe AS-2C, AS-6C, Lilly CPI-	Follow-up period: Outcome Measures:	Both treatments were associated with a significant lowering of mean blood glucose levels ( $P < 0.05$ vs	There was no difference between the two groups with respect to outpatient mean glucose levels,	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
SM;Holford T;Tamborlane WW; 1986 Feb 225		conventional insulin therapy. 11 women randomised to insulin pump therapy	Country:	9100).  Comparison: Intensive conventional therapy	Maternal hypoglycaemia: Mild (responded to snack) Moderate (required another person's assistance) Severe required glucagon or IV glucose, usually in an emergency room setting). Mean blood glucose HbA <sub>1c</sub> Hyperglycaemia (>6.6)	prerandomisation). Values of HbA <sub>1c</sub> fell to within the normal range in all patients.  Insulin requirements did not differ significantly between the two groups before treatment assignment. During the second and third trimesters, however, pump treated subjects required significantly less insulin than did Intensive conventional treatment group ( $P < 0.05$ ).  There were no other differences between groups.  There were no pump problems or episodes of ketoacidosis. One pump-treated subject experienced two days of hyperglycaemia and ketonuria during a viral infection.	symptomatic hypoglycaemia, glycosylated haemoglobin levels, inpatient mean blood glucose levels, glycaemic excursions, chemical hypoglycaemia or hyperglycaemia.	
Gabbe SG;Holing E;Temple P;Brown ZA; 2000 Jun 230	Study Type: Cohort  Evidence level: 2++	24 women who started continuous subcutaneous insulin infusion (CSII) during pregnancy 24 pregnant women using multiple daily injections (MDI) 12 women who were already using CSII before pregnancy	Pregnant women with type 1 diabetes. CSII used in women who did not have acceptable control using MDI or who requested a pump.  Country:	Intervention: CSII initiated during pregnancy  Comparison: MDI CSII initiated before pregnancy	Follow-up period:  Outcome Measures: Mean blood glucose (from SBGM) HbA <sub>1c</sub> Diabetic ketoacidosis (DKA) Severe hypoglycaemia (requiring assistance of another person and treatment with glucagon). Caesarean delivery Gestational age at delivery Birth weight LGA SGA Neonatal hypoglycaemia Respiratory distress syndrome Malformations Perinatal death	CSII was initiated at a mean of 16.8 weeks gestation.  HbA <sub>1c</sub> declined in all study groups in the 2nd and 3rd trimesters. There was no difference in maternal or perinatal outcomes.  Before starting CSII, 8/24 women had 17 episodes of severe hypoglycaemia. After starting CSII one patient had 2 episodes ( $P < 0.01$ ).  6/24 women on MDI had 8 episodes of severe hypoglycaemia.  There were no episodes of severe hypoglycaemia in 12 women who had started CSII before pregnancy.  2 patients who began CSII during pregnancy required hospitalisation for mild DKA. Both cases were attributed to localised inflammation or fibrosis at the tip of the infusion catheter. 12/24 women had pump-related problems (pump malfunction or site infection) 5/12 women who started CSII before	CSII was initiated during pregnancy without deterioration in glycaemic control and was associated with maternal and perinatal outcomes comparable to those among women who were already using the pump before pregnancy or who received MDI.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						pregnancy had pump-related problems.		
						<p>Follow-up data collected for 19/24 women who started CSII in pregnancy and 10/12 women who started CSII before pregnancy.</p> <p>18/19 women who had started CSII during pregnancy had continued to use CSII after pregnancy. 9/10 women who had started CSII before pregnancy had continued using pump therapy.</p> <p>HbA<sub>1c</sub> following pregnancy was significantly lower in women using CSII than in women using MDI (<math>P = 0.02</math>).</p>		
Nosari I;Maglio ML;Lepore G;Cortinovis F;Pagani G; 1993 433	Study Type: RCT Evidence level: 1++	16 women using continuous subcutaneous insulin infusion (CSII) 16 women using intensive conventional insulin therapy (ICT)	pregnant women with Type 1 diabetes Country: Italy	Intervention: CSII Comparison: ICT	Follow-up period: Outcome Measures: 24 hour mean BG under a day hospital regimen Mean home monitored BG Frequency of home-monitored plasma values outside the target range (3.3 mmol/l-6.6 mmol/l) during pregnancy (%) HbA <sub>1c</sub> Ketoacidosis (blood glucose >16.5 mmol/l, high positivity of urinary ketone reagent strips with arterial pH <7.2). Severe hypoglycaemia (coma or seizure or a situation requiring hospitalisation or IV glucose or glucagons). Progression of retinopathy Microalbuminuria Macro-proteinuria Gestational age at delivery	<p>Good glycaemic control was achieved in both groups in the 1st trimester and maintained in the 2nd and 3rd trimester. There were no significant differences in BG levels.</p> <p>The mean daily insulin requirements increased similarly in both groups.</p> <p>Ketoacidosis: CSII: 3 ICT: 0, NS</p> <p>The 3 cases of ketoacidosis were due to catheter occlusion (one case) catheter leakage (one case) and pump failure (one case).</p> <p>Severe hypoglycaemia: CSII: 3 ICT: 1, NS</p> <p>Intrauterine death: CSII: 2 ICT: 1, NS</p> <p>No differences in any other outcome</p>	CSII and ICT are equally effective strategies for the treatment of pregnant diabetic women.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					Caesarean section Perinatal mortality Neonatal hypoglycaemia Respiratory distress syndrome Congenital malformations Macrosomia LGA SGA			
Simmons D;Thompson CF;Conroy C;Scott DJ;  2001 Dec  229	Study Type: Case-control  Evidence level: 2+	30 women using insulin pump 60 using conventional therapy	Polynesian women with insulin-requiring GDM/type 2 with persistent hyperglycaemia despite multiple injections of subcutaneous insulin. Controls matched for ethnicity, type of diabetes and peak insulin dosage.  Country: New Zealand	Intervention: Insulin pumps (Nipro)  Comparison: Women treated with tablets or multiple daily injections	Follow-up period:  Outcome Measures: 2 hour postprandial glucose Neonatal birthweight Neonatal hypoglycaemia Caesarean section	Women in the pump group had a higher peak insulin dosage than women in the non pump group.  Mean 2 hour post prandial glucose (mmol/l) Pump user: 6.6±1.8 Non pump user: 6.4±1.6 P=0.550  There was no difference in perinatal outcomes  Women using pumps put on more weight from referral (10.6±8.8 kg vs 5.0±4.9 kg, $P < 0.0001$ ) and were more likely to have baby admitted to special care baby unit (56.3%vs25.0%, $P = 0.033$ ).	Perinatal outcomes were comparable to those in women with less hyperglycaemia and lower insulin requirements  Insulin pump therapy seems to be safe and effective for maintaining glycaemic control in pregnancies complicated by GDM/type 2 diabetes and requiring large doses of insulin.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Rodgers BD;Rodgers DE; 1991 219	Study Type: OtherCase series  Evidence Level: 3	Intervention:  Comparison:	37 admissions for DKA during pregnancy	Country:		Emesis and the use of $\beta$ -sympathomimetic drugs were considered etiologic in 57% of cases. Patient noncompliance and physician management errors were considered etiologic in 24% 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.  30% of patients admitted with emesis had had a prepregnancy history of diabetic gastroenteropathy, thus identifying that group at particularly high risk for DKA.		
Zarkovic M;Nesovic M;Marisavljevic D;Ciric J;Stojanovic M; 1995 216	Study Type: OtherCase study  Evidence Level: 3	Intervention: Parenteral nutrition (PN)  Glucose limited. Basal and additional insulin requirements independently assessed.  Comparison:	A pregnant woman with type 1 diabetes and hyperemesis gravidarum	Country:		Vomiting was significantly reduced after the PN started but it stopped completely after 15 days. Three days later the patient started taking small quantities of food and the PN was terminated after 23 days. There was no fetal morbidity.	This case demonstrates that optimal diabetes control during PN is feasible in pregnancy. Previous experience of a medical team in treating pregnant diabetic patients is of great value in assessing daily changes in insulin requirements	
Carroll MA;Yeomans ER; 2005 218	Study Type: OtherCase study  Evidence Level: 3	Intervention:  Comparison:	A 23 year old woman of 31 weeks gestation not known to be diabetic.	Country:		On presentation heart rate was 128 beats per min. Serum blood glucose was 41.8 mmol/l. urine and serum ketones were negative. The patient was admitted with a diagnosis of pyelonephritis and hyperglycemia.  Five hours after admission IV fluid and insulin were started.  Ten hours after admission fetal death		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Leveno KJ;Fortunato SJ;Raskin P;Williams ML;Whalley PJ; 1988 Apr 6 {Leveno, 1988 33988 /id}	Study Type: OtherCase series  Evidence Level: 3	Intervention: Insulin pump (autosyringe AS-2C and AS-6C  Comparison: Conventional insulin therapy	28 women offered pump therapy	Women who used pumps were generally from the private sector and in better glucose control at entry.  Country:	Fasting preprandial or postprandial plasma glucose measurements performed during clinics. Macrosomia Neonatal hypoglycaemia Respiratory distress syndrome	was confirmed. 15/28 women offered pump therapy accepted. 5/15 subsequently discontinued use. 1 woman developed ketoacidosis after abruptly discontinuing pump use.  Gestational age at delivery was significantly less in women refusing pump therapy (35.9 weeks vs 37.5 weeks, $P < 0.05$ ). Three malformations (2 ventricular septal defects and 1 clubfoot) in women who declined pump therapy. No malformations in women who accepted pump therapy.		Outdated technology
Brimacombe J; 1995 Apr {Brimacombe, 1995 34000 /id}	Study Type: OtherCase report  Evidence Level: 3	Intervention: Parenteral nutrition  Midazolam Prochlorperazine  Comparison:	A woman with diabetes and Hyperemesis Gravidarum presenting at 17 weeks gestation	Country:		No other differences between groups. Prochlorperazine was discontinued on day three when the patient developed mild extrapyramidal symptoms Parenteral nutrition was ceased on day 6 and the midazolam on day 7. By day 8 the patient was on a full diet with slight nausea. The patient discharged herself on day 10. At 28 weeks the mother was readmitted with severe recurrent symptoms and requested C-section. TPN and pharmacotherapy reinstated (although ondansetron not midazolam due to different clinician). After 10 days woman became febrile and developed peripheral oedema. Normal 1.5 kg baby delivered.	The combination of midazolam, prochlorperazine and TPN resulted in an improvement in symptoms which were sustained for some weeks after therapy ceased.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Nachum Z; Ben Shlomo I; Weiner E; Shalev E;  1999 Nov 6  {Nachum, 1999 17336 /id}	Study Type: RCT  Evidence level: 1++	392 women	Women with gestational or pre-existing diabetes.  Country: Israel	Intervention: Three doses of regular insulin before meals and an intermediate insulin dose before bedtime (four times daily regimen).  Comparison: Regular and intermediate insulin in the morning and evening (twice-daily regimen).	Follow-up period:  Outcome Measures: 1. Mean daily insulin 2. HbA <sub>1c</sub> levels 3. Caesarean section rate 4. Preterm delivery 5. Hypoglycaemia in infants 6. Apgar score	Glycaemic control was better with the four times daily regimen than with the twice-daily regimen: in women with gestational diabetes mean blood glucose concentrations decreased by 0.19 mmol/l (95% CI 0.13 to 0.25), HbA <sub>1c</sub> by 0.3% (95% CI 0.2% to 0.4%), and fructosamine by 41 micromol/l (95% CI 37 to 45), and adequate glycaemic control (mean blood glucose concentration <5.8 mmol/l) was achieved in 17% more women (95% CI 8% to 26%); in women with pre-existing diabetes mean blood glucose concentration decreased by 0.44 mmol/l (95% CI 0.28 to 0.60), HbA <sub>1c</sub> by 0.5% (95% CI 0.2% to 0.8%), and fructosamine by 51 micromol/l (95% CI 45 to 57), and adequate glycaemic control was achieved in 31% more women (95% CI 15% to 47%).  Rates of maternal severe hypoglycaemic events, caesarean section, preterm birth, macrosomia, and low Apgar scores were similar in both groups.  In women with gestational diabetes the four times daily regimen resulted in a lower rate of overall neonatal morbidity than the twice-daily regimen (RR 0.59, 95% CI 0.38 to 0.92), and the RRs for hyperbilirubinaemia and hypoglycaemia were lower (RR 0.51, 95% CI 0.29 to 0.91 and RR 0.12, 95% CI 0.02 to 0.97, respectively). The RR of	Four times daily rather than twice-daily insulin improves glycaemic control and perinatal outcomes without increasing rates of hypoglycaemia and caesarean section in the mother.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Farrar D; Tuffnell D; West J. 2007 224	Study Type: Systematic review - meta-analysis  Evidence level: 1+	Two studies, involving 60 women with 61 pregnancies.	Pregnant women with pre-existing diabetes or gestational diabetes.  Country: Both studies carried out in Italy	Intervention: This systematic review compared continuous subcutaneous insulin infusion with multiple daily injections for the treatment of diabetes during pregnancy.  Comparison:	Follow-up period:  Outcome Measures: Perinatal mortality, fetal anomalies, hypoglycemic /hyperglycemic episodes, hospital admission and LOS.  Additional maternal and perinatal outcomes included.	hypoglycaemia in newborn infants of women with pregestational diabetes was 0.17 (95% CI 0.04 to 0.74).  No significant differences were found for the main outcome measures.  For peri-natal outcomes no significant differences in outcomes were found.  Maternal outcomes showed no significant differences in outcomes.	Provides inconclusive evidence in either direction.	Neither trial included participants with GDM.  There may be serious limitations with the designs of these studies. The first trial did not describe randomization and included 2 women who had used CSII pre-conceptually. The second trial that described randomization, recruited only women with type 1 DM, described as being highly motivated.

## 5.4 Retinal assessment during pregnancy

### Q.18 When and how often should women be offered retinal assessment?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Diabetes Prevention Program Research Group: Nathan,D.M.; Chew,E.; Christophi,C.A.; Davis,M.D.; Fowler,S.; Goldstein,B.J.; Hamman,R.F.; Hubbard,L.D.; Knowler,W.C.; Molitch,M.E.	Study Type: RCT Evidence level: 1++	302	Patients with impaired glucose tolerance and with new-onset diabetes of known duration in the Diabetes Prevention Program (DPP) cohort.  The patients recruited had elevated fasting glucose (5.3–6.9 mmol/l) and impaired glucose tolerance, and no history of diagnosed diabetes, other than gestational diabetes not persisting after pregnancy.  Country: USA	Intervention: Patients with diabetes  Comparison: Patients without diabetes	Follow-up period: Over 3 years  Outcome Measures: Incidence of retinopathy	Retinopathy consistent with diabetic retinopathy was detected in 12.6% and 7.9% of the diabetic and non-diabetic participants, respectively ( $P = 0.03$ ).  Systolic blood pressure and HbA <sub>1c</sub> were higher at baseline in the participants with diabetes who developed retinopathy compared to the participants with diabetes but no retinopathy.	Retinopathy characteristic of diabetes is present in persons with elevated fasting glucose and impaired glucose tolerance and no known history of diabetes. The prevalence of retinopathy is significantly higher in persons who develop diabetes.	The study is not based on the right population for the guideline, but the information is useful.
2007  {Diabetes Prevention Program Research Group., 2007 36651 /id}								
2000  {The Diabetes Control and Complications Trial Research Group, 2000 28167 /id}	Study Type: RCT Evidence level: 1+	180 women who had pregnancies during the trial and 500 women who did not become pregnant during the trial	13–39 years of age, type 1 diabetes for 1–15 years, generally in good health	Intervention: Pregnancy  Comparison: Women who did not become pregnant	Follow-up period: Average 6.5 years  Outcome Measures: Progression of retinopathy	In the intensive treatment group 693/2950 (23%) non pregnant women had progression of retinopathy compared to 39/124 (31%) pregnant women OR 1.62 95% CI 1.01–2.59, $P < 0.05$ . In the conventional treatment group 1742/5605 (31%) non pregnant women had progression of retinopathy compared to 37/73 pregnant women OR 2.54, 95% CI 1.59–4.03, $P < 0.0001$ .  5 women in the intensive treatment group and 8 in the conventional treatment group developed severe retinopathy changes; 3 subjects in the	The pregnant state, rather than the institution of intensive diabetes treatment, is the primary cause of worsened diabetic retinopathy. Nonetheless a minor effect of rapid improvement of glycaemic control on worsening of retinopathy was seen. In addition, the adverse effect of pregnancy on retinopathy was greater in the conventionally treated group compared with the intensively treated group, showing that the effects of pregnancy are additive to the effects of poor metabolic control. The worsening of	The diabetes complications and control trial is a multicenter controlled clinical trial that compared intensive treatment with conventional diabetes therapy. This paper reports on an ancillary study of the effects of pregnancy on retinopathy.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						conventional treatment group required laser photocoagulation. 9/13 cases progressed even further postpartum before they improved. In only one of these cases was proliferative disease present before pregnancy.	retinopathy during pregnancy can be quite significant, occasionally requiring photocoagulation during pregnancy.	
Chew EY;Mills JL;Metzger BE;Remaley NA;Jovanovic-Peterson L;Knopp RH;Conley M;Rand L;Simpson JL;Holmes LB;Aarons JH;  1995  {Chew, 1995 28173 /id}	Study Type: Cohort  Evidence level: 2++	155 pregnant women with type 1 diabetes		Intervention: Metabolic control  Comparison:	Follow-up period: 1 month postpartum  Outcome Measures: Metabolic control (HbA <sub>1c</sub> assessed weekly during first trimester and then monthly) Progression of reinopathy (clinical groups: No retinopathy; microaneurysms or blot hemorrhages only; mild nonproliferative retinopathy; Moderate nonproliferative reinopathy; severe nonproliferative retinoapthy; Proliferative retinopathy). Progression: ≥ 2 step change in retinopathy.	Baseline and postdelivery photographs available for 140 women. 15 patients who had proliferative retinopathy at baseline were excluded. Group 1 no retinopathy: ≥ 2 step progression in 4/39 (10.3%) of patients with no retinopathy, 8/38 (21.1%) patients with microaneurysms only, 5/32 (18.8%) patients with mild NPDR, and 17/31 (54.8%) patients with moderate NPRD. Patients with more severe retinopathy were more likely to show progression than those with no retinopathy at baseline ( $\chi^2$ for trend, $P < 0.001$ ).  Retinopathy progressed by two or more steps in 55% of patients with ≤ 15 years duration of diabetes and 50% of patients with >15 years duration of diabetes. However, proliferative retinopathy developed in 18% of patients with ≤15 years duration of diabetes and 39% of patients with > 15 years duration of diabetes.  Patients with no retinopathy or only microaneurysms at conception did not develop proliferative retinopathy. Proliferative retinopathy developed in 2/32 (6.3%) patients with mild NPDR at	It is possible that the duration of diabetes may not be as important as baseline severity of retinopathy for ≥ 2 step progression of retinopathy during pregnancy. But duration of diabetes may be a more important risk factor for the development of proliferative retinopathy.  The effect of the institution of tight glycaemic control is impossible to separate from the effect of elevated glycosylated hemoglobin levels at conception because patients who were most likely to have progression had both the poorest control at baseline and the largest improvement during early pregnancy. A further confounding factor is the correlation of increasing severity of retinopathy with increasing poor glucose control at baseline.  Women with moderate or more severe retinopathy at conception are at greater risk of progression of retinopathy during pregnancy. Patients with significant retinopathy and poor metabolic control at conception are at greatest risk. Proliferative retinopathy may develop and careful ophthalmic monitoring is indicated. Improving metabolic control before pregnancy to	The diabetes in early pregnancy (DIEP) study was a multicenter collaborative study. Women with and without T1 diabetes were enrolled before (86%) or within 21 days (14%) of conception.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>baseline and 9/31 (29%) patients with moderate NPRD at baseline.</p> <p>Univariate analysis: Severity of retinopathy at baseline (<math>P = 0.001</math>) Initial HBA<sub>1c</sub> (<math>P = 0.048</math>) and duration of diabetes (<math>P &lt; 0.001</math>) were significant risk factors for progression of retinopathy.</p> <p>Multivariate analysis: Only baseline severity of retinopathy and initial glucose control were significant.</p> <p>Baseline severity of retinopathy (moderate NPDR compared with mild NPDR or less) OR 5.7, 95% CI 2.1–15.7, <math>P &lt; 0.001</math></p> <p>Initial glucose control (<math>\geq 6</math> SD above control mean compared with normal range of 2 SD of control mean) OR 2.7, 95% CI 1.1–7.2, <math>P = 0.039</math>.</p>	<p>prevent progression of retinopathy offers the best opportunity for favourable outcome for the mother and infant.</p>	
<p>Dibble CM;Kochenour NK;Worley RJ;</p> <p>1982</p> <p>{Dibble, 1982 28176 /id}</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2+</p>	55 women with T1 diabetes	Patients who were hypertensive were excluded	<p>Intervention: Pregnancy</p> <p>Comparison:</p>	<p>Follow-up period: 8 weeks postpartum</p> <p>Outcome Measures: Retinopathy Glucose control</p>	<p>Group 1 (no retinopathy) <math>n = 23</math>, 0% progressing. Group 2 (background retinopathy) <math>n = 19</math>, 3(16%) progressing, Group 3A (proliferative retinopathy - no photocoagulation prior to pregnancy) <math>n = 7</math>, 6 (86%) progressing, Group 3B (proliferative retinopathy, photocoagulation prior to pregnancy) <math>n = 6</math>, 1 (17%) progressing.</p> <p>The average duration of diabetes in those patient without retinopathy was 7.5 years whereas the duration in those with retinopathy was 16 years (<math>P &lt; 0.01</math>). In the groups with retinopathy, patients whose retinopathy progressed during pregnancy were found</p>	<p>Photocoagulation before pregnancy may protect against rapidly progressive proliferative retinopathy and that aggressive treatment of poliferative retinopathy early in pregnancy may prevent further progression of the disease.</p>	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Klein BE;Moss SE;Klein R; 1990 Jan {Klein, 1990 7910 /id}	Study Type: Cohort Evidence level: 2++	171 pregnant women with T1 diabetes, 298 nonpregnant women with T1 diabetes		Intervention: Pregnancy Comparison: Nonpregnant women with type 1 diabetes	Follow-up period: 9.4 ± 6.6 weeks postpartum Outcome Measures: Retinopathy (10 levels of severity - based on grading of fundus photographs) glycosylated haemoglobin, duration of diabetes, current age, diastolic blood pressure, number of past pregnancies, current pregnancy status	to have diabetes longer than those whose retinopathy did not progress ( $P < 0.05$ ). There were 133 pregnant and 241 nonpregnant women who had gradable fundus photographs at both visits. Non pregnant women on average were older; had diabetes for more years; had higher glycosylated haemoglobin, blood pressure and blood glucose levels; and took less insulin each day than pregnant women. Within each quartile of glycosylated haemoglobin, pregnant women had a greater tendency to have progression of retinopathy ( $P < 0.005$ , adjusted odds ratio 2.3). Within each quartile of diastolic blood pressure, pregnant women had a greater tendency to have progression ( $P=0.062$ , adjusted odds ratio 2.3). Ordinal multivariate logistic analysis: Outcome variable=change in severity of retinopathy between visits. Scale= (1) ≥2 steps improvement (2) 1 step improvement (3) no change (4) 1 step progression (5) ≥2 steps progression. Exposure variables= HbA <sub>1c</sub> , pregnancy, blood pressure, age, duration of diabetes, number of previous pregnancies. Significant variables= HbA <sub>1c</sub> ( $P < 0.0001$ , OR 1.7, 95% CI 1.4–2.2) and pregnancy ( $P < 0.02$ , OR 1.8, 95% CI 1.1–2.8). When scale for outcome variable was collapsed to progression of retinopathy or	Pregnancy was a strong predictor of the progression of diabetic retinopathy.	Loss to follow-up: There were 38 pregnant women lost to follow-up. There was no difference in severity of retinopathy at the first visit. There were 57 nonpregnant women lost to follow-up. They had less severe retinopathy at baseline than those that did. Mean age, duration of diabetes, and blood pressure were no different at base-line for pregnant women with and without follow-up. The difference for glycosylated haemoglobin was of borderline significance. Mean age and duration of diabetes was significantly less for nonpregnant women lost to follow-up. Mean blood pressures and glycosylated haemoglobin were not different. Likely direction of bias: underestimate of effect.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						not, diastolic bloodpressure reached a level of statistical significance.		
						Change in visual acuity: Pregnant women were significantly more likely to have a decrease in visual acuity than the non pregnant group ( $P < 0.05$ )		
Lauszus F;Klebe JG;Bek T; 2000 {Lauszus, 2000 28193 /id}	Study Type: Cohort Evidence level: 2++	112 women with type 1 diabetes		Intervention: Tight glycaemic control during pregnancy  Comparison:	Follow-up period:  Outcome Measures: Changes in retinopathy (Ophthalmologic examination before pregnancy, once in each trimester and 4 months after birth) 24-h blood pressure, glucose control, albuminuria, outcome of pregnancy	At all examinations during pregnancy HbA <sub>1c</sub> was significantly lower than before and after pregnancy ( $P < 0.01$ ). There was an association between grade of retinopathy and HbA <sub>1c</sub> in the period before pregnancy (Spearman's rho=0.49, $P < 0.04$ ) and after pregnancy (Spearman's rho=0.42, $P < 0.02$ ) but no such correlation was found at any examination during pregnancy where there was tight glycaemic control. None of the women showed progression of retinopathy requiring photocoagulation. Significantly more women experienced progression of retinopathy after pregnancy than during pregnancy ( $P < 0.001$ ).  Women who had progression of retinopathy had significantly earlier onset of diabetes ( $14 \pm 8$ years, range 1–27) than women with improvement or no progression of retinopathy ( $19 \pm 8$ years, range 1–36, $P < 0.04$ ). No association was found between progression of retinopathy and blood pressure, albumin excretion rate or adverse perinatal outcome.	Tight glycaemic control is recommended to avoid progression of retinopathy. Attention should be given to the period after delivery where the tight regulation may be difficult to achieve. Women with Type 1 diabetes should be encouraged to plan pregnancies early in life.	75/112 women attended prepregnancy clinic
Maayah J;Shammas	Study Type: Cohort	60 women with T1		Intervention: Pregnancy	Follow-up period:	35/60 (58%) of pregnant		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
A;Haddadin A; 2001 {Maayah, 2001 28197 /id}	Evidence level: 2+	diabetes 80 non pregnant women with T1 diabetes (controls)		Comparison:	Outcome Measures:	women had retinopathy at first examination compared to 24/80 controls (30%). None of the controls experienced progression of retinopathy during the 9 month period.  Pregnant women: Group 1 no retinopathy ( $n = 25$ ): None developed retinopathy during pregnancy.  Group 2 Background retinopathy ( $n = 20$ ): 3 (15%) progressed to PDR.  Group 3 PDR ( $n = 15$ ): Group 3A Photocoagulation prior to pregnancy: 2/7(29%) progressed Group 3B Untreated: 5/8 progressed (63%)  Duration of diabetes significant factor in progression ( $p < 0.005$ ).		
Phelps RL;Sakol P;Metzger BE; 1986 {Phelps, 1986 28203 /id}	Study Type: Cohort Evidence level: 2+	35 women with type 1 diabetes(38 pregnancies)	All women were enrolled in intensive education, monitoring, diet and insulin program to improve metabolic regulation.	Intervention: Pregnancy Comparison:	Follow-up period: Two weeks post partum  Outcome Measures: Retinopathy (graded from fundus photographs according to Airlee House classification system). Plasma glucose	3/10 patients with no retinopathy at baseline developed retinopathy during pregnancy 13/20 with background retinopathy at baseline showed progression of retinopathy during pregnancy. 2/20 developed proliferative retinopathy. All five patients with proliferative retinopathy at baseline deteriorated during pregnancy.  Patients without proliferative retinopathy at entry: A significant relationship was found between diabetic control at entry and the increase in total background retinopathy	Retinal changes sufficient to be a severe threat to vision developed rarely in patients who were free of proliferative disease at presentation and did not occur in any patients with normal fundi.  Our results provide the first detailed evidence that changes in background retinopathy in women without proliferative retinopathy may be related to the degree of diabetic control achieved over the course of pregnancy. We emphasise that this should not militate against the institution of intensive therapy. The established benefits of excellent diabetic control during gestation clearly	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Rosenn B;Miodovnik M;Kranias G;Khoury J;Combs CA;Mimouni F;Siddiqi TA;Lipman MJ;  1992  {Rosenn, 1992 28206 /id}	Study Type: Cohort  Evidence level: 2++	154 women with T1 diabetes	Tight glycaemic control	Intervention: Hypertension in pregnancy  Comparison:	Follow-up period:  Outcome Measures: Retinopathic progression (examinations once each trimester and 6 to 12 weeks post partum). Defined as retinopathy de novo or upgrading of retinopathy from first or second trimester to later trimesters or post partum or changes in women with grade 6 retinopathy requiring additional photocoagulation.	during pregnancy ( $r = 0.509$ , $P = 0.002$ ). The magnitude of improvement in glycaemic control was also correlated ( $r = 0.649$ , $P < 0.001$ ).  Progression of retinopathy was significantly associated with duration of diabetes ( $P = 0.04$ ) and with first trimester retinal grade ( $P = 0.01$ ). First trimester mean glycohemoglobin and the magnitude of decrease in mean glycohemoglobin from first to second trimester were also significantly associated with retinal changes ( $P = 0.01$ ).  Women with pregnancy-induced hypertension were significantly more likely than normotensive women to have progression of retinopathy. Women with chronic hypertension (with or without superimposed pregnancy induced hypertension) were at high risk for progression of retinopathy during pregnancy.  Seven women with pre-existing background retinopathy had proliferative changes during the course of pregnancy that necessitated photocoagulation therapy. 13/51 women who had retinopathic progression during pregnancy experienced postpartum regression of the changes. None of the women who had proliferative changes during pregnancy had spontaneous regression of the lesions.  Multiple logistic regression: Magnitude of decrease in glycohaemoglobin from first to	outweigh the relatively minor effects noted in in the fundi of the majority of patients who do not have pre-existing proliferative retinopathy.  The presence of any sort of hypertensive disorder of pregnancy is associated with progression of diabetic retinopathy.  The duration of diabetes and the severity of existing retinopathy are major determinants of the progression of retinal disease.  The progression of retinopathy during pregnancy may be associated with either of the following factors: institution of rapid glycaemic control in the first trimester or, alternatively, poor glycaemic control early in pregnancy. We believe the latter hypothesis to be true and advocate the pursuit of good glycaemic control in diabetic women as early in pregnancy as possible, because the association of poor glycaemic control with adverse pregnancy outcomes is now widely recognised.  In some women with T1 diabetes who experience progression of background retinopathy during pregnancy, postpartum regression of these changes may be expected.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						second trimester ( $P = 0.004$ ), pregnancy-induced hypertension ( $P = 0.01$ ) and chronic hypertension ( $P = 0.02$ ) were all associated with retinopathic progression. Higher first trimester glycohaemoglobin concentrations were associated with greater decreases in glycohaemoglobin from first to second trimester (correlation = 0.71, $P = 0.0001$ ). Odds ratios: chronic hypertension 2.1 (1.7–3.6), pregnancy-induced hypertension 1.8 (1.1–3.1), decrease >2% in glycohaemoglobin in women with first trimester values >8.5% 1.4 (0.9 - 2.2).		
Temple RC;Aldridge VA;Sampson MJ;Greenwood RH;Heyburn PJ;Glenn A;  2001  {Temple, 2001 28212 /id}	Study Type: Cohort  Evidence level: 2++	179 pregnancies in 139 women with T1 diabetes	No hypertension	Intervention: Pregnancy  Comparison:	Follow-up period:  Outcome Measures: Progression retinopathy (dilated fundal examination performed at booking, 24 weeks, and 34 weeks or 4–6 weekly if retinopathy present at booking. Retinopathy classed as: (1) No or minimal background retinopathy; (2) moderate or severe background retinopathy or; (3) proliferative diabetic retinopathy) HbA <sub>1c</sub>	Of 179 pregnancies 91% had no or minimal BDR at booking, 5.6% had moderate or severe BDR and 3.4% had PDR. Progression of retinopathy occurred in 9 pregnancies (5%) in 7 women. Two women with mild BDR at baseline and two women with moderate BDR at baseline developed PDR and all four were treated with laser therapy. Progression of retinopathy was significantly increased in women with duration of diabetes 10–19 years compared with duration <10 years (10% vs 0%, $P = 0.007$ ) and in women with moderate to severe background retinopathy at booking (30% vs 3.7%, $P = 0.01$ ).	The low rate of progression of retinopathy (5%) compared to earlier studies (17–70%) could be due to the fact that earlier studies had higher levels of retinopathy at booking. Our results support those from earlier studies that suggest that risk of development or progression of retinopathy is low in women with minimal or no retinopathy in early pregnancy. In our study glycaemic control at booking was very good (mean HbA <sub>1c</sub> 6.6%) which may be another factor in the low incidence of progression in our population. Our finding that risk of progression of retinopathy is increased in women with longer duration of diabetes and increased retinopathy at baseline supports previous observations. However our study included 20 pregnancies in women with duration of diabetes >20 years who had no	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
xer-Siegel R;Hod M;Fink-Cohen S;Kramer M;Weinberger D;Schindel B;Yassur Y;  1996  {Axer-Siegel, 1996 28214 /id}	Study Type: Cohort  Evidence level: 2+	65 pregnant patients with T1 diabetes	Age 21–42 years (mean 28.6 ± 4.6 years). 37 were prepared before conception and 28 were first seen after conception.	Intervention: Pregnancy  Comparison:	Follow-up period: 12 months postpartum  Outcome Measures: Progression of retinopathy (an increase in severity of more than one grade) Duration of diabetes HbA <sub>1c</sub> Systolic blood pressure	No retinopathy at conception ( <i>n</i> = 38): No change: 28 (74%) Mild progression: 10 (26%) Progression to proliferative diabetic retinopathy (PDR): 0  Nonproliferative diabetic retinopathy (NPDR) at conception ( <i>n</i> = 22): No change: 5 (22.5%) Mild progression: 12 (55%) Progression to PDR: 5 (22.2%)  Patients with no retinopathy at conception who progressed to mild NPDR ( <i>n</i> = 10): 5 had total regression postpartum Patients with NPDR at conception who progressed to severe NPDR ( <i>n</i> = 12): 2 had total regression postpartum  The glycohemoglobin was higher in the progression group than the nonprogression group ( <i>P</i> = 0.04 in third trimester) Duration was longer in the progression group than the nonprogression group ( <i>P</i> < 0.01) The systolic blood pressure was higher in the progression group ( <i>P</i> < 0.005).	or mild retinopathy at booking and only one of those showed progression. This would suggest that retinopathy at baseline may be a more important factor than duration of diabetes. Any patient with retinopathy more severe than minimal should have 4–6 weekly fundal examinations.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Chan WC;Lim LT;Quinn MJ;Knox FA;McCance D;Best RM;  2004  {Chan, 2004 28169 /id}	Study Type: Other  Evidence Level: 3	Intervention: Pregnancy  Comparison:	8	Women with t1 diabetes who developed sight threatening retinopathy during pregnancy		14/16 eyes showed signs of progression of retinopathy during pregnancy. 4 eyes progressed from background retinopathy to preproliferative retinopathy and 10 eyes progressed to proliferative retinopathy. 15 eyes did not show signs of post partum regression. In all, 13 eyes progressed to proliferative retinopathy in the post partum period. All eyes that did not show signs of regression required treatment.	Sigh threatening retinopathy associated with pregnancy is rare but it can have dire consequences. We recommend that pregnant patients who exhibit progression of retinopathy to severe preproliferative changes be considered for laser photocoagulation. Proliferate diabetic retinopathy may not regress postpartum. Close follow up should be extended in the postpartum period in this group of patients until the retinopathy is stabilised.	

## 5.5 Renal assessment during pregnancy

### Q.19 When and by what method should women be offered renal assessment?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Ekbohm P;Damm P;Feldt-Rasmussen B;Feldt-Rasmussen U;Molvig J;Mathiesen ER;  2001 Oct  {Ekbohm, 2001 35115 /id}	Study Type: Cohort  Evidence level: 2++	240	type 1 diabetes  Country: Denmark	Intervention: Microalbuminuria  Comparison: Normal urinary albumin excretion ,nephropathy	Follow-up period:  Outcome Measures: Preterm birth SGA Preeclampsia	203 (85%) had normal urinary albumin excretion 26 (11%) had microalbuminuria 11 (5%) had diabetic nephropathy  Preeclampsia: n (%) Normal: 12 (6) Microalbuminuria: 11 (42) Diabetic nephropathy: 7 (64) <i>P</i> < 0.01  SGA: n (%) Normal: 4 (2) Microalbuminuria: 1 (4) Diabetic nephropathy: 5 (45) <i>P</i> < 0.001  Pre-term birth (< week 37) n (%) Normal: 71 (35) Microalbuminuria: 16 (62) Diabetic nephropathy: 10 (91) <i>P</i> < 0.001  Pre-term birth (< week 34) n (%) Normal: 12 (6) Microalbuminuria: 6 (23) Diabetic nephropathy: 5 (45) <i>P</i> < 0.001	The prevalence of preterm birth is considerably increased in women with microalbuminuria, mainly caused by preeclampsia.	
Rosenn, B., Miodovnik, M.  2003  {Rosenn, 2003 29318 /id}	Study Type: Systematic review - meta-analysis  Evidence level: 2++	Effect of pregnancy on diabetes 11 studies 178 subjects  Effect of nephropathy on pregnancy outcome 10 studies 370	Diabetes and pregnancy  Country:	Intervention:  Comparison:	Follow-up period:  Outcome Measures: Progression of nephropathy Chronic hypertension Preeclampsia C section IUGR	8/11 longitudinal studies determined that pregnancy did not alter the rate of decline in renal function. 3 studies found accelerated progression in women with advanced nephropathy. Only one study used non-pregnant controls (this study did not find	Most studies suggest that pregnancy is not associated with the development of nephropathy or with accelerated progression of pre-existing nephropathy, but some data suggest that in patients with moderate or advanced renal disease, pregnancy may	

Bibliographic Information	Study Type & Evidence Level	Number of Patients subjects	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					Delivery <34 weeks delivery 34–36 weeks Delivery >36 weeks	accelerated progression) the other studies compared the average rate of decline in renal function to the expected rate of decline in the general nonpregnant population of subjects with diabetic nephropathy.  Outcome of pregnancy in women with diabetic nephrology (from 10 published studies) Chronic hypertension (%) 23–77 Preeclampsia (%) 15 - 64 Caesarean section (%) 63–86 IUGR (%) 9–45 Delivery <34 weeks (%) 16–45	accelerate progression to end-stage renal disease.  The presence of diabetic retinopathy significantly affects the outcome of pregnancy for three reasons (1) the increased risk of hypertensive complications (2) the increased risk of fetal prematurity due to deteriorating maternal hypertension and Preeclampsia; and (3) the increased risk of fetal growth restriction and fetal distress.	
Nielsen LR;Muller C;Damm P;Mathiesen ER;  2006  {Nielsen, 2006 36282 /id}	Study Type: Cohort  Evidence level: 2++	46 pregnant women with type 1 diabetes	Pregnant women with type 1 diabetes who were referred before gestational age 17 weeks. All were Caucasian women.  Country: Sweden	Intervention:  Comparison:	Follow-up period:  Outcome Measures: 1. Prevalence of preterm delivery before 34 weeks 2. Pre-eclampsia 3. Perinatal mortality 4. Birth weight	The cohorts were comparable with regard to age, diabetes duration, pre-pregnancy body mass index, HbA <sub>1c</sub> , mean (SD) blood pressure 121 (13)/71 (8) vs. 121 (14)/73 (8) mmHg and early UAE geometric mean (range) 69 (16–278) vs. 74 (30–287) mg/24 h).  The prevalence of preterm delivery before 34 weeks was reduced from 23% to zero ( $P = 0.02$ ), preterm delivery before 37 weeks from 62% to 40% ( $P = 0.15$ ) and pre-eclampsia from 42% to 20% ( $P = 0.11$ ). Perinatal mortality occurred in 4% vs. 0%. Birth weight was 3124 (767) g vs. 3279 (663) g.	Introduction of early antihypertensive treatment with methyldopa in normotensive pregnant women with type 1 diabetes and microalbuminuria resulted in a significant reduction in preterm delivery before gestational week 34.	

