Antenatal care

routine care for the healthy pregnant woman

2008 update

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

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Evidence tables

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

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Abbreviations

AC	abdominal circumference
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG	American College of Obstetricians and Gynecologists
ACTH	adrenocorticotrophic hormone
ADA	American Diabetes Association
AFG	adequate fetal growth
AFI	amniotic fluid index
AFP	alpha-fetoprotein
AIDS	acquired immune deficiency syndrome
ALPHA	Antenatal Psychosocial Health Assessment
ANC	antenatal care
APEC	Action on Pre-eclampsia
APH	antepartum haemorrhage
ASB	asymptomatic bacteriuria
BD	twice a day
BERR	Department for Business, Enterprise and Regulatory Reform
BMC	bone mineral content
BMI	body mass index
BP	blood pressure
BPD	biparietal diameter or bronchopulmonary dysplasia
BV	bacterial vaginosis
BW	birthweight
CAMP	Christie, Atkinson, Munch, Peterson test
cBG$_{120\ min}$	capillary blood glucose 120 minutes after glucose load
CDSC	Communicable Disease Surveillance Centre
CEGEN	Confidential Enquiry into Counselling for Genetic Disorders
cFBG	capillary fasting blood glucose
CFGC	customised fetal growth chart
cfu/ml	colony-forming units per millilitre
CHO	carbohydrate
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMV	cytomegalovirus
CNS	central nervous system
COMA	Committee on Medical Aspects of Food Policy
CPC	choroid plexus cyst
CRL	crown–rump length
CRP	C-reactive protein
CS	caesarean section
CTG	cardiotocography
DA	direct agglutination test
DARE	Database of Abstracts and Reviews of Effectiveness
df	degrees of freedom
DFA	direct fluorescent antibody test
DNA	deoxyribonucleic acid
DR	detection rate
DS	Down's syndrome
Dx	Diagnosis
eAg	hepatitis e antigen
EB	elementary body
ECV	external cephalic version
EEA	European Economic Area

EFW	estimated fetal weight
EIA	enzyme immunoassay
EL	evidence level
ELISA	enzyme-linked immunosorbent assay
EOGBS	early-onset group B streptococcus
EPDS	Edinburgh Postnatal Depression Scale
EPIC	external intermittent pneumatic compression
EU	European Union
FBC	full blood count
FFN	fetal fibronectin
FGM	female genital mutilation
FGR	fetal growth restriction
fl	femtolitre (10^{-15} litres)
FL	femur length
FPG	fasting plasma glucose
FPR	false positive rate
FTA-abs	fluorescent treponemal antibody – absorbed test
GA	gestational age
GBS	group B streptococcus
GCT	glucose challenge test
GD	gestational diabetes
GDG	Guideline Development Group
GDM	gestational diabetes mellitus
GPP	good practice point
GTT	glucose tolerance test
H/O	history of
HADS	Hospital Anxiety and Depression Scale
Hb	haemoglobin
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	head circumference
hCG	human chorionic gonadotrophin (can be total or free beta)
β-hCG	beta-human chorionic gonadotrophin
HCV	hepatitis C virus
HDN	haemolytic disease of the newborn
HEED	Health Economic Evaluations Database
HELLP	haemolysis, elevated liver enzymes and low platelet count
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HPLC	high-performance liquid chromatography
HSI	health sector initiative
HT	hypertension
HTA	Health Technology Assessment
ICD-9	International Classification of Diseases, 9th edition
ICER	incremental cost-effectiveness ratio
IFG	inadequate fetal growth
IGT	impaired glucose tolerance
IL	interleukin
IM	intramuscular(ly)
IMDA	interactive multimedia decision aid
IPC	intrapartum care
IPV	intimate partner violence
IU	international unit
IUGR	intrauterine growth restriction
LA	latex agglutination test
LBW	low birthweight
LCR	ligase chain reaction
LE	leucocyte esterase

LGA	large for gestational age
LMP	last menstrual period
LR	likelihood ratio
LR–	negative likelihood ratio
LR+	positive likelihood ratio
LSHTM	London School of Hygiene & Tropical Medicine
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MeSH	medical subject headings
MIDIRS	Midwives Information and Resource Service
MMIC	Multidimensional Measure of Informed Choice
MoM	multiples of the median
MOMP	major outer membrane protein
MSAFP	maternal serum alpha-fetoprotein
MSHCG	maternal serum beta-human chorionic gonadotrophin
MSS	maternal serum screening
MSU	midstream urine sample
MTCT	mother-to-child transmission
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NCRSP	National Congenital Rubella Surveillance Programme
NEC	necrotising enterocolitis
NFG	normal fetal growth
NHS EED	NHS Economic Evaluations Database
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NNT	number needed to treat
NPI	Neonatal Perception Inventory
NPV	negative predictive value
NS	not significant
NSC	(UK) National Screening Committee
NSF	National Service Framework
NT	nuchal translucency
NTD	neural tube defect
OGTT	oral glucose tolerance test
OH	oligohydramnios
25-OHD	25-hydroxyvitamin D
ONS	Office for National Statistics
OR	odds ratio
OTC	over-the-counter
oz	fluid ounce (28.41 ml)
PAI	Prenatal Attachment Inventory
PAPP-A	pregnancy-associated plasma protein-A
PCR	polymerase chain reaction
PCT	primary care trust
PE	pre-eclampsia
pg	picogram (10^{-12} grams)
PHLS	Public Health Laboratory Service
PI	pulsatility index
PIH	pregnancy-induced hypertension
PPV	positive predictive value
PROM	preterm rupture of the membranes
PTD	preterm delivery
QID	four times a day
RBC	red blood cell
RBG	random blood glucose
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RhD	rhesus D

RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
ROC	receiver operating characteristic
ROP	retinopathy of prematurity
RPG	random plasma glucose
RPR	rapid plasmin reagin test
RR	relative risk
RST	reagent strip testing
S/D	systolic/diastolic
SACN	Scientific Advisory Committee on Nutrition
SD	standard deviation
SE	socio-economic(ally)
SFH	symphysis–fundal height
SGA	small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network
SP	specificity
SPD	symphysis pubis dysfunction
SPTB	spontaneous preterm birth
ST	sensitivity
STAI	Spielberger State-Trait Anxiety Inventory
T 21/18/13	trisomy 21, 18 or 13
TDS	three times a day
TGA	tranposition of the great arteries
TPHA	*Treponema pallidum* haemagglutination assay
TVS	transvaginal sonography
uE3	unconjugated estriol
UHT	ultra-high-temperature processing
UK	United Kingdom
US CDC	United States Centers for Disease Control and Prevention
US	ultrasound
USPSTF	US Preventive Services Task Force
USS	ultrasound scan
UTI	urinary tract infection
VDRL	Venereal Disease Research Laboratory (test for syphilis)
VE	vaginal examination
WHO	World Health Organization
WMD	weighted mean difference

3 Woman-centred care and informed decision making

3.2 Provision of information

Clinical question: What, how and when information should be offered during the antenatal period to inform women's decisions about care during pregnancy, labour, birth and the postnatal period?

Effectiveness of information provision

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Dyson *et al*., 2005	637	7 RCTS involving 1388 women	To examine the interventions that aim to encourage women to breastfeed, to evaluate their effectiveness	The number of women who initiate breastfeeding and any other effects of such interventions.	5 trials involving 582 women showed that breastfeeding education had a significant effect on increasing initiation rates compared to routine care RR 1.53 [95% CI 1.25–1.88].	Cochrane review. The 7 studies suffered from a high overall risk of bias due to unclear or inadequate allocation concealment. 3 of 7 studies reported breastfeeding initiation for all participants, the remaining 4 studies had up to 25% losses to follow up between recruitment and breastfeeding initiation.	Systematic review of RCTs	1+
Fairbank *et al*., 2000	638	59 studies of which 14 were RCTs, 16 non-RCTs and 29 before–after studies. Intervention were grouped into categories: health education; health	Evaluation of evidence to identify which promotion programmes are effective at improving breastfeeding rates.	The number of women who start to breastfeed, duration and exclusivity of breastfeeding.	There is limited impact on initiation rates of breastfeeding by giving breastfeeding literature alone, or combined with a more formal, non-interactive method of health education. Small, informal, group health education classes, delivered in the antenatal period, can be an effective intervention to increase initiation rates, and in some cases the duration of breastfeeding, among women from different income or ethnic	Health Technology Assessment	Extensive literature review	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		sector initiatives (HSI) – general; HSI Baby Friendly Hospital Initiative (BFHI); HSI-training of health professionals; HSI – US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); HSI – social support from health professionals; peer support; media campaigns; and multifaceted interventions.			groups. Amedia campaign as a stand-alone intervention, and particularly television commercials, may improve attitudes towards, and increase initiation rates of breastfeeding. Multifaceted interventions comprising a media campaign and/or a peer support programme combined with structural changes to the health sector (HSI) or, in fewer cases, combined with health education activities are effective in increasing initiation rates (and duration and exclusivity of breastfeeding).			
Lavender *et al.*, 2005	[639]	Women who expressed a desire to breastfeed at the start of their pregnancy booked at an inner-city teaching hospital. Sample *n* = 1249	To evaluate the effect of an antenatal breastfeeding intervention on breastfeeding duration (delivered as an extra antenatal class session). Comparison group: usual antenatal classes	Main outcome: proportion of women who fulfilled their expectation of breastfeeding.	No difference between the groups in the proportion of women who attained their expected duration of breastfeeding (OR 1.2, 95% CI 0.89–1.6). There were no differences between the groups in the uptake of breastfeeding on discharge (OR 1.2, 95% CI 0.8–1.7) or exclusively at four months (OR 1.1, 95% CI 0.6–1.8).	UK	Cluster RCT	1−
Mattar *et al.*, 2007	[640]	'Low-risk' women booked at a tertiary referral centre May 2002 to December 2004. Sample *n* = 401	To evaluate the impact of breastfeeding educational material and breastfeeding coaching on breastfeeding practice.	Duration of exclusive and predominant breastfeeding.	Women who received simple antenatal instruction with a short, single, individual counselling session combined with educational material were practiced exclusive and predominant breastfeeding more often than women receiving routine care alone at 3 months (odds ratio [OR] 2.6, 95% CI 1.2–5.4) and 6 months (OR 2.4, 95% CI 1.0–5.7) postpartum. More women practiced exclusive and predominant breastfeeding at 6 months among women receiving individual counselling compared with women exposed to educational material alone (OR 2.5, 95% CI 1.0–6.3).	Singapore Note: There was contamination between the groups and women in the control group came to know about the interventions offered to the other groups simply by speaking to women in those groups. The study was	RCT	1−

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
						underpowered.		
Noel-Weiss *et al.*, 2006	[641]	Nulliparous women with an uncomplicated pregnancy. Sample *n* = 110	To evaluate the effects of a breastfeeding workshop on breastfeeding self-efficacy and duration.	Maternal breastfeeding self-efficacy (measured with a revised breastfeeding self-efficacy scale) and breastfeeding duration (measured at 4 weeks and 8 weeks postpartum).	Maternal breastfeeding scores increased in both groups. Self-efficacy scores (mean (std. dev.)): At registration: Intervention 42.73 (9.2) vs control 42.02 (9.7); t= -0.345 [95% CI -4.76 to 3.35]; *P* = 0.731. At 4 weeks postpartum: Intervention 57.98 (8.6) vs control 53.38 (9.1); t= -2.32 [95% CI -8.53 to -0.65]; *P* = 0.023. At 8 weeks postpartum: Intervention 61.70 (5.8) vs control 58.91 (9.1); t= -1.60 [95% CI -6.28 to -0.70]; *P* = 0.115. Exclusive breastfeeding at 8 weeks: Intervention 33/47 vs control 26/45; χ^2 = 8.41, *P* = 0.135.	Canada	RCT	1−
Reifsnider and Eckhart, 1996	[642]	Women who expressed a wish to breastfeed and who qualified for the US WIC programme living in rural areas of Oklahoma. Intervention group *n* = 14 Comparison group *n* = 17	To investigate the effects of antenatal breastfeeding education on breastfeeding incidence and duration.	Breastfeeding incidence and duration.	A significantly higher percentage of women still breastfeeding at 3 and 4 months postpartum in the experimental group versus the control group. The control group breastfed for 29.5 ± 43.6 days, while the experimental group breastfed for 76 days ± 104.3 (*P* = 0.05).	USA	Non-randomised trail	1−
Wiles, 1984	[643]	Nulliparous women expressing a wish to breastfeed. Sample *n* = 40	Evaluation of antenatal breastfeeding education programme.	Woman's own perception of breastfeeding 'success'. Woman's perceptions of her baby (measured using the Neonatal Perception Inventory (NPI)) Outcomes measured 1–2 days postpartum and	At 1–2 days: Intervention group had lower NPI scores than comparison group (U=125.5, *P* = 0.05) At 1 month: Intervention group had significantly higher NRI scores than comparison group (U=94, *P* = 0.01)	USA	Prospective cohort study	2