## 5.6 Screening for congenital malformations

### Q.20 When and by what method should women be offered screening for congenital malformations and counselling?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Spencer K;Cicero S;Atzei A;Otigbah C;Nicolaidis KH; 2005 Oct {Spencer, 2005 28809 /id}	Study Type: Cross-sectional Evidence level: 2++	195 women with type 1 diabetes. 79 had NT and serum biochemistry results, 127 had NT only.  33301 nondiabetic controls. 16366 had NT and maternal serum biochemistry results and 16305 had NT only.		Intervention: Type 1 diabetes  Comparison:	Follow-up period:  Outcome Measures: Nuchal translucency (NT)  β-hCG  PAPP-A	NT (mean, delta values) Type 1 diabetes: 0.0358 Control: 0.0002, $P = 0.418$  β-hCG (median, weight corrected) Type 1 diabetes: 0.87 MoM (95% CI 0.75–1.16) Control: 1.00 MoM, $P = 0.52$  PAPP-A (median, weight corrected) Type 1 diabetes: 1.02 MoM (95% CI 0.83–1.05) Control: 1.01 MoM, $P = 0.36$	There were no significant differences between the diabetic and control groups in median weight corrected free β-hCG, median maternal weight corrected PAPP-A or mean delta NT.  In pregnancies complicated by type 1 diabetes first trimester screening for chromosomal defects does not require adjustments for NT. However more data are required before the possible reduction in maternal serum free β-hCG and the reduction of PAPP-A suggested by the published world series can be considered sufficiently important to take into account in the calculation of risks for chromosomal defects.	
Huttly, W. et al 2004 {Huttly, 2004 28956 /id}	Study Type: Systematic review - meta-analysis Evidence level: 2+	AFP: 2453 uE3: 687 Total hCG: 1350 Free β-hCG: 126 Inhibin 445:	Type 1 diabetes	Intervention: Type 1 diabetes  Comparison: Non diabetic pregnant women	Follow-up period:  Outcome Measures: AFP uE3 Total hCG Free β-hCG Inhibin	AFP 14 studies ( $n = 2453$ ) Weight corrected median MoM in women with type 1 diabetes: 0.92  uE3 6 studies ( $n = 687$ ) Weight corrected median MoM in women with type 1 diabetes: 0.94  Total hCG 9 studies ( $n = 1350$ ) Weight corrected median MoM in women with type 1 diabetes: 0.96	There remains a case for adjusting AFP and uE3 levels in women with IDDM in Antenatal screening programmes for Down's syndrome.	Confidence intervals and statistical significance were not reported for meta-analysis

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Free $\beta$ -hCG 1 study ( $n = 126$ ) Weight corrected median MoM in women with type 1 diabetes: 0.96		
						Inhibin 3 studies ( $n = 445$ ) Weight corrected median MoM in women with type 1 diabetes: 1.03		
Pedersen, JF., et al 1998 {Pedersen, 1998 28961 /id}	Study Type: Cross-sectional  Evidence level: 2+	79 women with type 1 diabetes 93 non diabetic pregnant women		Intervention: Type 1 diabetes  Comparison:	Follow-up period:  Outcome Measures: PAPP-A	Levels of PAPP-A were significantly lower in diabetic women than in non diabetic women $z=2.263$ , $P = 0.024$ .	We have seen no other studies of PAPP-A in first trimester of diabetic pregnancy but if other studies confirm that PAPP-A levels are lower, then values for diabetic women should be adjusted up before interpretation.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Albert TJ;Landon MB;Wheller JJ;Samuels P;Cheng RF;Gabbe S;  1996 May  {Albert, 1996 28777 /id}	Study Type: Other  Evidence Level: 2++	Intervention: Comprehensive program to detect fetal anomalies in pregnancies complicated by diabetes. Protocol for all women as follows: 1). Initial HbA1 (normal range 4.5% - 8.0%). A receiver operator curve was constructed to demonstrate the relationship between sensitivity and the false-positive rate by use of several selected cut-off points. 2) AFP offered at 15–18 weeks (from 1992 as part of triple test). AFP and UE3 were adjusted by factors of 0.77 and 0.92 respectively. 1.5MOM was used as upper limit of normal for reported maternal serum AFP values in patients with insulin-dependent diabetes. 3) Fetal sonogram performed with a General Electric Advantage 3200 at 18 weeks by a staff perinatologist. The scan included standard 4 chamber cardiac view. 4) Detailed multiimage fetal echocardiography at 22 weeks with either Acuson 128/XP or HP Sonos 1000.	289 insulin-dependent women			29/289 (10%) had a major congenital malformation. 12 cardiac lesions 14 noncardiac lesions 3 both cardiac and noncardiac lesions  21/29 (72%) infants with anomalies were diagnosed antenatally.  12/15 cardiac (80%) 10/17 noncardiac (59%) were identified antenatally.  2 infants with cardiac lesions were identified postnatally. Each had a four chamber view at US but did not have echocardiogram performed. An infant with a largescundum-type atrial septal defect and coexistent skeletal abnormalities, and several other infants with noncardiac lesions were not identified antenatally. US evaluation of the fetuses in many of these cases was compromised by maternal obesity.  A statistically significant difference in HbA1 was noted between pregnancies with anomalous and nonanomalous fetuses at a cutoff of 8.0% ( $P = 0.017$ ). Sensitivity 85%, specificity 43%, PPV 14% NPV 96%. The receiver operator curve found no optimal HbA1 value that could be used to determine which patients are at greatest risk for malformations.  AFP sensitivity 17%, specificity, 7%, PPV 7% and NPV 89%.  Comprehensive US: 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%. No false positives. The majority of 'missed' cardiac defects involved lesions of the cardiac septum	Overall this program of Antenatal diagnostic testing attained a sensitivity of 72.4% a specificity of 99.5% a PPV of 95.5% and a NPV of 97%.  Sensitivity increased from 59% to 73% from US to echocardiogram  2/15 (13%) fetuses with abnormal initial HbA1 had cardiac defects  Transvaginal US may help in cases of maternal obesity.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						and outflow tracts.  Fetal echocardiography: Sensitivity 92%, Specificity 99%, PPV 92%, NPV 99%. The single false-positive diagnosis involved a perimembranous and muscular ventriculospetal defect that was confirmed antenatally with the use of colour flow Doppler studies. However the defect was not identified at the time of postnatal echocardiographic testing and was presumed to have therefore closed before birth.		
Muller PR;James A;Feldman K;Herlong JR;  2005 Apr  {Muller, 2005 28796 /id}	Study Type: Other  Evidence Level: 2++	Intervention: 2nd trimester comprehensive anatomy ultrasound (experienced obstetric sonographer) including 4-chamber/left ventricular outflow tract views.  Followed by comprehensive fetal echocardiogram at 17–30 weeks (experienced paediatric echocardiographer and paediatric cardiologist with expertise in fetal echocardiography)  Comparison:	725 women referred for echocardiogram following the evaluation of four-chamber/left ventricular outflow tract	Reasons for referral: 226 pre-gestational diabetes (alone); 130 fetal anomalies; 133 family history of congenital heart disease; 236 other indication for referral.	Ultrasound result: normal, abnormal, suboptimal  Echocardiogram result: normal, abnormal, suboptimal  Major congenital heart disease (MCHD) is defined as that which would require cardiac surgery in the first year of life	4 chamber/LVOT views at ultrasound were obtained in 86% of fetuses. 6% were reported as abnormal.  Fetal echocardiograms were reported as suboptimal in 2% of cases and abnormal in 4% of cases ( $n = 29$ ).  The ultrasound 4 chamber/LVOT views correctly predicted an abnormal fetal echocardiogram in 66% (19/29) of cases with a false positive rate of 4.1% (28/683).  No abnormal fetal echocardiograms were reported in patients with isolated pre-existing diabetes mellitus.  Review of 29 cases with abnormal fetal echocardiogram: Indications for fetal echocardiogram were an abnormal four chamber/LVOT view at ultrasound (66%); aneuploidy (14%), other fetal anomaly (17%) and fetal arrhythmia (3%).  The four chamber/LVOT view at ultrasound was reported as abnormal in 19/29 cases, suboptimal in 4/29 and normal in 6/29 (2 had ventricular septal defect).	Of 725 fetal echocardiograms carried out for specific indications, two major cardiac congenital malformations were not seen on 4-chamber/LVOT views at prior ultrasound. Other fetal congenital malformations however were seen in these two fetuses at ultrasound.  There would appear to be little yield from the addition of fetal echocardiogram in mothers with pre-existing diabetes and a previous normal comprehensive anatomy ultrasound (including 4-chamber/LVOT view).  Training all obstetric sonographers in the expanded fetal	Limitation of the study is that neonatal outcomes of normal echocardiograms is not known  Highly trained operators

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
							cardiac evaluation at ultrasound might reduce the need to refer all high risk patients for echocardiogram, except in those cases where an abnormality is found.	
							Patients would benefit from referral for fetal echocardiogram with abnormal four chamber/LVOT view, suboptimal views in high risk patients, other fetal anomalies or suspected aneuploidy.	
Giancotti A; Ferrero A; Marceca M; Donati L; Gallo G; Gallo F;  1995  {Giancotti, 1995 28785 /id}	Study Type: Other  Evidence Level: 2++	Intervention: Echocardiogram between 20–22 weeks. All examinations were performed by experienced ultrasonographers. The standard 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 views of the aortic arch. Insertion of the vena cava was also evaluated. Rescanning was suggested when the optimal view was not obtained throughout the ultrasound session. Fetal heart examination was completed at the first	250 women with type 1 diabetes			There were 22/250 (8.8%) fetal malformations.  A cardiac malformation was diagnosed in 8/250 (3.2%) of fetuses. 6 detected antenatally by echocardiogram (5 inter-ventricular defects and 1 transposition of the great arteries). There was one false positive and one false negative. One fetus had an apparently normal heart at 21 weeks but was found at birth to have a small atrial-septal defect. The false positive was a case of perimembranous ventricular-septal defect. The test sensitivity was 85.7% and specificity was 99.5%	We believe that the multiple heart view is an optimal methodology for high risk pregnancy scanning, in order to improve the Antenatal detection of congenital heart disease.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
		scanning session in 90% and after 2 scanning sessions in 100% of patients.						
Greene MF;Benacerraf BR; 1991 Apr {Greene, 1991 28787 /id}	Study Type: Other Evidence Level: 2++	Intervention: Ultrasound between 12–23 weeks using Acuson 128. The scans included detailed evaluation of the four chamber of the heart and great vessels.  AFP determinations between 16 and 18 weeks. Values were corrected for diabetes.  Comparison:	432 women with type 1 diabetes  432 examined with ultrasonography (US) 393 also screened with maternal serum alpha fetoprotein (AFP)		Major malformations	At delivery 32 infants had 38 major congenital malformations  18/32 (52%) detected by ultrasonography between 12 and 23 weeks  8 heart anomalies of which 5 detected  All 6 CNS abnormalities were detected  The lesions most commonly missed by sonography were ventricular septal defect, abnormal hand or foot, unilateral renal abnormality, and cleft palate without cleft lip.  US: Sensitivity 56% Specificity 99.5% PPV 90% NPV 97%  AFP Sensitivity 34% Specificity 86% PPV 17% NPV 94%	The majority of major malformations and all life threatening defects can be correctly identified by an experienced sonographer before 24 weeks.  All fetal malformations that MSAFP is designed to identify were detected accurately by routine ultrasonography before 24 weeks. None of the amniocenteses that were precipitated by elevated MSAFP results were useful for diagnosis in this population.	
Smith RS;Comstock CH;Lorenz RP;Kirk JS;Lee W; 1997 Oct 275	Study Type: Other Evidence Level: 2++	Intervention: Echocardiogram views.  Ultrasound examinations were performed by sonographers under physician supervision using Acuson models 128 or 128/XP  Comparison:	223 women diabetes requiring insulin (128 type 1, 47 type 2 and 48 gestational diabetes)		Cardiac defects	171 women had one visit only, 42 had two visits, 8 had three visits and 2 had four visits.  There were 11 congenital heart defects, 9 were detected antenatally on the 4-chamber/outflow tract views. The two missed cases were in morbidly obese patients. Obtaining other views such as the ductal or aortic arches did not contribute to detection of a defect.  7 defects occurred in patients with type 1 diabetes, 3 in women with type 2	The sensitivity increased from 73% with the four chamber view to 82% with the addition of the aortic root view. Other views did not improve the ability to detect a cardiac defect.  The majority of cardiac defects in	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						<p>diabetes and 1 in a woman with gestational diabetes.</p> <p>Test performance for different views: 4 chamber: Attainment: 97% (217/223) Sensitivity: 73% (8/11) Specificity:100% PPV: 100% NPV: 99%</p> <p>4 ch+aortic outflow tract: Attainment: 96% (213/223) Sensitivity: 82% (9/11) Specificity: 100% PPV: 100% NPV: 99%</p> <p>4ch+aortic outflow tract+pulmonary outflow tract Attainment: 93% (207/223) Sensitivity: 82% (9/11) Specificity:100% PPV:100% NPV: (100%)</p>	<p>fetuses of insulin requiring women with diabetes will be detected by the four chamber view and by visualising both outflow tracts. Additional echocardiographic views should be attempted but may not be useful unless an abnormality has been detected on these essential views. If an abnormality has been detected additional views should be obtained to establish a diagnosis.</p>	
<p>Wong SF;Chan FY;Cincotta RB;Oats JJ;McIntyre HD;</p> <p>2002 Feb</p> <p>271</p>	<p>Study Type: Other</p> <p>Evidence Level: 2++</p>	<p>Intervention: Routine US between 16 and 24 weeks</p> <p>The ultrasound machines used were Toshiba SSA-250 and ATL-3000. The scans were performed by 5 obstetricians with a special interest in ultrasound, 3 maternal fetal medicine subspecialists and 3 qualified sonographers. Experience ranged from 0.5 to 12years. A checklist of anatomical regions based on guidelines of the Australasian Society of Ultrasound in Medicine. Ventricular outflow tracts were not included for the first 3 years.</p> <p>Comparison:</p>	<p>130 women with pre-existing diabetes and 12169 low risk women from same institution</p>	<p>Tertiary obstetric hospital</p> <p>All women with pre-existing diabetes (type 1 &amp; 2) who had routine ultrasound screening between 1 January 1993 and 31 December 1998. 85 with type 1 diabetes, 45 type 2.</p>	<p>Assessment of image quality was subjectively assessed as adequate/inadequate</p> <p>Ultrasound images were recorded as hard copies or on video if anomalies were suspected.</p> <p>The findings were entered into a database and compared to the outcome after delivery.</p> <p>Ultrasound scan reports were reviewed.</p> <p>Major congenital anomalies defined as malformations that are either lethal or significantly affect the individual's function or</p>	<p>10/130 major anomalies (7.7%) and 3/130 minor anomalies (2.3%) were present in the fetuses of diabetic women. There were 169/12169 anomalies in low risk controls (8% vs. 1.4%;P&lt;0.001).</p> <p>There was no difference in the incidence of congenital malformations between type 1 (5.9%) and type 2 (11.1%, P=0.3)</p> <p>Neural tube/spinal defects accounted for 30% of anomalies and cardiovascular for another 30%. Periconceptual HbA<sub>1c</sub> of &gt;9% was associated with a high prevalence of major anomalies(146/1000).When HbA<sub>1c</sub>&lt;9% no baby had major anomaly.</p> <p>Women with fetuses with major anomaly had significantly higher first trimester HbA<sub>1c</sub> (10.1% vs. 8.0%,</p>	<p>The detection rate of congenital anomalies for diabetic women was significantly lower than for the general population within the same institution (30% vs. 73%; P&lt;0.01).</p> <p>This group of women with diabetes had a higher BMI. Other reasons that may contribute to poor image quality include insulin injection given over lower abdomen and previous caesarean section scars.</p>	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
					appearance.	<p><math>P &lt; 0.05</math>) a significantly higher BMI (32.5 vs. 29 kg/m<sup>2</sup>; <math>P &lt; 0.05</math>) and a higher incidence of obesity (78% vs. 37%; <math>P &lt; 0.05</math>).</p> <p>Of the 130 scans performed 48 (37%) were classified as suboptimal because of maternal obesity (<math>n = 45</math>) early gestational age (<math>n = 2</math>) and fetal position (<math>n = 1</math>).</p> <p>The majority of women who had repeat ultrasound scans still had unsatisfactory image quality (19/22; 86%).</p> <p>Of 82 women whose image quality was judged to be adequate, 2 fetuses had major congenital anomalies. Both were detected antenatally (detection rate 100%).</p> <p>Among 48 women whose image was unsatisfactory there were eight major congenital anomalies. Only one was detected antenatally (detection rate 12.5%).</p> <p>The detection rate was significantly lower in diabetic women as compared with the low risk population (30% vs. 73%; <math>P &lt; 0.01</math>).</p> <p>After exclusion of defects that are undetectable (at the gestational age with current technology) from both groups of women the detection rate was still better in the low risk population (42% vs. 86%; <math>P = 0.01</math>).</p> <p>The mean BMI was significantly higher in the diabetic group than in the low risk group (29 vs. 23 kg/m<sup>2</sup>; <math>P &lt; 0.001</math>).</p>	<p>Image quality may be improved by harmonic imaging, transvaginal approach at 14–16 weeks, or full fetal echocardiogram.</p> <p>If image is unsatisfactory, late second-trimester full fetal echocardiogram may be necessary.</p>	

## 5.7 Monitoring fetal growth and wellbeing

### Q.21 When and by what methods should fetal growth and wellbeing be monitored?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Abramowicz JS;Rana S;Abramowicz S; 2005 Apr 434	Study Type: Cohort Evidence level: 2+	214 women in retrospective study 50 women in prospective study	214 women entered into a birth weight study 50 women ≥38 weeks gestation  Country: USA	Intervention: Cheek to cheek diameter (CCD). Abnormal defined as above 2 SD for GA).  Comparison:	Follow-up period:  Outcome Measures: EFW (Hadlock's formula) Actual BW Biparietal diameter (BPD) Caesarean delivery for nonprogress of labour 'Difficult' vaginal delivery	In 78% of patients with uncomplicated vaginal deliveries CCD was within the normal range vs 56% of patients with complicated vaginal or caesarean deliveries ( $P = 0.03$ ).  Based on evaluation of the chi squared tests, a cut off point of 7.9 cm was chosen for CCD, 0.88 for CCD/BPD ratio and 3940 g for BW.  Mean (SD) CCD was 7.13(0.89) in women with vaginal deliveries and 7.48 (1.0) in women with C/S, $P = 0.02$  BW was 3560 (550)g in women with vaginal deliveries and 3927 (520)g in women with C/S, $P < 0.0001$  Abnormal CCD to predict C/S (Prospective study) Sensitivity: 40% Specificity: 97% PPV: 80%  At term risk of C/S with a CCD >7.9 cm was 94%.	CCD, as a reflector of fetal adipose tissue, performs as well as actual birth weight and demonstrates good prediction for delivery by C/S.	Obstetrician blinded to CCD
Best G;Pressman EK; 2002 May 435	Study Type: Cohort Evidence level: 2+	133 diabetic women (pregestational and gestational) 1690 controls	Women with diabetes who underwent sonograms between 34 and 36.9 weeks Non diabetic control group who had sonograms in the	Intervention: Gestation-adjusted projection method (The ratio between the estimated fetal weight and the median fetal for the gestational age was	Follow-up period:  Outcome Measures: Birth weight error ( $\pm 5\%$ , $\pm 10\%$ , $\pm 15\%$ ) Prediction of macrosomia (>4000 g)	The mean absolute percent error was 7.4% $\pm 6.3\%$ in women with diabetes and 8.3% $\pm 6.6\%$ in the control group ( $P = 0.14$ ).  Birth weight error	In women with diabetes, the accuracy of fetal weight estimation near term is at least equal to that in women who are not diabetic.  Use of gestation-adjusted	Retrospective

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			same gestational age range  Country: USA	calculated. This ratio was then multiplied by the median birth weight at the gestational age of delivery to give the predicted birth weight) Hadlock formula  Comparison:	:Sensitivity, specificity, PPV and NPV)	±5% Diabetic women: 63 (47%) Controls: 702 (42%) P=0.19  ±10% Diabetic women: 95 (71%) Controls: 1187 (70%) P=0.77  ±15% Diabetic women: (121) 91% Controls: 1474 (87%) P=0.21  Prediction of Macrosomia by gestation-adjusted projection: Sensitivity Diabetic women 68% Controls: 52% Specificity: Diabetic women: 96% Controls: 95% PPV Diabetic women: 87% Controls: 52% NPP Diabetic women: 87% Controls: 95%	projection method allows improved accuracy of prediction over those previously reported.	
Bracero LA;Figueroa R;Byrne DW;Han HJ;  1996 Apr  298	Study Type: Cohort  Evidence level: 2++	207	Pregnant women with diabetes. Within 1 week of delivery.  Country: USA	Intervention: Nonstress test Biophysical profile (BP) Doppler velocimetry of the umbilical artery (systolic to diastolic ratio).  Comparison:	Follow-up period:  Outcome Measures: Adverse outcome: Delivery before 37 weeks gestation, fetal growth restriction Hypocalcemia Hypoglycaemia Hyperbilirubinemia Respiratory distress syndrome (RDS) Fetal risk requiring caesarean delivery	75/205 pregnancies (36.2%) had an adverse outcome. Outcomes: n (%) Growth restriction: 4 (1.9%) RDS: 10 (4.8%) Hypoglycaemia: 39 (18.8%) Hypocalcemia: 5 (2.4%) Hyperbilirubinemia: 19 (9.2%) Caesarean section for fetal risk 20 (9.7%) Preterm delivery: 33 (15.9%) 11 associated with pre-eclampsia, 7 with preterm labour, 9 with premature rupture of the membranes, 4 with fetal distress and 2 elective.  NST (nonreactive)	Umbilical artery Doppler velocimetry was superior to either nonstress test or biophysical profile in identifying the subgroup of pregnancies complicated by diabetes that resulted in adverse outcomes.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						Sensitivity:25.3% Specificity:88.6% PPV:55.9% NPV:67.6% RR:1.7 95% CI: 1.2–2.5 P value: 0.009		
						BP ( $\leq 6$ ) Sensitivity: 8.0% Specificity:97% PPV:60% NPV:65% RR:1.7 95% CI: 0.9–2.9 P value: 0.109		
						Umbilical artery velocimetry (systolic to diastolic ratio $\geq 3$ ) Sensitivity: 25.3% Specificity:96.2% PPV:79.2% NPV:69.4% RR: 2.6 95% CI: 1.9–3.5 P value P<0.001		
						Umbilical artery velocimetry (systolic to diastolic ratio $\geq 2.5$ ) Sensitivity: 65.3% Specificity:61.4% PPV:49.0% NPV:75.7% RR: 2.0 95% CI: 1.4–3.0 P value P<0.001		
						Predictive value of Doppler (S/D $\geq 3$ ) for specific outcomes: Fetal growth restriction: Sensitivity 75% Specificity:89.7% PPV:12.5% NPV:99.5% P value: <0.001		
						Caesarean delivery for fetal		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>risk: Sensitivity 45% Specificity:92% PPV:37.5% NPV:94% P value: &lt;0.001</p> <p>Respiratory distress syndrome: Sensitivity 60% Specificity:90.9% PPV:25% NPV:97.8% P value: &lt;0.001</p>		
Bracero LA;Haberman S;Byrne DW;  2002 Nov  436	Study Type: Cohort  Evidence level: 2+	277	Pregnant women with diabetes  Country: USA	Intervention: Doppler velocimetry (S:D ratio) obtained in third trimester.  Comparison:	Follow-up period:  Outcome Measures: NICU>2days Hypoglycaemia Macrosomia Cesarean delivery for fetal risk Hyperbilirubinemia Respiratory distress syndrome Congenital anomalies Cardiomyopathy IUGR Hypocalcemia Stillbirth	Adverse pregnancy outcome occurred in 51.6% of pregnancies (143/277). The umbilical artery S:D ratio was significantly higher in the pregnancies with adverse outcomes (2.6±0.6 vs 2.4±0.3, <i>P</i> < 0.001)  UI artery S:D was an independent predictor of adverse outcome after controlling for third-trimester HbA <sub>1c</sub> .  96% of patients with both abnormal Doppler findings and abnormal glycaemic control had an adverse pregnancy outcome.  Patients with one of these risk factors had a 63% adverse outcome.  Patients with neither of these risk factors had 40% adverse outcome.	Umbilical artery Doppler velocimetry improves the predictive value for adverse perinatal outcome, independently of glycaemic control.	Inclusion of macrosomia as an 'adverse outcome'.
Chauhan SP;Parker D;Shields D;Sanderson M;Cole JH;Scardo JA;  2006 Aug  437	Study Type: Cohort  Evidence level: 2+	1934 pregnant women	Inclusion: Singleton pregnancy, nonanomalous fetus, reliable gestational age, delivery within 4 weeks of biometric measurements.	Intervention: Sonographic EFW  Comparison:	Follow-up period:  Outcome Measures: EFW SGA (≤10% for gestational age) Normal for gestational	The mean error was 128 ± 370 g. Overall 60% (1170/1954) of predictions were within 10% of the actual body weight and 80% (1566/1954) were classified correctly as being normal, SGA	The LR of detecting SGA was 10.9 and identifying LGA was 17.4.  Accuracy of EFW is better when performed within 1 week of delivery and in infants with body	Retrospective review

# Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			Examinations performed by RDMS  Country: USA		age LGA (≥90%)	or LGA.  SGA Sensitivity: 64% (95% CI 59%-68%) Specificity 94% (95% CI 93%-95%) PPV 80% (95% CI 76%-94%) NPV 87% (95% CI 86%-89%) LR 10.9 (95% CI 8.7–13.5)  LGA Sensitivity 36% (95% CI 27%-45%) specificity 98% (95% CI 97%-98%) PPV: 53% (95% CI 42%-64%) NPV: 96% (95% CI 95%-97%) LR 17.4  Following logistical regression the 2 factors that significantly influenced accuracy (whether predicted body weight was within 10% of actual body weight) were EFW, with significantly improved accuracy if EFW was <2500 g, and the time interval between examination and delivery, with improved accuracy if the ultrasound was performed within a week of delivery.  The two factors that significantly influenced correct classification (SGA/NGA/LGA) were presence of hydramnios and gestational age (classification was more accurate before 37 weeks).	weight <2500 g. Classification (as SGA/NGA/LGA) more accurate in the presence of hydramnios and when the prediction is made before 37 weeks.	
Coomarasamy A;Connock M;Thornton J;Khan KS;  2005 Nov  278	Study Type: Systematic review - meta-analysis  Evidence level: 1++	63 accuracy studies (51 evaluating the accuracy of estimated fetal weight (EFW) and 12 accuracy of Abdomial	Country:	Intervention: Accuracy for predicting macrosomia.  Data were pooled to produce summary receiver operating characteristic curves	Follow-up period:  Outcome Measures: Birth weight over various test thresholds.	The sROC area for EFW was not different from the area for fetal AC (0.87 vs 0.85, $P = 0.91$ ).  For predicting a birthweight of over 4000 g the summary LR	There is no difference in accuracy between EFW and AC in the prediction of a macrosomic baby at birth.  A positive test result is more accurate for ruling in	Quality assessment using established checklists.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
		circumference (AC) including a total of 19117 women.		(sROC) for studies with various test thresholds. Summary likelihood ratios for positive and negative test results were generated for an EFW of 4000 g and an AC of 36 cm for predicting birth weight over 4000 g.		were 5.7 (95% CI 4.3–7.6) for a positive test and 0.48 (95% CI 0.38–0.60) for a negative test.	macrosomia than a negative test result for ruling it out.	
de I;Verdiales M; 2002 Jun 438	Study Type: Cohort Evidence level: 2+	1810 pregnancies ≥20 weeks gestation	Private clinic with mixed population of high and low risk pregnancies.  Country: USA	Intervention: High resolution sonography during each trimester. Fetal heart rate, position and amniotic fluid index assessed by limited sonographic scan at each visit. Additional sonographic studies whenever deemed necessary. Biophysical profile during third trimester and at any time deemed necessary.  Comparison:	Follow-up period:  Outcome Measures: Fetal death in utero	For ultrasound fetal AC of 36 cm the LR for a positive test for predicting birthweight over 4000 g was 6.9 (95% CI 5.2–9.0) the LR for a negative test was 3.7 (0.30–0.45).	There were 14 stillbirths. The stillbirth rate was 7.7/1000 births cf to US national average of 6.7–7.8/1000 births. The most common associated maternal complications were Diabetes (4 cases) and antiphospholipid syndrome (3 cases). All except one (lost at 37 weeks) had identifiable risk factor.	
Johnstone FD;Prescott RJ;Steel JM;Mao JH;Chambers S;Muir N; 1996 Aug 289	Study Type: Cohort Evidence level: 2++	181 women with diabetes	73% pregestational T1, remainder GDM. Women who delivered after 34 weeks.  Country: UK	Intervention: Ultrasound (US) prediction of Macrosomia (using abdominal and head circumference and largest liquor pool) vs. clinical prediction (symphysis fundal height. US carried out every 3 weeks from 28 weeks. Analysis compared 3 time points (28 weeks, 34 weeks, and last scan before delivery).  Comparison:	Follow-up period:  Outcome Measures: Birth weight (BW) Prediction of macrosomic births (>95th percentile) using ROC.	All measurements are poor predictors of eventual standardised BW. Measurement of fundal height is as useful as US measurement of AC. Prediction improves with closeness to delivery. Prediction is improved, but is still poor, by combining clinical and US information.	There is no difference in prediction power between clinical and US measurements	
Johnstone FD;Steel JM;Haddad NG;Hoskins PR;Greer IA;Chambers S;	Study Type: Cohort Evidence level: 2+	128 pregnant women with diabetes 170 non diabetic women with no pre-	21 women with gestational diabetes (all requiring insulin) 107 with pre-existing diabetes.	Intervention: Doppler Flow velocity waveform (resistance index) recorded every 2 weeks from 28 weeks.  Comparison:	Follow-up period:  Outcome Measures: HbA <sub>1c</sub> (normal range 6–8%)	The mean number of examinations per patient was 5.5.  The umbilical artery RI values	The non-diabetic range of umbilical artery resistance index values is appropriate for diabetic pregnancies. Abnormal UA RI is a significant predictor	HbA <sub>1c</sub> was associated with not related to umbilical artery FVW values, however very few women were poorly controlled.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1992 Feb 297		existing or pregnancy complications	Country:	Significantly Abnormal defined as 50% of recording >mean +2SD or a single recording > mean+4SD.  Comparison:		in women with uncomplicated diabetes ( $n = 68$ ) did not differ from nondiabetic controls.  HbA <sub>1c</sub> was not associated with RI.  Antenatal fetal compromise was detected in 7 pregnancies. All 7 were delivered immediately by emergency caesarean section. In 3 of these cases the FVW had been abnormal.  9/128 women had significantly abnormal FVW. Compared with other diabetic pregnancies these were significantly more likely to show evidence of fetal compromise ( $P < 0.01$ ) and to be associated with birth of babies weighing < 50th centile ( $P < 0.05$ ).	of fetal compromise in diabetic pregnancy, but fetal compromise can occur in association with normal RI values. Undue reliance should not be placed on normal FVW values in diabetic pregnancy.	
Leung WC;Lam H;Lee CP;Lao TT; 2004 295	Study Type: Cohort  Evidence level: 2++	138	Women with GDM (WHO criteria) Good glycaemic control with normal 2 hour postprandial BG levels.  Country:	Intervention: Doppler study: Umbilical artery pulsatility index (PI) Middle cerebral artery PI Peak systolic velocity Measured every 4 weeks from the time of diagnosis until delivery  Comparison:	Follow-up period:  Outcome Measures: Abnormal pregnancy outcomes: Placental abruption Pre-eclampsia Preterm delivery (<37 weeks) SGA (< 10th centile) 1 and 5 min Apgar scores (<7) Neonatal jaundice requiring treatment Sepsis Birth trauma Meconium aspiration syndrome Respiratory distress syndrome Neurological complications (seizures, intraventricular	38 women (27.5%) had one or more adverse outcomes: Placental abruption ( $n = 1$ ), pre-eclampsia ( $n = 3$ ), preterm delivery ( $n = 9$ ) SGA infants ( $n = 7$ ), 1 min Apgar score <7 ( $n = 7$ ), 5 min Apgar score <7 ( $n = 1$ ), neonatal jaundice requiring treatment (N=18) , sepsis ( $n = 5$ ), respiratory complications ( $n = 4$ ) meconium aspiration syndrome ( $n = 2$ ) neurological complications ( $n = 2$ ) and birth trauma ( $n = 1$ ).  The group with abnormal outcomes was compared with the group with no abnormal outcome. Scatter plots for Doppler measurements showed extensive overlap between the two groups and no clear distinction in the lines	Doppler measurement of uterine artery pulsatility index, middle cerebral pulsatility index and peak systolic velocity were not useful in the prediction of abnormal pregnancy outcome in GDM.	Clinician blind to Doppler results.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					hemorrhage, hypoxic ischemic encephalopathy) Metabolic complications (hypoglycaemia, hypocalcemia) Perinatal mortality	of best fit.		
Levine AB;Lockwood CJ;Brown B;Lapinski R;Berkowitz RL;  1992 Jan  281	Study Type: Cohort  Evidence level: 2+	406 pregnant women. 22% with diabetes (85 gestational, 5 pregestational	Ultrasound after 36 weeks gestation. Primary indication for 3rd trimester sonography was fetal weight estimation in women with previous caesarean deliveries or diabetes.  Country: USA	Intervention: Ultrasound estimation of fetal weight (performed by experienced technicians and reviewed by physicians) Hadlock formula  Comparison:	Follow-up period:  Outcome Measures: LGA (>90th percentile) Diagnosed labour abnormalities Use of epidural anaesthesia Caesarean deliveries Forceps delivery Induction Use of oxytocin	All ultrasounds were performed between 37 and 42 weeks (mean 38.3 weeks) 68/407 fetuses were classified as LGA.  Prediction of LGA Sensitivity: 50% Specificity: 90% PPV: 51.5% NPP: 89.6%	The incorrect sonographic diagnosis of an LGA fetus had a significant effect on both the diagnosis of labour abnormalities and the incidence of caesareans in pregnancies with AGA birth weights.	All data obtained retrospectively from computerised ultrasound and obstetric data bases
Parry S;Severs CP;Sehdev HM;Macones GA;White LM;Morgan MA;  2000 Jan  280	Study Type: Cohort  Evidence level: 2+	135 women with Ultrasound (US) estimation of fetal weight (EFW) $\geq 4000$ g 129 women with US EFW between 3000 g and 3,999 g.	At risk antenatal population with US EFW after 37 weeks gestation. Indications for US included postdate, diabetes, previous stillbirth etc. exclusions <3000 g.	Intervention: US prediction of Macrosomia ( $\geq 4000$ g) Comparison of false positives with true negatives  Comparison:	Follow-up period:  Outcome Measures: Caesareans section (C/S) rates	Accuracy of EFW Sensitivity: 76% Specificity: 66% PPV: 62% NPV: 80%	Even in nonmacrosomic infants the antenatal US diagnosis of suspected macrosomia is associated with a significant increase in caesarean delivery rates.	Retrospective

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			Country: USA			False positives: 52 (42.3%) True negatives: 103 (24.3%) RR 1.74, 95% CI 1.09–2.78. Difference remained after removing women with diabetes.		
Pietryga M;Brazert J;Wender-Ozegowska E;Dubiel M;Gudmundsson S;  2006  {Pietryga, 2006 35338 /id}	Study Type: Cohort  Evidence level: 2++	146	Women with gestational diabetes (117/146 requiring insulin)  Country: Poland and Sweden	Intervention: Umbilical and uterine artery Doppler velocimetry (pulsatility index according to Gosling et al). Z score of deviation from the normal mean was used for evaluation.  Comparison:	Follow-up period:  Outcome Measures: HbA <sub>1c</sub>  Adverse perinatal outcome: Operative delivery for fetal distress  Preterm delivery (before 37 weeks of gestation)  5 min Apgar score <7  umbilical vein <7.20  LGA (.95th percentile)	The average gestational age at last Doppler velocimetry examination was 35.2±5.5 weeks. The average time interval between examination and delivery was 7.9±6.4 days.  Abnormal umbilical artery blood flow velocity was seen in 5% of cases and abnormal uterine artery flow in 16%.  There were 33 LGA infants. Uterine and umbilical artery vascular impedance was significantly lower in LGA than AGA infants ( $P < 0.05$ ).  All 11 cases of preeclampsia demonstrated abnormal uterine artery Doppler. 2/11 had abnormal umbilical artery Doppler.  Abnormal uterine blood circulation strongly correlated with adverse perinatal outcome defined as: Operative delivery for fetal distress, 5 min Apgar score <7, umbilical vein pH <7.20, especially in cases with pre-eclampsia. Abnormal flow in the umbilical artery was also strongly correlated to parameters of perinatal outcome.	Abnormal placental vascular impedance is infrequent in pregnancies complicated by gestational diabetes.  Uterine and umbilical impedance in pregnancies complicated by gestational diabetes is related to birthweight and placental weight, but not HbA <sub>1c</sub> .  The value of Doppler in for fetal surveillance in pregnancies complicated by gestational diabetes can be questioned, unless complications such as preeclampsia and IUGR are present.	There was no information on the proportion of sample who had good glycaemic control
Weiner Z;Ben-Shlomo I;Beck-Fruchter R;Goldberg Y;Shalev E;  2002 Oct 10	Study Type: Cohort  Evidence level: 2+	3844 pregnant women	All pregnant women. Women who had elective C/S for indications other than large fetus were	Intervention: Protocol: Estimated fetal weight (EFW) by ultrasound (Shepard formula) when clinical weight estimate	Follow-up period:  Outcome Measures: Predictive values of fetal weight estimation	555/3844 (14.4%) clinically estimated as 3700 g or more. 315 women had US within 3 days of delivery. Predictive value of clinical and	Antenatal suspicion of macrosomia increased the C?S rate while the associated improvement in pregnancy outcomes remains	In the group who were given US there was a significantly higher proportion who were diabetic compared to the group who were not given US (9.2% vs. 3.5%)