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
				1 month postpartum.	18/20 women in intervention group fully breastfeeding vs 6/20 in the comparison group.			
Pugin *et al.*, 1996	644	Women attending university hospital for antenatal care. Intervention (antenatal skills-based session) *n* = 59 Comparison 1 (5 other breastfeeding interventions) *n* = 363 Comparison 2 (no interventions) *n* = 313	Evaluation of the effectiveness of an antenatal skill-based education session for breastfeeding.	Number of women fully breastfeeding at 6 months	Fully breastfeeding at 6 months: Intervention group: 47/59 (80%) Comaparison Group 1: 235/363 (65%) Comparison Group 2: 99/313 (32%) χ^2 analysis showed these differences to be statistically significant.	Chile	Prospective cohort study	2
Sheehan *et al.*, 2003	645	Purposive sample of 29 women interviewed antenatally.	To describe women's decision making regarding infant feeding.	What woman's decision is regarding feeding her baby. Influences on the decision to breastfeed. How the woman feels about breastfeeding Woman's expectations of what breastfeeding will feel like.	Thematic analysis revealed the following key themes: 1. Assuming I'll breastfeed 2. Definitely going to breastfeed 3. Playing it by ear 4. Definitely going to bottle-feed	Australia	Qualitative interview-based study	3
Gulick, 1982	646	Nulliparous women attending antenatal classes associated with 12 medical centres in both urban and rural areas. Sample *n* = 251	To investigate whether women with more breastfeeding knowledge antenatally breastfeed for longer than those with less antenatal knowledge.	Breastfeeding for longer than 4 weeks.	Women with more antenatal knowledge were more likely to breastfeed for longer than 4 weeks compared with those with less knowledge (t=2.72, *P* = 0.004. Degrees of freedom not reported).	USA	Prospective descriptive study	3
Kramer, 1996	65	4 RCTs including 1108 women	To assess the effects of advising pregnant women to increase their energy and protein intakes.	Main outcomes: Dietary intake, gestational weight gain and pregnancy outcomes	Advice to increase energy and protein intakes seems to be successful in achieving those goals, but the increases are lower than those reported in trials of actual protein/energy supplementation. The evidence regarding the effects on pregnancy outcome are not truly representative as available only from one trial with very narrow confidence intervals. None of	Cochrane systematic review	Systematic review	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					the trials reported any potential adverse effects that might accompany increased fetal size, such as an increased risk of prolonged labour or caesarean section.			
Campbell *et al.*, 2004	[647]	Sample *n* = 307 (response rate 74.8%). 96% participants were females, 20% were pregnant, and 50% were minorities (African American and other).	Evaluation of effectiveness of interactive CD-ROM consisting of targeted video soap opera, dietary assessment and individualised dietary feedback and strategies to help change.	Total fat and fruit and vegetable intake; knowledge of low-fat; infant feeding knowledge; self-efficacy. Outcomes measured at baseline and then 1–2 months post-intervention.	Low-fat knowledge (mean (SD)): Intervention group: baseline 1.94 (1.2) vs follow-up 2.76 (0.46); *P* < 0.05. Control group: baseline 1.86 (1.2) vs follow-up 2.63 (0.55); NS Infant feeding knowledge: Intervention group: baseline 2.29 (0.82) vs follow-up 2.62 (0.62); *P* < 0.01. Control group: baseline 2.25 (0.86) vs follow-up 2.40 (0.75); NS	USA	RCT	1+
Olsen *et al.*, 2004	[648]	Healthy pregnant women with normal or overweight body mass index. Intervention group *n* = 179 Comparison group (historical) *n* = 381	To evaluate the efficacy of an educational intervention aimed at keeping pregnancy weight gain within Institute of Medicine (IOM) recommended limits.	Proportion of women exceeding upper limit of the IOM recommended weight gain range for pregnancy.	Subgroup analysis performed for low-income and high-income groups: Gaining above IOM range: Low income group: OR 0.41 [95% CI 0.20 to 0.81] High income group: OR 1.15 [95% CI 0.69 to 1.93]	USA	Prospective cohort study	2+
Szwajcer *et al.*, 2005	[649]	5 groups of 12 women including women who wanted a child (but not yet pregnant), women in the first, second and third trimester of their first pregnancy and women in the first trimester of their second pregnancy.	Exploration of the nutrition-related information sources and information seeking behaviours of women during pregnancy.	Sources of information used by women and information seeking behaviours.	Women in the first trimester mainly sought nutrition information in the media, such as the internet, books, magazines, 9 month calendars and brochures. In the second trimester, nutrition information was sought from the 9 month calendar (fun and tips) and friends (experienced). Women in the third trimester sought information from friends (information on breastfeeding). Second-time pregnant women relied on their experience, the midwife and books for specific questions.	Netherlands	Qualitative group interview –based study	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Orstead *et al.*, 1985	650	Women attending antenatal clinic at inner-city hospital 1975–1981. Intervention group: *n* = 114 (1975–1977) Control group *n* = 86 (1979–1981)	Evaluation of an intensive nutritional education group programme comprising 15 minute film ('Inside my Mom'), basic dietary advice given by dietitian with explanation for increasing intake of particular foods during pregnancy. Leaflets also given out and women invited to meet with dietitian at each subsequent antenatal visit for further counselling and follow-up.	Main outcomes: Maternal weight ain during pregnancy Birthweight Gestational age at birth	Maternal weight gain: Control group 9.5 kg (± 0.5) vs intervention group 7.0 (± 0.6); *P* < 0.001. Birthweight: Control group 3130 g (± 50) vs intervention group 3231 g (± 47) Birthweight < 2500 g: Control group *n* = 11 vs intervention group *n* = 5, NS	USA Poor quality study design	Retrospective cross-sectional study	2−
Lumley *et al.*, 2004	651	Systematic review of 51 RCTs with 20, 931 pregnant women and 6 cluster RCTs with 7,500 pregnant women	Smoking cessation programmes implemented during pregnancy	Continuation of smoking in late pregnancy Birthweight Incidence of low birthweight Incidence of very low birthweight Preterm birth Stillbirths Perinatal mortality	Continuation of smoking in late pregnancy: RR 0.94 [95% CI 0.92 to 0.96] (*n* = 47 trials) but heterogeneity I²=59.7% Mean birthweight: RR 33.03 [95% CI 11.32 to 54.74] (*n* = 16 trials) Heterogeneity I²=19.8% Incidence of low birthweight (under 2500 g): RR 0.82 [95% CI 0.70 to 0.95] (*n* = 13 trials) Heterogeneity I²=0.0% Incidence of very low birthweight (under 1500 g): RR 1.26 [95% CI 0.69 to 2.32] (*n* = 3 trials) Heterogeneity I²=0.0% Preterm birth (under 37 or under 36 weeks): RR 0.84 [95% CI 0.72 to 0.98] (*n* = 11 trials) Heterogeneity I²=0.0% Stillbirths: RR 1.16 [95% CI 0.71 to 1.88] (*n* = 5 trials) NS Perinatal mortality: RR 1.13 [95% CI 0.72 to 1.77] (*n* = 3 trials) NS	Cochrane review	Systematic review	1++
Acharya *et al.*, 2002	652	Pregnant women	Leaflets and direct counselling given during	Average no. cigarettes	Av. no. cigarettes smoked per day:	UK	Prospective	2+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		booked at 2 inner-city hospitals who reported smoking during current pregnancy. Sample *n* = 63	first-trimester booking visit	smoked per day Smoking behaviour of partner Changes in smoking behaviour following booking anti-smoking intervention Whether or not had read the anti-smoking advice leaflet Receipt of smoking counselling	14 [95% CI 12 to 15] Smoking behaviour of partner: 53 women had partners who were also smokers. Changes in smoking behaviour following booking anti-smoking intervention: 53 women (84.1%) made no change 7 (11.1%) reduced smoking by 3–5 cigarettes per day 3 (4%) gave up smoking altogether Whether or not had read the anti-smoking advice leaflet: All women had seen the leaflet Receipt of smoking counselling: 39 active smokers (62%) reported receiving anti-smoking advice		study	
Rigotti *et al.*, 2006	[653]	Pregnant smokers 18+ years old , and at or below 26 weeks of pregnancy. Intervention *n* = 209 Control *n* = 212	Pregnancy-tailored telephone smoking counselling using motivational counselling compared with a brief counselling session. Phone calls made throughout pregnancy and for 2 months postpartum (mean no. calls=5, mean total contact=68 minutes).	Smoking cessation outcomes Tobacco abstinence (7 days) – cotinine validated and self-report Significant reduction (50% or more)	Cotinine-validated: End of pregnancy OR 1.37 [95% CI 0.69 to 2.70]; *P* = 0.39 3 months postpartum OR 0.93 [95% CI 0.44 to 1.99]; *P* = 1.00 Sustained abstinence OR 1.46 [95% CI 0.54 to 3.90]; *P* = 0.47 Self-report: End of pregnancy OR 1.48 [95% CI 0.88 to 2.48]; *P* = 0.15 3 months postpartum OR 1.11 [95% CI 0.60 to2.05]; *P* = 0.75 Sustained abstinence OR 1.70 [95% CI 0.78 to 3.70]; *P* = 0.18 Significant reduction: End of pregnancy OR 1.49 [95% CI 0.96 to 2.31]; *P* = 0.09 3 months postpartum OR 1.11 [95% CI 0.67 to 1.86]; *P* = 0.69	USA	RCT	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Byrd *et al*., 1993	654	Pregnant smokers selected from 2 community-based clinics Sample *n* = 57 Mean age 23 years (range 17–40) 79% of women black, 17% white. 70% single 77% unemployed	Smoking cessation booklet, videotape and nurse counselling	Smoking cessation outcomes (self-report): Quit Quit attempts Daily mean cigarette consumption Measured at 1 month follow-up, ninth month of pregnancy, 1 month postpartum.	1 month follow-up: Quit: 7 (14%) Quit attempt: 31 (54%) Mean cigarette consumption: 6.2 per day Ninth month of pregnancy: Quit: 10 (18%) Quit attempt: 23 (40%) Mean cigarette consumption: 5.7 per day 1 month postpartum: Quit: 5(9%) Quit attempt: 21 (37%) Mean cigarette consumption: 8.2 per day	USA	RCT	1+
McLeod *et al*., 2004	655	Pregnant women who smoked at the time of conception. Sample *n* = 283 Control group *n* = 57 Breastfeeding education *n* = 57 Smoking cessation education *n* = 68 Combined group *n* = 101	3 interventions: – Programme of education and support for smoking cessation and reduction provided by midwives – Programme of education and support fro breastfeeding provided by midwives – Both programmes	Smoking cessation Smoking reduction Rates of breastfeeding Measured at 28 weeks and 36 weeks of pregnancy, at midwife discharge, 6 weeks and 4 months postpartum	Maintenance of smoking change – Breastfeeding education group (*n* = 57) 28 weeks pregnancy: Adjusted OR 1.52 [95% CI 0.61 to 3.81] 36 weeks of pregnancy: Adjusted OR 1.98 [95% CI 0.80 to 4.86] Midwife discharge: Adjusted OR 0.76 [95% CI 0.32 to 1.79] 6 weeks postnatal: 0.76 [95% CI 0.27 to 2.16] 4 months postnatal: 1.54 [95% CI 0.53 to 4.40] Smoking education group (*n* = 68) 28 weeks pregnancy: Adjusted OR 2.61 [95% CI 1.13 to 6.04] 36 weeks of pregnancy: Adjusted OR 2.71 [95% CI 1.17 to 6.28] Midwife discharge: Adjusted OR 1.32 [95% CI 0.60 to 2.93] 6 weeks postnatal:1.81 [95% CI 0.72 to 4.51], 4 months postnatal: 1.95 [95% CI 0.72 to 5.28] Combined group (*n* = 101) 28 weeks pregnancy: Adjusted OR 1.65 [95% CI 0.74 to 3.67] 36 weeks of pregnancy: Adjusted OR 2.39	New Zealand	Cluster RCT	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					[95% CI 1.08 to 5.31] Midwife discharge: Adjusted OR 0.92 [95% CI 0.43 to 1.95] 6 weeks postnatal:1.48 [95% CI 0.62 to 3.52], 4 months postnatal: 1.48 [95% CI 0.57 to 3.86]			
Goodson *et al.*, 1985	656	Couples attending antenatal classes at 2 hospitals. Sample *n* = 136 Intervention group *n* = 76 Comparison group *n* = 60	Half hour lecture during antenatal classes including a discussion of car safety, demonstration of use of care restraints and car seats for infants, a film showing outcomes of car impact on unrestrained infants using reconstructions and follow up brochure to take home.	Use of care seats and car restraints as tested using a telephone-based questionnaire 4–6 months after birth. Primary questions: 'When riding in a car, how does your child usually ride?' 'The last time you and your baby were in a car, how did your baby ride?'	'How does your child usually ride?': Intervention group: 99% reported use of a child car safety seat. Comparison group: 90% reported use of a child car safety seat. 'The last time you and your baby were in a car, how did your baby ride?': Intervention group: Used a crash-tested car seat: 96.1% (*n* = 73) Comparison group: Used a crash-tested car seat: 78.3% (*n* = 47)	USA	Prospective cohort study	2+
Greenberg and Coleman, 1982	657	Postnatal women on day of discharge from one hospital. Sample *n* = 75 couples (completing 1 questionnaire)	Demonstration of car safety using a mannequin and approved car restraint in usual antenatal class plus 5 minute lecture on child mortality and morbidity associated with car accidents. For latter phase of study parents also received a postnatal car safety programme including short film and pamphlet to read and take home. Nurses on postnatal ward also encouraged to promote car safety.	Use of car safety restraints for baby's journey home from hospital.	Of 75 couples: 27 reported receiving only antenatal information re car safety 30 reported receiving both antenatal and postnatal information 11 reported receiving only postnatal information 7 did not recall receiving any information about car safety. 35/75 couples reported using car restraint on baby's first journey home. Nurses' reported observation of couple leaving hospital verified this for 78% of cases.	USA	Prospective cohort study	2−
Waterson and Murray-Lyon, 1990	658	Women attending antenatal clinic at an inner city hospital between May 1982 and January 1983. Study 1 Sample at 28 weeks of pregnancy *n* = 611 (response rate 59%)	Study 1: Written information (leaflet) regarding alcohol consumption during pregnancy including advice on recommended safe levels compared with written information plus verbal advice from doctor during antenatal consultation. Study 2: Written information (leaflet) regarding alcohol consumption during pregnancy including advice on recommended safe levels compared with written information	Self-reported alcohol consumption at 28 weeks of pregnancy and week before giving birth, measured using questionnaire.	No significant difference between groups. Study 1: Written information only: 63% of women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 6% of women reported an increase in pregnancy from pre-pregnancy levels. Written+verbal information: 68% of women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 8% of women reported an increase in pregnancy from pre-pregnancy levels.	UK	Prospective cohort study	2+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		Postpartum sample *n* = 766 (response rate 74%) Study 2 Sample at 28 weeks of pregnancy *n* = 532 (response rate 50%) Postpartum sample *n* = 361 (response rate 34%)	plus verbal advice from doctor during antenatal consultation plus 4 minute video.		Study 2: Written information only: 69% of women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 5% of women reported an increase in pregnancy from pre-pregnancy levels. Written+verbal+video information: 66% of women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 8% of women reported an increase in pregnancy from pre-pregnancy levels.			
Smits *et al*., 1995	659	Pregnant women with gestational diabetes attending one inner city hospital for antenatal care. Intervention group sample *n* = 82 Comparison group sample *n* = 80	An outpatient education programme (known as the nursing intervention) compared with usual care for women with gestational diabetes provided by obstetricians only. Both models include dietary counselling, training and support for self-monitoring of blood glucose and surveillance of fetal development.	'Healthy woman' – defined as: no pregnancy complications, no prematurity or postmaturity, normal birth, postnatal stay of 1–4 days. Abnormal pregnancy outcome – defined as: Polyhydramnios, pre-eclampsia, premature contractions, vaginal bleeding due to placenta praevia, birth at < 37 weeks or > 42 weeks, labour and birth complications such as induction of labour, caesarean section, forceps or vacuum birth, postnatal stay of 5 days or longer. 'Healthy baby' – defined as: APGAR 8–10 at 1 and 4 minutes, birthweight 10th – 90th centile, postnatal stay 1–4 days, no diagnosed complications. Abnormal outcomes for	A logistic regression procedure was used to control for confounding variables such as proportion of nulliparous women and women requiring medication for gestational diabetes since these were found to be significantly different between the 2 study groups. After controlling for confounding factors no significant differences were found between the 2 study groups regarding incidence of abnormal pregnancy or abnormal outcomes for the baby (figures not reported). Confounding variables were found to have a significant impact on outcomes: Nulliparous women had a 3.31 times greater risk of an abnormal pregnancy outcome. Women taking medication for gestational diabetes had a 2.69 times greater risk of an abnormal pregnancy outcome than women with gestational diabetes who were not taking medication. Women with gestational diabetes who experienced complications during pregnancy were found to have a 4.2 times greater risk of having a baby with one or more abnormal outcomes.	USA	Retrospective descriptive study	2−

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
				baby – defined as: APGAR 7 or less at 1 and 5 minutes, birthweight < 10th centile or > 90th centile, postnatal stay of 5 days or longer, hypoglycaemia (blood glucose < 2.1 mmol/litre (37 mg/100 ml), respiratory distress syndrome (requiring oxygen), polycythemia (haematocrit > 65%), birth trauma including shoulder dystocia.				

How information is provided antenatally

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Thornton *et al.*, 1995	12	Women booking before 15 weeks of gestation. Sample *n* = 1691 *n* = 567 in control group *n* = 563 in individual group *n* = 561 in class group	To compare routine information given in antenatal clinics at booking visit by the doctor or midwife (control group), extra information given individually before 16 weeks or at an extra hospital visit by a research midwife (individual group), and extra information given to a group of 4 to12 women separate from the routine antenatal clinics (class group)	Attendance at extra information sessions; uptake rates of prenatal tests; levels of anxiety; understanding; satisfaction with decisions taken.	Attendance at the extra sessions was low (overall 52%) and was lower at classes than at individual appointments (adj. OR 0.45, 95% CI 0.35 to 0.58). Uptake of ultrasound at 18 weeks was almost universal (99%) and not affected by either intervention. Low uptake of Down's syndrome screening in the control group improved slightly after the intervention in the individual group (OR 1.45, 95% CI 1.04–2.02) but was not affected by extra information given in classes. High uptake of cystic fibrosis screening at the baseline was lowered both in the individual group (OR 0.44, 95% CI 0.20–0.97) and the class group (OR 0.39, 95% CI 0.18–0.86). Women in the individual group were found to have significantly reduced levels of anxiety at 20 weeks (*P* = 0.02) compared to the control group, and thereafter anxiety was reduced but not significantly	UK	RCT	1+
Graham *et al.*, 2000	660	Low- and high-risk pregnant women booking appointment for antenatal care Initial sample *n* = 875 Only 64% of women returned all 3 questionnaires giving final samples of Control group *n* = 358 Intervention group *n* = 376	To compare touch screen information provision and information leaflet with leaflet only.	Primary outcome measured was women's informed decision making on prenatal testing as measured by their uptake and understanding of the purpose of 5 screening tests (ultrasound scan at booking, serum screening, detailed anomaly scan, amniocentesis and chorionic villus sampling). Secondary outcomes included woman's satisfaction with the information and their anxiety levels.	More women in the intervention group underwent detailed anomaly scan compared to the control group (94% versus 87%, *P* = 0.01), but for rest of the screening tests uptake rates were similar. All women in the trial had good baseline knowledge of the screening tests and this increased significantly in both the groups after the intervention, but no apparent greater gain in knowledge was seen among women in the intervention arm compared to the control arm. Levels of anxiety declined significantly among the nulliparous women in the intervention group (*P* < 0.001). Both groups reported high level of satisfaction with the information leaflets (> 95%), and a similar proportion of women in the intervention group reported that they would recommend the touch screen to other women. T	UK	RCT	1+
O'Cathain *et al.*, 2002	13	12 maternity units each having more than 1000 deliveries annually were grouped into 10 clusters	To assess the effect of 10 evidence-based leaflets on promoting informed choice in pregnant women.	Primary outcome measured was the change in proportion of women who reported exercising informed choice, while secondary outcomes were women's levels of knowledge, satisfaction with information, and possible consequences of informed	Proportion of women who reported exercising informed choice increased slightly after the intervention in both the units, but there was no significant difference in the change between the two groups for either the antenatal or the postnatal sample. A small increase in satisfaction with information was observed in the antenatal sample of the population in the intervention units compared to the control units (OR 1.40, 95% CI	UK	Cluster RCT	1−

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
				choice. Outcomes were assessed using a postal questionnaire	1.05 to 1.88). However due to operational difficulties, just 75% of the women in the intervention units reported receiving at least one of the information leaflets.			
Glazier, 1997	661	Women with singleton pregnancies less than 18 weeks gestational age, recruited from 6 different sites in both urban and rural areas.	To evaluate use of a pamphlet on triple-marker screening in the intervention group, or similar appearing pamphlet on daily activities during pregnancy in the control group.	The primary outcome was woman's knowledge as tested using the Maternal Serum Screening Knowledge Questionnaire (a validated 14-item scale).	Mean overall knowledge score was significantly higher in the intervention group (0.89 versus 0.52 on a scale from -2 to +2, $P < 0.001$) compared to the control group. Also women receiving pamphlet on triple screening had higher scores for the domains of test characteristics, ancillary tests, and target conditions ($P < 0.001$) but not for the domains of indication and timing of tests	Canada	RCT	1+
Bekker *et al.*, 2004	662	Pregnant women receiving a screen positive maternal serum screening (MSS) test for Down's syndrome (risk $\geq$ 1 in 250) Intervention *n* = 133 Control *n* = 64	Comparison of a decision analysis consultation using three prompts was employed – a decision tree representing test options and consequences, a utility elicitation question prompting women to choose between the burden of having a child with Down's syndrome and that of pregnancy termination, and a threshold graph identifying the alternatives with usual consultation.	Main outcomes measured were risk perception, test decision, subjective expected utilities, knowledge, informed decision making, conflict in decision making, anxiety, and perceived usefulness of consultation.	Similar proportion of women chose to have a diagnostic test – 47/58 (81%) in the control group versus 48/59 (81%) in the intervention group. Choice of test did not differ by group allocation, but decision analysis women evaluated more information during their consultation both positively and negatively than those in the control group (positive evaluation – mean score 3.18 versus 2.55, F=6.30, $P = 0.01$; negative evaluation – mean score 3.00 versus 2.37, F=5.98, $P = 0.02$). These women also perceived the risk more realistic ($P = 0.05$) and had a lower decisional conflict over time. Decision analysis consultations lasted about 6 minutes longer but women did not perceive consultations to be any more or less directive, useful or anxiety provoking than the routine ones	UK	RCT	1+
Leung *et al.*, 2004	663	All Chinese women attending a prenatal clinic in a tertiary hospital before 20 weeks of gestation. Intervention *n* = 100 Control *n* = 101	Comparison of information leaflet, 30 minute video and then browsing IMDA (intervention group) or information leaflet and watching 30 minute video only (control group).	Primary outcome evaluated was uptake of the screening test, and secondary outcomes measured were women's initial decision, understanding, and satisfaction with the information that they received.	There were no significant differences in the initial decision for and the final uptake of the screening test between the intervention and the control group (P value for all the tests > 0.05). After watching the video 54.1% of women in the control group and 55.1% in the intervention group reported that they had no more questions. After browsing the IMDA the proportion of women having no more questions increased to 77.0% ($P < 0.001$), and 86.6% of women agreed that IMDA was user-friendly and 78.9% that it was acceptable. A higher proportion of younger women (age < 35 years) accepted IMDA compared to those over 35 years of age ($P = 0.03$), but the difference was not significant after adjusting for confounding variables.	Hong Kong, China	RCT	1+
Hewison *et al.*, 2001	664	Consecutive pregnant women referred for antenatal care.	Comparison of video sent to women at home before the hospital booking visit (intervention group) with the control group who received usual care.	Outcomes evaluated were test uptake (using record linkage), knowledge (multiple-choice	No statistically significant difference was observed in the screening uptake rate between the two groups (64.2% versus 64.7%). Questionnaires were sent at 17–19 weeks only to the first 1200	UK	Quasi RCT	1−