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
{Weiner, 2002 35351 /id}			excluded.  Country: Israel	>3700 g.C/S recommended when EFW>4500 g. US repeated every 4 days  Comparison:	for diagnosing macrosomia (>4000 g) Caesarean section (C/S). Complications of delivery	<p>Ultrasound (US) prediction of macrosomia: Sensitivity: Clinical:68% US: 58%</p> <p>Specificity Clinical: 90% US: 68%</p> <p>PPV Clinical: 38% US: 56%</p> <p>NPV Clinical: 97% US: 90%</p> <p>C/S in macrosomic newborns: Macrosomia predicted: 22% Macrosomia not predicted: 11% (P&lt;0.05)</p> <p>In fetuses estimated by US to be macrosomic the C/S rate was 50.7% vs. 24.9% in fetuses estimated to be &lt;4000 g. (P&lt;0.05) although actual weight of 4.500 g was recorded in 10.6% and 8.5% of these groups respectively.</p> <p>There was one case of shoulder dystocia (0.5%) when estimation of fetal weight was &lt;4000 g and 2 cases (1.5%) when estimation of fetal weight was ≥4000 g.</p> <p>There were no cases of shoulder dystocia in macrosomic babies when macrosomia was not predicted vs. 2 cases in babies where macrosomia was predicted by US.</p>	questionable.  The contribution of US, added to routine clinical estimation of fetal weight, was clinically insignificant apart from a further increase in C/S rate.	When women with diabetes excluded the C?S rate was still higher (34.7% vs. 14%, P < 0.05).
Williams	Study Type: RCT	649 Doppler testing	Pregnant women	Intervention: Doppler.	Follow-up period:	16/1356 women were lost to	Umbilical artery Doppler as a	Sample size based on power

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
KP;Farquharson DF;Bebbington M;Dansereau J;Galerneau F;Wilson RD;Shaw D;Kent N;  2003 May  {Williams, 2003 35352 /id}	Evidence level: 1++	691 Nonstress testing	referred due to perceived increased fetal antepartum risk at gestational age $\geq 32$ weeks. Main indications were postdates (43%) decreased fetal movement (22%) diabetes (11%) hypertension (10%) and IUGR (7%). Exclusions: Premature rupture of membranes, Multiple pregnancies, fetal death in utero, lethal or cardiovascular anomaly.  Country:	When the Doppler was normal the frequency of repeat testing was 2/week. When the S/D ratio was $\geq 90$ th percentile an assessment of amniotic fluid was done. When there was absent or reverse end diastolic blood flow a recommendation was made to proceed to induction/delivery within 24 hours.  Comparison: Non Stress testing	Outcome Measures: Caesarean delivery for fetal distress in labour	follow up.  The incidence of caesarean delivery for fetal distress was 30 (4.6%) in the Doppler group compared with 60 (8.7%) in the nonstress testing group ( $P < 0.006$ ).  The greatest reduction in caesarean deliveries for fetal distress was in the subgroups in which the indication for testing was hypertension and suspected intrauterine growth restriction.	screening test for fetal well-being in a high risk population was associated with a decreased incidence of caesarean delivery for fetal distress compared to the nonstress test, with no increase in neonatal morbidity.	calculation
Wong SF;Chan FY;Cincotta RB;Oats JJ;McIntyre HD;  2001 Nov  {Wong, 2001 35353 /id}	Study Type: Cohort  Evidence level: 2+	56 nondiabetic women 19 diabetic women (11 pregestational, 8 GDM)	Babies weighing more than 4000 g at birth. Women who had a scan within 1 week of delivery.  Country: Australia	Intervention: Ultrasound (US) estimation of fetal weight (EFW) in women with diabetes. Hadlock formula.  Comparison: Ultrasound (US) estimation of fetal weight (EFW) in nondiabetic women.	Follow-up period:  Outcome Measures: Mean simple error (actual birthweight - estimated fetal weight) Mean standardised absolute error (absolute value of simple error/actual birthweight) Percentage estimation within 15% of actual birthweight	Mean simple error (SD) g Diabetic: 378 (403) Nondiabetic: 16 (371) $P = 0.002$  Standardised absolute error (SD) g/kg Diabetic: 79 (87) Nondiabetic: 20 (85)  Percentage of weight difference Diabetic: 7.9% Nondiabetic: 0.2% ( $P = 0.002$ )  Percentage estimation within 15% of actual birthweight Diabetic: 14 (74%) Nondiabetic: 52 (93%) OR 4.6 (1.1–19.6).  In the diabetic group 26.3% of the birth weights were underestimated by >15% compared to 5.4% in the non-diabetic group ( $P < 0.05$ ).	The prediction accuracy of fetal weight estimation using standard formulae in macrosomic fetuses is significantly worse in diabetic pregnancies compared to nondiabetic pregnancies.	
Wong SF;Chan	Study Type: Cohort	104	Type 1 and 2 diabetes	Intervention: Umbilical	Follow-up period:	57/104 (55%) pregnancies had	The majority of diabetic	Obstetricians were not blinded to

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
FY;Cincotta RB;McIntyre DH;Stone M;  2003 Aug {Wong, 2003 35354 /id}	Evidence level: 2++		in pregnancy. Pregnancies where the babies had major congenital anomalies were excluded  Country: Australia	artery Doppler velocimetry at 28, 32, 36 and 38 weeks gestation (Abnormal results defined as pulsatility index (PI) $\geq$ 95th centile for gestation.  Comparison:	Outcome Measures: Adverse pregnancy outcomes: SGA (<10th percentile) Caesarean section for non-reassuring cardiotocography Fetal academia at delivery 1 min Apgar score $\leq$ 3 5-min Apgar score <7 Hypoxic ischaemic encephalopathy Perinatal death	Doppler carried out within 1 week of delivery and 83 (80%) had Doppler studies carried out within 2 weeks of delivery.  23/104 women (22.1%) had an elevated PI.  If the scans were carried out within 2 weeks of delivery, 71% of pregnancies with abnormal umbilical Doppler had adverse outcomes (P<0.0006; likelihood ratio 4.2). If the scans were carried out within 1 week of delivery 80% of pregnancies with elevated umbilical Doppler PI had adverse outcomes (P<0.01).  Scans carried out within 1 week of delivery: Sensitivity: 35% Specificity 94% PPV 80% NPP: 68%  Of women with an adverse outcome, 30% had abnormal umbilical arterial Doppler flow.	pregnancies with adverse perinatal outcomes have normal umbilical Doppler.	results of Doppler
Zimmermann P;Kujansuu E;Tuimala R;  1992 Nov 19 {Zimmermann, 1992 35355 /id}	Study Type: Cohort  Evidence level: 2+	53	Pregnant women diabetes with good glycaemic control  Country:	Intervention: Doppler velocimetry of the umbilical artery (resistance index calculated according to Pourcelot). Patients were examined on average 3 times (range 1–7) during pregnancy on average in 3–4 week intervals from 17 weeks to delivery.  Comparison:	Follow-up period:  Outcome Measures: LGA ( $\geq$ 90th percentile) Birthweight (g) 1 min Apgar <7 5 min Apgar <7 Umbilical artery pH <7.2 Hypoglycaemia Hypocalcemia Polycythemia Hyperbilirubinemia Respiratory distress	27/50 (53%) liveborn infants showed some sort of treatment-demanding perinatal morbidity.  None of the fetuses showed signs of fetal distress antenatal when the last Doppler measurement was performed, whereas 6 fetuses (12%) suffered fetal distress in labour.  The majority of Doppler flow velocity readings were within the normal range.  Pathological FVW were recorded in 1 patient at 22	Doppler FVW in the umbilical artery of diabetic pregnancies do not differ significantly from a non-diabetic healthy population.  In a small well-controlled diabetic sample Doppler was of little predictive value with respect to specific diabetic fetal morbidity.	There was no morbidity in this sample which is usually detected by Doppler.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Neilson, J., Alfirevic, Z. 2007 {Neilson, 2000 35739 /id}	Study Type: Systematic review - meta-analysis  Evidence level: 1++	11 studies involving 7000 women	High risk pregnancies  Country:	Intervention: Doppler ultrasound to investigate flow velocity waveforms in the umbilical artery (+/- uteroplacental artery)  Comparison: No Doppler	Follow-up period:  Outcome Measures: Perinatal morbidity and mortality and indices of obstetric outcome.	weeks of gestation. This pregnancy ended with sudden intrauterine death due to placental infarction.  Doppler ultrasound in high risk pregnancies (especially those complicated by hypertension or presumed impaired fetal growth) was associated with a trend to a reduction in perinatal deaths (OR 0.71, 95% CI 0.50 to 1.01) fewer inductions of labour (OR 0.83, 95% CI 0.74 to 0.93) and fewer admissions to hospital (OR 0.56, 95% CI 0.43–0.72).	The use of Doppler ultrasound in high risk pregnancies appears to improve a number of obstetric care outcomes and appears promising in helping to reduce perinatal deaths.	
Ben-Ami M;Battino S;Geslevich Y;Shalev E;  1995 Nov {Ben-Ami, 1995 35302 /id}	Study Type: RCT  Evidence level: 1+	92 diabetic pregnant women.	92 diabetic pregnant women between 28 and 40 weeks' gestation.  Country: Israel	Intervention: Doppler study.  Comparison:	Follow-up period:  Outcome Measures: Perinatal outcomes: 1. Normal outcome (Group A) 2. Poor outcome (Group B).	The sensitivity and specificity of the Doppler studies as a predictor of poor perinatal outcome were 39% and 92%, respectively.  The positive and negative predictive values were 54% and 86%, respectively.	The systolic to diastolic ratio of the umbilical artery offers no advantage over other well-established tests in the management of diabetic pregnancies.	
Combs,C.A.; Rosenn,B.; Miodovnik,M.; Siddiqi,T.A.  2002 {Combs, 2000 36051 /id}	Study Type: Cohort  Evidence level: 2+	165 women with gestational or pre-existing diabetes.	165 women with gestational or pre-existing diabetes who had sonograms to estimate fetal weight after 36 weeks' gestation and within 2 weeks of delivery.  Country:	Intervention: Estimated fetal weight.  Comparison:	Follow-up period:  Outcome Measures: 1. Rate of macrosomia	Macrosomia occurred in 49 cases (30%).  Using this "best" formula, an estimated fetal weight (EFW) of 4,000 g or more had a sensitivity of 45% to predict macrosomia and a positive predictive value of 81%.  To achieve 90% sensitivity with this formula would have required diagnosis of macrosomia with an EFW of 3,535 g or more, but this would have comprised 46% of the population with a 42% false-positive rate.  All 31 formulas were better at predicting macrosomia than predictions based on gestational age alone, and 28	All 31 formulas for estimating fetal weight had comparably poor accuracy for prediction of macrosomia.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Demiroren K;Cam L;Oran B;Koc H;Baspinar O;Baysal T;Karaaslan S;  2005  {Demiroren, 2005 36287 /id}	Study Type: Cohort  Evidence level: 2++	83 infants	83 infants, admitted to our Neonatology Unit. Thirty-three were infants of women with diabetes.  Country: Turkey	Intervention: Thirty-three infants of women with diabetes (including both macrosomic and nonmacrosomic) comprised Group A.  25 macrosomic infants of nondiabetic mothers comprised group B.  Comparison: 25 healthy full term AGA infants comprised group C.	Follow-up period:  Outcome Measures: 1. Left ventricular end-systolic diameter 2. Left ventricular end-diastolic diameter 3. Ventricular wall thickness	were better than predictions based on abdominal circumference alone.  The left ventricular end-systolic/left ventricular end-diastolic diameter ratio of group A was significantly smaller than that of group C ( $P < 0.05$ ).  The interventricular septum/posterior wall thickness ratios of groups A and B were greater than those of group C ( $P < 0.05$ ).  The left ventricular mass index of group A was greater than those of groups B and C ( $P < 0.05$ ).  The shortening fraction and ejection fraction of group A were increased in comparison to group C ( $P < 0.05$ ).	The study suggests that underlying mechanisms common to both macrosomic infants of nondiabetic mothers and infants of mothers with diabetes lead to fewer cardiac alterations in macrosomic infants of nondiabetic mothers than in infants of mothers with diabetes.	
Kofinas AD;Penry M;Swain M;  1991 Jul  {Kofinas, 1991 35325 /id}	Study Type: Cohort  Evidence level: 2+	65 pregnant women:  1. Gestational diabetes (n = 31) 2. Type 1 diabetes (n = 34)	65 pregnant women with gestational (n = 31) and type 1 diabetes (n = 34).  Country: USA	Intervention: Doppler flow velocity waveform.  Comparison:	Follow-up period:  Outcome Measures: 1. HbA <sub>1c</sub> 2. Capillary blood sugars during the third trimester of pregnancy	There was no difference in various clinical and Doppler parameters between women with good glycaemic control and those with poor control.  In contrast, the same clinical and Doppler parameters were significantly different in women with preeclampsia than in those without preeclampsia, regardless of glycaemic control.  There was a weak positive linear correlation ( $r = 0.30$ , $P < 0.02$ ) between maternal HbA <sub>1c</sub> and umbilical artery flow velocity waveforms (systolic/diastolic ratio).  Proteinuria correlated better with umbilical artery	Doppler flow velocity waveform analysis may be clinically useful only in diabetic pregnancies complicated by preeclampsia.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
<p>Reece EA;Hagay Z;Assimakopoulos E;Moroder W;Gabielli S;DeGennaro N;Homko C;O'Connor T;Wiznitzer A;</p> <p>1994 Feb</p> <p>{Reece, 1994 35341 /id}</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2+</p>	56 pregnant women with diabetes.	<p>56 pregnant women with diabetes, 14 of whom had varying degrees of vascular complications.</p> <p>Country: USA</p>	<p>Intervention: Doppler ultrasonography.</p> <p>Comparison:</p>	<p>Follow-up period:</p> <p>Outcome Measures:</p> <ol style="list-style-type: none"> <li>1. Mean Doppler values</li> <li>2. Pregnancy adverse outcomes</li> </ol>	<p>systolic/diastolic ratio (<math>r = 0.49</math>, <math>P &lt; 0.001</math>).</p> <p>The mean Doppler values were higher in women with diabetes complicated by vasculopathy than in women without diabetes (controls) or in women with diabetes but no vasculopathy.</p> <p>The third trimester systolic/diastolic (S/D) ratio was greater than 3.0 in almost 50% of women with vasculopathy. A tendency toward adverse outcomes was observed at S/D ratios approaching 4.0.</p> <p>Intrauterine growth retardation and neonatal metabolic complications were also significantly correlated with elevated Doppler indices.</p> <p>There was, however, no correlation between Doppler indices and glucose values, although most were within a euglycaemic range.</p>	<p>Increased resistance circuit among diabetics with vasculopathy may reflect a relative reduction in basal uteroplacental blood flow and the need for cautious interpretation of Doppler indices in these women.</p>	
<p>Colman A;Maharaj D;Hutton J;Tuohy J;</p> <p>2006</p> <p>{Colman, 2006 36286 /id}</p>	<p>Study Type: Cohort</p> <p>Evidence level: 2+</p>	1117 pregnant women of which 48 had gestational diabetes.	<p>Women with a singleton pregnancy <math>\geq 37</math> weeks' gestation who had undergone ultrasound estimation of fetal weight and who delivered <math>&lt; 7</math> days after the ultrasound.</p> <p>Country: New Zealand</p>	<p>Intervention: Ultrasound estimation of fetal weight.</p> <p>Comparison: Actual fetal weight.</p>	<p>Follow-up period:</p> <p>Outcome Measures: Fetal weight</p>	<p>Three-quarters of estimations were within 10% of birth weight.</p> <p>Ultrasonic estimation of fetal weight tended to overestimate the weight of small infants (<math>&lt; 2500</math> g; mean signed error = <math>+3.5\% \pm 9.1\%</math>, <math>n = 98</math>) and underestimate the weight of large infants (<math>\geq 4000</math> g; mean signed error = <math>-3.3\% \pm 8.7\%</math>, <math>n = 170</math>).</p> <p>Both large and normal weight infants of women with diabetes tended to have their weight underestimated (mean signed</p>	<p>As the reliability of ultrasound estimation of fetal weight to detect larger babies was poor, its use in the management of suspected macrosomia should be avoided.</p>	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						error = -5.1+/-9.2%, $n = 48$ ).		
						Sensitivity, specificity, positive predictive value, and negative predictive value for ultrasonic detection, of fetal weight $\geq 4000$ g in non-diabetic women were 61%, 96%, 69% and 94%, respectively.		
						For detection of fetal, weight $\geq 4500$ the figures were 50%, 98%, 47%, and 98%, respectively.		
Reece EA;Hagay Z;Moroder W;DeGennaro N;Homko C;Wiznitzer A;  1996 Jun  {Reece, 1996 35342 /id}	Study Type: Cohort  Evidence level: 2+	30 pregnant women.	30 pregnant women with type 1 diabetes.  Country: USA	Intervention: Fetal aortic velocity waveforms.  Comparison:	Follow-up period:  Outcome Measures: 1. Fetal distress during labour 2. Apgar score	Infants with presumed fetal distress during labour and neonates with respiratory abnormalities (respiratory distress syndrome, persistent fetal circulation, or transient tachypnea of the newborn) showed statistically significant elevations of aortic Doppler indices ( $P < 0.031$ and $< 0.011$ , respectively). However, these correlations lacked clinical relevance.  The infants demonstrated no evidence of fetal distress at birth since Apgar scores were $> 7$ at 5 min in all but one neonate.  No relationship was found between the mean third trimester fetal aortic systolic-diastolic ratios and perinatal death, preterm deliveries, birth weight, Apgar scores at 1 and 5 min, and neonatal metabolic abnormalities.	The data demonstrate a poor correlation between fetal aortic Doppler waveform analysis and fetal outcome. Therefore, fetal aortic Doppler velocimetry cannot be used as a means of assessing impending fetal compromise in offspring of diabetic mothers.	
Farrell,T.; Owen,P.; Kernaghan,D.; Ola,B.; Bruce,C.; Fraser,R.	Study Type: Cohort  Evidence level: 2+	93 women:  1. Type 1 diabetes (n = 26) 2. Type 2 diabetes (n= 7)	Pregnant women with pre-existing diabetes, gestational diabetes (GDM) or impaired glucose tolerance (IGT) attending the	Intervention: Ultrasound fetal biometry.  Comparison: No comparison	Follow-up period: Not reported.  Outcome Measures: 1. Mean growth velocity	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 -0.17 to 0.95], $P = 0.04$ ), significantly	Ultrasound measures of fetal size and growth are not sufficiently accurate to predict those infants likely to be at risk from adverse effects of fetal hyperinsulinaemia.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
{Farrell, 2007 36722 /id}		3. Gestational diabetes (n= 19) 4. Impaired glucose tolerance (n= 41)	Royal Hallamshire Hospital in Sheffield and whose amniotic fluid insulin levels were measured at time of delivery.  Country: UK		2. Mean fetal weight 3. Mean birth weight 4. Mean amniotic fluid insulin levels 5. Fetal deaths 6. Congenital anomalies	greater mean estimated fetal weight (EFW) Z score prior to delivery (2.36 [95% CI 1.82 to 2.9] versus 1.38 [95% CI 1.02 to 1.74], $P = 0.002$ ) and greater mean birthweight centile (82 [95% CI 0.74 to 0.89] versus 67 [95% C: 58 to 76], $P = 0.02$ ) than those with GDM/IGT.  Amniotic fluid insulin levels demonstrated a similar significant difference between the pre-existing and GDM/IGT groups (20.5, [95% CI 12.9–28.1], versus 8.5 [95% CI 5.4 to 11.7], $P = 0.001$ ).  Positive likelihood ratios were 1.67 and 2.08, respectively, for the prediction of liquor insulin greater than the 95th centile in women with pre-existing diabetes.		

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Study Summary	Reviewer comment
Kernaghan,D.; Ola,B.; Fraser,R.B.; Farrell,T.; Owen,P. 2007 {Kernaghan, 2007 36725 /id}	Study type: Diagnostic  Evidence level: 2+	242 women:  1. Type 1 diabetes (n= 61) 2. Type 2 diabetes (n= 14) 3. Gestational diabetes (n= 49) 4. Impaired glucose tolerance (n= 118)	Two hundred and forty-two consecutive women (61 type 1 diabetes mellitus, 14 type 2 diabetes mellitus, 49 gestational diabetics and 118 with impaired glucose tolerance) receiving routine care at the combined diabetes/antenatal clinic, Jessop Hospital for Women, Sheffield.  Country: UK	Test: 1. Estimated fetal weight alone. 2. Fetal growth velocity alone.  Reference test: Combined estimated fetal weight and fetal growth velocity.	Primary outcome: Large for gestational age at delivery  Secondary outcome: Neonatal hypoglycaemia	Estimated fetal weight has limited utility in the prediction of large for gestational age infants.  Fetal growth velocity does not identify the large for gestational age infant.  Estimated fetal weight and fetal growth velocity do not predict neonatal hypoglycaemia.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Macintosh,M.C.; Fleming,K.M.; Bailey,J.A.; Doyle,P.; Modder,J.; Acolet,D.; Golightly,S.; Miller,A.  2006  {Macintosh, 2006 36707 /id}	Study Type: Cohort  Evidence level: 2++	2359 pregnant women with type 1 or type 2 diabetes.	2359 pregnancies to women with type 1 diabetes (n = 1707) or type 2 diabetes (n = 652) who gave birth between 1 March 2002 and 28 February 2003.  Country: England, Wales and Northern Ireland.	Intervention: This is a study prospectively following pregnant women with diabetes to determine perinatal mortality and congenital anomalies occurring within this group.  Comparison: General population	Follow-up period: One year  Outcome Measures: 1. Stillbirth rates 2. Perinatal mortality 3. Neonatal mortality 4. Prevalence of congenital anomalies	Women with type 2 diabetes were more likely to come from a Black, Asian, or other ethnic minority group (type 2, 48.8%; type 1, 9.1%) and from a deprived area (type 2, 46.3% in most deprived fifth; type 1, 22.8%).  Perinatal mortality in babies of women with diabetes was 31.8/1000 births. Perinatal mortality was similar in babies of women with type 1 (31.7/1000 births) and type 2 diabetes (32.3/1000) and was nearly four times higher than that in the general maternity population.  141 major congenital anomalies were confirmed in 109 offspring. The prevalence of major congenital anomaly was 46/1000 births in women with diabetes (48/1000 births for type 1 diabetes; 43/1000 for type 2 diabetes), more than double that expected. This increase was driven by anomalies of the nervous system, notably neural tube defects (4.2-fold), and congenital heart disease (3.4-fold).  Anomalies in 71/109 (65%) offspring were diagnosed antenatally.  Congenital heart disease was diagnosed antenatally in 23/42 (54.8%) offspring; anomalies other than congenital heart disease were diagnosed antenatally in 48/67 (71.6%) offspring.	Perinatal mortality and prevalence of congenital anomalies are high in babies of women with type 1 or type 2 diabetes. The rates do not seem to differ between the two types of diabetes.	

## **5.8 Timetable of antenatal appointments**

### **Q.22 What timetable of antenatal appointments should be offered to women with diabetes?**

No specific searches were conducted for this clinical question and so there are no evidence tables.

## 5.9 Preterm labour in women with diabetes

### Q.23 What special considerations in relation to spontaneous or planned preterm birth are appropriate for women with diabetes?

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Mathiesen ER;Christensen AB;Hellmuth E;Hornnes P;Stage E;Damm P; 2002 Sep {Mathiesen, 2002 27426 /id}	Study Type: Non-random intervention study. Evidence Level: 2+	Intervention: An algorithm for administration of additional insulin during treatment with antenatal steroids	16: 8 women received additional insulin according to algorithm, 8 received additional insulin based on individual glucose levels.	Pregnant women with type 1 diabetes receiving antenatal steroids for fetal lung maturation.	Blood glucose. Maternal hypoglycaemia (<3 mmol/l).	<p>Cohort 1 (control group): Insulin dose (% increase from baseline). Median (range). Day 1: 6(0–40) Day 2: 38(20–106) Day 3: 36(25–125) Day 4: 27(0–60) Day 5 17(0–60)</p> <p>Blood glucose. Median (range). Day 1: 6.7 (3.5–23) Day 2: 14.3 (6.6–15) Day 3: 12.3 (10.5–13.4) Day 4: 7.7 (5.4–11.1) Day 5: 7.7 (5.3–11.1).</p> <p>Intervention group: Insulin dose (% increase from baseline). Median (range). Day 1: 27(0–40) Day 2: 45 (3–147) Day 3: 40 (16–19) Day 4: 31(19–113) Day 5: 11 (-6–40)</p> <p>Blood glucose. Median (range). Day 1: 7.7 (4.1–11.6) Day 2: 8.2 (6.7–12.7) <math>P &lt; 0.05</math> Day 3: 9.6 (6.3–13.1) <math>P &lt; 0.05</math> Day 4: 7.0 (5.1–9.8) Day 5: 7.4 (4.2–11.9).</p> <p>The total number of hypoglycaemic episodes per woman ranged from 0–2 (median 0) in the intervention group and from 0–5 (median 0.5) in the control group.</p>	<p>The median blood glucose during the second and third day was significantly reduced in the intervention group (<math>P &lt; 0.05</math>) and was close to acceptable levels.</p> <p>An algorithm with the s.c. Insulin dose increased by up to 40% shortly after glucocorticoid treatment for lung maturation in pregnant women with diabetes prevents severe dysregulation of glycaemic control.</p>	There were two perinatal deaths in the intervention group. An intrapartum death in week 27, 3 days after the first glucocorticoid dose; and an antepartum death in wk 27 in a severely growth-restricted fetus (340 g) 17 days after the first glucocorticoid dose.
Kaushal, K; Gibson, J; Raitlon A; Hounsborne B; New J; Young R; 2002.	Study type: Case series Evidence Level: 3	Protocol for improved glycaemic control following corticosteroid therapy in diabetic pregnancies. The protocol incorporates four	6 women receiving antenatal steroids	Women receiving dexamethasone in maternity unit.	Supplementary insulin requirement (median, range) Blood glucose values	<p>The median amount of supplementary IV insulin required was 74U (range 32–88U); the median glucose values achieved were 5.8–8.9 mmol/l. 75% of glucose measurements were within an acceptable range of 4–10 mmol/l.</p>	Large amounts of supplementary IV? insulin are required to achieve even moderate control. This protocol	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
		graded sliding scales. The initial scale is selected according to the patient's current s.c. insulin dose and advanced if blood glucose is $\geq 10.1$ mmol/l for 2 consecutive hours.					enables routine ward staff to manage this effectively.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Lauszus,F.F.; Fuglsang,J.; Flyvbjerg,A.; Klebe,J.G. 2006 303	Study Type: Cohort Evidence level: 2+	71 women with type 1 diabetes	During six years (1993- 1998), 198 out of 310 pregnancies with type 1 diabetes were enrolled prospectively by the Aarhus University Hospital in Denmark.  50 women were excluded due to albuminuria, 26 preeclampsia, 9 repeated pregnancies, 1 twin pregnancy and 40 due to insufficient clinical data.  Sufficient data was defined as available data on insulin dose, HbA <sub>1c</sub> , and albumin excretion rate in gestational week 12 and thereafter.  71 women with singleton pregnancies remained for this study.  Country: Denmark	Intervention: HbA <sub>1c</sub> , insulin dose, and albumin excretion rate checks from week 12 in women with type 1 diabetes, and every second week thereafter.  Comparison: Values from women without type 1 diabetes	Follow-up period: Conception to delivery  Outcome Measures: Indicators of deterioration of diabetes during pregnancy: 1. Progression of nephropathy 2. Retinopathy  Adverse perinatal outcomes: 1. Preeclampsia 2. Preterm delivery 3. Prematurity 4. Macrosomia 5. Intrauterine growth retardation 6. Neonatal hypoglycaemia	The preterm rate was 23% and women delivering preterm showed higher HbA <sub>1c</sub> throughout pregnancy.  Univariate regression analysis showed HbA <sub>1c</sub> was the strongest predictor of preterm delivery from week 6 to 32.  The same association was observed in multivariate analysis which included insulin dose, body mass index (BMI), age, duration of diabetes, and diurnal blood pressure.  The risk of delivering preterm was more than 40% when HbA <sub>1c</sub> was above 7.7% in week 8.  Diurnal blood pressure was not found to be associated with preterm delivery.	The quality of glycaemic control in early and mid-pregnancy is a major, independent risk factor for preterm delivery in normoalbuminuric diabetic women without preeclampsia.	

# 6 Intrapartum care

## 6.1 Timing and mode of birth

### Q.24 Does intervening in the timing and mode of birth improve outcomes for women with diabetes and their babies?

#### Comparative studies

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Bernstein IM;Catalano PM; 1994 Mar 317	Study Type: Cohort Evidence level: 3	166	Country: USA	Intervention: route of delivery of women with GDM		The study found that 110 women had vaginal births and 56 had caesarean. Multiple regression analysis showed that foetal position, maternal nulliparity, and foetal fat were factors associated with caesarean section.		
Conway DL;Langer O; 1998 May 325	Study Type: Case-control Evidence level: 2-	2604	Country: USA	Intervention: examined the outcome of elective caesarean births due to macrosomia in diabetic women. The study compared two time periods – one prior to a protocol, the other after the protocol was introduced. The protocol was based on ultrasound estimates of foetal weight, with foetuses appropriate for dates being managed expectantly, those > 4250 g being delivered via caesarean section, and those large for age but less than 4250 g being delivered vaginally after induction.		The rate of shoulder dystocia was lower (7.4% vs 18.8%, OR 2.9) in macrosomic babies in the induced grouped compared non-induced. The rate of caesarean section was higher (25.1% VS 21.7%, P < 0.04) post-protocol compared to pre-protocol.	The study recommended the use of ultrasound to estimate foetal weight and using this to determine method of delivery.	
Feig DS;Razzaq A;Sykora K;Hux JE;Anderson GM;	Study Type: Case-control Evidence level: 2-	776500	Country: Canada			The study found that the number of women with diabetes in 1996 was 8.42 per 100 deliveries but that this increased to 11.90 per 1000	The study concluded that women with pre-existing diabetes needed close	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
2006 Feb 315						deliveries by 2001. What the study found was women with diabetes were significantly more likely to have caesarean section or induced labour ( $P < 0.0001$ ) than women without diabetes. The study also found that women with diabetes were more likely to have obstructed labour ( $P = 0.01$ ), shoulder dystocia ( $P < 0.0001$ ), hypertension ( $P < 0.0001$ ), and pre-eclampsia ( $P < 0.0001$ ). However, the study also noted marked increases in all these outcomes in non-diabetic women between 1996 and 2001.	monitoring during pregnancy.	
Gonen O;Rosen DJ;Dolfin Z;Tepper R;Markov S;Fejgin MD; 1997 Jun 327	Study Type: RCT Evidence level: 1+	273	Country: Israel	Intervention: compared induction of labour against expectant management in macrosomia (4000 g to 4500 g).		At baseline the women in the induction group were significantly older than the expectant group (30.8 years vs 29.5 years, $P = 0.02$ ). The results showed in the induction group that: 91 were spontaneous vaginal births, 17 were instrumental, and 26 were caesarean. In the expectant group: 91 were spontaneous vaginal births, 18 were instrumental, and 30 were caesarean. There were no significant differences. The birth weight in the induced group was 4062.8 g compared to 4132.8 in the expectant group ( $P = 0.24$ ). There were 5 cases of shoulder dystocia in the induced group compared to 6 in the expectant group.	The study concluded that estimated fetal weight between 4000 g and 4500 g should not be considered an indication for inducing birth.	However, study was not explicitly conducted on women with diabetes.
Hod M;Bar J;Peled Y;Fried S;Katz I;Itzhak M;Ashkenazi S;Schindel B;Ben Rafael Z; 1998 Aug 324	Study Type: Cohort Evidence level:	1542	Country: Israel	Intervention: examined the effect of intensive management of diet and three protocols for active elective management of route of birth on outcomes in women with GDM.		The results for the three periods of different protocols (Period A [EFW for caesarean >4500 g], Period B - mean glucose < 5.8 mmol/l, EFW for caesarean >4000 g time of elective induction = 40 weeks, Period C - mean glucose 5.3 mmol/l, EFW for caesarean >4000 g time of elective induction = 38 weeks) were: macrosomia > 4000 g = 17.9%, 14.9% and 8.8%, LGA = 23.6%, 21.0% and 11.7%, caesarean section = 20.6%, 18.4% and 16.2%, shoulder dystocia = 1.5%, 1.2% and	The study concluded that intensive management of diet and active management of birth were beneficial to women and babies.	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Incerpi MH;Fassett MJ;Kjos SL;Tran SH;Wing DA; 2001 Oct 328	Study Type: RCT Evidence level: 1+	120	Country: USA	Intervention: compared the use of misoprostol against placebo for inducing birth in women with diabetes.		0.6%, induction of labour = 11.0%, 17.0% and 35.0%. There was no difference between the groups at baseline. The study found no difference between the groups during outpatient observation, labour period (time from induction to delivery [ $P = 0.23$ ], total oxytocin dose [ $P = 0.18$ ]) or neonatal characteristics.	The study concluded misoprostol was not beneficial for the induction of women with diabetes.	
Khonjandi M;Tsai M;Tyson JE; 1974 Jan 329	Study Type: Cohort Evidence level: 2+	84	Country: USA	Intervention: comparing the outcomes of caesarean section (n = 44) and vaginal births (n = 40, 26 spontaneous and 14 induced) in women with GDM (3 hour 100 g OGTT).		The recorded complications for caesarean versus vaginal were: morbidity (9 vs 0), blood transfusions (2 vs 0), wound separation (2 vs 0), fetal gigantism > 4000 g (5 vs 3), prematurity by weight (6 vs 5), neonatal infection (1 vs 1), neonatal hypoglycaemia (1 vs 0), hyperchloremic acidosis (1 vs 0).	The study concluded that there was no advantage to pre-term caesarean section in women with GDM.	
Kjos SL;Henry OA;Montoro M;Buchanan TA;Mestman JH; 1993 Sep 323	Study Type: RCT Evidence level: 1+	200	Country: USA	Intervention: compared the outcomes of active induced labour (n= 100) (accurate measurement of gestational development and induction of labour with intravenous oxytocin) and expectant management (n = 100)(close monitoring and insulin treatment) in women with insulin requiring diabetes.		Those enrolled were a mixture of GDM (n = 187) and pre-existing diabetics (n = 13). There were no differences between the groups at baseline. In the active induction group 70 were induced, 8 had caesarean section and 22 had spontaneous labours. In the expectant group 49 were induced, 7 had caesarean section and 44 had spontaneous labour. The results showed a greater level of 'large for gestational age' births in the expectant group compared to the active group (23% vs. 10%, $P = 0.02$ ). There were 3 cases of 'mild' shoulder dystocia in the expectant group and none in the active group. The study concluded that active induction of women at 38 weeks should be considered in women with diabetes requiring insulin therapy.  The caesarean section rate was not significantly different in the expectant management group (31%) from the active inductive group (25%). The mean birth weight (3672 ± 407 gm)	Active induction of labour at 38 weeks' gestation should be considered in women with diabetes requiring insulin therapy.  In women with uncomplicated insulin-requiring gestational or pre-existing diabetes, expectant management of pregnancy after 38 weeks' gestation did not reduce the incidence of caesarean section delivery. Moreover, there was an increased prevalence of large-for gestational-age infants (23% vs 10%) and shoulder dystocia (3% vs 0%).  Because of the risks, delivery should be contemplated at 38 weeks' gestation and, if not pursued, careful	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						and percentage large for gestational age, as defined by birth weight $\geq$ 90th percentile, of infants in the expectantly managed group (23%) was greater than those in the active induction group ( $3466 \pm 372$ gm), $P < 0.0001$ , 10% large for gestational age). This difference persisted after controlling for gestational age and maternal age and body weight ( $P < 0.01$ ).	monitoring of fetal growth should be performed.	
Lurie S;Insler V;Hagay ZJ; 1996 Jul 331	Study Type: Case-control Evidence level: 2-	260	Country: Israel	Intervention: compared inducing labour at 38–39 weeks or allowing pregnancy to continue naturally in women with type 1 diabetes.		In pre-existing diabetes, the expectant management of pregnancy after 38 weeks' gestation or more did not reduce the incidence of caesarean section, but rather led to an increased prevalence of large-for gestational-age infants (23% vs 10%) and shoulder dystocia (3% versus 0%).		
Naylor CD;Sermer M;Chen E;Sykora K; 1996 Apr 17 318	Study Type: Cohort Evidence level: 2+	3778	Country: Canada	Intervention: relationship between caesarean section rates and gestational glucose intolerance (3-hour, 100 g OGGT).  The study identified four groups: negative GDM (n = 2940), false-positive GDM (n = 580), untreated borderline GDM (n = 115) and known treated GDM (n = 143).		There were no differences between the groups at baseline. The study found the rate of shoulder dystocia was 1.4% in the induced group against 10.2% in the non-induced group ( $P < 0.05$ ). No difference in caesarean section rates was found. There was also no difference in the weight of babies at delivery (ns).  The study found that those with GDM had higher rates of macrosomia (28.7% vs 13.7%, $P < 0.001$ ) and caesarean delivery (29.6% vs 20.2%, $P = 0.02$ ). Treatment of GDM reduce rates of macrosomia (>4000 g) to 10.5% compared to 28.7% in the untreated group and 13.7% in the non-GDM group, but caesarean section rates were 33.6% compared to 29.6% in the untreated group and 20.2% in the non-diabetic group. Multivariate analysis found that being treated for GDM was the most significant factor in determining caesarean section delivery (OR = 2.1 [95%CI 1.3 to		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						3.6]), untreated GDM was not a significant risk factor (OR = 1.6 [95%CI 0.9 to 2.7]).		
						The study found no significant differences in gestational age at delivery (39.8 ± 1.8 weeks for women without diabetes, 39.8 ± 1.8 weeks for women with borderline diabetes, and 39.3 ± 1.6 weeks for women with gestational diabetes, <i>p</i> > 0.20). There were no differences in fetal distress and dystocia among the children of these mothers.		
Takoudes TC;Weitzen S;Slocum J;Malee M; 2004 Sep 330	Study Type: Case-control Evidence level: 2-	388	Country: USA	Intervention: examined the risk of wound complication after caesarean section in women with and without pre-gestational diabetes.		At baseline those in the diabetic group were more likely to be obese ( <i>P</i> <0.01) and have a positive group B streptococcus status ( <i>P</i> < 0.01). During caesarean section the diabetic group was more likely to have estimated blood loss > 1000 ml ( <i>P</i> < 0.01), postpartum haemorrhage ( <i>P</i> = 0.05) and longer in the operating theatre ( <i>P</i> = 0.01), but were less likely to have meconium present ( <i>P</i> = 0.01). The results of the study showed that 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 [OR 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.