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		n = 993 women in video group *n* = 1007 in control group		questionnaire with 12 items), worries (multiple-choice questionnaire with 16 items), and anxiety (Hospital Anxiety and Depression scale).	women randomised in the two groups, and after exclusions the sample size was 499 (video group) and 552 (control group). Rate of questionnaire completion was similar between the two groups. Knowledge about screening was increased in the video group with a mean score of 7.3 compared with 6.7 in the controls ($P = 0.0005$), but there was no difference between the two groups in specific worries about anomalies in the baby, and general anxiety.			
Andersen, 1989	[665]	All women beginning antenatal care by 36 weeks and not at high risk for preterm delivery were enrolled for the study and offered a class. *n* = 487	Class about recognising the signs and symptoms of preterm labour – 15 minute videotape presentation followed by a 15 minute discussion led by a registered nurse staff member where several printed educational materials were also given.	Outcome evaluated were the rates of preterm delivery and low birthweight.	There were no significant differences between the class attendees and non-attendees for the baseline demographic and obstetric variables. Women attending classes had babies with a higher mean birthweight ($P = 0.03$) and gestational age ($P = 0.12$), but improvement in gestational age did not reach statistical significance. The preterm birth rate was reduced by 17% and low birthweight rate by 27% among women attending the classes compared to the non-attendees, but these differences were statistically not significant	USA	Cohort study	2−
Simpson *et al*., 1998	[666]	All pregnant women booked in a tertiary hospital in the UK were invited to participate in the trial. Sample *n* = 3024	Four different combinations of providing information using a leaflet sent with booking information package ('all blood tests information' or 'HIV specific test information') and discussion with a midwife ('Minimal' or 'Comprehensive') were compared.	Main outcomes were uptake of testing and women's knowledge of HIV, satisfaction with consultation, and anxiety.	Uptake rates were 6% for the control group and each of the methods of directly offering the test resulted in a higher uptake than in the control group (χ^2 test, df = 4, $P < 0.0001$). However there was no significant difference between the four groups where the test was offered directly (χ^2 test, df = 3, $P = 0.37$). The best independent predictor of uptake was being directly offered the test. General knowledge of HIV was good and did not differ significantly by the method of offering testing, but specific knowledge about HIV and benefits of testing increased with the amount of information given (χ^2 test of linear trend, df = 4, $P < 0.001$). No significant difference was found regarding anxiety and satisfaction	UK	RCT	1+
Hunt *et al*., 2005	[667]	Sample *n* = 50 clinicians *n* = 40 pregnant women Observation of 101 genetic counselling sessions	To examine how clinicians assure informed consent prior to antenatal genetic testing and communicate information regarding genetics/inheritance and risk calculation.	Information provided during consultation.	Clinicians discussed all the essential elements of information giving in only 59% of the consultations. Elements most consistently covered were that the test is optional, risks of procedure, and risks for the anomaly, while the least covered elements were the nature of anomaly and alternatives to amniocentesis. Patients overall knowledge score averaged about 53% and the elements for which they showed most complete knowledge included reasons for doing amniocentesis, test is optional, nature of the invasive procedure, and what information can this test give. The elements least completely discussed included risk of anomaly,	USA	Qualitative descriptive study	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					alternatives to amniocentesis, and nature of the anomaly. But there was no statistical correlation between the completeness of information included in consultant's consultations and the level of knowledge exhibited by the patients during the interviews (Pearson correlation = 0.204, *P* = 0.289).			
Williams *et al.*, 2002	[668]	Health practitioners whose work was related directly or indirectly to perinatal care Sample *n* = 56	To explore the information given to pregnant women and their partners about Down's syndrome from the perspective of healthcare practitioners	Perceptions of healthcare providers of information given.	Practitioners felt that more time was spent explaining the complexities of the actual screening process rather than the condition being screened. Though many practitioners felt that their way of providing information influenced decision making by pregnant women, they seldom made any positive and realistic statement about the condition. Most practitioners themselves had little time and practical experience of dealing with DS cases. They relied on medical textbooks, leaflets and articles for knowledge and these sources usually focused on the potential problems of the syndrome and its management strategies.	UK	Qualitative descriptive study	3
Stapleton *et al.*, 2002	14	A total of 886 episodes of consultations with pregnant women were observed – 653 held by midwives, 167 by obstetricians and 66 by the obstetric ultrasonographers. 383 face-to-face interviews were conducted (173 childbearing women, 177 midwives, 28 obstetricians, 12 obstetric ultrasonographers, and 3 obstetric anaesthetists).	To examine the use of evidence-based information leaflets and to understand the social context in which the leaflets were used.	How the leaflets were used and how informed choice and decision making occurred in practice	Though the health professionals were positive about the leaflet and their potential in helping women make informed choices, they were seldom used to maximum effect in clinical practice. The various reasons observed were the time constraint, unavailability of choice in regular practice, disagreement of staff with its content or an option given in it, and their distribution usually in a concealed manner or 'wrapped' up with other advertising material. Health professionals were also observed to influence decision making in pregnant women towards technological intervention by conveying information which either minimised the risk of the intervention or emphasised the potential for harm without the intervention. They reinforced notions of 'right' and 'wrong' choices instead of 'informed choices' and this was promoted by their fear of litigation. A strong hierarchy was observed within the maternity services with the obstetricians at the top, midwives and health professionals other than doctors in the middle, and pregnant women at the bottom.	UK	Qualitative descriptive study	3
Jaques *et al.*, 2004	[669]	Pregnant women	To examine whom women perceived as influencing their decisions about antenatal	Women's reports of who influenced their decision	More than 90% of women in both the groups reported that they themselves had a strong	Australia	Retrospective cohort study	2+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		from eighteen hospitals in Australia at approximately 24 weeks gestational age and over 37 years of age at the estimated date of delivery. *n* = 539 women undergoing prenatal testing (tested group) *n* = 185 not going for prenatal testing (untested group).	testing for fetal anomalies, with whom they would have liked to have talked more and what sources of information they preferred.	making, who they would have liked to talk with more and preferred sources of information.	influence on their decision to be tested or not, and 70% reported their partner as strongly influencing their decision. Statistically no significant difference was observed between the two groups for the above parameters, but significantly higher proportion of women in the tested group were influenced by their doctor or genetic counsellor ($P < 0.001$ for both) and a friend or a nurse ($P < 0.01$ for both). 35.7% of women in the tested group were more likely to talk to other women who have had the tests as compared to 21% of women in the untested group ($P < 0.001$). Higher proportion of tested women would have preferred to talk to a genetic counsellor (9.5% versus 8.6%, $P = 0.002$), while women in the untested group were more likely to talk to a pastoral carer (2.5% versus 10.6%, $P < 0.001$). There were no significant differences between the groups with respect to a specialist, general practitioner, friend, nurse/midwife or other pregnant women. In both the tested and the untested groups, the preferred source of getting information was face-to-face discussion or counselling (69.1% tested group, 47.4% untested group), and the difference between the two groups was statistically significant ($P < 0.001$). The second preferred choice was pamphlet (48.7% tested group, 42.8% untested group, $P = 0.18$) followed by video (35.2% tested group, 24.9% untested group, $P = 0.01$).			

Women's views of general and specific antenatal information provision

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Bennett *et al.*, 2006	674	African-American women receiving Medicaid who had given birth in the previous 48 hours Sample *n* = 237	To explore effects of low literacy level on uptake and perceptions of antenatal care.	Uptake of antenatal care. Women's views and experiences of antenatal care. To determine literacy level women undertook a literacy (reading) assessment as part of the interview (Rapid Estimate of Adult Literacy in Medicine).	Cultural consensus analysis of findings (*n* = 9 women with low literacy level; *n* = 31 women with higher literacy) (from most to least salient): Finding out if everything is okay; long wait; questions (communication with carer); needles (blood tests); woman's weight and hearing the baby's heartbeat. Cultural consensus factor analysis returned a single factor (eigenvalue 0.881, SD 0.058) showing a high degree of shared knowledge among participants of lower and higher literacy level. Findings from the focus groups confirmed these salient factors across both subgroups. Items associated with communication between women and their carers were identified as central when women were discussing obstacles to care.	USA	Qualitative study – concurrent mixed methods (including individual face-to-face interviews and focus groups).	3
Vonderheid *et al.*, 2003	675	African-American and Mexican-American women living on a low income and booked to a 'low-risk' antenatal clinic. Sample *n* = 159 *n* = 112 African-American women *n* = 47 Mexican-American women. 72% younger than 24 years. 65% multiparous. 39% less than 12 years education 45% household incomes of less than $1000 per month.	To compare issues women to discuss during antenatal consultations with issues actually discussed.	Items identified by women as something they wanted or needed information about and whether or not the topic was discussed (identified from a list of 27 health promotion topics).	Note: Statistical analysis performed using the Sign test for paired data. Although *P* values are given values for the Sign statistic are not reported. Significantly more women wanted or needed information but did not discuss using seatbelts safely, dealing with stress and conflict, family planning, and caring for the new baby. Women did not want or feel they needed information but discussed taking vitamin/mineral supplements, eating specific food groups, drinking adequate amounts of water, stopping specific substance use. More differences were reported between information wanted or needed and information discussed for African-American women compared with Mexican-American women (adjusted regression analysis R^2=0.39, $P < 0.001$).	USA	Cross-sectional interview-based descriptive study.	3
Benn *et al.*, 1999	676	Volunteer sample of women planning a pregnancy (*n* = 7); pregnant	Investigation of women's information needs about pregnancy issues.	Identified information needs Sources of information	Information sources: Midwife (37%) Friends (23%) GP (13%).	New Zealand	Cross-sectional questionnaire survey	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		women (*n* = 30 and women in first 3 months postnatally.		Usefulness of information received	The theme of reassurance was prominent amongst women's responses. Topics that pregnant women wanted information about included: Knowing what is normal How to prepare for birth Coping with labour and birth How to look after the baby What to expect after birth. Multiparous women identified some different information needs including: Coping with morning sickness Self care during pregnancy Birth after caesarean section Financial needs and options.			
Ussher *et al.*, 2006	[677]	Pregnant smokers and pregnant recent ex-smokers. Sample *n* = 443	To identify perceived barriers to and benefits of a smoking cessation course.	Responses to a 20-item decisional-balance measure	Most frequently endorsed barriers to attending a smoking cessation course: 'I am afraid I would disappoint myself' (54.2%), 'I do not tend to seek help for this sort of thing' (40.6%), 'I do not have access to such a course' (40.5%) 'I do not have time to attend the appointments' (39.8%). The 2 statements with the least agreement were: 'People that are close to me would not support me attending such a course' (9.8%) and 'Stopping smoking is not particularly important to me' (7.6%). The most frequently endorsed benefits of attending a smoking cessation course were: 'Advice about managing my cigarette cravings would be useful' (74.2%); 'Praise and encouragement with stopping smoking would be helpful' (70.7%); 'Advice about safe medications to help me stop smoking would be useful' (69.2%) and 'Someone my checking my progress would be helpful' (64.5%). Respondents who agreed with the benefits of attending a smoking cessation course were significantly more likely to express an interest in receiving help of this kind (ANOVA, all at $P < 0.01$).	International (mainly UK and USA)	Web-based cross-sectional survey	3
Cates *et al.*, 2004	[678]	Pregnant women	Evaluation of women's responses to health education messages regarding listeriosis.	Knowledge regarding: Listeriosis infection	Few women reported receiving information about food safety from healthcare professionals	USA	Descriptive study – focus groups	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		Sample *n* = 63 64% multiparous 87% caucasian		Food safety Sources of information	contacted during pregnancy, and none remembered receiving information specifically about listeriosis. Commonly cited sources of information about food safety included books and magazines on antenatal care. Women suggested that written information on listeriosis be provided as part of the antenatal booking information package. Participants also felt that knowledge of listeriosis should be improved amongst the general population and suggested using the media to deliver public health food safety messages.			
Orr and Simmons, 1979	[679]	Women between 34 and 38 weeks of pregnancy. Sample *n* = 92	Investigation of women's perceptions of dietary information and advice provided during pregnancy.	Women's perceptions of need for dietary advice – generally and personally. Women's satisfaction with dietary advice received.	75% of women felt pregnant women in general needed dietary advice. 50% of women felt they personally needed such advice. The most common reasons for this response was that advice was remembered from a previous pregnancy (39%) or that the woman already had a good knowledge of dietary requirements (35%). Only 11% of women reported that they had acquired dietary information from other sources (eg. books/leaflets). One third of respondents reported that complying with dietary advice worried them 'a lot', with the most common concern being excessive weight gain during pregnancy. A similar proportion of women reported difficulty complying with dietary advice, especially that relating to dietary restrictions. When asked about their satisfaction with dietary information only 3 women reported any shortfall. Only 36 women (39%) were able to recall specific dietary information.	USA	Cross-sectional descriptive interview-based study.	3