Non-comparative studies

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Ehrenberg HM;Durnwald CP;Catalano P;Mercer BM; 2004 316	Study Type: Other Evidence Level: 3	Intervention: relationship of obesity and diabetes on risk of caesarean section.	12303	Country: USA		The study found that diet controlled GDM ( $P < 0.0001$ ), insulin controlled GDM ( $P < 0.0001$ ) 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.		
Holt VL;Mueller BA; 1997 Jan 333	Study Type: Other Evidence Level: 3	Intervention: Examined success of VBAC in women with previous complications, such as GDM.	10110	Country: USA		The study found that 62% of those who attempted VBAC were successful. The factors associated with unsuccessful VBAC were birth weight $> 4000$ g, cephalopelvic disproportion, prolonged labour, dysfunctional labour, diabetes (GDM and pre-existing), hypertension, induced labour, STD, foetal distress and breech birth.		
Levy AL;Gonzalez JL;Rappaport VJ;Curet LB;Rayburn WF; 2002 326	Study Type: Other Evidence Level: 3	Intervention: examined if induction of labour increased rates of caesarean section in women with diabetes.	108487	Country: USA		The study found an OR of 2.00 (95%CI 1.83 to 2.19) for women with diabetes having caesarean section compared to those without. The caesarean section rate was lower in women who were induced compared to those who were not (OR = 0.77, 95%CI = 0.50 to 0.89).		
Marchiano D;Elkousy M;Stevens E;Peipert J;Macones G; 2004 334	Study Type: Other Evidence Level: 3	Intervention: examined women with a previous history of caesarean section and GDM who attempted vaginal birth and were using diet only to control diabetes. The study compared women with or without GDM who had a history of caesarean section.	25079	Country: USA		The diabetic group was significantly older (31 vs 30, $P < 0.001$ ), higher proportion of $>4000$ g infants (18% vs 13%, $P < 0.05$ ), managed in a university hospital, to have chronic hypertension and have spontaneous labour. The study then with diet controlled GDM who attempted VBAC or had elective caesarean section. The VBAC group was younger (31.1 vs 32.2, $P < 0.001$ ), had higher previous pregnancies (3.4 vs 31, $P < 0.001$ ), different ethnic mix ( $P < 0.05$ ), different insurance profile ( $P < 0.001$ ), seen in university hospital (56% vs 42%, $P < 0.001$ ), previous vaginal birth or VBAC (40% vs 17%, $P < 0.001$ ), and birth weight $> 4000$ g (18% v 33%, $P < 0.001$ ). The study found that 295 of 423 attempted VBACs were successful in women with diet controlled GDM. Logistic regression showed that age, birth weight, ethnic origin (white), induced labour, augmented labour and previous vaginal birth were all predictors of successful VBAC, whilst diet-		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						controlled GDM, and chronic hypertension were not.  The gestational age at delivery between women without diabetes and those with diet-controlled gestational diabetes was $38.9 \pm 2$ vs $38.3 \pm 2.2$ , respectively, $P < 0.001$ )		
Naeye RL; 1978 Mar 30 {Naeye, 1978 35583 /id}	Study Type: Other  Evidence Level: 3	Intervention: examined the association between perinatal death and presence of GDM.	53518	Country: USA		Examined the association between peri-natal death and presence of GDM. The study found 1614 of 47745 (33.8 per 1000) peri-natal deaths in the non-diabetic group, and 46 of 652 (70.3 per 100) in the diabetic group. However, the rate in the diabetic women who were induced or had caesarean was 33.2 per 1000 compared to 14.8 per 100 in the spontaneous group. The study also found that babies of diabetic mothers who were equal to or greater than the 90 percentile in birth weight were more likely ( $P < 0.005$ ) to have retarded lung development. 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 neonate survival rate has improved.
Patel RR;Peters TJ;Murphy DJ; 2005 {Patel, 2005 35584 /id}	Study Type: Other  Evidence Level: 3	Intervention: examined prenatal risk factors associated with a woman having a caesarean section. The study found that having GDM inc	11791	Country: UK		The study found that having GDM increased the risk of having a caesarean (OR = 2.60; 95%CI 1.38 to 4.92) and having pre-existing diabetes increased the risk (OR = 8.50; 95%CI 4.27 to 16.9). However, a number of other factors were also identified, such obstetric history and medical history. In the multiple regression models, diabetes was a risk factor for caesarean, alongside maternal age, previous caesarean section, outcome of last pregnancy, parity, birth weight, neonatal head circumference, gestational age at delivery, and fetal presentation.		However, the study did not examine any health professional or healthcare related factors.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Modanlou,HD.; Dorchester,WP.  1987  {Modanlou, 1987 36205 /id}	Study Type: Cross-sectional  Evidence level: 3	10,369 deliveries between 1984-1985	Women who delivered during 1984-1985 in Miller Children's Hospital in California.  Country: USA	Intervention: No intervention, assessment of risk factors.  Comparison:	Follow-up period: No follow-up (cross-sectional study).  Outcome Measures: Delivery via: 1. Vaginal vertex 2. Breech vagina 3. Repeat caesarean section 4. Primary caesarean section	The study shows that diabetes is one of the diseases associated with increased caesarean section, resuscitation with positive pressure ventilation and low 1 and 5 minute Apgar score.  Diabetes, hypertension, premature labour, prolonged rupture of membrane and postdate were more common in women who underwent primary caesarean sections than in vaginal vertex births ( $P < 0.001$ ).  Very low Apgar score ( $\leq 3$ ) at 1 and 5 minutes was significantly more frequent in primary and repeat caesarean sections than in vaginal vertex births ( $P < 0.01$ ).  Resuscitation with positive pressure ventilation was more frequent in primary and repeat caesarean sections than in vaginal vertex births ( $P = 0.001$ ).	Given that diabetes is associated with many of the poor pregnancy outcomes, there is a need for a well trained neonatal team to be present for operative deliveries.	

## Q.25 Does intervening have any implications for future pregnancies and births?

## Comparative studies

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Bernstein IM;Catalano PM; 1994 Mar {Bernstein, 1994 35575 /id}	Study Type: Cohort Evidence level: 3	166	Country: USA	Intervention: route of delivery of women with GDM		The study found that 110 women had vaginal births and 56 had caesarean. Multiple regression analysis showed that foetal position, maternal nulliparity, and foetal fat were factors associated with caesarean section.		
Conway DL;Langer O; 1998 May {Conway, 1998 6282 /id}	Study Type: Case-control Evidence level: 2-	2604	Country: USA	Intervention: examined the outcome of elective caesarean births due to macrosomia in diabetic women. The study compared two time periods – one prior to a protocol, the other after the protocol was introduced. The protocol was based on ultrasound estimates of foetal weight, with fetuses appropriate for dates being managed expectantly, those > 4250 g being delivered via caesarean section, and those large for age but less than 4250 g being delivered vaginally after induction.		The rate of shoulder dystocia was lower (7.4% vs 18.8%, OR 2.9) in macrosomic babies in the induced group compared non-induced. The rate of caesarean section was higher (25.1% VS 21.7%, P < 0.04) post-protocol compared to pre-protocol.	The study recommended the use of ultrasound to estimate foetal weight and using this to determine method of delivery.	
Feig DS;Razzaq A;Sykora K;Hux JE;Anderson GM; 2006 Feb {Feig, 2006 35579 /id}	Study Type: Case-control Evidence level: 2-	776500	Country: Canada			The study found that the number of women with diabetes in 1996 was 8.42 per 100 deliveries but that this increased to 11.90 per 1000 deliveries by 2001. What the study found was women with diabetes were significantly more likely to have caesarean section or induced labour (P < 0.0001) than women without	The study concluded that women with pre-existing diabetes needed close monitoring during pregnancy.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Gonen O;Rosen DJ;Dolfin Z;Tepper R;Markov S;Feigin MD; 1997 Jun {Gonen, 1997 35580 /id}	Study Type: RCT Evidence level: 1+	273	Country: Israel	Intervention: compared induction of labour against expectant management in macrosomia (4000 g to 4500 g).		diabetes. The study also found that women with diabetes were more likely to have obstructed labour ( $P = 0.01$ ), shoulder dystocia ( $P < 0.0001$ ), hypertension ( $P < 0.0001$ ), and pre-eclampsia ( $P < 0.0001$ ). However, the study also noted marked increases in all these outcomes in non-diabetic women between 1996 and 2001. At baseline the women in the induction group were significantly older than the expectant group (30.8 years vs 29.5 years, $P = 0.02$ ). The results showed in the induction group that: 91 were spontaneous vaginal births, 17 were instrumental, and 26 were caesarean. In the expectant group: 91 were spontaneous vaginal births, 18 were instrumental, and 30 were caesarean. There were no significant differences. The birth weight in the induced group was 4062.8 g compared to 4132.8 in the expectant group ( $P = 0.24$ ). There were 5 cases of shoulder dystocia in the induced group compared to 6 in the expectant group.	The study concluded that estimated fetal weight between 4000 g and 4500 g should not be considered an indication for inducing birth.	However, study was not explicitly conducted on women with diabetes.
Hod M;Bar J;Peled Y;Fried S;Katz I;Itzhak M;Ashkenazi S;Schindel B;Ben Rafael Z; 1998 Aug {Hod, 1998 6024 /id}	Study Type: Cohort Evidence level:	1542	Country: Israel	Intervention: examined the effect of intensive management of diet and three protocols for active elective management of route of birth on outcomes in women with GDM.		The results for the three periods of different protocols (Period A [EFW for caesarean >4500 g], Period B - mean glucose < 5.8 mmol/l, EFW for caesarean >4000 g time of elective induction = 40 weeks, Period C - mean glucose 5.3 mmol/l, EFW for caesarean >4000 g time of elective induction = 38 weeks) were: macrosomia > 4000 g = 17.9%, 14.9% and 8.8%, LGA = 23.6% 21.0% and 11.7%, caesarean section = 20.6%, 18.4% and 16.2%, shoulder dystocia = 1.5%, 1.2% and 0.6%, induction of labour = 11.0%, 17.0% and 35.0%.  The gestational age at delivery for women with gestational diabetes was $39 \pm 2.5$ weeks and that of women without diabetes was $39 \pm 1.5$ weeks.	The study concluded that intensive management of diet and active management of birth were beneficial to women and babies.	
Incerpi MH;Fassett MJ;Kjos SL;Tran SH;Wing DA;	Study Type: RCT Evidence level: 1+	120	Country: USA	Intervention: compared the use of misoprostol against		There was no difference between the groups at baseline. The study found no difference between the groups during	The study concluded misoprostol was not beneficial for the	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
2001 Oct {Incerpi, 2001 35581 /id}				placebo for inducing birth in women with diabetes.		outpatient observation, labour period (time from induction to delivery [ $P = 0.23$ ], total oxytocin dose [ $P = 0.18$ ]) or neonatal characteristics.	induction of women with diabetes.	
Khonjandi M;Tsai M;Tyson JE; 1974 Jan {Khonjandi, 1974 6294 /id}	Study Type: Cohort Evidence level: 2+	84	Country: USA	Intervention: comparing the outcomes of caesarean section (n = 44) and vaginal births (n = 40, 26 spontaneous and 14 induced) in women with GDM (3 hour 100 g OGTT).		The recorded complications for caesarean versus vaginal were: morbidity (9 vs 0), blood transfusions (2 vs 0), wound separation (2 vs 0), fetal gigantism > 4000 g (5 vs 3), prematurity by weight (6 vs 5), neonatal infection (1 vs 1), neonatal hypoglycaemia (1 vs 0), hyperchloremic acidosis (1 vs 0).	The study concluded that there was no advantage to pre-term caesarean section in women with GDM.	
Kjos SL;Henry OA;Montoro M;Buchanan TA;Mestman JH; 1993 Sep {Kjos, 1993 6295 /id}	Study Type: RCT Evidence level: 1+	200	Country: USA	Intervention: compared the outcomes of active induced labour (n= 100) (accurate measurement of gestational development and induction of labour with intravenous oxytocin) and expectant management (n = 100) (close monitoring and insulin treatment) in women with insulin requiring diabetes.		Those enrolled were a mixture of GDM (n = 187) and pre-existing diabetics (n = 13). There were no differences between the groups at baseline. In the active induction group 70 were induced, 8 had caesarean section and 22 had spontaneous labours. In the expectant group 49 were induced, 7 had caesarean section and 44 had spontaneous labour. The results showed a greater level of 'large for gestational age' births in the expectant group compared to the active group (23% vs. 10%, $P = 0.02$ ). There were 3 cases of 'mild' shoulder dystocia in the expectant group and none in the active group. The study concluded that active induction of women at 38 weeks should be considered in women with diabetes requiring insulin therapy.		
Lurie S;Insler V;Hagay ZJ; 1996 Jul {Lurie, 1996 6301 /id}	Study Type: Case-control Evidence level: 2-	260	Country: Israel	Intervention: compared inducing labour at 38 to 39 weeks or allowing pregnancy to continue naturally in women with insulin dependent diabetes.		There were no differences between the groups at baseline. The study found the rate of shoulder dystocia was 1.4% in the induced group against 10.2% in the non-induced group ( $P < 0.05$ ). No difference in caesarean section rates was found. There was also no difference in the weight of babies at delivery (ns).		
Naylor CD;Sermer M;Chen E;Sykora K; 1996 Apr 17	Study Type: Cohort Evidence level: 2+	3778	Country: Canada	Intervention: relationship between caesarean section rates and gestational glucose intolerance (3-		The study found that those with GDM had higher rates of macrosomia (28.7% vs 13.7%, $P < 0.001$ ) and caesarean delivery (29.6% vs 20.2%, $P = 0.02$ ). Treatment of GDM reduce rates of macrosomia		

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
{Naylor, 1996 9614 /id}				hour, 100 g OGGT).  The study identified four groups: negative GDM (n = 2940), false-positive GDM (n = 580), untreated borderline GDM (n = 115) and known treated GDM (n = 143).		(>4000 g) to 10.5% compared to 28.7% in the untreated group and 13.7% in the non-GDM group, but caesarean section rates were 33.6% compared to 29.6% in the untreated group and 20.2% in the non-diabetic group. Multivariate analysis found that being treated for GDM was the most significant factor in determining caesarean section delivery (OR = 2.1 [95%CI 1.3 to 3.6]), untreated GDM was not a significant risk factor (OR = 1.6 [95%CI 0.9 to 2.7]).		
Takoudes TC;Weitzen S;Slocum J;Malee M;  2004 Sep  {Takoudes, 2004 35585 /id}	Study Type: Case-control  Evidence level: 2-	388	Country: USA	Intervention: examined the risk of wound complication after caesarean section in women with and without pre-gestational diabetes.  Comparison:	Follow-up period:  Outcome Measures:	At baseline those in the diabetic group were more likely to be obese ( $P < 0.01$ ) and have a positive group B streptococcus status ( $P < 0.01$ ). During caesarean section the diabetic group was more likely to have estimated blood loss $> 1000$ ml ( $P < 0.01$ ), postpartum haemorrhage ( $P = 0.05$ ) and longer in the operating theatre ( $P = 0.01$ ), but were less likely to have meconium present ( $P = 0.01$ ). The results of the study showed that 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 [OR 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.
Coleman TL;Randall H;Graves W;Lindsay M;  2001 May  {Coleman, 2001 35577 /id}	Study Type: Systematic review - meta-analysis  Evidence level: 2-	428	Country: USA	Intervention: examined vaginal birth after caesarean section in women with GDM.  Comparison:	Follow-up period:  Outcome Measures:	The GDM group was significantly older ( $P < 0.001$ ) and had a significantly different ethnic background ( $P = 0.006$ ) compared to the control group. The study found those with previous GDM were significantly more likely to have a future caesarean section (35.9% vs 22.8%, $P < 0.001$ ), less likely to have a vaginal birth (64.1% vs 77.2%, $P < 0.001$ ), and more likely to have an induced birth (38.5% vs 22.4%, $P < 0.001$ ). There was no difference in failure of VBAC in the induced group (63.2% vs 68.9%, $P = 0.540$ ) but significant difference in failure of VBAC in the spontaneous labour group (18.7% vs 9.5%, $P = 0.20$ ). There were no differences for pre-emclampsia, lacerations or shoulder dystocia. The birth weight in the GDM group was significantly greater than the control (3437.8 g vs		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						3191.9 g, $P = 0.001$ ), but no differences in outcome Apgar scores or neonatal deaths.		
						The mean gestational ages at delivery of women with gestational diabetes and control were similar ( $38.4 \pm 2.8$ vs $39 \pm 2.9$ weeks). There was no significance difference in the risk of shoulder dystocia, pre-eclampsia, pelvic laceration, or prolonged hospital stay after delivery between the two groups.		

### Non-comparative studies

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Ehrenberg HM;Durnwald CP;Catalano P;Mercer BM;	Study Type: Other Evidence Level: 3	Intervention: relationship of obesity and diabetes on risk of caesarean section.	12303	Country: USA		The study found that diet controlled GDM ( $P < 0.0001$ ), insulin controlled GDM ( $P < 0.0001$ ) and pre-existing diabetes ( $p < 0.0001$ ) were risk factors for having caesarean section.		
2004 {Ehrenberg, 2004 35578 /id}						However, multiple regression analysis showed that only pre-existing diabetes was an independent risk factor for having caesarean section.		
Holt VL;Mueller BA;	Study Type: Other Evidence Level: 3	Intervention: Examined success of VBAC in women with previous complications, such as GDM.	10110	Country: USA		The study found that 62% of those who attempted VBAC were successful. The factors associated with unsuccessful VBAC were birth weight $> 4000$ g, cephalopelvic disproportion, prolonged labour, dysfunctional labour, diabetes (GDM and pre-existing), hypertension, induced labour, STD, foetal distress and breech birth.		
1997 Jan {Holt, 1997 1889 /id}								
Levy AL;Gonzalez JL;Rappaport VJ;Curet LB;Rayburn WF;	Study Type: Other Evidence Level: 3	Intervention: examined if induction of labour increased rates of caesarean section in women with diabetes.	108487	Country: USA		The study found an OR of 2.00 (95%CI 1.83 to 2.19) for women with diabetes having caesarean section compared to those without. The caesarean section rate was lower in women who were induced compared to those who were not (OR = 0.77, 95%CI = 0.50 to 0.89).		
2002 {Levy, 2002 29258 /id}								
Marchiano D;Elkousy M;Stevens E;Peipert J;Macones G;	Study Type: Other Evidence Level: 3	Intervention: examined women with a previous history of caesarean section and GDM who	25079	Country: USA		The diabetic group was significantly older (31 vs 30, $P < 0.001$ ), higher proportion of $>4000$ g infants (18% vs 13%, $P < 0.05$ ), managed in a university hospital, to have chronic hypertension		

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
2004  {Marchiano, 2004 35582 /id}		attempted vaginal birth and were using diet only to control diabetes. The study compared women with or without GDM who had a history of caesarean section.				and have spontaneous labour. The study then with diet controlled GDM who attempted VBAC or had elective caesarean section. The VBAC group was younger (31.1 vs 32.2, $P < 0.001$ ), had higher previous pregnancies (3.4 vs 31, $P < 0.001$ ), different ethnic mix ( $P < 0.05$ ), different insurance profile ( $P < 0.001$ ), seen in university hospital (56% vs 42%, $P < 0.001$ ), previous vaginal birth or VBAC (40% vs 17%, $P < 0.001$ ), and birth weight > 4000 g (18% vs 33%, $P < 0.001$ ). The study found that 295 of 423 attempted VBACs were successful in women with diet controlled GDM. Logistic regression showed that age, birth weight, ethnic origin (white), induced labour, augmented labour and previous vaginal birth were all predictors of successful VBAC, whilst diet-controlled GDM, and chronic hypertension were not.		
Naeye RL;  1978 Mar 30  {Naeye, 1978 35583 /id}	Study Type: Other  Evidence Level: 3	Intervention: examined the association between perinatal death and presence of GDM.	53518	Country: USA		examined the association between peri-natal death and presence of GDM. The study found 1614 of 47745 (33.8 per 1000) peri-natal deaths in the non-diabetic group, and 46 of 652 (70.3 per 100) in the diabetic group. However, the rate in the diabetic women who were induced or had caesarean was 33.2 per 1000 compared to 14.8 per 100 in the spontaneous group. The study also found that babies of diabetic mothers who were equal to or greater than the 90 percentile in birth weight were more likely ( $P < 0.005$ ) to have retarded lung development. 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 neonate survival rate has improved.
Patel RR;Peters TJ;Murphy DJ;  2005  {Patel, 2005 35584 /id}	Study Type: Other  Evidence Level: 3	Intervention: examined prenatal risk factors associated with a woman having a caesarean section. The study found that having GDM inc	11791	Country: UK		The study found that having GDM increased the risk of having a caesarean (OR = 2.60; 95%CI 1.38 to 4.92) and having pre-existing diabetes increased the risk (OR = 8.50; 95%CI 4.27 to 16.9). However, a number of other factors were also identified, such obstetric history and medical history. In the multiple regression model, diabetes was a risk factor for caesarean, alongside maternal age, previous caesarean section, outcome of last pregnancy, parity, birth weight, neonatal head circumference, gestational age at delivery, and fetal presentation.		However, the study did not examine any health professional or healthcare related factors.

## 6.2 Analgesia and anaesthesia

### Q.26 What special considerations in relation to analgesia and anaesthesia are appropriate for women with diabetes?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Lattermann,R.; Carli,F.; Wykes,L.; Schricker,T.  2002  {Lattermann, 2002 37232 /id}	Study Type: RCT  Evidence level: 1+	16 patients  1. Intervention group (n = 8)  2. Control group (n = 8)	16 patients undergoing elective colorectal surgery for nonmetastatic carcinoma were admitted to the study.  All patients had a body mass index (BMI) of 20–27 kg/m <sup>2</sup> and maintained their body weight during the preceding 3 months (< 5% weight loss).  Exclusion criteria were any cardiac, hepatic, renal, endocrine, or metabolic disorders, ingestion of any medication known to affect metabolism, and history of severe sciatica or back surgery that contraindicated the use of epidural catheters. Further exclusions were patients with a plasma albumin concentration less than 35 g/l, with anaemia (haemoglobin < 10 g/dl), and patients who received chemotherapy during 6 months before surgery.	Intervention: A combination of epidural blockade with bupivacaine and general anaesthesia.  Comparison: General anaesthesia alone (control group).	Follow-up period:  Outcome Measures: Plasma concentrations of: 1. Glucose 2. Cortisol 3. Glucagon 4. Insulin	Epidural blockade blunted the perioperative increase in the plasma concentration of glucose, cortisol, and glucagon when compared to the control group ( $P < 0.05$ ).  Plasma concentrations of lactate, free fatty acids and insulin did not change.  Intra- and postoperative glucose production was lower in patients with epidural blockade than in control subjects (intraoperative, epidural blockade $8.2 \pm 1.9$ vs. control $10.7 \pm 1.4$ $\mu\text{mol/kg/min}$ , $P < 0.05$ ; postoperative, epidural blockade $8.5 \pm 1.8$ vs. control $10.5 \pm 1.2$ $\mu\text{mol/kg/min}$ , $P < 0.05$ ), whereas glucose clearance decreased by a similar extent in both groups ( $P < 0.05$ ).  Protein breakdown ( $P < 0.05$ ), protein synthesis ( $P < 0.05$ ), and amino acid oxidation ( $p > 0.05$ ) decreased with both anaesthetic techniques.	Epidural blockade attenuates the hyperglycaemic response to surgery through modification of glucose production whilst perioperative suppression of protein metabolism was not influenced by epidural blockade.	Patients undergoing elective colorectal surgery for nonmetastatic carcinoma, not women with diabetes.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Datta,S.; Kitzmiller,J.L.; Naulty,J.S.; Ostheimer,G.W.; Weiss,J.B.  1982  {Datta, 1982 34438 /id}	Study Type: Cohort  Evidence level: 2-	20 patients	Country: Canada  Rigidly controlled insulin-dependent women with diabetes and women without diabetes undergoing spinal anaesthesia for caesarean section.  Country: USA	Intervention: Spinal anaesthesia in women with diabetes  Comparison: Spinal anaesthesia in women without diabetes	Follow-up period:  Outcome Measures: 1 Acid-base values 2. Apgar scores	There were no significant differences in the acid-base values between the women with diabetes and women without diabetes and the infants of the mothers with diabetes compared to the control group.  There were no differences in the induction-delivery or uterine-incision delivery interval between the two groups  Apgar scores were also similar in the two groups.	If maternal diabetes is well controlled, dextrose-containing solutions are not used for intravascular volume expansion before delivery and hypotension is avoided, spinal anaesthesia can be used safely for women with diabetes undergoing caesarean section.	The sample size is very small, and the role of chance may not be excluded. Also the study is very old, conducted 1982 over 20 years ago
Hebl,J.R.; Kopp,S.L.; Schroeder,D.R.; Horlocker,T.T.  2006  {Hebl, 2006 36652 /id}	Study Type: Cohort  Evidence level: 2+	567 patients with a preexisting peripheral sensorimotor neuropathy or diabetic polyneuropathy.  1. Receiving anaesthesia (n = 325) 2. Epidural anaesthesia or analgesia (n = 214) 3. Continuous spinal anaesthesia (n = 24) 4. Combined spinal-epidural (n= 4)	567 patients with a preexisting peripheral sensorimotor neuropathy or diabetic polyneuropathy who subsequently underwent neuraxial anaesthesia or analgesia.  Country: USA	Intervention: Neuraxial anaesthesia or analgesia.  Comparison: General population undergoing the same procedure.	Follow-up period: At least six months.  Outcome Measures: 1. New or progressive postoperative neurological deficits. 2. Technical complications such as unintentional elicitation of a paresthesia. 3. Infectious complications 4. Haematologic complications	The majority of patients had chronically stable neurological signs or symptoms at the time of block placement, with very few reporting progression of their symptoms within the last 6 months.  Overall, two (0.4%; 95% CI 0.1% to 1.3%) patients experienced new or progressive postoperative neurological deficits, in the setting of an uneventful neuraxial technique.  In these patients, the neuraxial block may have contributed to the injury secondary to direct trauma or local anaesthetic neurotoxicity around an already vulnerable nerve.  Overall the risk of severe postoperative neurological dysfunction in patients with peripheral sensorimotor neuropathy or diabetic polyneuropathy undergoing neuraxial anaesthesia or	The risk of severe postoperative neurological dysfunction in patients with peripheral sensorimotor neuropathy or diabetic polyneuropathy undergoing neuraxial anaesthesia or analgesia is high. Hence clinicians should be aware of this potentially high-risk subgroup of patients when developing and implementing a regional anesthetic care plan.	Study involved general population of patients with peripheral sensorimotor neuropathy or diabetic polyneuropathy, not women with diabetes undergoing analgesia or anaesthesia.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						analgesia was found to be 0.4% (95% CI 0.1 to 1.3%).  Sixty-five (11.5%) technical complications occurred in 63 patients with the most common complication being unintentional elicitation of a paresthesia (7.6%), followed by traumatic (evidence of blood) needle placement (1.6%) and unplanned dural puncture (0.9%).  There were no infectious or haematologic complications.		
Ramanathan,S.; Khoo,P.; Arismendy,J.  {Ramanathan, 1991 35590 /id}	Study Type:  Cohort  Evidence level: 2+	50 women (20 with type 1 diabetes and 30 without diabetes)	20 women with type 1 diabetes and 30 women without diabetes undergoing elective caesarean section under lumbar epidural anaesthesia.  All the women were selected from the population.  The three groups were similar in age, weight and height.  Country: USA	Intervention: The usual insulin dosage plus epidural bupivacaine before caesarean section (Group 1).  Comparison: 1. Lactated ringer's solution plus dextrose in water (Group 2)  2. Lactated ringer's solution alone (Group 3)	Follow-up period: Not reported  Outcome Measures: Maternal outcomes: 1. Maternal vital statistics 2. Acid-base balance 3. Glucose levels 4. Blood lactate 5. Blood pyruvate 6. Blood excess lactate 6. Lactate/pyruvate ratio  Neonatal outcomes: 1. Neonatal complications (such as hypoglycaemia and respiratory distress) 2. Neonatal acid-base balance 3. Neonatal glucose levels 4. Blood lactate 5. Blood pyruvate 6. Blood excess lactate 7. Lactate/pyruvate ratio	None of the women with diabetes developed hypoglycaemia before delivery.  Seven infants in Group 1 developed (mild) hypoglycaemia which was treated only with early oral feeding.  Two infants developed hypoglycaemia within 1 hour. The remaining five infants developed hypoglycaemia at 3 hours.  Two infants from group 1 developed respiratory distress and required constant airway positive pressure breathing.  No neonatal deaths occurred.  No significant differences were observed in the maternal and neonatal blood pH, PO <sub>2</sub> , PCO <sub>2</sub> , or base excess at delivery.  At delivery the mean neonatal capillary blood glucose level (46 ± 3 mg/dL) was	The data show that epidural anaesthesia for caesarean section in women with diabetes is associated with satisfactory neonatal Apgar scores and acid-base status at the time of birth.  Epidural anaesthesia in women with diabetes is associated with normal acid-base status in the mother and the neonate. In women with diabetes, there is increased incidence of neonatal hypoglycaemia and altered maternal and neonatal glycolysis.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>significantly lower than both the umbilical venous (<math>135 \pm 12</math> mg/dL) and arterial (<math>103 \pm 8</math> mg/dL) blood glucose levels in Group 1 (<math>P = 0.01</math>).</p>		
						<p>Maternal venous blood glucose levels were greatest in the healthy women given glucose before epidural anaesthesia.</p>		
						<p>Blood lactate level was higher in mothers in Group 1 than the corresponding levels in group 2 and 3 mothers. Neonatal umbilical venous blood in group 2 contained significantly higher levels of lactate than group 1 or 3.</p>		
						<p>Blood pyruvate: The pyruvate levels in maternal venous blood were significantly lower in group 1 mothers than in group 2. Both the umbilical venous and arterial blood pyruvate levels in group 1 were significantly lower than the corresponding levels in then other two groups. Blood pyruvate levels in both umbilical vein and artery were greatest in group 2.</p>		
						<p>Blood Excesses lactate and lactate/pyruvate ratio: In maternal venous blood, excess lactate was significantly greater in group 1 compared to that in the other two groups. Groups 1 and 2 had greater concentrations of excess lactate in the neonatal umbilical venous blood. In the maternal venous and neonatal umbilical venous and arterial blood, lactate/pyruvate ratio was significantly greater</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Tsen,L.C. 2003 {Tsen, 2003 34440 /id}	Study Type: Other Evidence Level: 3	Intervention: Anaesthetic management of women with diabetes  Comparison: neuraxial anaesthesia and general anaesthesia		Pregnant women with cardiac disease and diabetes or gestational diabetes. For the purposes of the review, interest lies in those women with diabetes or gestational diabetes  Country: various	Umbilical cord, fetal and neonatal acidosis	than in group 1 than in the other groups.  No summary statistics provided	Management should be undertaken by a multidisciplinary team	The paper provided an important reference to a relevant study.
Rees,G.A.; Hayes,T.M.; Pearson,J.F. 1982 {Rees, 1982 34439 /id}	Study Type: Other Evidence Level: 3	Intervention: Anaesthesia for pregnant women with diabetes or gestational diabetes  Comparison: The authors discuss benefits and risks accompanying: general anaesthesia regional anaesthesia epidural analgesia		Women / mothers with gestational diabetes  Country: various	Type of anaesthetic metabolic issues (hyperglycaemia vs hypoglycaemia) obstetric and medical complications		Pregnant women with diabetes should be managed in specialist centres.  The care team should include an anaesthetist  Particular attention must be paid to diagnosing women who develop gestational diabetes.	The paper was useful in providing good background information

### 6.3 Glycaemic control during labour and birth

#### Q.27 How should glycaemic control be monitored and maintained during labour and birth?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Balsells M;Corcoy R;Adelantado JM;Garcia-Patterson A;Altirriba O;de Leiva A;  2000  347	Study Type: Cohort  Evidence level: 2+	85 women with gestational diabetes		Intervention: Maternal hyperglycaemia  Standardised protocol for metabolic control during labour: (1) IV glucose 8.3 g/hr (2) IV insulin infusion by syringe pump adjusted according to hourly CBG measurements (3) urine test for ketone bodies  The targets for metabolic control were capillary blood glucose between 2.8 and 6.9 mmol/l (ideally 3.3- 6.1 mmol/l).	Follow-up period:  Outcome Measures: Neonatal hypoglycaemia (2 or more glucose values <1.7 mmol/l for term babies of appropriate weight, <1.1 mmol/l for preterm or SGA babies)	Mean maternal capillary blood glucose during labour was 4.7 mmol/l and in 82.3% of the women it was in the desired range.  Logistic regression: Mean maternal blood glucose in the last two hours of labour was significantly associated with neonatal hypoglycaemia ( $P < 0.05$ ).	In this group of women with GDM the use of a standardised intrapartum management protocol was associated with fair metabolic control. CBG during labour was predictive of neonatal hypoglycaemia.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Carron Brown S; Kyne-Grzebalski D; Mwangi B; Taylor R.  1999  348	Study Type: Other  Evidence Level: 2+	Intervention: To compare the effect of a policy change following an intensive effort to improve pre-pregnancy counseling and a relaxation of targets for blood glucose control during labour.  Comparison:	120 Participants August 1989- July 1994 n= 80 November 1985 - July 1989 n= 40	Pregnant women with Type 1 diabetic mellitus  Country: UK	HbA <sub>1c</sub> Maternal blood glucose Neonatal blood glucose Birth weight Gestation at delivery Delivery type	Mean blood glucose in labour was 1.0 mmol/L higher than that of period one.  There was no relationship between neonatal blood glucose and HbA <sub>1c</sub> throughout the third trimester ( $r = -0.11$ ), mean HbA <sub>1c</sub> throughout pregnancy ( $r = 0.10$ ), or HbA <sub>1c</sub> at booking ( $r = 0.28$ ).  In period 1 neonatal hypoglycemia was recorded in seven infants (<2.2 mmol/L; intravenous glucose used in four), in period 2 neonatal blood glucose was measured as less than 2.2 mmol/L was 19 infants; with intravenous glucose used in 14).  Mean maternal blood glucose at delivery was $7.7 \pm 3.8$ mmol/L in the group with neonatal blood glucose levels <2.2 mmol/L, compared with $4.9 \pm 2.8$ mmol/L in all other women ( $P = 0.05$ ).  When maternal blood glucose was over 10 mmol/L, the infants blood glucose was always low ( $1.3 \pm 0.8$ versus $2.5 \pm 1.5$ for all others; $P < 0.02$ )	Provides evidence to suggest that HbA <sub>1c</sub> does not affect neonatal blood glucose levels.  Neonatal hypoglycemia occurred when maternal blood glucose was over 10 mmol/l.	
Taylor R; Choy Lee; Grzebalski D; Marshall S; Davison J  2002  349	Study Type: Other  Evidence Level: 3	Intervention: To define the relationship between maternal blood glucose control and neonatal hypoglycemia and macrosomia.  Comparison:	107 consecutive singleton pregnancies in women with type 1 diabetes between January 1, 1994 and January 31, 1999.	Mean age $28.6 \pm 5.2$ years Mean duration type 1 diabetes $12.9 \pm 6.8$ years  Diabetic retinopathy present in 23 women  106 women were white  Country: UK	HbA <sub>1c</sub> Pre pregnancy insulin requirement Type of insulin Maternal blood glucose Neonatal blood glucose Ultrasound estimated abdominal circumference Birth weight Blood pressure Creatinine clearance 24-hour protein excretion hemoglobin concentrations Congenital abnormalities Neonatal death	There was a significant correlation between neonatal blood glucose and mean maternal blood glucose in labor ( $R = -0.33$ , $P < 0.001$ )  The correlation for neonatal blood glucose and maternal blood glucose in the hour before delivery was $R = -0.29$ , $P < 0.01$ .  When maternal blood glucose stayed within the target of 4.0 – 8.0 mM there was no relationship with neonatal blood glucose.  When maternal blood glucose was greater than 8.0 mM, neonatal blood glucose was less than 2.5 mM, in all	Provides evidence to suggest that there is no correlation with neonatal blood glucose and maternal HbA <sub>1c</sub> throughout pregnancy, first second or third trimesters.  There was evidence to suggest that if a women's blood glucose during labour was over 9 mM then neonatal	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
						cases except two women.  If the maternal blood glucose was above 9.0 mM neonatal blood glucose was always less than 2.5 mM.	blood glucose would always be less than 2.5 mM.	
Curet LB;Izquierdo LA;Gilson GJ;Schneider JM;Perelman R;Converse J;  1997 Mar  344	Study Type: Other Observational  Evidence Level: 2++	Intervention: Maternal plasma glucose levels  Comparison:	233	77 (33%) T1 diabetes, 156 (67%) T2 diabetes. All received intensive insulin treatment aimed at maintaining the 2-hour postprandial plasma glucose level <150 mg/dl (8.3 mmol/l) and the intrapartum plasma glucose level <100 mg/dl (5.6 mmol/l).	Neonatal hypoglycaemia. Neonatal blood glucose was measured with a reflectance meter within 1/2 hour of delivery, every 30 minutes thereafter during the first 3 hours after delivery, and every 1 to 4 hours for the next 48 hours. A reading by the glucose oxidase method was obtained whenever the meter result was $\leq 40$ mg/dl or signs of hypoglycaemia were observed. Hypoglycaemia was defined as a plasma glucose concentration <30 mg/dl (1.7 mmol/l) as determined by the glucose oxidase method occurring during the first 24 hours of life. Neonates received external feedings or continuous glucose infusion as dictated by the clinical condition.	The incidence of neonatal hypoglycaemia was 16.5% (38 neonates). The degree of hypoglycaemia was mild and rarely necessitated admission of the infant to the special care nursery or treatment with IV glucose.  Neonatal normoglycaemic group: Maternal intrapartum plasma glucose concentrations $84 \pm 32$ mg/dl ( $4.7 \pm 1.8$ mmol/l)  Neonatal hypoglycaemic group: Maternal intrapartum plasma glucose concentrations $107 \pm 53$ mg/dl ( $5.9 \pm 2.9$ mmol/l). $P < 0.05$  Percentage of infants with neonatal hypoglycaemia according to maternal plasma glucose concentration: 1. Mean intrapartum concentration <100 mg/dl (5.6 mmol/l): Mean prenatal 2 hour postprandial concentration <150 mg/dl 10% Mean prenatal 2 hour postprandial concentration > 50 mg/dl 16%  2. Mean intrapartum concentration $\geq 100$ mg/dl: Mean prenatal 2 hour postprandial concentration <150 mg/dl 43% ( $P < 0.05$ ) Mean prenatal 2 hour postprandial concentration > 50 mg/dl 71% ( $P < 0.05$ )	Our data demonstrate that the lowest incidence of neonatal hypoglycaemia is observed when both the prenatal 2-hour postprandial and intrapartum maternal plasma glucose concentrations are kept <150 mg/dl (8.3 mmol/l) and <100 mg/dl (5.6 mmol/l) respectively. It appears however that intrapartum control is more important.  Tight regulation of the plasma glucose level during labour will significantly reduce the incidence of neonatal hypoglycaemia.	
Andersen O;Hertel J;Schmolker L;Kuhl C;  1985 Mar  342	Study Type: Other  Evidence Level: 2+	Intervention: Maternal plasma glucose concentrations  Comparison:	53 infants of mothers with T1 diabetes	The study was retrospective, inclusion criteria were that the plasma glucose concentration of an IDM was recorded at birth and 2 hr and that no calories	Neonatal plasma glucose concentrations Neonatal hypoglycaemia (plasma glucose $\leq 1.7$ mmol/l) Infants with glucose values <1.7 mmol/l were treated with IV	The maternal blood glucose at delivery correlated positively with the blood glucose of the infant at birth ( $-0.82$ , $P < 0.001$ ). A negative correlation was found between maternal plasma glucose concentration at delivery and the	The risk of neonatal hypoglycaemia in IDMs is closely related to the maternal plasma glucose concentrations at	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
				had been supplied to the infant. During delivery isotonic glucose was infused IV at rates of 60–90 ml per hr, increased to max. 180 ml if maternal hypoglycaemia observed.	glucose.	<p>plasma glucose concentration of the infant at 2 hours of age (<math>-0.46</math>, <math>P &lt; 0.001</math>).</p> <p>11/30 infants developed hypoglycaemia when maternal blood glucose at delivery was <math>\geq 7.1</math> mmol/l) whereas neonatal hypoglycaemia was not observed when maternal plasma blood glucose at delivery was <math>&lt;7.1</math> mmol/l.</p> <p>Maternal blood glucose at delivery was higher in caesarean section than vaginal birth (<math>P &lt; 0.05</math>).</p>	<p>delivery. In this series neonatal hypoglycaemia was not found if the maternal plasma glucose concentration at delivery was below 7.1 mmol/l</p> <p>Maternal plasma glucose should therefore be closely monitored before and during delivery especially in mothers who are subject to caesarean section.</p>	
Feldberg D;Dicker D;Samuel N;Peleg D;Karp M;Goldman JA; 1988 346	Study Type: OtherNon randomised intervention study  Evidence Level: 2++	Intervention: CSIIIP  Comparison: IV continuous insulin infusion during labour	28 women treated with CSIIIP throughout gestation and labour 37 women treated with conventional intensified insulin therapy during pregnancy and intravenous continuous insulin infusion during labour.	Type 1 diabetes	Maternal blood glucose Maternal HbA <sub>1c</sub> Neonatal blood glucose Hypoglycaemia (capillary blood glucose below 30 mg/dl (1.7 mmol/l)).	CSIIIP: In the first 8 hours of labour group mean blood glucose level was $4.77 \pm 0.61$ mmol/l (range 3.77 - 5.77 mmol/l). Acute fetal distress 14.3% 1 min Apgar score $8.4 \pm 0.7$ Caesarean section rate 25% Neonatal hypoglycaemia 0  Continuous IV insulin infusion: Group mean $7.16 \pm 1.11$ mmol/l (range 5.55 - 8.27 mmol/l) ( $P < 0.025$ ). Acute fetal distress 27% ( $p < 0.001$ ) 1 min Apgar score $7.4 \pm 0.6$ ( $P < 0.001$ ) Caesarean section rate 38% ( $P < 0.05$ ) Neonatal hypoglycaemia 8 ( $P < 0.05$ )  A paediatrician evaluated the baby immediately afterbirth. Blood glucose concentration was measured and heel stick capillary blood measurements were performed every 30–60 minutes during the first 4 hr of life, and less frequently thereafter with glucose- oxidase reagent strips. If hypoglycaemia occurred IV glucose was administered.	We feel that the establishment of firm metabolic control prepartum, and particularly at the crucial time of delivery, contributed to improved management of labour as well as to improved neonatal outcomes.  Our results indicate that when the two glucose techniques are compared, CSIIIP is superior in achieving and maintaining intrapartum optimal metabolic control, reducing the incidence of acute fetal distress, thus lowering the caesarean section rate and neonatal hypoglycaemia.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
							Consequently we concur with the recommendation that firm prepartum and intrapartum diabetic control is mandatory for successful management of labour in the diabetic patient.	
Lean ME;Pearson DW;Sutherland HW; 1990 Feb 345	Study Type: OtherObservational study  Evidence Level: 2++	Intervention: A standardized IV regimen for insulin and dextrose therapy in labour and delivery  Comparison:	25 women with insulin-treated diabetes		Blood glucose (mean $\pm$ SD)	<p>Blood glucose was <math>5.0 \pm 1.7</math> (2.9–9.0) at presentation in the labour suite and was maintained at <math>6.0 \pm 1.8</math> mmol/l for a mean 6.0 (1–29) h until delivery at which time blood glucose was <math>6.3 \pm 2.1</math> (3.0–9.0).</p> <p>Only one mild maternal hypoglycaemic episode was recorded.</p> <p>Infants who had blood glucose below 2.2 mmol/l on routine testing went on to have plasma glucose measured, and those with plasma glucose <math>&lt;2.0</math> mmol/l (<math>n = 11</math>, mean <math>1.5 \pm 0.3</math> (1.0–1.8) mmol/l) were all treated routinely with IV glucose for 3–24 h, although none was symptomatically hypoglycaemic. In this group maternal HbA<sub>1c</sub> was <math>4.7 \pm 0.7</math> (3.7–5.4) % and maternal blood glucose at delivery <math>7.6 \pm 1.7</math> (4.5–10) mmol/l compared with HbA<sub>1c</sub> <math>4.1 \pm 0.6</math> (2.9 - 5.2) % and maternal blood glucose at delivery <math>5.9-2.2</math> (3.0–9.3) mmol/l in mothers of infants who were not hypoglycaemic.</p> <p>There was an inverse correlation between neonatal blood glucose and both maternal HbA<sub>1c</sub> (<math>-0.47</math>, <math>n = 26</math>, <math>P &lt; 0.02</math>) and maternal blood glucose at delivery (<math>-0.58</math>, <math>n = 24</math>, <math>P &lt; 0.01</math>).</p>	<p>The present data provide fairly strong evidence relating maternal HbA<sub>1c</sub> and blood glucose at delivery, both inversely, to neonatal hypoglycaemia. It also appears that close blood glucose control in diabetic women reduces this problem, a marked decrease in the incidence of neonatal hypoglycaemia has been reported in this unit, from 68–39% of infants born to diabetic mothers (<math>P &lt; 0.01</math>) since the introduction of the present regimen.</p>	
Miodovnik M;Mimouni F;Tsang RC; 1987	Study Type: OtherObservational  Evidence Level: 2++	Intervention: Maternal capillary blood glucose  Comparison:	122 pregnancies in 100 women with type 1 diabetes	Well controlled type 1 diabetes. IV glucose and/or insulin was infused during labour to maintain capillary glucose	Neonatal hypoglycaemia Plasma glucose was determined at 0.5, 1,2and 4 hr afterdelivery. IV glucose was used when	<p>There was a significant correlation between the lowest infant plasma glucose concentration in the first 4 hours of life and the highest maternal capillary glucose concentration within 4</p>	<p>Although maternal blood glucose was maintained in a relatively normal range, the rate of</p>	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
343				concentration between 70 and 100 mg/dl (3.9 and 5.6 mmol/l).	plasma glucose fell below 30 mg/dl (1.7 mmol/l).	<p>hr before delivery. Mothers who had maximum blood glucose concentration &gt;90 mg/dl (5 mmol/l) during the last 4 hours before delivery had infants with hypoglycaemia rate of 47% (36/76) compared to mothers with blood glucose &lt;90 mg/dl, whose infants had 14% (6/42) rate of hypoglycaemia (<math>P = 0.003</math>).</p> <p>Total incidence of hypoglycaemia 44 (36%).</p>	<p>neonatal hypoglycaemia was still significant. We suggest that neonatal hypoglycaemia might not be totally prevented by strict glycaemic control during labour; presumably due to pre-existent fetal hyperinsulinism.</p> <p>Maintenance of normoglycaemia during labour and delivery may be important in reducing neonatal hypoglycaemia.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Rosenberg VA;Eglington GS;Rauch ER;Skupski DW; 2006 Oct 351	Study Type: RCT Evidence level: 1+	36 women	Women with gestational diabetes and in labour were recruited for this study. Country: USA	Intervention: Insulin drip Comparison: Rotating fluids	Follow-up period: Outcome Measures: The primary outcome measure was mean maternal capillary blood glucose (mg/dL).	Fifteen women were randomised to the rotating fluids protocol and 21 women to an insulin drip. There was no difference in mean intrapartum maternal capillary blood glucose levels in the rotating fluids and insulin drip group ( $103.9 \pm 8.7$ mg/Dl and $103.2 \pm 17.9$ mg/Dl,,respectively, $P = 0.89$ ). Neonatal outcomes were also similar between the 2 treatment groups.	In women with insulin-requiring gestational diabetes, intrapartum glycaemic control may be comparable with a standard adjusted insulin drip or a rotation of intravenous fluids between glucose and non-glucose containing fluids.	

# 7 Neonatal care

## 7.1 Initial assessment and criteria for admission to intensive or special care

### Q.28 What are the criteria for admission to intensive/special care?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Modanlou,HD.; Dorchester,WP.  1987  322	Study Type: Cross-sectional  Evidence level: 3	10,369 deliveries between 1984–1985	Women who delivered during 1984–1985 in Miller Children's Hospital in California.  Country: USA	Intervention: No intervention, assessment of risk factors.  Comparison:	Follow-up period: No follow-up (cross-sectional study).  Outcome Measures: Delivery via: 1. Vaginal vertex 2. Breech vagina 3. Repeat caesarean section 4. Primary caesarean section	The study shows that diabetes is one of the diseases associated with increased caesarean section, resuscitation with positive pressure ventilation and low 1 and 5 minute Apgar score.  Diabetes, hypertension, premature labour, prolonged rupture of membrane and postdate were more common in women who underwent primary caesarean sections than in vaginal vertex births ( $P < 0.001$ ).  Very low Apgar score ( $\leq 3$ ) at 1 and 5 minutes was significantly more frequent in primary and repeat caesarean sections than in vaginal vertex births ( $P < 0.01$ ).  Resuscitation with positive pressure ventilation was more frequent in primary and repeat caesarean sections than in vaginal vertex births ( $P = 0.001$ ).	Given that diabetes is associated with many of the poor pregnancy outcomes, there is a need for a well trained neonatal team to be present for operative deliveries.	
Dalgic N;Ergenekon E;Soysal S;Koc E;Atalay Y;Gucuyener	Study Type: Cohort  Evidence level: 2+	Exposure arm 94  Comparison arm - 0	Infants admitted to neonatal intensive care for	Intervention: Neuro-developmental outcome	Follow-up period: 2 years	Premature - 51.1% maternal diabetes or gestational diabetes - 34.1%	Routine screening for hypoglycaemia should be carried out on admission of high	This was not a true cohort study as there was no comparison group. The statistical analyses

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
K; 2002 Mar 361			hypoglycaemia  Country: Turkey	Comparison: none	Outcome Measures: risk factors of neonatal hypoglycaemia and their frequencies  Long-term neurodevelopmental outcome of promptly treated neonatal hypoglycaemia	SGA - 12.8% no known risk factor - 26.6%  48 infants underwent psychometric evaluation:  2 showed motor deficit at 6 months 1 showed language deficit at 24 months	risk infants to intensive care.  Clinicians need to be taught which populations are high risk, but neonatal hypoglycaemia may occur in low-risk populations as well  Early action can prevent long-term complications	were very basic and the sample size was too small to make the results generalisable.
Teramo K;Kari MA;Eronen M;Markkanen H;Hiilesmaa V; 2004 Oct 360	Study Type: Case-control  Evidence level: 2+	Cases - 157 women with type 1 diabetes delivered by caesarean section (CS) before the onset of labour had an amniotic fluid sample taken  Controls - 19 healthy, non-smoking women delivered by elective CS	Women with type 1 diabetes with at least one childbirth  Country: Finland	Intervention: amniotic fluid erythropoietin (EPO) levels  Comparison: Amniotic fluid EPO levels	Follow-up period:  Outcome Measures: umbilical artery pH and pO2 fetal macrosomia neonatal hypoglycaemia cardiomyopathy hyperbilirubinaemia admission to neonatal intensive care	Newborn infants in high EPO group were significantly more macrosomic ( $P = 0.0005$ ) and acidotic ( $P < 0.0001$ ), had significantly lower pO2 levels ( $P < 0.0001$ ) than newborns in the medium and low group.  Neonatal hypoglycaemia ( $P < 0.0001$ ), admission to neonatal intensive care ( $P = 0.03$ ) and hyperbilirubinaemia ( $P = 0.002$ ) occurred significantly more often in the high EPO group  EPO was independently related to low pH ( $P < 0.0001$ ) and neonatal hypoglycaemia ( $P = 0.002$ ) after adjustment.	Further studies are needed to evaluate the clinical usefulness of antenatal amniotic fluid EPO measurements in pregnancies complicated by diabetes	The authors needed to be clearer about the outcomes being measured
Halliday,H.L. 1981 363	Study Type: Other  Evidence Level: 3	Intervention: To determine the association between poorly controlled maternal diabetes and cardiomyopathy  Comparison: Comparisons between LGA infants and AGA infants	12  Group 1 - 10 LGA infants  Group 2 - 2 AGA infants	Newborn infants with respiratory distress and cardiomegaly  Country: United States Ireland	Hypertrophic cardiomyopathy	Incidence of hypertrophic cardiomyopathy in LGA group 100%. (cardiomyopathy only persisted for 2 weeks)  Incidence of hypertrophic cardiomyopathy in AGA group 0%	The authors are unsure whether the presence of hypertrophic cardiomyopathy could explain the respiratory difficulty observed in the infants. They felt that structural congenital heart disease could not explain the myocardial hypertrophy observed	This study is small, poorly designed and the association shown cannot be supported statistically
Watson D;Rowan J;Neale L;Battin MR; 2003 Dec	Study Type: Other  Evidence Level: 2+	Intervention: Admissions to NICU  Comparison: none	Records of 136 infants	Infants admitted to neonatal intensive care unit whose mothers had gestational diabetes or	Mode of delivery gestational age prematurity birthweight	Most common indications for admission to NICU:  hypoglycaemia - 51%	Pre-term delivery is an important contributing factor to high neonatal morbidity in women with type 3 diabetes and	The number of records used for the study are small, but the results are consistent with other evidence

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
364				type 2 diabetes Country: New Zealand	hypoglycaemia respiratory distress congenital anomaly days in NICU	respiratory distress - 40% pre-term delivery 46%  Difference in rates of respiratory distress in pre-term infants (39%) and term infants (43%) was not significant $P = 0.34$  Birthweights among infants of women with type 2 diabetes were significantly higher ( $P < 0.05$ ) than for the IGT group and significantly more common than in the IGT or normal group ( $P < 0.05$ )	gestational diabetes	
Cordero,L.; Treuer,S.H.; Landon,M.B.; Gabbe,S.G.  / /1998  362	Study Type: Other  Evidence Level: 2+	Intervention: Factors affecting admission of infants to NICU  Comparison:	530 infants born to 332 women with gestational diabetes and 177 women with type 1 diabetes	Infants born to mothers with gestational diabetes or type 1 diabetes  Country: United States	NICU admissions respiratory distress syndrome (RDS) congenital malformations intrauterine fetal growth hypoglycaemia other morbidities	247 infants admitted to NICU. Of these:  31% had gestational age <33 weeks  9% had congenital malformations  4% had miscellaneous conditions  42% had a gestational age >34 weeks and respiratory distress syndrome  1% had hypoglycaemia as the only diagnosis  Of 244 infants admitted to 'well baby' nurseries:  27 presented with RDS as the main reason for transfer to the NICU  43 presented with hypoglycaemia as the main reason for transfer to NICU	The use of guidelines must be flexible enough to allow the best care assignments for infants of mothers with gestational diabetes, while preventing delays in the recognition of neo- natal morbidities	

**Q.30** What initial assessment should babies undergo?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Aucott SW;Williams TG;Hertz RH;Kalhan SC;  1994  355	Study Type: Cohort  Evidence level: 2++	78 pregnant women with type 1 diabetes.	Pregnant women with type 1 diabetes attending the Cleveland Metropolitan General Hospital between 1984 and 1987. Women with multiple pregnancies or gestational diabetes were excluded.  Country: USA	Intervention: Women with diabetes receiving intensive antenatal care with either (1) infusion pump or (2) split-dose insulin therapy  Comparison: Women without diabetes and receiving normal antenatal care.	Follow-up period: Not reported.  Outcome Measures: 1. Mean HbA <sub>1c</sub> 2. Premature delivery 3. Pre-eclampsia 4. Caesarean section 5. Macrosomia 6. Hyperbilirubinemia 7. Respiratory distress 8. Hypoglycaemia 9. Apgar score 10. Mortality 11. Congenital malformations	Mean HbA <sub>1c</sub> in the first half of pregnancy was 8.49% ± 2.30%, and 7.34% ± 1.79% in the second half.  Women with type 1 diabetes had higher rates of premature delivery (31% vs 10%, <i>P</i> = 0.003), pre-eclampsia (15% vs 5%, <i>P</i> = 0.035), and caesarean section (55% vs 27%, <i>P</i> = 0.002).  Infants of women with diabetes had higher frequency of large for gestational age (24% vs 10%)  Complications including large size for gestational age (41% vs 16%, <i>P</i> = 0.0002), hypoglycemia (14% vs 1%, <i>P</i> = 0.0025), hyperbilirubinemia (46% vs 23%, <i>P</i> = 0.0002), and respiratory distress (12% vs. 1%, <i>P</i> = 0.008) were common in infants of mothers with diabetes  Apgar scores and mortality rates were similar in the intervention and control two groups.  Congenital malformations occurred in 6 (7.7%) of infants of mothers with diabetes and 1 (1.3%) of the mothers in the control group ( <i>P</i> = 0.05). All the mothers who had infants with congenital malformations presented after 8 weeks' gestation, past the period of organ formation.	Although the improved medical management of type 1 diabetes decreased neonatal mortality this did not translate into significant reduction in perinatal complications.	
Haworth JC, Dilling LA,	Study Type: Cohort	1. Group 1 (12	42 infants born to	Intervention:	Follow-up period:	One baby in Group 1 and	The hypothesis that	Information on study design and

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Vidyasagar D. 1973 356	Evidence level: 2+	infants) 2. Group 2A (7 infants) 3. Group 2B (4 infants)	women with diabetes, 30 developed who hypoglycaemia were suitable for this study. However, 23 were selected for treatment and follow-up.  Country: Canada	Group 2A received long-acting epinephrine given every 6 hours for 24 hours, then every 8 hours from 24 -48 hours, every 12 hours from 48- 72 hours and one dose on the fourth day.  The intervention group also received intravenous glucose.  Comparison: 1. Group 1 received only intravenous glucose.  2. Group 2B received long-acting epinephrine only.	72 hours post delivery.  Outcome Measures: 1. Mortality rate 2. Respiratory distress syndrome	another in group 2A developed mild respiratory distress.  Five of the 12 infants in Group 1, four of the 7 in Group 2A and 2 out of 4 in Group 2B had one or more recurrent episodes of hypoglycaemia, but the differences were not significant.  Epinephrine-treated infants had significantly higher lactate levels at 12, 24, 48 and 72 hours after delivery.  When lactate levels were analysed excluding the three infants with possible hypoxic respiratory distress, the results did not change.  Two epinephrine-treated infants developed metabolic acidosis, but neither had evidence of significant pulmonary distress.	epinephrine reduces the rate of mortality in infants born to women with diabetes could neither be confirmed nor rejected.	reporting is inadequate to allow a comprehensive quality assessment.
Van Howe RS, Storms MR 2006 357	Study Type: Case-control  Evidence level: 2+	66 infants born to mothers with long standing diabetes.	Infants of mothers with pre-existing diabetes or gestational diabetes at 36-42 weeks' gestation.  Country: USA	Intervention: No intervention, the study was to assess risk factors.  Comparison: Infants of the same birth cohort born to women without diabetes.	Follow-up period: Not reported.  Outcome Measures: Risk factors for neonatal hypoglycaemia	When compared to singletons of $\geq 36$ weeks' gestation in the same birth cohort, infants of mothers with diabetes were more likely to be born via caesarean section (43.94% versus 20.13%, OR 3.11, 95% CI 1.89 to 5.12).  Only 26 (39.39%) were breastfed exclusively.  Hundred blood glucose determinations in the first 90 minutes of life had a mean of 3.01 mmol/L (54.24 mg/dl, 95% CI 0.99 to 5.04 mmol/L [17.74 to 90.74 mg/dL] with a median value of 2.94 mmol/L (53 mg/dL).  313 blood glucose determinations from 91 minutes	The first 90 minutes of life is the period of greatest risk to the infant born to a woman with diabetes. The risk is determined mainly by maternal age and weight of the infant at delivery.	The analysis was detailed and well conducted.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>to 12.5 hours of age had a mean value of 3.29 mmol/L (59.20 mg/dL, 95% CI 1.70 to 4.87 mmol/L [30.68 to 78.72 mg/dL] and a median value of 3.17 mmol/L (57 mg/dL).</p> <p>107 blood glucose determinations after 12.5 hours of age had a mean value of 3.49 mmol/L (62.79 mg/Dl, 95% CI 1.97 to 5.01 mmol/L [35.50 to 90.09 mg/dL) with a median value of 3.33 mmol/L (60 mg/dL).</p> <p>Of the 66 infants born to mothers with diabetes, 39 had blood glucose determinations &lt; 2.2 mmol/L (40 mg/dL); 19 had blood glucose determinations &lt; 1.9 mmol/L (35 mg/dL), 9 had blood glucose determinations of &lt; 1.7 mmol/L (30 mg/dL), and 2 had &lt; 1.4 mmol/L (25 mg/dL).</p> <p>None of the low blood glucose determinations was associated with symptoms consistent with hypoglycaemia.</p> <p>19 (28.8%) of the patients received interventions with oral feeding for low glucose level, none required intravenous fluids.</p> <p>Analysis with marginal mixed models with repeated measurements indicated age at which blood glucose was measured as highly significant (<math>t= 3.97</math>; <math>P &lt; 0.0001</math>), with the value increasing by 0.021 mmol/L (0.37 mg/dL) for each hour of age.</p> <p>In the Poisson regression,</p>		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						episodes of blood glucose determinations < 1.7 mmol/L (30 mg/dL) were more likely to occur with decreasing maternal age (adjusted relative risk [RR, 0.87, 95% CI, 0.79 to 0.94]) and more likely to occur with large weight infants.  None of the other maternal or obstetric factors were statistically significant.		
Alam M; Raza SJ; Sherali AR; Akhtar AS;  2006  358	Study Type: Cross-sectional  Evidence level: 2-	40 infants of mothers with diabetes	Singleton infants born to mothers with diabetes at the Federal Government Services Hospital, Islamabad and National Institute of Child Health, Karachi, from August 1999 to January 2000.  Country: Pakistan.	Intervention: Infants born to mothers with diabetes were immediately admitted to the neonatal intensive care unit after delivery.  Comparison: No comparison	Follow-up period: Cross-sectional study, no follow-up.  Outcome Measures: 1. Mode of delivery 2. Birth injuries 3. Birth asphyxia 4. Congenital abnormalities 5. Weight of infant at delivery 6. Hypoglycaemia 7. Hypocalcemia 8. Hyperbilirubinemia 9. Respiratory distress syndrome	22 (55%) of women had a caesarean section.  7 (17.5%) of mothers who gave birth to large babies vaginally experienced birth injuries.  15% of the infants born to mothers with diabetes experienced birth asphyxia.  Congenital anomalies were found in 10 (25%) of infants.  18 (45%) of infants were macrosomic and 2 (5%) were small for gestational age.  Hypoglycaemia was observed in 35% and hypocalcemia in 15% of the infants.  12 (30%) had hyperbilirubinemia.  Mortality rate was 7.5%.	Mothers with diabetes should be offered regular antenatal follow-up to maintain good glycaemic control during pregnancy.  All deliveries of mothers with diabetes should be attended by experienced pediatricians to minimise complications.  Caesarean section may be allowed especially with clinical evidence of macrosomia to avoid birth injury and asphyxia.	
Akera C;Ro S;  2003  354	Study Type: Other  Evidence Level: 3	Intervention:  Comparison:		Neonates  Country: Various	Outcome measures of interest are hyperbilirubinaemia and hypoglycaemia		A clinician's awareness of the prenatal history of the mother can provide early detection and intervention of many conditions leading to good prognosis	This paper was not specific to infants of women with gestational diabetes
Jones CW;  2001 Sep  359	Study Type: Other  Evidence Level: 3	Intervention: For this non-systematic review, the following have been included:		The review population is neonates  Country: various	The review considers the following:  macrosomia respiratory distress	Incidences are reported for:  macrosomia: 20- 30% respiratory distress syndrome: 25-38%	The author considers the following as key:  early recognition of symptoms in the mother and appropriate	The review is non-systematic and therefore the information must be considered carefully

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
		textbook chapters case reports scientific studies diagnostic studies prospective studies  Comparison:			syndrome cardiomyopathy hypoglycaemia hypocalcaemia and hypomagnesaemia polycythaemia and hyperviscosity	hypoglycaemia - 25% hypocalcaemia - 50% polycythaemia - >65%	treatment for improved outcomes in the infant  education of mothers with gestational diabetes for better long term health  early monitoring and intervention in infants may decrease neonatal morbidity related to gestational diabetes	

## 7.2 Prevention and assessment of neonatal hypoglycaemia

### Q.29 How should neonatal hypoglycaemia be prevented and treated?

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Wharton BA;Bower BD; 1965 Nov 13 <sup>370</sup>	Study Type: Intervention study non random. Evidence Level: 2+	Immediate feed (within 3 hours) with undiluted breast milk (if <4lb 6oz) or half cream evaporated milk (if >4lb 6oz) .	239 premature babies:118 immediate feed, 121 later feed.	Inclusion: All babies admitted to the unit weighing <5lb Exclusion: Death within two hours of birth, >than 8 hours old on admission. During second phase ill babies also excluded.	Symptomatic hypoglycaemia (blood sugar level <20 mg per 100 ml (1.1 mmol/l) in a baby with one or more of the following features: Convulsions, cyanotic attacks, irritability, and collapse). Aymptomatic hypoglycaemia (estimated blood sugar<20 mg per 100 ml (1.1 mmol/l)).	Symptomatic hypoglycaemia in 4/121 'later' fed and 0/118 'immediate' fed. Blood sugar estimated in 98 babies: The lowest level was <20 mg per 100 ml in 10/54 'later' fed and 5/44 'immediate' fed. Statistical significance was not reported.	Immediate feeding reduces hypoglycaemia.	The mortality in the immediate group was 17% cf 6% in later group. Difference likely due to relatively large volumes of milk and inhalation of vomit.
Beard AG;Panos TC;Marasigan BV;Eminians J;Kennedy HF;Lamb J; 1966 Mar <sup>369</sup>	Study Type: Intervention study non random. Evidence Level: 2+	Feeding at 6 hours	68 premature infants without complications: 41 fed at 72 hours 27 fed from 6 hours.		Blood glucose measured at 1, 3, 24, 48 and 72 hours of age.	In feeding withheld group 14 had blood glucose <25 mg per 100 ml (1.4 mmol/l) at 48 hours and 24 had values <25 mg per 100 ml (1.4 mmol/l) at 72 hours. Values below 25 mg per 100 ml (1.4 mmol/l) at both 48 and 72 hours were seen in 11 infants. Among early fed infants none had blood glucose measurements <25 mg per 100 ml (1.4 mmol/l).	Early feeding of newborn premature infants decreases hypoglycaemia.	
Lucas A;Boyes S;Bloom SR;ynsley-Green A; 1981 Mar <sup>372</sup>	Study Type: intervention study - non random. Evidence Level: 2+	Breast fed	45 breast fed, 34 formula fed.	6 days old.	Plasma concentrations of insulin, glucagon and gastric inhibitory polypeptide (GIP) blood levels of glucose, ketone bodies, pyruvate, lactate and glycerol measured pre- and post-prandially.	Breast fed infants had higher basal and postprandial blood ketones. $P < 0.001$ (difference in overall mean values of beta-hydroxybutyrate) and $P < 0.05$ (difference in overall mean values of acetacetate).  Formula fed infants had a greater insulin and GIP response to feeding and a significantly greater post feed rise in lactate and pyruvate concentrations.	It is possible that breast feeding enhances ketogenesis. Ketones may be important alternative substrates to glucose for brain metabolism in the neonatal period.	

Bibliographic information	Study level and evidence type	Aim of study	Number of patients and patient characteristics	Population characteristics	Outcome measures	Results	Study summary
Ferris AM;Neubauer SH;Bendel RB;Green KW;Ingardia CJ;Reece EA; 1993 Jul <sup>381</sup>	Study Type:Case control . Evidence level: 2+		33 women with type 1 diabetes 33 women without diabetes matched on gestational age of infant, method of delivery, sex of the infant, and prior lactation experience 11 healthy reference subjects who delivered vaginally	Follow-up period: 2, 3, 7, 14, 42 and 84 days postpartum. Outcome Measures: Percentage of time mother spent with infant from birth to day 2 (% of h possible) Time mother spent with infant (h) Mothers perception of time when milk came in after delivery (h) Time from delivery that infant was first breastfed (h) Number of times infant breastfed in first 12 h after birth Duration of breastfeeding Frequency of breastfeeding Type of feeding Perceived problems with feeding	Percentage of time mother spent with infant from birth to day 2 (% of h possible): Type1D 18.8±2.8, Control 31.9±2.7, Reference 47.6±4.6, $P < 0.05$ . Time mother spent with infant (h) Day 2: Type1D 8.0±0.6, Control 10.7±0.6, Reference 16.6±1.1, $P < 0.05$ . Day3: Type1D 11.1±0.6, Control 15.2±0.6, Reference 23.6±1.1, $P < 0.05$ . Mothers perception of time when milk came in after delivery (h): Type1D 78.2±4.5, Control 72.2±4.2, Reference 54.4±7.1, $P < 0.05$ . Time from delivery that infant was first breast fed (h): Type1D 26.1±2.8, Control 11.4±2.7, Reference 4.6±4.7, $P < 0.05$ . Number of times infant breastfed in first 12 h after birth: Type1D 0.5±0.2, Control 1.0±0.2, Reference 1.4±0.3, $P < 0.05$ . Significantly more women with type1 diabetes than control or reference mothers stopped breastfeeding before 42d postpartum ( $P < 0.01$ ). Infants of mothers with type1D were supplemented with formula significantly more than were infants of control or reference mothers ( $P < 0.01$ ). Women with type1 diabetes breastfed less frequently than either the control or reference women from days 2 to 42 postpartum ( $P < 0.0001$ ). At 7 and 14 d postpartum more women with Type1D perceived that they had infants with feeding problems (44% and 33%) perceived that they had infants with feeding problems than did control (6% and 6%) and reference women (10% and 20%) $P < 0.05$ .	Differences in feeding patterns attributed to: Routine admission of IDM to neonatal units, increased rate of CS in diabetic mothers, increased rate of macrosomic baby in diabetic mothers.	Diabetic mothers cited infant sleepiness as the most common infant-feeding problem. A sleepy infant was not identified as a problem by any of the control mothers and by only one reference mother.

Bibliographic information	Study type and evidence level	Number of patients and patient characteristics	Aim of study	Outcome measures	Results	Study summary	Reviewer comments
Hawdon JM;Ward Platt MP;ynsley-Green A; 1992 Apr <sup>371</sup>	Study Type: Cross sectional Evidence level: 2+	156 term infants, 62 preterm infants	Type of delivery Method of feeding Feeding frequency Feed volume Postnatal age	Follow-up period: 6 days. Outcome Measures: Whole blood concentrations of glucose Gluconogenic precursors (pyruvate, alanine, lactate, glycerol) Ketone bodies Plasma concentrations of NEFA	Term infants ( $n = 156$ , 71 breast fed, 61 formula fed). Breastfed infants had significantly lower blood glucose concentration (mean 3.6 mmol/l, range 1.5–5.3 mmol/l) than formula fed (mean 4 mmol/l, range 2.5–6.2 mmol/l; $P < 0.05$ ). Breast fed infants had significantly higher blood ketone body concentrations (0.76 mmol/l) than formula fed (0.15 mmol/l, $P < 0.05$ ). Breast fed infants had significantly higher total glucogenic substrate concentrations (mean 2.2 mmol/l) than formula fed infants (mean 1.9 mmol/l; $P < 0.01$ ).  Multiple regression analysis with method of feed, between feed interval, volume of feed, and postnatal age as independent variables demonstrated that only between feed interval was significantly correlated with blood glucose concentration ( $B = -0.003$ , $SE = 0.001$ , $\beta = -0.32$ ; $P < 0.05$ ).	The major determinant of blood glucose concentration was the interval between feeds, with lower blood concentrations when feed intervals were prolonged. Breast fed infants, who had the lowest blood glucose concentrations demonstrated effective counter regulation. This is reassuring in the light of current policies which encourage demand feeding of infants and exclusivity of breast feeding when this is the mother's preference.	
Lucas A;Morley R;Cole TJ; 1988 Nov 19 <sup>367</sup>	Study Type: Cohort Evidence level: 2+	661 preterm babies	hypoglycaemia defined as plasma blood glucose concentration $< 2.6$ mmol	Follow-up period: 18 months. Outcome Measures: Bayley motor and mental development scales Hypoglycaemia ( $< 2.6$ mmol/l) Number of days plasma blood glucose concentration $< 2.6$ mmol/l	433/661 had plasma glucose $< 2.6$ mmol/l. Regression analysis: Maximum slope and significance were seen for motor development ( $P < 0.002$ ) and mental development ( $P < 0.005$ ) when a cut off of 2.5 mmol/l was used. Reduced developmental scores were associated independently with the number of days on which plasma glucose concentration was 0–1.5 mmol/l ( $P < 0.01$ ) and the number of days on which it was 1.6 to 2.5 mmol/l ( $P < 0.01$ ) whereas no relation was detected when it was in the range 2.6 to 4.0 mmol/l.	Moderate hypoglycaemia ( $< 2.6$ mmol/l) is associated with adverse neurodevelopmental outcomes.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Plagemann A, Harder T, Franke K, Kohlhoff R.  2002  374	Study Type: Cohort  Evidence level: 2+	112 children of women with diabetes (type 1 diabetes, n = 83 and gestational diabetes, n = 29).	Children born to women with diabetes who were delivered during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf.  They were part of the prospective cohort study on consequences of maternal diabetes during pregnancy for the children's development.  Country: Germany	Intervention: Feeding on diabetic breast milk only.  Comparison: 1. Feeding on some diabetic breast milk.  2. Banked donor breast milk	Follow-up period: 2.5 years  Outcome Measures: 1. Nutritional:  2. Anthropometrical:  3. Glucose levels	There was a positive correlation between the volume of diabetic breast milk 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 ingested was inversely correlated to body weight at follow-up ( $P = 0.001$ ).  Risk of childhood impaired glucose tolerance 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 diabetic breast milk to be the only significant predictor of relative body weight at 2 years of age ( $P = 0.001$ ).	Early neonatal ingestion of breast milk from diabetic mothers may increase risk of becoming overweight and, consequently, developing impaired glucose tolerance during childhood.  Additional studies are needed to assess long-term consequences that might result from the type of neonatal nutrition in children of diabetic mothers.	This is a well designed and executed study taking into account potential confounding factors.  The sample size is reasonable and the likelihood of the role of chance is expected to be significantly small.
Rodekamp E;Harder T;Kohlhoff R;Franke K;Dudenhausen JW;Plagemann A;  2005  375	Study Type: Cohort  Evidence level: 2+	317 children of women with type 1 diabetes.	The participants of this study came from a population of 741 children of women with diabetes during pregnancy (type 1 diabetes and gestational diabetes) who delivered during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf.  They were part of the prospective cohort study on consequences of maternal diabetes during pregnancy for	Intervention: Diabetic breast milk only.  Comparison: 1. Some diabetic breast milk.  2. No diabetic breast milk.	Follow-up period: 2.5 years.  Outcome Measures: 1. Nutritional:  2. Anthropometrical:  3. Glucose levels	Regression analysis showed no significant influence of maternal third trimester glucose on the child's body weight (OR 0.86, 95% CI 0.58 to 1.27) or impaired glucose tolerance (OR 0.97, 95% CI 0.56 to 1.67).  Relative body weight was lowest in children who had not ingested diabetic breast milk during the neonatal period and highest in those fed with diabetic breast milk only.  Exclusive breast-feeding was associated with	Neither late neonatal diabetic breast milk intake nor the duration of breast-feeding has an independent influence on childhood risk of overweight or impaired glucose tolerance in children of women with diabetes. The 1st week of life appears to be the critical window for nutritional programming in children of women with diabetes by ingestion of maternal diabetic breast milk.	The study was generally well designed with detailed background information and statistical analysis and reporting of results.  The only issue not clear is "some diabetic breast milk", the authors did not explain.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			<p>the children's development.</p> <p>A total of 112 infants (83 born to mothers with pre-existing diabetes and 29 with gestational diabetes) were followed-up with complete data on nutrition throughout the neonatal period, i.e., both the early neonatal period (1st neonatal week) and the late neonatal period (2nd–4th neonatal week), as well as data on duration of breast-feeding.</p> <p>Gestational diabetes was diagnosed between the 26th and 28th gestational weeks.</p> <p>Country: Germany</p>			<p>increased childhood relative body weight (<math>P = 0.011</math>).</p> <p>Breast-fed children of women with diabetes had increased risk of overweight (OR 1.98, 95% CI 1.12 to 3.50).</p> <p>Breast-feeding duration was positively associated with childhood relative body weight (<math>P = 0.004</math>) and 120-min blood glucose during an oral glucose tolerance test (<math>P = 0.022</math>).</p> <p>Adjustment for the breast milk volume ingested during the early neonatal period (1st week of life) eliminated all these relationships with late neonatal breast-feeding and its duration.</p> <p>No relationship was observed between maternal blood glucose in the middle of the third trimester and the subsequent outcome.</p>		
Gerstein HC; 1994 Jan  378	Study Type: Systematic review - meta-analysis  Evidence level: 2++	3575 people who had diminished duration of breastfeeding or early exposure to cow's milk.	<p>People who were had diminished duration of breastfeeding or early exposure to cow's milk.</p> <p>Country: Data come from different countries.</p>	<p>Intervention: Short duration of breastfeeding or early cow's milk exposure.</p> <p>Comparison: Long duration of breastfeeding.</p>	<p>Follow-up period: Not reported.</p> <p>Outcome Measures: Development of type 1 diabetes.</p>	<p>Patients with type 1 diabetes were more likely to have been breastfed for &lt; 3 months (overall OR 1.43, 95% CI 1.15 to 1.77) and to have been exposed to cow's milk before 4 months (overall OR 1.63, 95% CI 1.22 to 2.17).</p>	<p>Early cow's milk exposure may be an important determinant of subsequent type 1 diabetes and may increase the risk approximately 1.5 times.</p>	
Norris, J.M.; Scott, F.W. 1996	Study Type: Systematic review - meta-analysis	21039 participants 1. Cases (n=4656)	Children who were either breast fed or introduced to cow's milk constituents.	<p>Intervention: Early breast feeding.</p> <p>Comparison:</p>	<p>Follow-up period:</p> <p>Outcome Measures: 1. Ever breastfed 2.</p>	<p>The summary results showed a moderate effect of exposure to breast milk substitutes (OR 1.38, 95% CI</p>	<p>The results showed that the effect of exposure to breast milk substitutes on type 1 diabetes is small.</p>	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
379	Evidence level: 2++	2. Controls (n = 16383)	Country: Various countries	Early cow's milk exposure.	Never breastfed. 2. Breast feeding duration. 3. Age at first exposure to breast milk substitutes.	1.18 to 1.61])and cow's milk substitutes (OR = 1.61, 95% CI = 1.31 to 1.98) before 3 months of age.		
						The studies using existing records demonstrated little association compared to the studies relying on long-term recall.		
						Studies in which the controls had a participation rate more than 20% lower than the cases showed a stronger diabetogenic effect of never being breastfed (OR = 1.58) than studies whose cases and controls had similar participation rates (OR = 1.06).		
Gagne,M.P.; Leff,E.W.; Jefferis,S.C.  1992  382	Study Type: Case-control  Evidence level: 2+	22 women with type 1 diabetes.	Twenty-two mothers who were identified as having type 1 diabetes before pregnancy and who had given birth in the past 2 years.  Country: USA	Intervention: Infant feeding practices of women with diabetes.  Comparison: Infant feeding practices of women without diabetes.	Follow-up period:  Outcome Measures: 1. Early breast-feeding 2. Early exposure to bottle feeding	Diabetes was not a principal factor in the decision to breastfeed or bottle-feed for the majority of the women.  Participants who considered diabetes in their decision to breastfeed had on average 2 years' more education than those who did not (14.82 years versus 12.94 years).	Diabetes was not a determinant of breast feeding experiences or early exposure to cow's milk.	
Meloni,T.; Marinero,A.M.; Mannazzu,M.C.; Ogana,A.; La,Vecchia C.; Negri,E.; Colombo,C.	Study Type: Case-control  Evidence level: 2+	200  100 children with diabetes and 100 without diabetes who were matched	The study subjects comprised children with type 1 diabetes and controls selected from children admitted at the	Intervention: Risk-factor assessment  Comparison:	Follow-up period:  Outcome Measures: 1. Duration of complete or partial breastfeeding.	A larger proportion of the children with diabetes rather than the control children had been breastfed.  The risk of type 1 diabetes	The data do not support the existence of a protective effect of breast-feeding on the risk of type 1 diabetes, nor do the data indicate that early exposure to cow's milk and	