The effectiveness of antenatal education/classes

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gagnon, 2001	[27]	5 RCTs including 168 women	Any structured educational programme relating to preparation for childbirth, caring for a baby or parenthood.	Knowledge acquisition Anxiety Sense of control Participation in decision making Pain and pain relief Obstetric interventions during labour Breastfeeding Psychological adjustment following childbirth	The only outcomes reported were knowledge acquisition and competencies relating to care of baby. Satisfaction with preparation for motherhood improved following maternal role preparation vs no preparation: WMD 21.59 points [CI 11.23 to 31.95] (1 study, *n* = 16, response rate 73%). Maternal attachment behaviour more frequent when maternal attachment preparation included in classes: WMD 52.60 points [CI 21.82 to 83.38] (1 study, *n* = 10. Knowledge acquisition: Fathers' preparation classes vs no classes WMD 9.55 [CI 1.25 to 17.85] (1 study, *n* = 28) Expanded childbirth education classes vs traditional classes: WMD 1.62 [CI 0.49 to 2.75] (1 study, *n* = 48)	Meta-analysis not possible due to heterogeneity of studies.	Systematic review of RCTs	1+
Spiby *et al*., 2003	[680]	Women who had given birth to their first baby in the preceding 72 hours Sample *n* = 121	3 coping strategies taught during antenatal classes during labour, and reasons for discontinuing where appropriate.	Women's reports of using and discontinuing the following coping strategies: Breathing technique Postural change Relaxation techniques	88% of women (*n* = 106) used 'sighing out slowly' breathing, 51% (*n* = 61) used change of position and 40% (*n* = 48) used a relaxation technique. Relaxation techniques were reported by 33% of the women who used it as being effective in providing relaxation. Only 12% of women who used this technique reported that it provided a distraction. Change of position was reported by 14% of women as providing a distraction, while only 6% found it relaxing. Change in position was the most effective in terms of pain relief with 22% of women reporting that it provided some pain relief. 19% of women who used 'sighing out slowly' breathing and 12% of those who used relaxation techniques reported that they provided some pain relief.	UK	Retrospective descriptive interview-based survey	3
Maestas L, 2003	[681]	Women attending 10 sets of antenatal classes Sample *n* = 57 pre-test questionnaire Sample *n* = 42	Antenatal classes.	Women's beliefs and perceptions of childbirth: Fear of childbirth; childbearing locus of control; passive compliance vs active participation in childbirth; personal values about childbearing and childrearing	Women's mean scores for fear of childbirth and passive compliance vs active participation decreased significantly after participation in the antenatal classes: Fear (*n* = 37) 9.68 vs 8.32, *P* < 0.05; Compliance vs active participation (*n* = 38) 3.84 vs 2.89, *P* < 0.02). No significant change in scores for locus of control (*n* = 41;	USA	Descriptive before–after study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		post-test questionnaire.			x=1.98 vs 1.49) and personal values about childbearing (*n* = 39; x=4.03 vs 3.97).			
Hart M, 1994	682	Couples enrolled in antenatal classes at a tertiary hospital. Sample *n* = 119 couples	Antenatal classes.	Self-care agency as measured using the Appraisal of Self-Care Agency scale (Evers, 1986)	Self-care agency was very high in women and men both before and after attendance at a series of antenatal classes. Women: no significant difference between scores obtained before and after antenatal classes (mean score pre-class 97.1; post class 97.5). Men: significant increase following class attendance (mean scores 91.3 and 94.7).	USA	Descriptive before–after study	3
Rolls and Cutts, 2001	683	Couples enrolled in antenatal classes in a public hospital Sept. – Oct. 1998. Sample *n* = 70 couples *n* = 34 participant-led classes (intervention) *n* = 34 traditional classes (comparison)	Participant-led antenatal classes compared with traditional classes	Knowledge of pregnancy issues eg. smoking, alcohol intake, diet; Information for labour eg. birth positions, pain relief, role of the midwife; Postnatal issues eg. body changes after birth, relationships with partner; Infant care eg. bathing, dressing, holding and settling a baby.	Women who attended participant-led antenatal classes reported significantly higher levels of increased knowledge relating to childbirth, baby care and becoming a parent than women attending traditional classes (F (1, 59)=11.89, *P* < 0.01). This difference was not evident for men attending the classes (F (1, 57)=2.59, NS). Women in the intervention group also reported higher level of preparedness for the experience of pregnancy (t=3.05, *P* < 0.01) and for self-care following birth (t=3.12, *P* < 0.01). No differences were found for preparedness for labour, birth, mood and lifestyle changes following birth, or caring for the baby.	Australia	Prospective longitudinal before–after study	3
Redman *et al.*, 1991	684	Phase 1: All nulliparous women giving birth in a large teaching hospital in a 4 month period. Sample *n* = 325 women (response rate 91%) Phase 2 : Women and their partners attending classes over a 3 month period. Sample *n* = 117 women (response rate 82%) Sample *n* = 82 men (response rate	Antenatal education programme	Phase 1: Characteristics of attenders Phase 2: Changes in knowledge (eg. what to do when you think you are in labour; care during labour and what to expect during labour; what to expect after the birth) Satisfaction of participants	Phase 1: 82% nulliparous women attended antenatal classes. Women who chose to attend classes were older, of a higher educational level, more likely to be married or living as married, and more likely to have private health insurance than women who chose not to attend. Phase 2: Women's and men's knowledge of issues relating to pregnancy and childbirth increased significantly following attendance at antenatal classes across all topic areas measured. Most of the course components were rated as either 'very' or 'quite' useful by the majority of respondents. Of the 24 items included, 17 were rated as very or quite useful by at least 70% of participants. Items relating to labour were rated as very or quite useful by over 90% of participants. Items with fewer ratings of very or quite useful were: family planning; baby health centres; and nutrition and weight gain.	Australia	Phase 1: Cross-sectional survey Phase 2: Before–after longitudinal questionnaire-based study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		(58%).						
Schmied *et al.*, 2002	685	First-time parents participating in hospital's antenatal programme Sample *n* = 59 (21 couples plus 2 single women) Response rate = 64% for the intervention group and 47% for the comparison group.	Expanded course of antenatal classes aimed at preparing couples for parenting and early lifestyle changes following childbirth compared with traditional classes.	Satisfaction with care eg. 'Labour managed as I liked' 'Pain managed as I liked'. Psychological outcomes following birth eg. 'Evaluation of parenting experience'; 'Life change''	Significantly more women in the intervention group stated that their labour had been 'managed as [they] liked' (84% vs 43%; $\chi^2 = 5.4$, $P < 0.05$). No significant differences were found between the 2 groups regarding women's experience of pain or views of pain relief used during labour (again figures not given). Women in the intervention group were also more likely to rate their parenting experience more highly than women in the control group (mean score on parenting rating scale x=89.4 vs x=83.6; t(31)=2.06, $P < 0.05$). No significant difference was seen between the 2 groups regarding adjustment to life change following birth (mean score x=38.0 vs 37.0; t(31)=0.36, NS).	Australia	Descriptive cross-sectional study	3

Women's experiences and views of antenatal classes

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Schneider Z, 2001	686	Pregnant women attending antenatal classes Sample *n* = 13 Most women well educated (12/13 had a degree or diploma) 11 were in full-time employment. 12 of the women were Caucasian and 1 was Australian-Chinese. All were booked for a hospital birth.	Antenatal classes	Women's experience of classes, what they considered to be important and usefulness of information provided.	Most women were satisfied with the amount of information provided about labour and pain relief. For some women the emphasis some antenatal teachers placed on labouring without drugs was a concern. Women were less pleased with the amount of information provided concerning breastfeeding and care of the new baby, and they contrasted this lack of information with the large amount of information given about labour and birth. Women's responses indicated that more practical advice, including practical advice on breastfeeding and what to expect when feeding, would have been welcome. The women felt classes had not prepared them for labour. The preference for more practical information and advice about infant feeding (not just breastfeeding), how to handle and communicate with your baby and general baby care (eg. bathing, playing with your baby) was also commonly expressed. Lack of information about discomfort following birth was also noted.	Australian	Longitudinal qualitative study – grounded theory approach	3
Lee H, 1998	687	All women giving birth at the 2 study hospitals in a 1 month period in 1997. 143 completed questionnaires were returned, a response rate of 62% (56%of the target population). Of the respondents, 50 had attended antenatal classes (35%). Sample *n* = 33 women who had attended all essions.	Antenatal classes	Women's reasons for attending classes, expectations of classes and whether expectations were being met.	All women stated that they attended classes in order to gain information. Other important reasons for attending classes were: 'to reduce anxiety or increase confidence' (94%), 'to have partner present and involved' (85%); and 'to have a more positive emotional experience' (76%). Expectations had been met for the majority of women. Most women reported that they felt the amount of information was right regarding normal labour (97%), pain relief in labour (91%), choices in decision making during childbirth (88%), and complications/interventions during labour and birth (91%). There were 3 areas where a fair proportion of women reported that the amount of information proved was too little: relaxation and breathing for labour (33%), nutrition/diet (27%), and infant care (21%).	Australia	Retrospective cross-sectional questionnaire survey	3
Stewart P, 1993	688	All women attending antenatal classes in the study	Antenatal classes including community-based	Women's reasons for not attending early (first-trimester) antenatal classes and women's interest in	3 most common reasons women gave for not attending early pregnancy classes were: insufficient knowledge about the classes (69%); early classes were not considered useful	Canada	Cross-sectional questionnaire survey	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		area during one specified week in 1990. At the time the survey was undertaken 46% of the classes were in the early pregnancy section of the course. Sample *n* = 437, a response rate of 98.9%.	and hospital-based classes, some of which charged a registration fee. All courses included early pregnancy classes which focused on pregnancy and healthy lifestyle issues, although women could choose when to join the course.	attending early classes	(29%); and early classes not convenient (18%) (women were invited to give multiple responses if appropriate). An open-ended question asking for ideas on how to encourage women to attend early classes elicited the following responses: encourage doctors to promote early classes and using a public awareness programme to advertise the content and availability of the classes. Women reported that they would like information in early classes on how the baby develops, signs and symptoms of miscarriage, nutrition and exercise.			