Bibliographic Information	Study Type & Evidence Level	Number of Patients for age and sex.	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
1997 380			Department of Pediatrics of the University of Sassari in Italy.  Country: Italy			among children who had not been breastfed was < 1 (OR 0.41; 95% CI 0.19 to 0.91).  No clear difference was observed between children with diabetes and those without diabetes in the duration of breastfeeding (medians: 3 and 2 months, respectively).  Although a larger proportion of control children rather than children with diabetes had been given cow's milk-derived formula and solid food before the age of 3 months, there was no time-risk relationship.	dairy products has any influence on the development of type 1 diabetes in a high-risk population.	
2005 377	Study Type: Cohort  Evidence level: 2++	242 children of mothers with diabetes.	Subjects were participants of the Kaulsdorf Cohort Study, a prospective cohort study on short- and long-term consequences of maternal diabetes during pregnancy and lactation for the children's development.  Country: Germany	Intervention: Glucose homeostasis monitoring.  Women maintaining mean 24-hour profiles < 5.5 mmol/l were treated with diet, but when a woman's mean profile was > 5.5 mmol/l, insulin therapy was initiated.  Comparison:	Follow-up period:  Outcome Measures: 1. Mean maternal blood glucose 2. Gestational age 3. Birthweight 4. Neonatal hypoglycaemia 5. Apgar score at 1, 5, and 10 min postpartum	Children of mothers 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 mothers with diabetes had a delayed onset of speaking compared to those with lower milk intake ( $P = 0.002$ ).	Ingesting larger volumes of milk of mothers with diabetes may normalise early psychomotor development in infants of these mothers, but may delay onset of speaking.	
1988 373	Study Type: Cohort  Evidence level: 2-	22 women	Eleven women with type 1 diabetes and 11 age-matched controls without diabetes.  Country: Germany	Intervention: Women with diabetes were treated with intensified conventional insulin therapy according to the standard by Jovanovic and Peterson (1980) by intermediate-acting or multiple injections of short-acting insulin (lente and actrapid).	Follow-up period:  Outcome Measures: 1. HbA1 values 2. Birthweight	Although a near-normoglycaemic control of diabetic mothers was accomplished by intensified insulin treatment, the HbA1 value was significantly higher in comparison to non-diabetic mothers ( $8.1 \pm 0.9\%$ versus $6.2 \pm 0.5\%$ ; $P < 0.01$ ).  The glucose concentration of	The data suggest that breastfeeding infants of mothers with diabetes is not associated with an increased glucose concentration in breastmilk and thus is not of importance as a possible mechanism to sustain a hyperinsulinaemic state in newborns.	Sample size too small to exclude the role of chance.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
				Comparison: Control group without insulin therapy.		breast milk did not differ between mothers with diabetes and mothers without diabetes ( $0.68 \pm 0.50$ versus $0.66 \pm 0.55$ mmol/l).  No correlation was found between glucose concentration of breast milk and relevant blood glucose concentration as well as HbA <sub>1c</sub> of the mother.		
Rodekamp,E.; Harder,T.; Kohlhoff,R.; Dudenhausen,J.W.; Plagemann,A.  2006  376	Study Type: Cohort  Evidence level: 2++	242 children of mothers with diabetes.	Subjects were participants of the Kaulsdorf Cohort Study (KCS), a prospective cohort study on short and long-term consequences of maternal diabetes during pregnancy and lactation on the child's development.  Country: Germany	Intervention: Late neonatal intake of breast milk of mothers with diabetes.  Comparison:	Follow-up period: Up to 12 months.  Outcome Measures: 1. Developmental milestone as measured by Denver Developmental 2. Onset of speaking 3. Onset of walking	Ingestion of breast milk delayed onset of speaking: in children who did not take breast milk of mothers with diabetes, the median onset of speaking was 44 weeks (range 31–72 weeks); in children who took some breast milk of mothers with diabetes the median onset of speaking was 48 weeks (range 24–100 weeks);and in children who had only breast milk of mothers with diabetes, the median onset of speaking was 52 weeks (range 28–84 weeks); $P = 0.037$ .  Ingestion of breast milk of mothers with diabetes halved the probability of the time of speaking at any time point (hazard ratio 0.53, 95% CI 0.31 to 0.91).  Adjustment for volume of breast milk of mothers with diabetes ingested during the early neonatal period weakened the hazard ratio towards non-significance.	Neonatal diabetic breast milk ingestion, particularly during the first week of life, may delay speech development, an important indicator of cognitive development.	
van Beusekom,C.M.; Zeegers,T.A.; Martini,I.A.; Velvis,H.J.;	Study Type: Cohort  Evidence level: 2-	6 women with type 1 diabetes	Six women with tightly controlled type 1 diabetes mellitus (median glycosylated	Intervention: Insulin treatment  Comparison: Women	Follow-up period:  Outcome Measures: Macronutrients:	No abnormalities in concentrations of macronutrients (triglycerides, lactose, and protein),	The data suggest that there are no differences in macronutrient concentration between tightly controlled	Sample size small, and the role of chance cannot be ruled out

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Visser,G.H.; van Doormaal,J.J.; Muskiet,F.A.  1993  383			haemoglobin concentrations at parturition of 5.2% [range 4.9–5.3%], reference range 4.9–6.6%) and five women without diabetes  Country: The Netherlands	without diabetes and not receiving insulin.	1. Triglycerides 2. Lactose 3. Protein 4. Cholesterol 5. Glucose 6. Myoinositol concentrations 7. Fatty acid composition  8. Duration of lactation	cholesterol, glucose, and myoinositol nor in fatty acid composition were found.  The duration of colostrum lactation was the same for women with diabetes and those without diabetes (3–5 days in both groups).  Two of three longitudinally studied women showed rather constant ratios between glucose concentrations in milk and capillary blood.	glycaemic levels of women with diabetes and those without diabetes.	

# 8 Postnatal care

## 8.1 Breastfeeding and effects on glycaemic control

### Q.31 How does breastfeeding affect glycaemic control?

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Saez de Ibarra, I., Gaspar, R., Obesso, A., Herranz, L.  2003  389	Study Type: Cohort  Evidence level: 2+	36 women with type 1 diabetes	Type 1 diabetes, mean age 32 ±3 years, mean duration of diabetes 15±7 years. All women were on multiple dialy injections (3 to 4 per day) with short and intermediate acting insulins. Patients given instructions on maintaining good glycaemic control, including advice to eat before baby feeding times (or to have a glass of juice or milk if this is not possible).  Country: Spain	Intervention: Breastfeeding (Patients were asked to keep a daily record of breastfeeding hours and if juice or milk was taken before breastfeeding).  Comparison: Not breastfeeding	Follow-up period:  Outcome Measures: Glycaemic control in four periods: Preconception period, first seven days postpartum, first month postpartum, second month postpartum. Measured using glucose meters (4 times daily capillary blood glucose self monitoring).  Hypoglycaemic episodes (these were considered to be related to a breastfeeding session when it occurred during breastfeeding or up to 30 minutes after).	28 women breastfed in the first month. 24 women breastfed in the second month.  Mean glucose values were significantly lower during the first week postpartum (6.7±1.1 mmol/l) than at preconception (7.7±0.9 mmol/l) or during the second month postpartum (7.6±1.3 mmol/l). The percentage of glucose reading below 3 mmol/l did not differ during the four periods.  Insulin requirements were significantly lower during the first postpartum week (0.56±0.15U/kg/day) than the preconception period (0.68±0.16U/kg/day) and remained significantly lower over the first (0.56±0.15 U/kg/day) and second (0.56±0.11 U/kg/day) postpartum months.  Breastfeeding mothers had lower mean glucose levels during the first postpartum week (borderline significance, 6.6±0.6 vs 7.0±0.9 mmol/l; P = 0.050). There was no	Insulin requirements after delivery and throughout the first two months postpartum are lower than before pregnancy. Glucose levels are lower during the first week postpartum. These changes apply both to breastfeeding and non-breastfeeding mothers.  Hypoglycaemic episodes do not occur more frequently during or immediately after nursing sessions.	The comparison between breastfeeding and bottlefeeding mothers may be limited by small numbers of bottlefeeding mothers.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
						<p>significant difference between breastfeeding and nonbreastfeeding mothers in mean glucose levels in the first or second months postpartum, in the mean standard deviation of blood glucose readings or in insulin dose.</p> <p>The 13 women who kept records of breastfeeding hours had fewer hypoglycaemic episodes related to breastfeeding sessions (<math>4.0 \pm 3.5</math>) than unrelated to breastfeeding sessions (<math>12.2 \pm 7.1</math>, <math>P = 0.002</math>).</p>		
Ferris, A., Dalidowitz, M., Ingardia, C. et al 1988 390	Study Type: Cohort Evidence level: 2+	30 (16 breastfeeding and 14 bottle feeding)	Type 1 diabetes Country: USA	Intervention: Breastfeeding Comparison: Bottle feeding	Follow-up period: 6 weeks Outcome Measures: Insulin dose Fasting blood glucose levels (mean)	<p>Insulin doses did not differ between the two groups.</p> <p>6-week postpartum mean fasting plasma glucose levels: Mothers who exclusively breastfed (<math>n = 6</math>) <math>4.6 \pm 2.2</math> mmol/L Stopped before 6 weeks (<math>n = 9</math>) <math>8.1 \pm 2.1</math> mmol/l Bottle fed (<math>n = 14</math>) <math>6.7 \pm 1.7</math> mmol/l</p>	Mothers with type 1 diabetes who exclusively breastfed had lower fasting blood glucose levels by 6 weeks postpartum than mothers who stopped breastfeeding or mothers who bottle fed.	Small numbers in subgroups. P values not given.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Davies, A., Clark, J., Dalton, K., Edwards, O. 1989	Study Type: OtherCase series Evidence Level: 3	Intervention: Breastfeeding Comparison: Not breastfeeding	24 insulin dependent women	Country: UK	Insulin requirements	Breastfeeding was established after 18 pregnancies and continued in 16 cases until the visit to the postnatal clinic six weeks later.  Mean (SD) insulin dose Breastfeeding In early pregnancy: 44(15) At end of pregnancy: 96 (36) Postpartum: 33 (13) At 6 week postnatal clinic: 37(13)  Bottlefeeding: In early pregnancy: 46(10) At end of pregnancy: 72(8) Postpartum 41(10) At postnatal clinic 46(12)  The mean reduction in insulin dose in breastfeeding mothers from prepregnancy dose was 11.6 units (95% CI 8.9 to 14.3 units) and 5.2 units (1.1 to 9.3 units) in women who bottlefed.		The study is too small to show a difference in the mean reduction in insulin between breastfeeding and bottlefeeding mothers.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Briggs,G.G.; Ambrose,P.J.; Nageotte,M.P.; Padilla,G.; Wan,S.  2005  392	Study Type: Cohort  Evidence level: 2-	7 women:  5 women with type 2 diabetes  2 controls (women without diabetes)	Five women with type 2 diabetes and two controls (women without diabetes) who were started on metformin on the first day after caesarean section  Country: USA	Intervention: Metformin use after caesarean section  Comparison: Women without diabetes who were also started on metformin after caesarean section	Follow-up period: Not reported  Outcome Measures: Metformin concentration in serum and milk  Blood glucose concentrations in the neonate	The mean peak and trough serum metformin concentrations were 1.06 µg/mL (range 0.68–1.90 µg/mL) and 0.42 µg/mL (range 0.26–0.51 µg/mL), respectively, whereas the mean peak and trough metformin concentrations in breast milk were 0.42 µg/mL (range 0.38–0.46 µg/mL) and 0.39 µg/mL (range 0.31–0.52 µg/mL), respectively.  The mean milk:serum ratio was 0.63 (range 0.36–1.00) and the mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.65% (range 0.43–1.08%).  In 3 infants, the blood glucose concentrations 4 hours after feeding were within the normal limit, ranging from 47–77 mg/dL.	Metformin is excreted into breast milk, but the amounts seem to be clinically insignificant.	
Feig,D.S.; Briggs,G.G.; Kraemer,J.M.; Ambrose,P.J.; Moskovitz,D.N.; Nageotte,M.; Donat,D.J.; Padilla,G.; Wan,S.; Klein,J.; Koren,G.  2005  393	Study Type: Cohort  Evidence level: 2+	8 mothers with type 2 diabetes from Toronto.  13 mothers with type 2 diabetes from Long Beach	The study cohorts included women with type 2 diabetes who had recently delivered at Mount Sinai Hospital in Toronto, Canada or at the Women's Pavilion, Miller Children's Hospital in Long Beach, Canada and who were currently breast-feeding.  In Toronto, the women were put on insulin therapy during pregnancy and continued using	Intervention: Glyburide and glipizide.  Comparison: Standard breast milk or serum concentrations of glyburide (ng/ml) and a fixed concentration of tolbutamide for breast milk and serum).	Follow-up period: Two years.  Outcome Measures: Detection of glyburide and glipizide in breast milk.	Neither glyburide nor glipizide were detected in the breast milk and blood glucose was normal in the three infants (one glyburide and two glipizide) who were wholly breast-fed when the drug concentrations were at steady state.  In the single-dose glyburide study, the mean maximum theoretical infant dose as a percent of the weight-adjusted maternal dose was < 1.5% and < 0.7% for the 5 mg and 10 mg doses, respectively.  The mean maximum	Neither glyburide nor glipizide were detected in breast milk, and hypoglycemia was not observed in the three nursing infants. Both glyburide and glipizide, at the doses tested, appear to be compatible with breast-feeding.	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			<p>insulin after delivery.</p> <p>In Long Beach, the women were treated with insulin during pregnancy and were changed to nonmicronised glyburide (5 mg/day) or immediate-release glipizide (5 mg/day) immediately after delivery by their personal physicians independently of the study.</p>			<p>theoretical infant dose as the percent of weight-adjusted maternal dose was &lt; 28% and &lt; 27% for the glyburide and glipizide subjects, respectively.</p>		
Country: Canada								

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Plagemann A, Harder T, Franke K, Kohlhoff R.  2002  374	Study Type: Cohort  Evidence level: 2+	112 children of women with diabetes (type 1 diabetes, n = 83 and gestational diabetes, n = 29).	Children born to women with diabetes who were delivered during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf.  They were part of the prospective cohort study on consequences of maternal diabetes during pregnancy for the children's development.  Country: Germany	Intervention: Feeding on diabetic breast milk only.  Comparison: 1. Feeding on some diabetic breast milk.  2. Banked donor breast milk	Follow-up period: 2.5 years  Outcome Measures: 1. Nutritional:  2. Anthropometrical:  3. Glucose levels	There was a positive correlation between the volume of diabetic breast milk 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 ingested was inversely correlated to body weight at follow-up ( $P = 0.001$ ).  Risk of childhood impaired glucose tolerance 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 diabetic breast milk to be the only significant predictor of relative body weight at 2 years of age ( $P = 0.001$ ).	Early neonatal ingestion of breast milk from diabetic mothers may increase risk of becoming overweight and, consequently, developing impaired glucose tolerance during childhood.  Additional studies are needed to assess long-term consequences that might result from the type of neonatal nutrition in children of diabetic mothers.	This is a well designed and executed study taking into account potential confounding factors.  The sample size is reasonable and the likelihood of the role of chance is expected to be significantly small.
Rodekamp E;Harder T;Kohlhoff R;Franke K;Dudenhausen JW;Plagemann A;  2005  375	Study Type: Cohort  Evidence level: 2+	317 children of women with type 1 diabetes.	The participants of this study came from a population of 741 children of women with diabetes during pregnancy (type 1 diabetes and gestational diabetes) who delivered during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf.  They were part of the prospective cohort study on consequences of maternal diabetes during pregnancy for the children's	Intervention: Diabetic breast milk only.  Comparison: 1. Some diabetic breast milk.  2. No diabetic breast milk.	Follow-up period: 2.5 years.  Outcome Measures: 1. Nutritional:  2. Anthropometrical:  3. Glucose levels	Regression analysis showed no significant influence of maternal third trimester glucose on the child's body weight (OR 0.86, 95% CI 0.58 to 1.27) or impaired glucose tolerance (OR 0.97, 95% CI 0.56 to 1.67).  Relative body weight was lowest in children who had not ingested diabetic breast milk during the neonatal period and highest in those fed with diabetic breast milk only.  Exclusive breast-feeding was associated with increased childhood relative	Neither late neonatal diabetic breast milk intake nor the duration of breast-feeding has an independent influence on childhood risk of overweight or impaired glucose tolerance in children of women with diabetes. The 1st week of life appears to be the critical window for nutritional programming in children of women with diabetes by ingestion of maternal diabetic breast milk.	The study was generally well designed with detailed background information and statistical analysis and reporting of results.  The only issue not clear is "some diabetic breast milk", the authors did not explain.

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
			<p>development.</p> <p>A total of 112 infants (83 born to mothers with pre-existing diabetes and 29 with gestational diabetes) were followed-up with complete data on nutrition throughout the neonatal period, i.e., both the early neonatal period (1st neonatal week) and the late neonatal period (2nd–4th neonatal week), as well as data on duration of breast-feeding.</p> <p>Gestational diabetes was diagnosed between the 26th and 28th gestational weeks.</p> <p>Country: Germany</p>			<p>body weight (<math>P = 0.011</math>).</p> <p>Breast-fed children of women with diabetes had increased risk of overweight (OR 1.98, 95% CI 1.12 to 3.50).</p> <p>Breast-feeding duration was positively associated with childhood relative body weight (<math>P = 0.004</math>) and 120-min blood glucose during an oral glucose tolerance test (<math>P = 0.022</math>).</p> <p>Adjustment for the breast milk volume ingested during the early neonatal period (1st week of life) eliminated all these relationships with late neonatal breast-feeding and its duration.</p> <p>No relationship was observed between maternal blood glucose in the middle of the third trimester and the subsequent outcome.</p>		

## 8.2 Information and follow-up after birth

**Q.32** What information and follow-up should be offered to women with gestational diabetes after birth?

**Q.33** What information and follow up should be offered to women with type 1 and type 2 diabetes after birth?

These two clinical questions were addressed together.

### Comparative studies

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Kim C;Newton KM;Knopp RH;  2002 Oct  394	Study Type: Systematic review - meta-analysis  Evidence level: 2+	28 studies included	Inclusion criteria: GDM and incidence of type 2 diabetes  Country: Various	Epidemiological risk factors for developing type 2 diabetes after having GDM	Follow-up period: Various  Outcome Measures:		The included studies report rates of type 2 conversion 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. The results of fasting glucose levels from oral glucose tolerance test administered during pregnancy were predictive of developing type 2 diabetes after pregnancy. There was no clear pattern for risks factors such as BMI, maternal age, previous history of GDM, family history of diabetes, or parity. The review highlighted that included studies varied in ethnicity, length of follow-up, and criteria for gestational diabetes and type 2 diabetes, which made comparison and generalisation of results difficult.	
Tuomilehto et al  2001  405	Study Type: RCT  Evidence level: 1+	522 randomised. 265 to intervention group and 257 to control group.	Country: Finland	Intervention = detailed education and targets for lifestyle change; one-to-one support sessions  control = general information on diet	Follow-up period: Up to 6 years  Outcome Measures: Diabetes status; weight change; plasma glucose		Diabetes status: Intervention group = 32 per 1000 person years Control group = 78 per 1000 person years	

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
					change; serum insulin change; serum lipids change; blood pressure change			
Diabetes prevention program research group 2002 404	Study Type: RCT Evidence level: 1+	3234 randomised. 1082 = placebo, 1073 = metformin, 1079 = lifestyle	Entry criteria: Men and women; aged = 25 years; BMI $\geq$ 24; plasma glucose concentration of 5.3 to 6.9 mmol/l in fasting state; and 7.8 to 11.0 mmol/l after 2 hour 75 g OGTT  Baseline characteristics (n = 3234): Female = 67.7% Family history of diabetes = 69.4% Age = 50.6 History of GDM = 16.1% of women BMI = 34.0  Country: USA	Placebo and standard lifestyle recommendations;  metformin and standard lifestyle recommendations;  Intensive lifestyle intervention (24 week programme, including one-to-one counselling)	Follow-up period: Up to 4 years  Outcome Measures: Incidence of diabetes; change in weight; change in physical activity	Incidence of diabetes(per100 person years) Placebo = 11.0 Metformin = 7.8 Lifestyle = 4.8  all statistically different ( $P < 0.05$ )		
Gillies CL, Abrahams KR et al. 2007 407	Study Type: Systematic review - meta-analysis Evidence level: 1+	21 RCTs met the inclusion criteria out of which 17 trials with 8084 people with impaired glucose tolerance gave enough results for analysis	Randomized controlled trials  Country:	Intervention: Interventions to delay or prevent type 2 diabetes in individuals with impaired glucose tolerance.  Comparison:	Follow-up period:  Outcome Measures: Development of type 2 diabetes and related adverse events	Meta-analyses showed: Pooled hazard ratios 0.51, 95% CI 0.44 to 0.60 for lifestyle interventions vs standard advice, 0.70, 95% CI 0.62 to 0.79 for oral diabetes drugs vs control, 0.44, 95% CI 0.28 to 0.69 for orlistat vs control, and 0.32, 95% CI 0.03 to 3.07 for the herbal remedy jiangtang bushen recipe vs standard diabetes advice. These correspond to numbers needed to treat for benefit (NNT) and harm (NNH) of 6.4 for lifestyle (95% credible interval, NNT 5.0 to 8.4), 10.8 for oral diabetes drugs (NNT 8.1 to NNT 15.0), 5.4 for orlistat (NNT 4.1 to NNT 7.6), and 4.0 for jiangtang bushen (NNH 16.9 to NNT 24.8).	In people with impaired glucose tolerance lifestyle and pharmacological interventions reduce the rate of progression to type 2 diabetes. Lifestyle interventions seem to be at least as effective as drug treatment.	No separate analyses for women and men were reported in this study

## Diagnostic studies

Bibliographic Information	Study type & Evidence level	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Study Summary	Reviewer comment
Holt RI;Goddard JR;Clarke P;Coleman MA; 2003 Jul <sup>408</sup>	Study type: Diagnostic Evidence level: III	152	Women with WHO defined GDM  Country: UK	Fasting plasma glucose test versus 75 g OGTT for identifying diabetes		Using a cut-off for fasting plasma glucose of 6.0 mmol/l, the specificity was 100% and specificity was 94% for identifying those who have diabetes compared to OGTT.	
Tan YY;Yeo SH;Liauw PC; 1996 Aug <sup>409</sup>	Study type: Diagnostic Evidence level: III	298	Women with WHO defined GDM  Country: Singapore	Test: 75 g OGTT testing antenatal versus 75 g OGTT testing postnatal to detect postnatal diabetes		The results showed that at a cut-off of 4.5 mmol/l the sensitivity was 73.9% and specificity was 70.3%.  For a 2-hour OGTT the cut-off was 10.5 mmol/l with a sensitivity of 55.1% and a specificity of 84.7.	

Non-comparative studies

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Aberg AE;Jonsson EK;Eskilsson I;Landin-Olsson M;Frid AH;  2002 Jan  400	Study Type: Other Epidemiological comparative cohorts  Evidence Level: 2+	Examine following risk factors: BMI, weight increase, estimated foetal weight and birth weight, 2 hour OGTT value and HbA <sub>1c</sub> at diagnosis, use of insulin during pregnancy	468, 315 cases, 153 controls	Women with or without European Association for the Study of Diabetes criteria for classification  Country: Sweden	Incidence of diabetes	At 1 year follow up 50 of 229 (22%) cases and 1 of 60 (1.6%) controls had developed type 2 diabetes ( $P < 0.001$ ). Further results were that 24 of 90 insulin users against 23 of 132 (17%) non-insulin users had 2 hour OGTT value of 7.8 to 11.0 ml and 18 of 90 (20%) and 3 of 132 (2%) had >11.0 mmo/l, respectively. The study found 2 hour OGTT value and HbA <sub>1c</sub> st diagnosis were associated with diabetes at 1 year, but BMI, weight increase, estimated foetal weight and birth weight were not associated with developing diabetes. Multiple regression analysis found on OGTT test during pregnancy was predictive.		
Jarvela IY;Juutinen J;Koskela P;Hartikainen AL;Kulmala P;Knip M;Tapanainen JS;  2006 Mar  401	Study Type: Other Epidemiological comparative cohorts  Evidence Level: 2+	Examine following risk factors: age, use of insulin treatment, positive ICA, positive GAD Antibodies and being positive for more than one antibody	435 with and 435 without GDM	Women with Finnish Diabetes Association classification for GDM  Country: Finland	Incidence of developing diabetes	The study found that 43 of 435 in the case group had developed diabetes (either type 1 or type 2) whereas none of the control group had developed diabetes. Women treated with insulin during pregnancy were more likely ( $P < 0.0001$ ) than those not. The women in the control group were significantly younger (27.2 versus 34.0, $P < 0.001$ ). Regression analysis showed that age, use of insulin treatment, positive ICA, positive GADA and being positive for more than one antibody were all predictive of developing diabetes.		
Lauenborg J;Hansen T;Jensen DM;Vestergaard H;Molsted-Pedersen L;Hornnes P;Locht H;Pedersen O;Damm P;  2004 May  395	Study Type: Other Epidemiological cohorts  Evidence Level: 2-	Examine following risk factors: BMI, ethnic origin, pre-existing diabetes	481. 330 in new cohort (1987 to 1996). 151 in old cohort (1978 to 1985)	Women with WHO defined GDM.  Country: Denmark	Incidence of diabetes	The study found that overall 192 (40.0%) diabetes (type 1 or type 2) and 130 (27.0%) had impaired glucose tolerance/impaired fasting glucose. Comparing the cohorts, 40.9% in the new cohort had diabetes (type 1 or type 2) compared to 18.3% in the old cohort. Multiple regression analysis showed that membership of the new cohort, being overweight pre-pregnancy (BMI => 25 kg/m <sup>2</sup> ) and IGT postpartum		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Lee CP;Wong HS;Chan FY;Pun TC;To WK;Lam YH;Baldwin S;Wong VCW;  1994  398	Study Type: Other Epidemiological  Evidence Level: 3	Examine following risk factors: Age, BMI, family history of diabetes, baby greater 4 kg	193	Women with WHO defined GDM  Country: Hong Kong	Incidence of diabetes	were identified as statistical significant risk factors in developing diabetes ( $P < 0.05$ ).  The study found that 56 of 193 (29.0%) women with GDM had impaired glucose tolerance ( $n = 38$ ) or diabetes ( $n = 18$ ) by 6 years follow-up compared to 8 (5 and 3, respectively) of 58 (13.8%) in women without GDM. The study found that age, BMI, abnormal OGTT at 6 weeks postpartum, diabetes in first degree relative, macrosomia, recurrent GDM and use of oral contraceptives were not predictive of later developing diabetes.		
Lobner K;Knopff A;Baumgarten A;Mollenhauer U;Marienfeld S;Garrido-Franco M;Bonifacio E;Ziegler A;  2006  396	Study Type: Other Epidemiological  Evidence Level: 3	Examine following risk factors: first-degree relative with diabetes, age, duration of pregnancy, birth weight of child and number of previous pregnancies, insulin during pregnancy, BMI >30 and serum CRP at 9 months in 2 to 4th quartiles	302	Women with ADA defined GDM  Country: Germany	Association between risk factors and incidence of diabetes;	The study found that insulin during pregnancy, BMI >30 and serum CRP at 9 months in 2 to 4th quartiles were statistically significant predictors of developing diabetes. The study found that first-degree relative with diabetes, age, duration of pregnancy, birth weight of child and number of previous pregnancies was not predictive of subsequent diabetes. The study recommended that prospective diabetes assessment and intervention should be considered in women with GDM who are autoantibody positive, require insulin treatment during pregnancy or who are obese.		
Pettitt DJ;Narayan KM;Hanson RL;Knowler WC;  1996 Nov  402	Study Type: Other Comparative cohort  Evidence Level: 2-	Examine following risk factors: Pregnant or not	317	Women with impaired glucose tolerance test results  Country: USA	Incidence of diabetes	The study found that 114 of 244 (46%) of non-pregnant women and 17 of 73 (23%) pregnant women 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.		
Wein P;Beischer NA;Sheedy MT;  1997 Nov  397	Study Type: Other Epidemiological  Evidence Level: 3	Examine following risk factors: BMI, antenatal GTT results, insulin during pregnancy, severity of GD and ethnic origin, age, macrosomic infants and booking status (private or not)	2957	Women with WHO defined GDM  Country: New Zealand	Incidence of diabetes	The study found that BMI, antenatal GTT results, insulin during pregnancy, severity of GD and ethnic origin were all predictive of women developing diabetes. However, age, macrosomic infants and booking status (private or not) were not predictive of future diabetes. Multivariate analysis found		

## Diabetes in pregnancy: evidence tables

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Study Summary	Reviewer Comment
Linne et al  399	Study Type: Other Epidemiological case-control study  Evidence Level: 2-	Examine following risk factors: weight, BMI, fasting blood sugar and HBA <sub>1c</sub>	70. 28 women with GDM and 52 controls	Women with and without GDM  Country: Sweden	Incidence of diabetes	that severity of GD, Asian origin, 1-hour plasma glucose were predictive of developing diabetes, but tat insulin during pregnancy, BMI and foetal macrosomia were not. The study found that 10 of 28 (35%) women with GDM had developed type 2 diabetes but none of 52 controls had developed diabetes ( $P < 0.001$ ). The study found that weight, BMI, fasting blood sugar and HBA <sub>1c</sub> ( $P < 0.05$ ) were all significant predictors of women with GDM developing diabetes compared to women with GDM that did not develop diabetes.		

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Study Summary	Reviewer Comments
Smith BJ;Cheung NW;Bauman AE;Zehle K;McLean M;  2005  406	Study Type: Cross-sectional  Evidence level: 3	226	Inclusion criteria: Women who had attended diabetes clinics for the treatment of GDM, had given birth 6–24 months earlier and were able to speak English Exclusion criteria: Women who had given birth within 6 months  Country: Australia	Intervention: Survey by telephone  Comparison:	Follow-up period:  Outcome Measures: Physical activity behaviours, self-efficacy, social support, and barriers to participation.	Mean age of women was 33.4 years. 26.5% were classified as sedentary, and only 33.6% reported sufficient physical activity as recommended by health authorities. Walking was the most popular physical activity, and most women reported no other moderate- or vigorous-intensity activity. Most common barriers to physical activity were lack of assistance with child care (49.1%) and insufficient time (37.6%). The type of social support most often reported was verbal encouragement (39.1%). Self-efficacy for physical activity was lowest when women were under time pressure or tired. Sufficient physical activity was associated with high social support (OR 2.5, 95% CI 1.21–3.79) and high self-efficacy (OR 2.09, CI 1.06–3.20)	There was low prevalence of physical activity and it was strongly related to social support and self-efficacy	

# References

---

1. Office for National Statistics. *Key Population and Vital Statistics 2005. Local and Health Authority Areas*. No. Series VS, No 32. Basingstoke: Palgrave Macmillan; 2007.
2. CEMACH. *Confidential Enquiry into Maternal and Child Health: Pregnancy in Women with Type 1 and Type 2 Diabetes in 2002–03, England, Wales and Northern Ireland*. London: CEMACH; 2005.
3. King H. Epidemiology of glucose intolerance and gestational diabetes in women of childbearing age. *Diabetes Care* 1998;21(Suppl 2): B9–13.
4. Casson IF. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *British Medical Journal* 1997;315:275–8.
5. Hawthorne G. Prospective population based survey of outcome of pregnancy in diabetic women: results of the Northern Diabetic Pregnancy Audit, 1994. *British Medical Journal* 1997;315:279–81.
6. NHS Executive. *Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS*. London: HMSO; 1996.
7. National Institute for Clinical Excellence. *Type 1 Diabetes: Diagnosis and Management of Type 1 Diabetes in Children, Young People and Adults*. London: NICE; 2004.
8. National Institute for Health and Clinical Excellence. *Type 2 Diabetes: the Management of Type 2 Diabetes (Update)*. London: NICE [publication expected April 2008].
9. National Collaborating Centre for Women's and Children's Health. *Antenatal Care: Routine Care for the Health Pregnant Woman (2008 Update)*. 2nd ed. London: RCOG Press; 2008.
10. National Collaborating Centre for Women's and Children's Health. *Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth*. London: RCOG Press; 2007.
11. National Collaborating Centre for Primary Care. *Postnatal Care: Routine Postnatal Care of Women and Their Babies*. London: NICE; 2006.
12. Royal College of Obstetricians and Gynaecologists. *Induction of Labour*. London: RCOG Press; 1998.
13. National Collaborating Centre for Women's and Children's Health. *Caesarean Section*. London: RCOG Press; 2004.
14. National Institute for Clinical Excellence. *Guidance on the Use of Continuous Subcutaneous Insulin Infusion for Diabetes*. London: NICE; 2003.
15. National Institute for Clinical Excellence. *Guidance on The Use of Glitazones for the Treatment of Type 2 Diabetes*. London: NICE; 2003.
16. National Institute for Clinical Excellence. *Guidance on the Use of Long-Acting Insulin Analogues for the Treatment of Diabetes – Insulin Glargine*. London: NICE; 2002.
17. National Institute for Clinical Excellence. *Guidance on the Use of Patient-Education Models for Diabetes*. London: NICE; 2003.
18. National Institute for Health and Clinical Excellence. *Improving the Nutrition of Pregnant and Breastfeeding Mothers and Children in Low- Income Households*. NICE public health guidance 11. London: NICE; 2008.
19. Department of Health. *National Service Framework for Diabetes: Standards*. London: Department of Health; 2002.
20. National Institute for Clinical Excellence. *Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers*. London: NICE; 2005.
21. National Institute for Health and Clinical Excellence. *The Guidelines Manual 2006*. London: NICE; 2006.
22. National Institute for Health and Clinical Excellence. *The Guidelines Manual 2007*. London: NICE; 2007.
23. Oxman AD, Sackett DL and Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1993;270(17):2093–5.
24. Guyatt GH, Sackett DL and Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1993;270(21):2598–601.
25. Guyatt GH, Sackett DL and Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994;271(1):59–63.
26. Jaeschke R, Guyatt G and Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994;271(5):389–91.
27. Jaeschke R, Guyatt GH and Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA: the journal of the American Medical Association* 1994;271(9):703–7.
28. Sackett DL, Straus SE, Richardson WS, et al. *Evidence-based medicine. How to practice and teach EBM*. 2nd ed. Edinburgh: Churchill Livingstone; 2000.
29. Scottish Intercollegiate Guidelines Network. *A guideline developers' handbook*. No. 50. Edinburgh: SIGN; 2001.
30. World Health Organization and Department of Noncommunicable Disease Surveillance. *Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus*. Geneva: World Health Organization; 1999.
31. CEMACH. *Confidential enquiry into maternal and child health: Maternity services in 2002 for women with type 1 and type 2 diabetes*. London: RCOG Press on behalf of CEMACH; 2004.
32. Confidential Enquiry into Maternal and Child Health. *Diabetes in pregnancy: are we providing the best care? Findings of a national enquiry: England, Wales and Northern Ireland*. London: CEMACH; 2007.
33. Drummond MF, Sculpher M, Torrance GW, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.