4 Provision and organisation of care

4.6 Gestational age assessment

Clinical question: What is the diagnostic value and effectiveness of screening methods in determining gestational age?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Alexander, 1995	690	A sample size of 150 898 cases that contained both clincal examination- and LMP-based values with a range of 20 to 45 weeks were selected.	Examined the comparability of the LMP-based and the clinical examination of gestational age as collected on one state (South Carolina's) vital records. They also investigated the concordance between these measures and explored whether socio-demographic or delivery hospital characteristics influenced their agreement.		LMP-based measure produced higher percentages of preterm and post-term births. More than 60% of the last menstrual period-based preterm births were classified as preterm by the clinical estimate. The sensitivity of the clinical estimate was 27% for post-term births. The overall concordance (the percentage of cases with the same value for both measures) was 47%, but it varied considerably by gestational age. Between 30 and 35 weeks, the clinical estimate exceeded the last menstrual period-based value by 2 weeks or more for more than 40% of the cases. Concordance also varied by race of mother, hospital delivery size, trimester prenatal care began, and birthweight.		Retrospective study	II
Olesen, 2006	691	657 spontaneous deliveries were used for analysis, *n* = 339 and 318 in the certain and uncertain LMP groups, respectively. Healthy women who were enrolled at the first visit during their pregnancy underwent ultrasound	compared the predicted date of delivery LMP, CRL and BPD with the actual date of delivery in a population of pregnant women divided into those with certain and those with uncertain LMP		median prediction errors (predicted – actual date of delivery) estimated by ultrasonography in the first and second trimesters and by corrected LMP according to cycle length were 2.32, 0.16, and 3.00 days, respectively,		Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		examinations in the first and second trimesters.			in women with certain LMP, and 1.71, 0.00, and 3.00 days, respectively, in women with uncertain LMP. The median gestational age at delivery estimated by ultrasonography in the first and second trimesters and by corrected LMP according to cycle length was 282, 280, and 283 days, respectively, in both groups.			
Taipale, 2001	692	17 221 non-selected singleton pregnancies at 8–16 completed weeks were scanned by ultrasound. The last menstrual period (LMP) was considered certain in 13 541 and uncertain in 3680 cases.	Compared different ultrasound measurements CRL, BPD, and FL, for predicting the day of delivery at 8–16 weeks of gestation. Also compared them to prediction by certain and uncertain LMP		at all gestational ages, ultrasound was superior to certain LMP in predicting the day of delivery to at least 1.7 days. CRL of 15–60 mm was superior to BPD, but at a later gestation BPD (at least 21 mm) was more precise. Regression models using a combination of any two or three ultrasonic variables did not improve accuracy of prediction. When ultrasound was used instead of certain LMP, the number of post-term pregnancies decreased from 10.3% to 2.7% ($P < .001$).		Prospective study	II
Savitz, 2002	53	The women were enrolled at 24 to 29 weeks of gestation. 3147 women had both LMP and early ultrasound scan and were recruited and interviewed in the comparisons of pregnancy dating.	4 algorithms were compared: LMP only, ultrasound scans only, use of LMP except when there was a disparity of ≥ 7 days in the estimated date of confinement in which case ultrasound scanning was used and the use of LMP except when there was a disparity of ≥ 14 days in the estimated date of confinement in which case ultrasound scanning was used.	Accuracy of algorithms for the assignment of gestational age with the use of the last menstrual period and early ultrasound information. There was an evaluation of digit preference in the last menstrual period dates and a comparison of mean gestational age, preterm and post-term categories with the use of kappa statistics, difference between actual and expected delivery date, and birthweight among subgroups with discrepant assignments.	last menstrual period reports showed digit preference, assign gestation 2.8 days longer on average than ultrasound scanning, yield substantially more post-term births (12.1% vs 3.4%), and predict delivery among term births less accurately. Misclassification of births as post-term was more common in younger women, those of non-optimal pre-pregnancy body weight, cigarette smokers, and women who reported last menstrual period using preferred dates of the month.		Prospective cohort study	II
Neufeld, 2006	693	Gestational age at birth was	Regression modelling was used to	Best method for gestational age	Gestational age estimated by	When trained field personnel	Longitudinal	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		determined by an early second-trimester measure of BPD, LMP, the Capurro neonatal examination and symphysis–fundal height (SFH) for 171 woman–infant pairs	determine which method provided the best estimate of gestational age using ultrasound as the reference.	estimation	LMP was within ±14 days of the ultrasound estimate for 94% of the sample. LMP-estimated gestational age explained 46% of the variance in gestational age estimated by ultrasound whereas the neonatal examination explained only 20%.	assist women to recall their date of LMP, this date provides the best estimate of gestational age. SFH measured during the second trimester may provide a reasonable alternative when LMP is unavailable.	study	
Mustafa, 2001	694	476 034 computerised birth records from 20–44 weeks of gestation	Concordance between gestational age data obtained by clinical estimate with data calculated from the date of the last menstrual period (LMP) as recorded on birth certificates		The overall exact concordance of 46% between the two measurements. For +1 week it was 78%, and for +2 weeks it was 87%. The incidence of prematurity with menstrual gestational age was 16%, while it was 12% with the clinical estimate. About 47% of the LMP-based preterm births were classified as term by clinical estimate. 83% of clinically estimated preterm births were also preterm by LMP-based gestation.	Agreement between menstrual and clinical estimates of gestational age occurs most often close to term, with significant disagreement in preterm and post-term births.	Retrospective study	II
Johnsen, 2006	695	4179 consecutive women attending the second-trimester routine ultrasound examination at 17–20 weeks of gestation were included	The difference between the time of delivery and the predicted date of delivery calculated with HC and BPD (based on pregnancy duration of 282 days) was noted.	Whether the HC predicts the day of confinement better than BPD	for the group of spontaneous onset of labour (*n* = 3336), 5.6% were post-term (≥ 296 days) according to HC and 5.7% according to BPD. Premature births (< 37 weeks) were 3.9% with HC measurement and 3.6% with BPD method. For the entire group, the median differences between actual and predicted delivery with HC and BPD were 0.9 and 1.2 days, respectively. In the spontaneous onset of labour group the corresponding differences were 0.9 and 1.4 days. The difference between the HC and BPD methods was significant (*P*< 0.0001).		Prospective study	II
Nguyen, 1999	696	14 805 spontaneous	Compared the error in the predicted		The average discrepancy	It was found that none of the	Retrospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		deliveries with a reliable LMP were included and their predicted dates of delivery were calculated using two assumptions: average length of pregnancy of 280 and of 282 days.	date of delivery using BPD with the error using the LMP		between predicted date of delivery from BPD and LMP and date of spontaneous delivery was 7.96 and 8.63 days, respectively ($P < 0.0001$). Adding 282 instead of 280 days to the first day of the LMP reduced the error of the LMP method from 8.63 to 8.41 days, reduced the percentage of classified post-term deliveries from 7.9 to 5.2% and increased the preterm births from 3.96 to 4.48%.	models of combined use of LMP and BPD were superior to the use of BPD alone.	study	
Rowlands, 1993	697	106 women	The two methods compared were: a calculation based on LMP or a prediction based on the measurement by ultrasound scan	Determine the most accurate predictor of the date of delivery for pregnant women in a community-based population	At an error of ±5 days, the scan prediction is accurate in 52% of cases and last menstrual period in 37%, a difference of 15% (95% CI 4% to 23%).	The scan accuracy is significantly better than LMP accuracy.	Prospective study	II
Okonofua, 1989	698	84 Nigerian women who had no complications of pregnancy and delivered infants whose birthweights were appropriate for 40 weeks were assessed		Accuracy of gestational age using the locally produced normogram and compared with predictors based on menstrual dates	ultrasound dating was more accurate than menstrual dating as evident from the number of women who delivered on and within 1 or 2 weeks of predicted delivery dates. 12/84 (14.3%) women delivered on the days predicted by ultrasound whereas only 3/84 (3.6%) delivered on days estimated by LMP. 69/84 (82.1%) ultrasound predictions were correct to within 1 week of predicted dates as compared to 42/84 (50%) predictions based on LMP. The difference reached statistical significance $P < 0.05$.		Prospective study	II
Campbell, 1985	699	4257 consecutive pregnancies were scanned in 4246 patients as part of a routine antenatal two-tier ultrasonic screening	The first-tier scans were performed before 20th week of gestation, whereas the second-tier scans were performed between 26 weeks and term. The estimated date of	Determine if a single ultrasonic measurement performed in a technician oriented routine screening programme was more accurately predictive of gestational age than menstrual history.	84.7% patients with optimal menstrual history delivered within ±2 weeks of the predicted date. Only 69.7% delivered within ±2 weeks of		Population study	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		programme.	confinement based on ultrasound measurements was compared with menstrual history in its ability to predict the actual onset of spontaneous labor.	In addition they determined whether a single BPD or CRL measurement was more predictive of gestational age and how the predictive accuracy of these measurements changed throughout pregnancy.	the estimate date of confinement based on suspect menstrual history. CRL measurements were as predictive (84.6%) as optimal menstrual history. BPD measurements done between 12 and 18 weeks of gestation were significantly more accurate in gestational predictions (89.4%) than those based on menstrual history (*P*< .001).			
Kopta, 1983	[700]	27 women	The actual delivery date was compared with the estimated date of confinement predicted by the CRL and the BPD.	Compared the relative accuracy of estimated dates of confinement predicted by first-trimester CRL versus second-trimester BPD measurements	No difference of mean error between predicting the actual date of delivery by CRL (7.73 days) and BPD (7.65 days). In both methods there was a greater tendency to overestimate the actual date of delivery.		Prospective study	II
Selbing, 1983	[701]	53 women with regular, 28 day interval menstrual cycles were extracted consecutively from the register of the ultrasound laboratory.		Evaluation of the fetal CRL screening programme	25% of pregnant women had a difference between menstrual age and gestational age estimated on the basis of CRL, exceeding 7 days. Regular menstrual cycles and reliable menstrual history reduced this to 19%. Post-mature deliveries > 294 days were reduced from 1 in 15 to 1 in 300 by using CRL.		Prospective study	II
Bennett KA, 2004	[702]	Low-risk population	Routine first-trimester ultrasound screening	Induction of labour	5/104 women in the first-trimester screening group and 12/92 women in the second-trimester screening group had labour induced for post-term pregnancy (*P*= 0.04, RR 0.37, 95% CI 0.14–0.96).		RCT	1+
Crowther, 1999	52	648 women attending for their first antenatal visit at less than 17 weeks of gestation with no previous ultrasound scan in	Eligible consenting women were enrolled by telephone randomisation into either the ultrasound at first visit group, who had an ultrasound at the	efficacy of an ultrasound scan at the first antenatal visit	9% of women in the ultrasound at first visit group needed adjustment of their expected date of delivery as a		Randomised clinical trial	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		the pregnancy, who were expected to give birth at the hospital, and for whom there was no indication for an ultrasound at their first visit.	time of their first antenatal visit, or the control group in whom no ultrasound assessment was done at their first antenatal visit.		result of the 18 to 20 week ultrasound, compared with 18% of women in the control group (RR 0.52, 95% CI 0.34–0.79; *P* = 0.002). Fewer women in the ultrasound at first visit group reported feeling worried about their pregnancy (RR 0.80, 95% CI 0.65–0.99; *P* = 0.04) or not feeling relaxed about their pregnancy (RR 0.73, 95% CI 0.56–0.96; *P* = 0.02), compared with women in the control group.		
Waldenstrom, 1988	703	4997 women were randomised into a screening group where women had an ultrasound scan at about 15 weeks and a control/non-screening group where women did not have a scan before 19 weeks	All women in the screening group had gestational age and expected date of delivery estimation from BPD with charts derived from a Swedish population. For the control group, last menstrual period with specialty calibrated calendars was used.	effectiveness of one-stage screening in the second trimester in pregnant women with no clear indication for elective scanning	that labour was less often induced among screened women both for all reasons 5.9% vs 9.1%, *P* < 0.0001 and for suspected post-term pregnancy 1.7% vs 3.7%, *P* < 0.0001. Among babies born to screened women, fewer had a birthweight < 2500 g (59 vs 95, *P* = 0.005) and mean birthweight was 42 g higher (*P* = 0.008).		RCT	1+
Eik-Nes, 2000	704	825 women were allocated to an ultrasound scan between 18–32 weeks of gestation in addition to receiving routine antenatal care.	Standard antenatal care, but could only be referred for ultrasound examination on clinical indication.	Benefits of the routine use of ultrasound screening in pregnancy	incidence of induced labor due to apparent post-term pregnancies was 70% lower in the ultrasound-screened group. Inductions from all causes were also less frequent among ultrasound-screened women. There were six perinatal deaths among the screened and seven among the controls after excluding three lethal malformations among the controls. The proportion of infants with Apgar score less than 8 after 5 minutes was lower among the screened group (*P* = 0.04). The need for positive pressure		RCT	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					ventilation for more than 1 minute was lower among the screened group (P = 0.02).			
Morin, 2005	[705]	46 514 women with both menstrual and early ultrasound-based gestational age estimates.		Association between maternal and fetal characteristics, discrepancy between last normal menstrual period and early (< 20 weeks) ultrasound-based gestational age and the association between discrepancies and pregnancy outcomes	positive discrepancies between LMP and early ultrasound scan were more likely in multiparous mothers and those with diabetes, small stature or high pre-pregnancy body mass index. The proportion of women with discrepancies ≥+7 days was significantly higher among chromosomally malformed and female fetuses. With increasingly positive differences between LMP and ultrasound scan, the mean birthweight declined and the risk of low birthweight increased. Associations with fetal growth measures were more plausible with early ultrasound estimates.		Cohort study	2++
Neilson, 1999	57	Nine good quality trials were included		Assessed whether routine early pregnancy ultrasound influences the diagnosis of fetal malformations and of multiple pregnancies, the rate of clinical interventions, and the incidence of adverse fetal outcome compared with its selective use.	Routine ultrasound examination significantly reduced the rates of induction of labour for post-term pregnancy (OR 0.61, 95% CI 0.52–0.72).		Systematic review	1+