35. Suhonen L, Hiilesmaa V and Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type 1 diabetes mellitus. *Diabetologia* 2000;43(1):79–82.
36. Kitzmiller JL, Gavin LA, Gin GD, et al. Preconception care of diabetes. Glycemic control prevents congenital anomalies. *JAMA: the journal of the American Medical Association* 1991;265(6):731–6.
37. Dornhorst A and Frost G. Nutritional management in diabetic pregnancy: a time for reason not dogma. In: Hod M, Jovanovic L, Di Renzo GC, de Leiva A, Langer O, eds. *Diabetes and Pregnancy*. London: Taylor & Francis Group; 2003. p. 340–58.
38. Brand-Miller J, Hayne S, Petocz P, et al. Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care* 2003;26(8):2261–7.
39. Kaplan JS, Iqbal S, England BG, et al. Is pregnancy in diabetic women associated with folate deficiency? *Diabetes Care* 1999;22(7):1017–21.
40. Gillmer MD, Maresh M, Beard RW, et al. Low energy diets in the treatment of gestational diabetes. *Acta Endocrinologica, Supplementum* 1986;277:44–9.
41. Ray JG, Vermeulen MJ, Shapiro JL, et al. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: The DEPOSIT study. *QJM: monthly journal of the Association of Physicians* 2001;94(7):347–56.
42. Moore LL, Singer MR, Bradlee ML, et al. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology* 2000;11(6):689–94.
43. Kieffer EC, Tabaei BP, Carman WJ, et al. The influence of maternal weight and glucose tolerance on infant birthweight in Latino mother-infant pairs. *American Journal of Public Health* 2006;96(12):2201–8.
44. Stotland NE, Cheng YW, Hopkins LM, et al. Gestational weight gain and adverse neonatal outcome among term infants. *Obstetrics and Gynecology* 2006;108(3 Pt 1):635–43.
45. Ricart W, Lopez J, Mozas J, et al. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. *Diabetologia* 2005;48(9):1736–42.
46. Moore H, Summerbell C, Hooper L, et al. Dietary advice for the prevention of type 2 diabetes mellitus in adults. (Cochrane Review). In: *Cochrane Database of Systematic Reviews*. Chichester: Wiley Interscience; 2005.
47. Ceysens G, Rouiller D and Boulvain M. Exercise for diabetic pregnant women. (Cochrane Review). In: *Cochrane Database of Systematic Reviews*. Chichester: Wiley Interscience; 2006.
48. Expert Advisory Group. *Folic acid and the prevention of neural tube defects*. Department of Health; Scottish Office, Home and Health Department; Welsh Office; Department of Health and Social Services, Northern Ireland; 1992.
49. The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. *American Journal of Obstetrics and Gynecology* 1996;174(4):1343–53.
50. Goldman JA, Dicker D, Feldberg D, et al. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *American Journal of Obstetrics and Gynecology* 1986;155(2):293–7.
51. Steel JM, Johnstone FD, Hepburn DA, et al. Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *British Medical Journal* 1990;301(6760):1070–4.
52. Fuhrmann K, Reiher H, Semmler K, et al. The effect of intensified conventional insulin therapy before and during pregnancy on the malformation rate in offspring of diabetic mothers. *Experimental and Clinical Endocrinology* 1984;83(2):173–7.
53. Fuhrmann K. Treatment of pregnant insulin-dependent diabetic women. *Acta Endocrinologica Supplementum* 1986;277:74–6.
54. Diabetes and Pregnancy Group F. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. *Diabetes Care* 2003;26(11):2990–3.
55. Greene MF, Hare JW, Cloherty JP, et al. First-trimester hemoglobin A<sub>1c</sub> and risk for major malformation and spontaneous abortion in diabetic pregnancy. *Teratology* 1989;39(3):225–31.
56. Ylinen K, Aula P, Stenman UH, et al. Risk of minor and major fetal malformations in diabetics with high haemoglobin A<sub>1c</sub> values in early pregnancy. *British Medical Journal* 1984;289(6441):345–6.
57. Miller E, Hare JW, Cloherty JP, et al. Elevated maternal hemoglobin A<sub>1c</sub> in early pregnancy and major congenital anomalies in infants of diabetic mothers. *New England Journal of Medicine* 1981;304(22):1331–4.
58. Lucas MJ, Leveno KJ, Williams ML, et al. Early pregnancy glycosylated hemoglobin, severity of diabetes, and fetal malformations. *American Journal of Obstetrics and Gynecology* 1989;161(2):426–31.
59. Key TC, Giuffrida R and Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. [Erratum appears in *Am J Obstet Gynecol* 1987;157(6):1460]. *American Journal of Obstetrics and Gynecology* 1987;156(5):1096–100.
60. Rosenn B, Miodovnik M, Combs CA, et al. Glycemic thresholds for spontaneous abortion and congenital malformations in insulin-dependent diabetes mellitus. *Obstetrics and Gynecology* 1994;84(4):515–20.
61. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *New England Journal of Medicine* 1988;319(25):1617–23.
62. Rosenn B, Miodovnik M, Combs CA, et al. Pre-conception management of insulin-dependent diabetes: improvement of pregnancy outcome. *Obstetrics and Gynecology* 1991;77(6):846–9.
63. Dicker D, Feldberg D, Samuel N, et al. Spontaneous abortion in patients with insulin-dependent diabetes mellitus: the effect of preconceptional diabetic control. *American Journal of Obstetrics and Gynecology* 1988;158(5):1161–4.
64. Miodovnik M, Mimouni F, Tsang RC, et al. Glycemic control and spontaneous abortion in insulin-dependent diabetic women. *Obstetrics and Gynecology* 1986;68(3):366–9.
65. Miodovnik M, Skillman C, Holroyde JC, et al. Elevated maternal glycohemoglobin in early pregnancy and spontaneous abortion among insulin-dependent diabetic women. *American Journal of Obstetrics and Gynecology* 1985;153(4):439–42.
66. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care* 2004;27(12):2819–23.
67. Gold AE, Reilly R, Little J, et al. The effect of glycemic control in the pre-conception period and early pregnancy on birth weight in women with IDDM. *Diabetes Care* 1998;21(4):535–8.
68. Rosenn BM, Miodovnik M, Holcberg G, et al. Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstetrics and Gynecology* 1995;85(3):417–22.
69. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *British Medical Journal* 2002;325:746–8.
70. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1993;329(14):977–86.

71. Gutzin SJ, Kozler E, Magee LA, et al. The safety of oral hypoglycemic agents in the first trimester of pregnancy: A meta-analysis. *Canadian Journal of Clinical Pharmacology* 2003;10(4):179–83.
72. Hawthorne G. Metformin use and diabetic pregnancy – has its time come? *Diabetic Medicine* 2006;23(3):223–7.
73. Gilbert C, Valois M and Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertility and Sterility* 2006;86(3):658–63.
74. Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *New England Journal of Medicine* 2000;343(16):1134–8.
75. Elder AT. Contraindications to use of metformin. Age and creatinine clearance need to be taken into consideration. *British Medical Journal* 2003;326(7392):762.
76. Ekpebegh CO, Coetzee EJ, van der ML, et al. A 10-year retrospective analysis of pregnancy outcome in pregestational Type 2 diabetes: comparison of insulin and oral glucose-lowering agents. *Diabetic Medicine* 2007;24(3):253–8.
77. Briggs GG, Freeman RK and Yaffe SJ. *Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk*. 7th ed. Philadelphia: Lippincott, Williams and Wilkins; 2005.
78. Joint Formulary Committee. *British National Formulary*. 53rd ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2007.
79. Mathiesen E, Kinsley B, McCance D, et al. Maternal hyperglycemia and glycemic control in pregnancy: a randomized trial comparing insulin aspart with human insulin in 322 subjects with type 1 diabetes. *Diabetes* 2006;55(Suppl 1):A40.
80. Jovanovic L, Howard C, Pettitt D, et al. Insulin aspart vs. regular human insulin in basal/bolus therapy for patients with gestational diabetes mellitus: safety and efficacy. *Diabetologia* 2005;48(Suppl 1):A317.
81. Kinsley BT, Al-Agha R, Murray S, et al. A comparison of soluble human insulin vs rapid acting insulin analogue in type 1 diabetes mellitus in pregnancy. *Diabetes* 2005;54(Suppl 1):A461 (Abstract).
82. Balaji V and Seshiah V. Insulin aspart – safe during pregnancy. *Diabetes* 2005;54(Suppl 1):A787 (Abstract).
83. Boskovic R, Feig DS, Derewlany L, et al. Transfer of insulin lispro across the human placenta: In vitro perfusion studies. *Diabetes Care* 2003;26(5):1390–4.
84. Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Archives of Internal Medicine* 2005;165(12):1337–44.
85. Mecacci F, Carignani L, Cioni R, et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2003;111(1):19–24.
86. Persson B, Swahn ML, Hjertberg R, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Research and Clinical Practice* 2002;58(2):115–21.
87. Simmons D. The utility and efficacy of the new insulins in the management of diabetes and pregnancy. *Current Diabetes Reports* 2002;2(4):331–6.
88. Kitzmiller JL and Jovanovic L. Insulin therapy in pregnancy. In: Hod M, Jovanovic L, Di Renzo GC, de Leiva A, Langer O, eds. *Textbook of Diabetes and Pregnancy*. London: Martin Dunitz; 2003. p. 359–78.
89. Garg SK, Frias JP, Anil S, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocrine Practice* 2003;9(3):187–93.
90. Masson EA, Patmore JE, Brash PD, et al. Pregnancy outcome in Type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabetic Medicine* 2003;20(1):46–50.
91. Wyatt JW, Frias JL, Hoyme HE, et al. Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabetic Medicine* 2005;22(6):803–7.
92. Cypriak K, Sobczak M, Pertynska-Marczewska M, et al. Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Medical Science Monitor* 2004;10(2):PI29–32.
93. Gallen IW and Jaap AJ. Insulin glargine use in pregnancy is not associated with adverse maternal or fetal outcomes. *Diabetes* 2006;55(Suppl 1):A417–1804-P (Abstract).
94. Poyhonen-Alho M, Saltevo J, Ronnema T, et al. Insulin glargine during pregnancy. *Diabetes* 2006;55(Suppl 1):A417 (Abstract).
95. Price N, Bartlett C and Gillmer MD. Use of insulin glargine during pregnancy: A case-control pilot study. *BJOG: an international journal of obstetrics and gynaecology* 2007;114(4):453–7.
96. Di CG, Volpe L, Lencioni C, et al. Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 2005;28(4):982–3.
97. Woolderink JM, van Loon AJ, Storms F, et al. Use of insulin glargine during pregnancy in seven type 1 diabetic women. *Diabetes Care* 2005;28(10):2594–5.
98. Graves DE, White JC and Kirk JK. The use of insulin glargine with gestational diabetes mellitus. *Diabetes Care* 2006;29(2):471–2.
99. Al-Shaikh AA. Pregnant women with type 1 diabetes mellitus treated by glargine insulin. *Saudi Medical Journal* 2006;27(4):563–5.
100. Holstein A, Plaschke A and Egberts EH. Use of insulin glargine during embryogenesis in a pregnant woman with Type 1 diabetes. *Diabetic Medicine* 2003;20(9):779–80.
101. Caronna S, Cioni F, Dall'Aglio E, et al. Pregnancy and the long-acting insulin analogue: A case study. *Acta Bio-Medica de l Ateneo Parmense* 2006;77(1):24–6, 62.
102. Conway DL and Longer O. Selecting antihypertensive therapy in the pregnant woman with diabetes mellitus. *Journal of Maternal-Fetal Medicine* 2000;9(1):66–9.
103. Hod M, van Dijk DJ, Karp M, et al. Diabetic nephropathy and pregnancy: the effect of ACE inhibitors prior to pregnancy on fetomaternal outcome. *Nephrology Dialysis Transplantation* 1995;10(12):2328–33.
104. Bar J, Chen R, Schoenfeld A, et al. Pregnancy outcome in patients with insulin dependent diabetes mellitus and diabetic nephropathy treated with ACE inhibitors before pregnancy. *Journal of Pediatric Endocrinology* 1999;12(5):659–65.
105. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *New England Journal of Medicine* 2006;354(23):2443–51.
106. Lip GY, Churchill D, Beevers M, et al. Angiotensin-converting-enzyme inhibitors in early pregnancy. *Lancet* 1997;350(9089):1446–7.
107. Steffensen FH, Nielsen GL, Sorensen HT, et al. Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet* 1998;351(9102):596.
108. Centers for Disease Control and Prevention (CDC). Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987–1995. *MMWR - Morbidity and Mortality Weekly Report* 1997;46(11):240–2.

109. Bar J, Hod M and Merlob P. Angiotensin converting enzyme inhibitors use in the first trimester of pregnancy. *International Journal of Risk and Safety in Medicine* 1997;10(1):23–6.
110. Magee LA, Schick B, Donnenfeld AE, et al. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. *American Journal of Obstetrics and Gynecology* 1996;174(3):823–8.
111. Belfort MA, Anthony J, Buccimazza A, et al. Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. *Obstetrics and Gynecology* 1990;75(6):970–4.
112. Holing EV, Beyer CS, Brown ZA, et al. Why don't women with diabetes plan their pregnancies? *Diabetes Care* 1998;21(6):889–95.
113. Janz NK, Herman WH, Becker MP, et al. Diabetes and pregnancy. Factors associated with seeking pre-conception care. *Diabetes Care* 1995;18(2):157–65.
114. St James PJ, Younger MD, Hamilton BD, et al. Unplanned pregnancies in young women with diabetes. An analysis of psychosocial factors. *Diabetes Care* 1993;16(12):1572–8.
115. Casele HL and Laifer SA. Factors influencing preconception control of glycemia in diabetic women. *Archives of Internal Medicine* 1998;158(12):1321–4.
116. Harris K and Campbell E. The plans in unplanned pregnancy: Secondary gain and the partnership. *British Journal of Medical Psychology* 1999;72(1):105–20.
117. Barrett G and Wellings K. What is a 'planned' pregnancy? Empirical data from a British study. *Social Science and Medicine* 2002;55(4):545–57.
118. Charron-Prochownik D, Sereika SM, Falsetti D, et al. Knowledge, attitudes and behaviors related to sexuality and family planning in adolescent women with and without diabetes. *Pediatric Diabetes* 2006;7(5):267–73.
119. Charron-Prochownik D, Sereika SM, Wang SL, et al. Reproductive health and preconception counseling awareness in adolescents with diabetes: what they don't know can hurt them. *Diabetes Educator* 2006;32(2):235–42.
120. Feig DS, Cleave B and Tomlinson G. Long-term effects of a diabetes and pregnancy program: does the education last? *Diabetes Care* 2006;29(3):526–30.
121. Ray JG, O'Brien TE and Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: A meta-analysis. *Quarterly Journal of Medicine* 2001;94(8):435–44.
122. Pedersen J. Weight and length at birth of infants of diabetic mothers. *Acta Endocrinologica* 1954;16(4):330–42.
123. Hod M, Rabinerson D and Peled Y. Gestational diabetes mellitus: Is it a clinical entity? *Diabetes Reviews* 1995;3(4):602–13.
124. Scott DA, Loveman E, McIntyre L, et al. Screening for gestational diabetes: a systematic review and economic evaluation. *Health Technology Assessment* 2002;6(11):1–172.
125. Dornhorst A, Paterson CM, Nicholls JSD, et al. High prevalence of gestational diabetes in women from ethnic minority groups. *Diabetic Medicine* 1992;9:820–5.
126. Ostlund I and Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. *Acta Obstetrica et Gynecologica Scandinavica* 2003;82(2):103–8.
127. Rayner M, Petersen S, Buckley C, et al. *Coronary Heart Disease Statistics: Diabetes Supplement*. London: British Heart Foundation; 2001.
128. Moses R, Griffiths R and Davis W. Gestational diabetes: do all women need to be tested? *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1995;35(4):387–9.
129. Davey RX and Hamblin PS. Selective versus universal screening for gestational diabetes mellitus: an evaluation of predictive risk factors. *Medical Journal of Australia* 2001;174(3):118–21.
130. Doherty DA, Magann EF, Francis J, et al. Pre-pregnancy body mass index and pregnancy outcomes. *International Journal of Gynecology and Obstetrics* 2006;95(3):242–7.
131. Keshavarz M, Cheung NW, Babaee GR, et al. Gestational diabetes in Iran: incidence, risk factors and pregnancy outcomes. *Diabetes Research and Clinical Practice* 2005;69(3):279–86.
132. Griffin ME, Coffey M, Johnson H, et al. Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. *Diabetic Medicine* 2000;17(1):26–32.
133. Schytte T, Jorgensen LG, Brandslund I, et al. The clinical impact of screening for gestational diabetes. *Clinical Chemistry and Laboratory Medicine* 2004;42(9):1036–42.
134. Weijers RN, Bekedam DJ, Goldschmidt HM, et al. The clinical usefulness of glucose tolerance testing in gestational diabetes to predict early postpartum diabetes mellitus. *Clinical Chemistry and Laboratory Medicine* 2006;44(1):99–104.
135. Coustan DR, Nelson C, Carpenter MW, et al. Maternal age and screening for gestational diabetes: A population-based study. *Obstetrics and Gynecology* 1989;73(4):557–61.
136. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *JAMA: the journal of the American Medical Association* 1997;278(13):1078–83.
137. Kim C, Berger DK and Chamany S. Recurrence of gestational diabetes mellitus: a systematic review. *Diabetes Care* 2007;30(5):1314–19.
138. Major CA, DeVeciana M, Weeks J, et al. Recurrence of gestational diabetes: who is at risk? *American Journal of Obstetrics and Gynecology* 1998;179(4):1038–42.
139. Spong CY, Guillermo L, Kuboshige J, et al. Recurrence of gestational diabetes mellitus: identification of risk factors. *American Journal of Perinatology* 1998;15(1):29–33.
140. Clarke P, Norman P, Coleman MA, et al. The introduction of a specific request form for the diagnosis of gestational diabetes (GDM) improves understanding of GDM amongst clinicians but does not increase its detection. *Diabetic Medicine* 2005;22(4):507–8.
141. Agarwal MM, Dhatt GS, Punnose J, et al. Gestational diabetes: dilemma caused by multiple international diagnostic criteria. *Diabetic Medicine* 2005;22(12):1731–6.
142. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004;27(Suppl 1):S5–10.
143. Tallarigo L, Giampietro O, Penno G, et al. Relation of glucose tolerance to complications of pregnancy in nondiabetic women. *New England Journal of Medicine* 1986;315(16):989–92.
144. Weiss PAM, Haeusler M, Tamussino K, et al. Can glucose tolerance test predict fetal hyperinsulinism? *BJOG: an international journal of obstetrics and gynaecology* 2000;107(12):1480–5.
145. Sacks DA, Greenspoon JS, bu-Fadil S, et al. Toward universal criteria for gestational diabetes: the 75-gram glucose tolerance test in pregnancy. *American Journal of Obstetrics and Gynecology* 1995;172(2 Pt 1):607–14.
146. Mello G, Parretti E, Cioni R, et al. The 75-gram glucose load in pregnancy: relation between glucose levels and anthropometric characteristics of infants born to women with normal glucose metabolism. *Diabetes Care* 2003;26(4):1206–10.

147. Sermer M, Naylor CD, Farine D, et al. The Toronto Tri-Hospital Gestational Diabetes Project. A preliminary review. *Diabetes Care* 1998;21(Suppl 2):B33–42.
148. Langer O, Brustman L, Anyaegbunam A, et al. The significance of one abnormal glucose tolerance test value on adverse outcome in pregnancy. *American Journal of Obstetrics and Gynecology* 1987;157(3):758–63.
149. Jensen DM, Damm P, Sorensen B, et al. Proposed diagnostic thresholds for gestational diabetes mellitus according to a 75-g oral glucose tolerance test. Maternal and perinatal outcomes in 3260 Danish women. *Diabetic Medicine* 2003;20(1):51–7.
150. Ostlund I, Hanson U, Bjorklund A, et al. Maternal and fetal outcomes if gestational impaired glucose tolerance is not treated. *Diabetes Care* 2003;26(7):2107–11.
151. Saldana TM, Siega-Riz AM, Adair LS, et al. The association between impaired glucose tolerance and birth weight among black and white women in central North Carolina. *Diabetes Care* 2003;26(3):656–61.
152. Cheng YW, Esakoff TF, Block-Kurbisch I, et al. Screening or diagnostic: markedly elevated glucose loading test and perinatal outcomes. *Journal of Maternal-Fetal and Neonatal Medicine* 2006;19(11):729–34.
153. Crowther CA, Hiller JE, Moss JR, et al.; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine* 2005;352(24):2477–86.
154. Dornhorst A and Frost G. The principles of dietary management of gestational diabetes: reflection on current evidence. *Journal of Human Nutrition and Dietetics* 2002;15(2):145–56.
155. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *New England Journal of Medicine* 1995;333(19):1237–41.
156. Fraser RB. The effect of pregnancy on the normal range of the oral glucose tolerance in Africans. *East African Medical Journal* 1981;58(2):90–4.
157. Fraser RB, Ford FA and Lawrence GF. Insulin sensitivity in third trimester pregnancy. A randomized study of dietary effects. *British Journal of Obstetrics and Gynaecology* 1988;95(3):223–9.
158. Clapp JF 3rd. Effect of dietary carbohydrate on the glucose and insulin response to mixed caloric intake and exercise in both nonpregnant and pregnant women. *Diabetes Care* 1998;21(Suppl 2):B107–12.
159. Clapp JF 3rd. Maternal carbohydrate intake and pregnancy outcome. *Proceedings of the Nutrition Society* 2002;61(1):45–50.
160. Gillen L, Tapsell LC, Martin GS, et al. The type and frequency of consumption of carbohydrate-rich foods may play a role in the clinical expression of insulin resistance during pregnancy. *Nutrition and Dietetics: Journal of the Dietitians Association of Australia* 2002;59(2):135–43.
161. Nolan CJ. Improved glucose tolerance in gestational diabetic women on a low fat, high unrefined carbohydrate diet. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1984;24(3):174–7.
162. Ostman EM, Frid AH, Groop LC, et al. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. *European Journal of Clinical Nutrition* 2006;60(3):334–41.
163. Sacks DA, Chen W, Wolde-Tsadik G, et al. When is fasting really fasting? The influence of time of day, interval after a meal, and maternal body mass on maternal glycemia in gestational diabetes. *American Journal of Obstetrics and Gynecology* 1999;181(4):904–11.
164. Dornhorst A, Nicholls JS, Probst F, et al. Calorie restriction for treatment of gestational diabetes. *Diabetes* 1991;40(Suppl 2):161–4.
165. Rae A, Bond D, Evans S, et al. A randomised controlled trial of dietary energy restriction in the management of obese women with gestational diabetes. *The Australian and New Zealand Journal of Obstetrics and Gynaecology* 2000;40(4):416–22.
166. Algert S, Shragg P and Hollingsworth DR. Moderate caloric restriction in obese women with gestational diabetes. *Obstetrics and Gynecology* 1985;65(4):487–91.
167. Peterson CM and Jovanovic-Peterson L. Randomized crossover study of 40% vs. 55% carbohydrate weight loss strategies in women with previous gestational diabetes mellitus and non-diabetic women of 130–200% ideal body weight. *Journal of the American College of Nutrition* 1995;14(4):369–75.
168. Jovanovic-Peterson L, Durak EP and Peterson CM. Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes. *American Journal of Obstetrics and Gynecology* 1989;161(2):415–19.
169. Brankston GN, Mitchell BF, Ryan EA, et al. Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2004;190(1):188–93.
170. Lesser KB, Gruppuso PA, Terry RB, et al. Exercise fails to improve postprandial glycemic excursion in women with gestational diabetes. *Journal of Maternal-Fetal Medicine* 1996;5(4):211–17.
171. Symons DD and Ulbrecht JS. Understanding exercise beliefs and behaviors in women with gestational diabetes mellitus. *Diabetes Care* 2006;29(2):236–40.
172. Persson B, Stangenberg M, Hansson U, et al. Gestational diabetes mellitus (GDM). Comparative evaluation of two treatment regimens, diet versus insulin and diet. *Diabetes* 1985;34(Suppl 2):101–4.
173. Thompson DJ, Porter KB, Gunnells DJ, et al. Prophylactic insulin in the management of gestational diabetes. *Obstetrics and Gynecology* 1990;75(6):960–4.
174. Wechter DJ, Kaufmann RC, Amankwah KS, et al. Prevention of neonatal macrosomia in gestational diabetes by the use of intensive dietary therapy and home glucose monitoring. *American Journal of Perinatology* 1991;8(2):131–4.
175. Botta RM, Di Giovanni BM, Cammilleri F, et al. Predictive factors for insulin treatment in women with diagnosis of gestational diabetes. *Annali Dell'Istituto Superiore di Sanita* 1997;33(3):403–6.
176. Bochner CJ, Medearis AL, Williams J 3rd, et al. Early third-trimester ultrasound screening in gestational diabetes to determine the risk of macrosomia and labor dystocia at term. *American Journal of Obstetrics and Gynecology* 1987;157(3):703–8.
177. Buchanan TA, Kjos SL, Montoro MN, et al. Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care* 1994;17(4):275–83.
178. Kjos SL, Schaefer-Graf U, Sardesi S, et al. A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care* 2001;24(11):1904–10.
179. Schaefer-Graf UM, Kjos SL, Fauzan OH, et al. A randomized trial evaluating a predominantly fetal growth-based strategy to guide management of gestational diabetes in Caucasian women. *Diabetes Care* 2004;27(2):297–302.
180. Bonomo M, Cetin I, Pisoni MP, et al. Flexible treatment of gestational diabetes modulated on ultrasound evaluation of intrauterine growth: a controlled randomized clinical trial. *Diabetes and Metabolism* 2004;30(3):237–44.
181. Rossi G, Somigliana E, Moschetta M, et al. Adequate timing of fetal ultrasound to guide metabolic therapy in mild gestational diabetes mellitus. Results from a randomized study. *Acta Obstetrica et Gynecologica Scandinavica* 2000;79(8):649–54.

182. Bertini AM, Silva JC, Taborda W, et al. Perinatal outcomes and the use of oral hypoglycemic agents. *Journal of Perinatal Medicine* 2005;33(6):519–23.
183. Jacobson GF, Ramos GA, Ching JY, et al. Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. *American Journal of Obstetrics and Gynecology* 2005;193(1):118–24.
184. Conway DL, Gonzales O and Skiver D. Use of glyburide for the treatment of gestational diabetes: the San Antonio experience. *Journal of Maternal-Fetal and Neonatal Medicine* 2004;15(1):51–5.
185. Kremer CJ and Duff P. Glyburide for the treatment of gestational diabetes. *American Journal of Obstetrics and Gynecology* 2004;190(5):1438–9.
186. Yogev Y, Ben-Haroush A, Chen R, et al. Undiagnosed asymptomatic hypoglycemia: diet, insulin, and glyburide for gestational diabetic pregnancy. *Obstetrics and Gynecology* 2004;104(1):88–93.
187. Jovanovic L, Ilic S, Pettitt DJ, et al. Metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care* 1999;22(9):1422–7.
188. Poyhonen-Alho M, Teramo K and Kaaja R. Treatment of gestational diabetes with short- or long-acting insulin and neonatal outcome: a pilot study. *Acta Obstetrica et Gynecologica Scandinavica* 2002;81(3):258–9.
189. Pettitt DJ, Ospina P, Kolaczynski JW, et al. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003;26(1):183–6.
190. Sameshima H, Kamitomo M, Kajiya S, et al. Insulin-meal interval and short-term glucose fluctuation in tightly controlled gestational diabetes mellitus. *The Journal of Maternal-Fetal Medicine* 2001;10(4):241–5.
191. Smits MW, Paulk TH and Kee CC. Assessing the impact of an outpatient education program for patients with gestational diabetes. *Diabetes Educator* 1995;21(2):129–34.
192. Mires GJ, Williams FL and Harper V. Screening practices for gestational diabetes mellitus in UK obstetric units. *Diabetic Medicine* 1999;16(2):138–41.
193. Hod M, Jovanovic L, Di Renzo GC, et al. *Textbook of Diabetes and Pregnancy*. London: Martin Dunitz; 2003.
194. Langer O, Rodriguez DA, Xenakis EM, et al. Intensified versus conventional management of gestational diabetes. *American Journal of Obstetrics and Gynecology* 1994;170(4):1036–46.
195. Landon MB, Gabbe SG, Piana R, et al. Neonatal morbidity in pregnancy complicated by diabetes mellitus: predictive value of maternal glycemic profiles. *American Journal of Obstetrics and Gynecology* 1987;156(5):1089–95.
196. Wyse LJ, Jones M and Mandel F. Relationship of glycosylated hemoglobin, fetal macrosomia, and birthweight macrosomia. *American Journal of Perinatology* 1994;11(4):260–2.
197. Valuk J. Factors influencing birth weight in infants of diabetic mothers. *Diabetes* 1986;35:96A.
198. Jovanovic L, Druzin M and Peterson CM. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *American Journal of Medicine* 1981;71(6):921–7.
199. Evers IM, De Valk HW, Mol BWJ, et al. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* 2002;45(11):1484–9.
200. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development – Diabetes in Early Pregnancy Study. *American Journal of Obstetrics and Gynecology* 1991;164(1 Pt 1):103–11.
201. Combs CA, Gunderson E, Kitzmiller JL, et al. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 1992;15(10):1251–7.
202. Manderson JG, Patterson CC, Hadden DR, et al. Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. *American Journal of Obstetrics and Gynecology* 2003;189(2):507–12.
203. Parretti E, Mecacci F, Papini M, et al. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth. *Diabetes Care* 2001;24(8):1319–23.
204. Karlsson K and Kjellmer I. The outcome of diabetic pregnancies in relation to the mother's blood sugar level. *American Journal of Obstetrics and Gynecology* 1972;112(2):213–20.
205. Miodovnik M. High spontaneous premature labour rate in insulin-dependent diabetic women: An association with poor glycaemic control. *Scientific abstracts of the seventh Annual Meeting of the Society for Perinatal Obstetrics* Lake Buena Vista, Florida, 5–7 February 1987 (Abstract).
206. Rosenn B. Minor congenital malformations in infants of insulin-diabetic women: association with poor glycaemic control. *Obstetrics and Gynecology* 1990;76:745–9.
207. Nielsen GL, Moller M and Sorensen HT. HbA<sub>1c</sub> in early diabetic pregnancy and pregnancy outcomes: A Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes Care* 2006;29(12):2612–16.
208. Fotinos C, Dodson S and French L. Does tight control of blood glucose in pregnant women with diabetes improve neonatal outcomes?. *Journal of Family Practice* 2004;53(10):838–41.
209. Yogev Y, Chen R, Ben-Haroush A, et al. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstetrics and Gynecology* 2003;101(4):633–8.
210. Kerssen A, De Valk HW and Visser GH. Do HbA<sub>1c</sub> levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus? *Diabetologia* 2006;49(1):25–8.
211. Jovanovic L. The role of continuous glucose monitoring in gestational diabetes mellitus. *Diabetes Technology and Therapeutics* 2000;2(Suppl 1):S67–71.
212. di Biase N, Napoli A, Sabbatini A, et al. Telemedicine in the treatment of diabetic pregnancy. *Annali Dell'Istituto Superiore di Sanita* 1997;33(3):347–51.
213. Inkster ME, Fahey TP, Donnan PT, et al. Poor glycated haemoglobin control and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: Systematic review of observational studies. *BMC Pregnancy and Childbirth* 2006;6:30.
214. Diamond MP, Reece EA, Caprio S, et al. Impairment of counterregulatory hormone responses to hypoglycemia in pregnant women with insulin-dependent diabetes mellitus. *American Journal of Obstetrics and Gynecology* 1992;166(1 Pt 1):70–7.
215. Rosenn BM, Miodovnik M, Khoury JC, et al. Counterregulatory hormonal responses to hypoglycemia during pregnancy. *Obstetrics and Gynecology* 1996;87(4):568–74.
216. Zarkovic M, Nesovic M, Marisavljevic D, et al. Short term parenteral nutrition in a pregnant diabetic woman with hyperemesis gravidarum. *Archives of Gastroenterohepatology* 1995;14(1–2):33–5.
217. Brimacombe J. Midazolam and parenteral nutrition in the management of life-threatening hyperemesis gravidarum in a diabetic patient. *Anaesthesia and Intensive Care* 1995;23(2):228–30.
218. Carroll MA and Yeomans ER. Diabetic ketoacidosis in pregnancy. *Critical Care Medicine* 2005;33(10 Suppl):S347–53.

219. Rodgers BD and Rodgers DE. Clinical variables associated with diabetic ketoacidosis during pregnancy. *Journal of Reproductive Medicine* 1991;36(11):797–800.
220. Levetan CS, Passaro MD, Jablonski KA, et al. Effect of physician specialty on outcomes in diabetic ketoacidosis. *Diabetes Care* 1999;22(11):1790–5.
221. National Collaborating Centre for Chronic Conditions. *Type 1 diabetes in adults - national clinical guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians; 2004.
222. Nachum Z, Ben Shlomo I, Weiner E, et al. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *British Medical Journal* 1999;319(7219):1223–7.
223. Gonzalez C, Santoro S, Salzberg S, et al. Insulin analogue therapy in pregnancies complicated by diabetes mellitus. *Expert Opinion on Pharmacotherapy* 2005;6(5):735–42.
224. Farrar D, Tuffnell DJ and West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database of Systematic Reviews* 2007;(3).
225. Coustan DR, Reece EA, Sherwin RS, et al. A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. *JAMA : the journal of the American Medical Association* 1986;255(5):631–6.
226. Laatikainen L, Teramo K and Hieta-Heikurainen H. A controlled study of the influence of continuous subcutaneous insulin infusion treatment on diabetic retinopathy during pregnancy. *Acta Medica Scandinavica* 1987;221(4):367–76.
227. Burkart W, Hanker JP and Schneider HP. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. *Gynecologic and Obstetric Investigation* 1988;26(2):104–12.
228. Lapolla A, Dalfrà MG, Masin M, et al. Analysis of outcome of pregnancy in type 1 diabetics treated with insulin pump or conventional insulin therapy. *Acta Diabetologica* 2003;40(3):143–9.
229. Simmons D, Thompson CF, Conroy C, et al. Use of insulin pumps in pregnancies complicated by type 2 diabetes and gestational diabetes in a multiethnic community. *Diabetes Care* 2001;24(12):2078–82.
230. Gabbe SG, Holing E, Temple P, et al. Benefits, risks, costs, and patient satisfaction associated with insulin pump therapy for the pregnancy complicated by type 1 diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2000;182(6):1283–91.
231. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Archives of Ophthalmology* 1984;102(4):520–6.
232. Diabetes Prevention Program Research Group., Nathan DM, Chew E, et al. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the diabetes prevention program. *Diabetic Medicine* 2007;24(2):137–44.
233. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial the diabetes control and complications trial research group. *Diabetes Care* 2000;23(8):1084–91.
234. Maayah J, Shammass A and Haddadin A. Effect of pregnancy on diabetic retinopathy. *Bahrain Medical Bulletin* 2001;23(4):163–5.
235. Klein BE, Moss SE and Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care* 1990;13(1):34–40.
236. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy: The Diabetes in Early Pregnancy Study. *Diabetes Care* 1995;18(5):631–7.
237. Phelps RL, Sakol P and Metzger BE. Changes in diabetes retinopathy during pregnancy. Correlations with regulation of hyperglycemia. *Archives of Ophthalmology* 1986;104(12):1806–10.
238. Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. *Ophthalmology* 1996;103(11):1815–19.
239. Rosenn B, Miodovnik M, Kraniias G, et al. Progression of diabetic retinopathy in pregnancy: Association with hypertension in pregnancy. *American Journal of Obstetrics and Gynecology* 1992;166(4):1214–18.
240. Dibble CM, Kochenour NK and Worley RJ. Effect of pregnancy on diabetic retinopathy. *Obstetrics and Gynecology* 1982;59(6):699–704.
241. Temple RC, Aldridge VA, Sampson MJ, et al. Impact of pregnancy on the progression of diabetic retinopathy in Type 1 diabetes. *Diabetic Medicine* 2001;18(7):573–7.
242. Lauszus F, Klebe JG and Bek T. Diabetic retinopathy in pregnancy during tight metabolic control. *Acta Obstetrica et Gynecologica Scandinavica* 2000;79(5):367–70.
243. Diabetes Control and Complications Trial (DCCT) Research Group. Early worsening of diabetic retinopathy in the DCCT. *Archives of Ophthalmology* 1998;116:874–86.
244. Kroc Collaborative Study Group. Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. *JAMA: the journal of the American Medical Association* 1988;260(1):37–41.
245. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, et al. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *British Medical Journal* 1985;290(6471):811–15.
246. Lauritzen T, Frost-Larsen K, Larsen HW, et al. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. *Lancet* 1983;1(8318):200–4.
247. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. *Archives of Ophthalmology* 1985;103:1796–806.
248. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987;94(7):761–74.
249. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 1991;98(5 Suppl):766–85.
250. Bailey CC, Sparrow JM, Grey RH, et al. The National Diabetic Retinopathy Laser Treatment Audit. I. Maculopathy. *Eye* 1998;12(Pt 1):69–76.
251. Bailey CC, Sparrow JM, Grey RH, et al. The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical outcomes. *Eye* 1999;13(Pt 2):151–9.
252. The Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the Diabetic Retinopathy Study. *Archives of Ophthalmology* 1979;97(4):654–5.
253. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report Number 8. *Ophthalmology* 1981;88(7):583–600.
254. Chase HP, Garg SK, Jackson WE, et al. Blood pressure and retinopathy in type I diabetes. *Ophthalmology* 1990;97(2):155–9.
255. Joner G, Brinchmann-Hansen O, Torres CG, et al. A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1992;35(11):1049–54.
256. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;105(10):1801–15.

257. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. [Erratum appears in *BMJ* 1999;318(7175):29]. *British Medical Journal* 1998;317(7160):703–13.
258. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44(2):156–63.
259. Estacio RO, Jeffers BW, Gifford N, et al. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23(Suppl 2):B54–64.
260. Matthews DR, Stratton IM, Aldington SJ, et al. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Archives of Ophthalmology* 2004;122(11):1631–40.
261. Mogensen CE, Christensen CK and Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 1983;32(Suppl 2):64–78.
262. Rosenn BM and Miodovnik M. Diabetic vascular complications in pregnancy: nephropathy. In: Hod M, Jovanovic L, Di Renzo GC, de Leiva A, Langer O, eds. *Diabetes and Pregnancy*. London: Taylor & Francis Group; 2003. p. 486–94.
263. Ekblom P, Damm P, Feldt-Rasmussen B, et al. Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care* 2001;24(10):1739–44.
264. Nielsen LR, Muller C, Damm P, et al. Reduced prevalence of early preterm delivery in women with Type 1 diabetes and microalbuminuria – Possible effect of early antihypertensive treatment during pregnancy. *Diabetic Medicine* 2006;23(4):426–31.
265. McLeod L and Ray JG. Prevention and detection of diabetic embryopathy. *Community Genetics* 2002;5(1):33–9.
266. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales and Northern Ireland: population based study. *British Medical Journal* 2006;333(7560):177.
267. EUROCAT Central Registry. *European Registration of Congenital Anomalies: report 8: surveillance of congenital anomalies in Europe 1980–1999*. Newtownabbey: University of Ulster; 2002.
268. Huttly W, Rudnicka A and Wald NJ. Second-trimester prenatal screening markers for Down syndrome in women with insulin-dependent diabetes mellitus. *Prenatal Diagnosis* 2004;24(10):804–7.
269. Spencer K, Cicero S, Atzei A, et al. The influence of maternal insulin-dependent diabetes on fetal nuchal translucency thickness and first-trimester maternal serum biochemical markers of aneuploidy. *Prenatal Diagnosis* 2005;25(10):927–9.
270. Pedersen JF, Sorensen S and Molsted-Pedersen L. Serum levels of human placental lactogen, pregnancy-associated plasma protein A and endometrial secretory protein PP14 in first trimester of diabetic pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 1998;77(2):155–8.
271. Wong SF, Chan FY, Cincotta RB, et al. Routine ultrasound screening in diabetic pregnancies. *Ultrasound in Obstetrics and Gynecology* 2002;19(2):171–6.
272. Greene MF and Benacerraf BR. Prenatal diagnosis in diabetic gravidas: utility of ultrasound and maternal serum alpha-fetoprotein screening. *Obstetrics and Gynecology* 1991;77(4):520–4.
273. Albert TJ, Landon MB, Wheller JJ, et al. Prenatal detection of fetal anomalies in pregnancies complicated by insulin-dependent diabetes mellitus. *American Journal of Obstetrics and Gynecology* 1996;174(5):1424–8.
274. Giancotti A, Ferrero A, Marceca M, et al. Mid-second trimester fetal echocardiographic examination for detecting cardiac malformations in pregnancies complicated by pregestational diabetes. *Italian Journal of Gynaecology and Obstetrics* 1995;7(2):79–82.
275. Smith RS, Comstock CH, Lorenz RP, et al. Maternal diabetes mellitus: which views are essential for fetal echocardiography? *Obstetrics and Gynecology* 1997;90(4 Pt 1):575–9.
276. Muller PR, James A, Feldman K, et al. Utility of fetal echocardiogram in high-risk patients. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2005;45(2):117–21.
277. Stratton JF, Scanhill SN, Stuart B, et al. Are babies of normal birth weight who fail to reach their growth potential as diagnosed by ultrasound at increased risk? *Ultrasound in Obstetrics and Gynecology* 1995;5(2):114–18.
278. Coomarasamy A, Connock M, Thornton J, et al. Accuracy of ultrasound biometry in the prediction of macrosomia: a systematic quantitative review. *BJOG: an international journal of obstetrics and gynaecology* 2005;112(11):1461–6.
279. Hadlock FP, Harrist RB, Fearnelyhough TC, et al. Use of femur length/abdominal circumference ratio in detecting the macrosomic fetus. *Radiology* 1985;154(2):503–5.
280. Parry S, Severs CP, Sehdev HM, et al. Ultrasonographic prediction of fetal macrosomia. Association with cesarean delivery. *Journal of Reproductive Medicine* 2000;45(1):17–22.
281. Levine AB, Lockwood CJ, Brown B, et al. Sonographic diagnosis of the large for gestational age fetus at term: does it make a difference? *Obstetrics and Gynecology* 1992;79(1):55–8.
282. Wong SF, Chan FY, Cincotta RB, et al. Sonographic estimation of fetal weight in macrosomic fetuses: diabetic versus non-diabetic pregnancies. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2001;41(4):429–32.
283. Bancerraf BR. Sonographically estimated fetal weights: accuracy and limitations. *American Journal of Obstetrics and Gynecology* 1988;159:118–21.
284. Kehl RJ, Krew MA, Thomas A, et al. Fetal growth and body composition in infants of women with diabetes mellitus during pregnancy. *Journal of Maternal-Fetal Medicine* 1996;5(5):273–80.
285. Combs CA, Rosenn B, Miodovnik M, et al. Sonographic EFW and macrosomia: is there an optimum formula to predict diabetic fetal macrosomia? *Journal of Maternal-Fetal Medicine* 2000;9(1):55–61.
286. Colman A, Maharaj D, Hutton J, et al. Reliability of ultrasound estimation of fetal weight in term singleton pregnancies. *New Zealand Medical Journal* 2006;119(1241):U2146.
287. Farrell T, Owen P, Kernaghan D, et al. Can ultrasound fetal biometry predict fetal hyperinsulinaemia at delivery in pregnancy complicated by maternal diabetes? *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2007;131(2):146–50.
288. Kernaghan D, Ola B, Fraser RB, et al. Fetal size and growth velocity in the prediction of the large for gestational age (LGA) infant in a glucose impaired population. *European Journal of Obstetrics and Gynecology* 2007;132(2):189–92.
289. Johnstone FD, Prescott RJ, Steel JM, et al. Clinical and ultrasound prediction of macrosomia in diabetic pregnancy. *British Journal of Obstetrics and Gynaecology* 1996;103(8):747–54.
290. Williams KP, Farquharson DF, Bebbington M, et al. Screening for fetal well-being in a high-risk pregnant population comparing the nonstress test with umbilical artery Doppler velocimetry: a randomized controlled clinical trial. *American Journal of Obstetrics and Gynecology* 2003;188(5):1366–71.
291. Neilson JP and Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. (Cochrane Review). In: *Cochrane Database of Systematic Reviews*. Chichester: Wiley Interscience; 2000.
292. Bricker L and Neilson JP. Routine doppler ultrasound in pregnancy. (Cochrane Review). In: *Cochrane Database of Systematic Reviews*. Chichester: Wiley Interscience; 2001.

293. Salvesen K. Routine ultrasound scanning in pregnancy. *British Medical Journal* 1993;307(6911):1064.
294. Wong SF, Chan FY, Cincotta RB, et al. Use of umbilical artery Doppler velocimetry in the monitoring of pregnancy in women with preexisting diabetes. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2003;43(4):302–6.
295. Leung WC, Lam H, Lee CP, et al. Doppler study of the umbilical and fetal middle cerebral arteries in women with gestational diabetes mellitus. *Ultrasound in Obstetrics and Gynecology* 2004;24(5):534–7.
296. Zimmermann P, Kujansuu E and Tuimala R. Doppler velocimetry of the umbilical artery in pregnancies complicated by insulin-dependent diabetes mellitus. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1992;47(2):85–93.
297. Johnstone FD, Steel JM, Haddad NG, et al. Doppler umbilical artery flow velocity waveforms in diabetic pregnancy. *British Journal of Obstetrics and Gynaecology* 1992;99(2):135–40.
298. Bracero LA, Figueroa R, Byrne DW, et al. Comparison of umbilical Doppler velocimetry, nonstress testing, and biophysical profile in pregnancies complicated by diabetes. *Journal of Ultrasound in Medicine* 1996;15(4):301–8.
299. Ben-Ami M, Battino S, Geslevich Y, et al. A random single Doppler study of the umbilical artery in the evaluation of pregnancies complicated by diabetes. *American Journal of Perinatology* 1995;12(6):437–8.
300. Kofinas AD, Penry M and Swain M. Uteroplacental Doppler flow velocity waveform analysis correlates poorly with glycemic control in diabetic pregnant women. *American Journal of Perinatology* 1991;8(4):273–7.
301. Reece EA, Hagay Z, Assimakopoulos E, et al. Diabetes mellitus in pregnancy and the assessment of umbilical artery waveforms using pulsed Doppler ultrasonography. *Journal of Ultrasound in Medicine* 1994;13(2):73–80.
302. Reece EA, Hagay Z, Moroder W, et al. Is there a correlation between aortic Doppler velocimetric findings in diabetic pregnant women and fetal outcome? *Journal of Ultrasound in Medicine* 1996;15(6):437–40.
303. Lauszus FF, Fuglsang J, Flyvbjerg A, et al. Preterm delivery in normoalbuminuric, diabetic women without preeclampsia: The role of metabolic control. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2006;124(2):144–9.
304. Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction of an algorithm]. *Acta Obstetrica et Gynecologica Scandinavica* 2002;81(9):835–9.
305. Kaushal K, Gibson J and Railton A. A protocol for improved glycaemic control following corticosteroid therapy in diabetic pregnancies. *Diabetic Medicine* 2003;20(1):73–5.
306. Royal College of Obstetricians and Gynaecologists. Tocolytic drugs for women in preterm labour. London, RCOG Press; 2002.
307. Giugliano D, Passariello N, Torella R, et al. Effects of acetylsalicylic acid on plasma glucose, free fatty acid, betahydroxybutyrate, glucagon and C-peptide responses to salbutamol in insulin-dependent diabetic subjects. *Acta Diabetologica Latina* 1981;18(1):27–36.
308. Fredholm BB, Lunell NO, Persson B, et al. Actions of salbutamol in late pregnancy: plasma cyclic AMP, insulin and C-peptide, carbohydrate and lipid metabolites in diabetic and non-diabetic women. *Diabetologia* 1978;14(4):235–42.
309. Lenz S, Kuhl C, Wang P, et al. The effect of ritodrine on carbohydrate and lipid metabolism in normal and diabetic pregnant women. *Acta Endocrinologica* 1979;92(4):669–79.
310. Tibaldi JM, Lorber DL and Nerenberg A. Diabetic ketoacidosis and insulin resistance with subcutaneous terbutaline infusion: a case report. *American Journal of Obstetrics and Gynecology* 1990;163(2):509–10.
311. Halpren EW, Soifer NE, Haenel LC, et al. Ketoacidosis secondary to oral ritodrine use in a gestational diabetic patient: Report of a case. *Journal of the American Osteopathic Association* 1988;88(2):241–4.
312. Richards SR and Klingelberger CE. Intravenous ritodrine as a possibly provocative predictive test in gestational diabetes. *A case report. Journal of Reproductive Medicine* 1987;32(10):798–800.
313. Mordes D, Kreutner K, Metzger W, et al. Dangers of intravenous ritodrine in diabetic patients. *JAMA: the journal of the American Medical Association* 1982;248(8):973–5.
314. Schilthuis MS and Aarnoudse JG. Fetal death associated with severe ritodrine induced ketoacidosis. *Lancet* 1980;1(8178):1145.
315. Feig DS, Razzaq A, Sykora K, et al. Trends in deliveries, prenatal care, and obstetrical complications in women with pregestational diabetes: a population-based study in Ontario, Canada, 1996–2001. *Diabetes Care* 2006;29(2):232–5.
316. Ehrenberg HM, Durnwald CP, Catalano P, et al. The influence of obesity and diabetes on the risk of cesarean delivery. *American Journal of Obstetrics and Gynecology* 2004;191(3):969–74.
317. Bernstein IM and Catalano PM. Examination of factors contributing to the risk of cesarean delivery in women with gestational diabetes. *Obstetrics and Gynecology* 1994;83(3):462–5.
318. Naylor CD, Sermer M, Chen E, et al. Cesarean delivery in relation to birth weight and gestational glucose tolerance. Pathophysiology or practice style? *JAMA: the journal of the American Medical Association* 1996;275(15):1165–70.
319. Kolderup LB, Laros RK, Jr. and Musci TJ. Incidence of persistent birth injury in macrosomic infants: association with mode of delivery. *American Journal of Obstetrics and Gynecology* 1997;177(1):37–41.
320. Naeye RL. The outcome of diabetic pregnancies: a prospective study. *Ciba Foundation symposium* 1978;(63)227–41.
321. Patel RR, Peters TJ and Murphy DJ. Prenatal risk factors for Caesarean section. Analyses of the ALSPAC cohort of 12 944 women in England. *International Journal of Epidemiology* 2005;34(2):353–67.
322. Modanlou H and Dorchester W. Maternal, fetal and immediate neonatal morbidity and operative delivery. *Neonatal Epidemiology & Followup* 1987;400A.
323. Kjos SL, Henry OA, Montoro M, et al. Insulin-requiring diabetes in pregnancy: a randomized trial of active induction of labor and expectant management. *American Journal of Obstetrics and Gynecology* 1993;169(3):611–15.
324. Hod M, Bar J, Peled Y, et al. Antepartum management protocol. Timing and mode of delivery in gestational diabetes. *Diabetes Care* 1998;21(Suppl 2):B113–17.
325. Conway DL and Langer O. Elective delivery of infants with macrosomia in diabetic women: reduced shoulder dystocia versus increased cesarean deliveries. *American Journal of Obstetrics and Gynecology* 1998;178(5):922–5.
326. Levy AL, Gonzalez JL, Rappaport VJ, et al. Effect of labor induction on cesarean section rates in diabetic pregnancies. *Journal of Reproductive Medicine* 2002;47(11):931–2.
327. Gonen O, Rosen DJ, Dolfin Z, et al. Induction of labor versus expectant management in macrosomia: a randomized study. *Obstetrics and Gynecology* 1997;89(6):913–17.
328. Incerpi MH, Fassett MJ, Kjos SL, et al. Vaginally administered misoprostol for outpatient cervical ripening in pregnancies complicated by diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2001;185(4):916–19.
329. Khonjandi M, Tsai M and Tyson JE. Gestational diabetes: the dilemma of delivery. *Obstetrics and Gynecology* 1974;43(1):1–6.
330. Takoudes TC, Weitzen S, Slocum J, et al. Risk of cesarean wound complications in diabetic gestations. *American Journal of Obstetrics and Gynecology* 2004;191(3):958–63.
331. Lurie S, Insler V and Hagay ZJ. Induction of labor at 38 to 39 weeks of gestation reduces the incidence of shoulder dystocia in gestational diabetic patients class A2. *American Journal of Perinatology* 1996;13(5):293–6.

332. Coleman TL, Randall H, Graves W, et al. Vaginal birth after cesarean among women with gestational diabetes. *American Journal of Obstetrics and Gynecology* 2001;184(6):1104–7.
333. Holt VL and Mueller BA. Attempt and success rates for vaginal birth after caesarean section in relation to complications of the previous pregnancy. *Paediatric and Perinatal Epidemiology* 1997;11(Suppl 1):63–72.
334. Marchiano D, Elkousy M, Stevens E, et al. Diet-controlled gestational diabetes mellitus does not influence the success rates for vaginal birth after cesarean delivery. *American Journal of Obstetrics and Gynecology* 2004;190(3):790–6.
335. Rees GA, Hayes TM and Pearson JF. Diabetes, pregnancy and anaesthesia. *Clinics in Obstetrics and Gynaecology* 1982;9(2):311–32.
336. Lattermann R, Carli F, Wykes L, et al. Epidural blockade modifies perioperative glucose production without affecting protein catabolism. *Anesthesiology* 2002;97(2):374–81.
337. Tsen LC. Anesthetic management of the parturient with cardiac and diabetic diseases. *Clinical Obstetrics and Gynecology* 2003;46(3):700–10.
338. Ramanathan S, Khoo P and Arismendy J. Perioperative maternal and neonatal acid-base status and glucose metabolism in patients with insulin-dependent diabetes mellitus. *Anesthesia and Analgesia* 1991;73(2):105–11.
339. Hebl JR, Kopp SL, Schroeder DR, et al. Neurologic complications after neuraxial anesthesia or analgesia in patients with preexisting peripheral sensorimotor neuropathy or diabetic polyneuropathy. *Anesthesia and Analgesia* 2006;103(5):1294–9.
340. Saravanakumar K, Rao SG and Cooper GM. Obesity and obstetric anaesthesia. *Anaesthesia* 2006;61(1):36–48.
341. Datta S, Kitzmiller JL, Naulty JS, et al. Acid-base status of diabetic mothers and their infants following spinal anesthesia for cesarean section. *Anesthesia and Analgesia* 1982;61(8):662–5.
342. Andersen O, Hertel J, Schmolker L, et al. Influence of the maternal plasma glucose concentration at delivery on the risk of hypoglycaemia in infants of insulin-dependent diabetic mothers. *Acta Paediatrica Scandinavica* 1985;74(2):268–73.
343. Miodovnik M, Mimouni F and Tsang RC. Management of the insulin-dependent diabetic during labor and delivery. Influences on neonatal outcome. *American Journal of Perinatology* 1987;4(2):106–14.
344. Curet LB, Izquierdo LA, Gilson GJ, et al. Relative effects of antepartum and intrapartum maternal blood glucose levels on incidence of neonatal hypoglycemia. *Journal of Perinatology* 1997;17(2):113–15.
345. Lean ME, Pearson DW and Sutherland HW. Insulin management during labour and delivery in mothers with diabetes. *Diabetic Medicine* 1990;7(2):162–4.
346. Feldberg D, Dicker D, Samuel N, et al. Intrapartum management of insulin-dependent diabetes mellitus (IDDM) gestants. A comparative study of constant intravenous insulin infusion and continuous subcutaneous insulin infusion pump (CSII). *Acta Obstetrica et Gynecologica Scandinavica* 1988;67(4):333–8.
347. Balsells M, Corcoy R, Adelantado JM, et al. Gestational diabetes mellitus: Metabolic control during labour. *Diabetes, Nutrition and Metabolism - Clinical and Experimental* 2000;13(5):257–62.
348. Carron Brown S, Kyne-Grzebalski D, Mwangi B, et al. Effect of management policy upon 120 Type 1 diabetic pregnancies: policy decisions in practice. *Diabetic Medicine* 1999;16(7):573–8.
349. Taylor R, Lee C, Kyne-Grzebalski D, et al. Clinical outcomes of pregnancy in women with type 1 diabetes. *Obstetrics and Gynecology* 2002;99(4):537–41.
350. Mimouni F. Perinatal asphyxia in infants of diabetic mothers is associated with maternal vasculopathy and hyperglycaemia in labour. *Neonatal Epidemiology & Follow-up* 1987;400A.
351. Rosenberg VA, Eglinton GS, Rauch ER, et al. Intrapartum maternal glycemic control in women with insulin requiring diabetes: a randomized clinical trial of rotating fluids versus insulin drip. *American Journal of Obstetrics and Gynecology* 2006;195(4):1095–9.
352. Fuloria M and Kreiter S. The newborn examination: Part I. Emergencies and common abnormalities involving the skin, head, neck, chest, and respiratory and cardiovascular systems. *American Family Physician* 2002;65(1):61–8.
353. Edstrom CS and Christensen RD. Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clinics in Perinatology* 2000;27(3):623–41.
354. Akera C and Ro S. Medical concerns in the neonatal period. *Clinics in Family Practice* 2003;5(2):265–92.
355. Aucott SW, Williams TG, Hertz RH, et al. Rigorous management of insulin-dependent diabetes mellitus during pregnancy. *Acta Diabetologica* 1994;31(3):126–9.
356. Haworth JC, Dilling LA and Vidyasagar D. Hypoglycemia in infants of diabetic mothers: effect of epinephrine therapy. *The Journal of Pediatrics* 1973;82(1):94–7.
357. Van Howe RS and Storms MR. Hypoglycemia in infants of diabetic mothers: experience in a rural hospital. *American Journal of Perinatology* 2006;23(2):105–10.
358. Alam M, Raza SJ, Sherali AR, et al. Neonatal complications in infants born to diabetic mothers. [Erratum appears in *J Coll Physicians Surg Pak* 2006;16(8):566 Note: Akhtar, SM [corrected to Akhtar, ASM]. *Journal of the College of Physicians and Surgeons – Pakistan: JCPSP* 2006;16(3):212–15.
359. Jones CW. Gestational diabetes and its impact on the neonate. *Neonatal Network - Journal of Neonatal Nursing* 2001;20(6):17–23.
360. Teramo K, Kari MA, Eronen M, et al. High amniotic fluid erythropoietin levels are associated with an increased frequency of fetal and neonatal morbidity in type 1 diabetic pregnancies. *Diabetologia* 2004;47(10):1695–703.
361. Dalgic N, Ergenekon E, Soysal S, et al. Transient neonatal hypoglycemia—long-term effects on neurodevelopmental outcome. *Journal of Pediatric Endocrinology* 2002;15(3):319–24.
362. Cordero L, Treuer SH, Landon MB, et al. Management of infants of diabetic mothers. *Archives of Pediatrics and Adolescent Medicine* 1998;152(3):249–54.
363. Halliday HL. Hypertrophic cardiomyopathy in infants of poorly-controlled diabetic mothers. *Archives of Disease in Childhood* 1981;56(4):258–63.
364. Watson D, Rowan J, Neale L, et al. Admissions to neonatal intensive care unit following pregnancies complicated by gestational or type 2 diabetes. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2003;43(6):429–32.
365. Scottish Intercollegiate Guidelines Network. *Management of diabetes. A national clinical guideline*. Edinburgh: SIGN; 2001. 366. Williams AF. Hypoglycaemia of the newborn: a review. *Bulletin of the World Health Organization* 1997;75(3):261–90.
367. Lucas A, Morley R and Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *British Medical Journal* 1988;297(6659):1304–8.
368. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000;105(5):1141–5.
369. Beard AG, Panos TC, Marasigan BV, et al. Perinatal stress and the premature neonate. II. Effect of fluid and calorie deprivation on blood glucose. *The Journal of Pediatrics* 1966;68(3):329–43.

370. Wharton BA and Bower BD. Immediate or later feeding for premature babies? *A controlled trial. Lancet* 1965;2(7420):769–72.
371. Hawdon JM, Ward Platt MP and Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *Archives of Disease in Childhood* 1992;67(4 Spec No):357–65.
372. Lucas A, Boyes S, Bloom SR, et al. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. *Acta Paediatrica Scandinavica* 1981;70(2):195–200.
373. Ratzmann KP, Steindel E, Hildebrandt R, et al. Is there a relationship between metabolic control and glucose concentration in breast milk of type 1 (insulin-dependent) diabetic mothers? *Experimental and Clinical Endocrinology* 1988;92(1):32–6.
374. Plagemann A, Harder T, Franke K, et al. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care* 2002;25(1):16–22.
375. Rodekamp E, Harder T, Kohlhoff R, et al. Long-term impact of breast-feeding on body weight and glucose tolerance in children of diabetic mothers: role of the late neonatal period and early infancy. *Diabetes Care* 2005;28(6):1457–62.
376. Rodekamp E, Harder T, Kohlhoff R, et al. Impact of breast-feeding on psychomotor and neuropsychological development in children of diabetic mothers: role of the late neonatal period. *Journal of Perinatal Medicine* 2006;34(6):490–6.
377. Plagemann A, Harder T, Kohlhoff R, et al. Impact of early neonatal breast-feeding on psychomotor and neuropsychological development in children of diabetic mothers. *Diabetes Care* 2005;28(3):573–8.
378. Gerstein HC. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. *Diabetes Care* 1994;17(1):13–19.
379. Norris JM and Scott FW. A meta-analysis of infant diet and insulin-dependent diabetes mellitus: do biases play a role? *Epidemiology* 1996;7(1):87–92.
380. Meloni T, Marinaro AM, Mannazzu MC, et al. IDDM and early infant feeding. Sardinian case-control study. *Diabetes Care* 1997;20(3):340–2.
381. Ferris AM, Neubauer SH, Bendel RB, et al. Perinatal lactation protocol and outcome in mothers with and without insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1993;58(1):43–8.
382. Gagne MP, Leff EW and Jefferis SC. The breast-feeding experience of women with type I diabetes. *Health Care for Women International* 1992;13(3):249–60.
383. van Beusekom CM, Zeegers TA, Martini IA, et al. Milk of patients with tightly controlled insulin-dependent diabetes mellitus has normal macronutrient and fatty acid composition. *American Journal of Clinical Nutrition* 1993;57(6):938–43.
384. Cox SG. Expressing and storing colostrum antenatally for use in the newborn periods. *Breastfeeding Review* 2006;14(3):16. 386. Screening guidelines for newborns at risk for low blood glucose. *Paediatrics and Child Health* 2004;9(10):723–40.
387. CREST. *Management of Diabetes in Pregnancy*. Belfast: CREST; 2001. p. 1–74.
388. Rennie JM. *Robertson's Textbook of Neonatology*. Edinburgh: Churchill Livingstone; 2005.
389. Saez-de-Ibarra L, Gaspar R, Obesso A, et al. Glycaemic behaviour during lactation: postpartum practical guidelines for women with type 1 diabetes. *Practical Diabetes International* 2003;20(8):271–5.
390. Ferris AM, Dalidowitz CK, Ingardia CM, et al. Lactation outcome in insulin-dependent diabetic women. *Journal of the American Dietetic Association* 1988;88(3):317–22.
391. Davies HA, Clark JD, Dalton KJ, et al. Insulin requirements of diabetic women who breast feed. *British Medical Journal* 1989;298(6684):1357–8.
392. Briggs GG, Ambrose PJ, Nageotte MP, et al. Excretion of metformin into breast milk and the effect on nursing infants. *Obstetrics and Gynecology* 2005;105(6):1437–41.
393. Feig DS, Briggs GG, Kraemer JM, et al. Transfer of glyburide and glipizide into breast milk. *Diabetes Care* 2005;28(8):1851–5.
394. Kim C, Newton KM and Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;25(10):1862–8.
395. Lauenborg J, Hansen T, Jensen DM, et al. Increasing incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. *Diabetes Care* 2004;27(5):1194–9.
396. Lobner K, Knopff A, Baumgarten A, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes* 2006;55(3):792–7.
397. Wein P, Beischer NA and Sheedy MT. Studies of postnatal diabetes mellitus in women who had gestational diabetes. Part 2. Prevalence and predictors of diabetes mellitus after delivery. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1997;37(4):420–3.
398. Lee CP, Wong HS, Chan FY, et al. Long-term prognosis of women with abnormal glucose tolerance in pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1994;34(5):507–10.
399. Linne Y, Barkeling B and Rossner S. Natural course of gestational diabetes mellitus: Long term follow up of women in the SPAWN study. *BJOG: an international journal of obstetrics and gynaecology* 2002;109(11):1227–31.
400. Aberg AE, Jonsson EK, Eskilsson I, et al. Predictive factors of developing diabetes mellitus in women with gestational diabetes. *Acta Obstetrica et Gynecologica Scandinavica* 2002;81(1):11–16.
401. Jarvela IY, Juutinen J, Koskela P, et al. Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: predictive role of autoantibodies. *Diabetes Care* 2006;29(3):607–12.
402. Pettitt DJ, Narayan KM, Hanson RL, et al. Incidence of diabetes mellitus in women following impaired glucose tolerance in pregnancy is lower than following impaired glucose tolerance in the non-pregnant state. *Diabetologia* 1996;39(11):1334–7.
403. Stage E, Ronneby H and Damm P. Lifestyle change after gestational diabetes. *Diabetes Research and Clinical Practice* 2004;63(1):67–72.
404. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine* 2002;346(6):393–403.
405. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* 2001;344(18):1343–50.
406. Smith BJ, Cheung NW, Bauman AE, et al. Postpartum physical activity and related psychosocial factors among women with recent gestational diabetes mellitus. *Diabetes Care* 2005;28(11):2650–4.
407. Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *British Medical Journal* 2007;334(7588):299–302.
408. Holt RI, Goddard JR, Clarke P, et al. A postnatal fasting plasma glucose is useful in determining which women with gestational diabetes should undergo a postnatal oral glucose tolerance test. *Diabetic Medicine* 2003;20(7):594–8.

409. Tan YY, Yeo SH and Liauw PC. Is postnatal oral glucose tolerance testing necessary in all women with gestational diabetes. *Singapore Medical Journal* 1996;37(4):384–8.
410. Elixhauser A, Weschler JM, Kitzmiller JL, et al. Cost-benefit analysis of preconception care for women with established diabetes mellitus. *Diabetes Care* 1993;16(8):1146–57.
411. Shearer A, Bagust A, Sanderson D, et al. Cost-effectiveness of flexible intensive insulin management to enable dietary freedom in people with Type 1 diabetes in the UK. *Diabetic Medicine* 2004;21(5):460–7.
412. Gregory R and Tattersall RB. Are diabetic pre-pregnancy clinics worth while? *Lancet* 1992;340(8820):656–8.
413. Odibo AO, Coassolo KM, Stamilio DM, et al. Should all pregnant diabetic women undergo a fetal echocardiography? A cost-effectiveness analysis comparing four screening strategies. *Prenatal Diagnosis* 2006;26(1):39–44.
414. Wren C, Birrell G and Hawthorne G. Cardiovascular malformations in infants of diabetic mothers. *Heart* 2003;89(10):1217–20.
415. Sullivan ID. Prenatal diagnosis of structural heart disease: does it make a difference to survival? *Heart* 2002;87(5):405–6.
416. Ritchie K, Boynton J, Bradbury I, et al. *Routine Ultrasound Scanning Before 24 Weeks of Pregnancy*. Consultation report. NHS Quality Improvement; 2003 [www.nhshealthquality.org/nhsqis/files/Ultrasound%20CAR.pdf].
417. Ogge G, Gaglioti P, Maccanti S, et al. Prenatal screening for congenital heart disease with four-chamber and outflow-tract views: A multicenter study. *Ultrasound in Obstetrics and Gynecology* 2006;28(6):779–84.
418. Bonnet D, Coltri A, Butera G, et al. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. *Circulation* 1999;99(7):916–18.
419. Bonnet D, Jouannic JM and Fermont L. Impact of prenatal diagnosis on perinatal care of transposition of the great arteries. *Ultrasound in Obstetrics and Gynecology* 2003;22(S1):66–7.
420. Kumar RK, Newburger JW, Gauvreau K, et al. Comparison of outcome when hypoplastic left heart syndrome and transposition of the great arteries are diagnosed prenatally versus when diagnosis of these two conditions is made only postnatally. *American Journal of Cardiology* 1999;83(12):1649–53.
421. Schaefer-Graf UM, Buchanan TA, Xiang A, et al. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *American Journal of Obstetrics and Gynecology* 2000;182(2):313–20.
422. Checa MA, Requena A, Salvador C, et al. Insulin-sensitizing agents: Use in pregnancy and as therapy in polycystic ovary syndrome. *Human Reproduction Update* 2005;11(4):375–90.
423. Hod M, Visser GHA, Damm P, et al. Safety and perinatal outcome in pregnancy: a randomized trial comparing insulin aspart with human insulin in 322 subjects with type 1 diabetes. *Diabetes* 2006;55(Suppl 1):A 417.
424. Halaska M, Martan A, Voigt R, et al. Tolerance and effectiveness of propiverine hydrochloride in 752 patients with symptoms of hyperactivity of the detrusor, increased sensitivity and irritability of the urinary bladder: Results of an investigation of the use of a drug. *Ceska Gynekologie* 1997;62(5):259–64.
425. Glueck CJ, Goldenberg N, Wang P, et al. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: Prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. *Human Reproduction* 2004;19(3):510–21.
426. Langer O, Yogev Y, Most O, et al. Gestational diabetes: the consequences of not treating. *American Journal of Obstetrics and Gynecology* 2005;192(4):989–97.
427. Wang Y, Storlien LH, Jenkins AB, et al. Dietary variables and glucose tolerance in pregnancy. *Diabetes Care* 2000;23(4):460–4.
428. Catalano PM, Thomas A, Huston-Presley L, et al. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *American Journal of Obstetrics and Gynecology* 2003;189(6):1698–704.
429. Simmons D and Robertson S. Influence of maternal insulin treatment on the infants of women with gestational diabetes. *Diabetic Medicine* 1997;14(9):762–5.
430. Drexel H, Bichler A, Sailer S, et al. Prevention of perinatal morbidity by tight metabolic control in gestational diabetes mellitus. *Diabetes Care* 1988;11(10):761–8.
431. Stainton MC, Lohan M, Fethney J, et al. Women's responses to two models of antepartum high-risk care: Day stay and hospital stay. *Women and Birth* 2006;19(4):89–95.
432. Carta Q, Meriggi E, Trossarelli GF, et al. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabète & Métabolisme* 1986;12(3):121–9.
433. Nosari I, Maglio ML, Lepore G, et al. Is continuous subcutaneous insulin infusion more effective than intensive conventional insulin therapy in the treatment of pregnant diabetic women? *Diabetes, Nutrition and Metabolism - Clinical and Experimental* 1993;6(1):33–7.
434. Abramowicz JS, Rana S and Abramowicz S. Fetal cheek-to-cheek diameter in the prediction of mode of delivery. *American Journal of Obstetrics and Gynecology* 2005;192(4):1205–11.
435. Best G and Pressman EK. Ultrasonographic prediction of birth weight in diabetic pregnancies. *Obstetrics and Gynecology* 2002;99(5 Pt 1):740–4.
436. Bracero LA, Haberman S and Byrne DW. Maternal glycemic control and umbilical artery Doppler velocimetry. *Journal of Maternal-Fetal and Neonatal Medicine* 2002;12(5):342–8.
437. Chauhan SP, Parker D, Shields D, et al. Sonographic estimate of birth weight among high-risk patients: feasibility and factors influencing accuracy. *American Journal of Obstetrics and Gynecology* 2006;195(2):601–6.
438. de la Vega A and Verdiales M. Failure of intensive fetal monitoring and ultrasound in reducing the stillbirth rate. *Puerto Rico Health Sciences Journal* 2002;21(2):123–5.
439. Smith MC, Moran P, Ward MK, et al. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG: an International Journal of Obstetrics and Gynaecology* 2008;115(1):109–12.
440. Pan W, Wu GP, Li YF, et al. The experience of diagnosis the abnormal fetal heart by fetal echocardiography to 900 fetuses. Guangzhou, China: Guangdong Cardiovascular Institute; undated [available from www.unepa.org/china/ab/1327.HTM; accessed 30 August 2006].
441. Poncet B, Touzet S, Rocher L, et al. Cost-effectiveness analysis of gestational diabetes mellitus screening in France. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2002;103(2):122–9.
442. Di CG, Volpe L, Casadidio I et al. Universal screening and intensive metabolic management of gestational diabetes: cost-effectiveness in Italy. *Acta Diabetologica* 2002;39(2):69–73.
443. Nicholson WK, Fleisher LA, Fox HE et al. Screening for gestational diabetes mellitus: a decision and cost-effectiveness analysis of four screening strategies. *Diabetes Care* 2005;28(6):1482–4.
444. Reed BD. Screening for gestational diabetes—analysis by screening criteria. *Journal of Family Practice* 1984;19(6):751–5.

- 
445. Massion C, O'Connor PJ, Gorab R et al. Screening for gestational diabetes in a high-risk population. *Journal of Family Practice* 1987;25(6):569–75.
  446. Lavin JP, Barden TP and Miodovnik M. Clinical experience with a screening program for gestational diabetes. *American Journal of Obstetrics and Gynecology* 1981;141(5):491–4.
  447. Larijani B, Hossein-nezhad A and Vassigh A-R. Effect of varying threshold and selective versus universal strategies on the cost in gestational diabetes mellitus. *Archives of Iranian Medicine* 2004;7(4):267–71.
  448. National Collaborating Centre for Women's and Children's Health. *Fertility: Assessment and Management for People with Fertility Problems*. London: RCOG Press; 2004.
  449. Reichelt AJ, Spichler ER, Branchtein L, Nucci LB, Franco LJ, Schmidt MI. Fasting plasma glucose is a useful test for the detection of gestational diabetes. Brazilian Study of Gestational Diabetes (EBDG) Working Group. *Diabetes Care* 1998;21:1246–9.
  450. Ostlund I and Hanson U. Repeated random blood glucose measurements as universal screening test for gestational diabetes mellitus. *Acta Obstetrica et Gynecologica Scandinavica* 2004;83(1):46–51.
  451. Seshiah V, Balaji V, Balaji MS, et al. Gestational diabetes mellitus in India. *Journal of the Association of Physicians of India*. 2004;52:707–11.
  452. Coustan DR. Methods of screening for and diagnosing of gestational diabetes. *Clinics in Perinatology* 1993;20(3):593–602.
  453. Weeks JW, Major CA, de Veciana M et al. Gestational diabetes: Does the presence of risk factors influence perinatal outcome? *American Journal of Obstetrics and Gynecology* 1994; 171:1003–7.
  454. Danilenko-Dixon D, Van Winter J, Nelson R, Ogburn P. Universal versus selective gestational diabetes screening: application of 1997 American Diabetes Association recommendations. *American Journal of Obstetrics and Gynecology* 1999;181:798–802.
  455. Williams CB, Iqbal S, Zawacki CM, Yu D, Brown MB, Herman WH. Effect of selective screening for gestational diabetes. *Diabetes Care* 1999;22:418–21.
  456. Curtis L, Netten A. *Unit Costs of Health and Social Care*. Canterbury: Personal and Social Services Research Unit University of Kent at Canterbury; 2006.
  457. Joint Formulary Committee. *British National Formulary*. 52nd ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2006.
  458. Davies L and Drummond M. Management of labour: consumer choice and cost implications. *Journal of Obstetrics and Gynaecology* 1991;11(Suppl 1):s28–s33.
  459. Davies L and Drummond M. *The Costs of Induction of Labour by Prostaglandin E<sub>2</sub> or Oxytocin: Refining the Estimates*. York: University of York; 1993.
  460. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.
  461. Goetzl L and Wilkins I. Glyburide compared to insulin for the treatment of gestational diabetes mellitus: A cost analysis. *Journal of Perinatology* 2002;22(5):403–6.
  462. Williams CB, Iqbal S, Zawacki CM, et al. Effect of selective screening for gestational diabetes. *Diabetes Care* 1999;22:418–21.

Other NICE guidelines produced by the National Collaborating Centre for Women's and Children's Health include:

- Antenatal care: routine care for the healthy pregnant woman
- Fertility: assessment and treatment for people with fertility problems
- Caesarean section
- Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people
- Long-acting reversible contraception: the effective and appropriate use of long-acting reversible contraception
- Urinary incontinence: the management of urinary incontinence in women
- Heavy menstrual bleeding
- Feverish illness in children: assessment and initial management in children younger than 5 years
- Urinary tract infection in children: diagnosis, treatment and long-term management
- Intrapartum care: care of healthy women and their babies during childbirth
- Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years
- Surgical management of otitis media with effusion in children

Guidelines in production include:

- Induction of labour (update)
- Surgical site infection
- Diarrhoea and vomiting in children under 5
- When to suspect child maltreatment
- Meningitis and meningococcal disease in children
- Neonatal jaundice
- Idiopathic constipation in children
- Hypertension in pregnancy
- Socially complex pregnancies
- Autism in children and adolescents

Enquiries regarding the above guidelines can be addressed to:

**National Collaborating Centre for Women's and Children's Health**

King's Court  
Fourth Floor  
2–16 Goodge Street  
London  
W1T 2QA  
enquiries@ncc-wch.org.uk

A version of this guideline for women with diabetes and the public is available from the NICE website ([www.nice.org.uk/CG063](http://www.nice.org.uk/CG063)) or from NICE publications on 0845 003 7783; quote reference number N1485.

ISBN 978-1-904752-47-9



9 781904 752479

Published by the Royal College of  
Obstetricians and Gynaecologists.  
To purchase further copies and for  
a complete list of RCOG Press titles,  
visit: [www.rcogbookshop.com](http://www.rcogbookshop.com)