5 Lifestyle considerations

5.5 Nutritional supplements

Clinical question: What is the effectiveness of antenatal vitamin D supplementation during pregnancy

Stand-alone vitamin D supplementation

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
(Brooke *et al.*. 1980)[971] London (51.5° N), UK RCT Evidence level: 1+ Associated references (Brooke 1981 [974], Maxwell 1981 [973])	Asian pregnant women (Indian, Pakistan, Bangladesh, Sri Lanka, Mauritius an east Africa) living in Tooting, south London (51.5° N) No significant differences between the two groups in age, parity, height, vegetarian status, country of origin, serum 25-OHD levels (range from undetectable to 92 nmol/litre; 71% of vegetarians and 12% of non-vegetarians had undetectable levels, *P* < 0.01) 126 Asian women Calciferol group: 59 Placebo group: 67 Randomisation by hospital pharmacy on the basis of women's hospital number	Study Question: What are the effects of vitamin D on maternal and infant calcium homeostasis and fetal growth? Statistical Analysis: Comparative analysis between a treatment group and a placebo group	Vitamin D supplements (calciferol 1000 IU/day[25 microg rams/day]) given during the third trimester vs placebo	Intention-to-treat analysis performed Mothers: Mean plasma 25-OHD concentration (nmol/litre) Calciferol group:168 ± 96.0 Placebo group: 16.2 ± 22.1 (WMD 151.80, 95% CI 126.74 to 176.86) Results 'pooled' from samples taken in summer months and winter months separately, no significant difference between the two lots of samples, though mean levels were higher in summer months in mothers at 28 weeks, at term and also in cord blood Significant correlation in 25-OHD levels between maternal and cord blood (*r* = 0.93, *P* < 0.01) Mean daily weight gain (g): Calciferol group: 63.3 ± 20.70 Placebo group: 46.4 ± 29.50 (WMD 16.9, 95% CI 8.08 to 25.72) Infants: Mean birthweight (g) Calciferol group: 3157 ± 468.5	Though likely to be applicable to pregnant Asian women in regions of similar latitude and sunlight hours. This is the only RCT assessing the effect of vitamin D in Asian women	This RCT was conducted in 1977 during autumn-winter, throughout 1978 and Spring-summer 1979 Allowance made for seasonal variation No allocation details

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
				Placebo group: 3034 ± 523.9 (WMD 123.0, 95% CI —50.29 to 296.39) No harmful/adverse effects documented No long-term follow-up data		
(Stephens *et al*.. 1981)[983] Rochdale (53.6° N), UK RCT Evidence level: 1−	Asians living in Rochdale with vitamin D deficiency 24 Asian men and women Oral vitamin D (*n* = 12) IM vitamin D (*n* = 12) Oral group: 2 men and 10 women, aged 15—46 years, mean 32 years IM group: 5 men and 7 women, aged 16—46 years, mean 33 years No sig diff between the two groups in pre-treatment serum 25-OHD levels Subjects were given strict instructions to avoid vit D preparations for the next 6 months	Study Question: What are the effects of a single dose of ergocalciferol orally or intramuscularly during the autumn on serum 25-OHD? Statistical Analysis: comparison analysis of the two treatment groups	A single dose of oral ergocalciferol 2.5 mg (100 000 IU) vs. a single dose of intramuscular calciferol given in the Spring for 5 months	Serum 25-OHD before and after vit D treatment (nmol/litre) Pre-treatment (Spring 1980) Oral vit D: 8.3 ± 2.8 IM vit D: 7.3 ± 3.5 (NS) Pre-treatment (Autumn 1980) Oral vitaminD: 16.5 ± 8.5 IM vitamin D: 14.0 ± 7.3 (NS) At 1 month: Oral vitamin D: 52.5 ± 12.0 IM vitamin D: 32.5 ± 13.8 (WMD 20.0, 95% CI 9.65 to 30.35) At 3 months: Oral vitaminD: 29.5 ± 7.0 IM vitamin D: 25.8 ± 8.8 (NS) At 5 months (Spring 1981): Oral vitamin D: 24.5 ± 5.3 IM vitamin D: 23.5 ± 11.6 (NS) Pre-treatment vs 5 months after treatment Oral: WMD 8.00, 95% CI 2.33 to 13.67 IM: WMD 9.50, 95% CI 1.75 to 17.25 The range produced by oral vitamin D was much less than the range produced by IM vitamin D (mean 24.5, range 19.3 —34.3 nmol/litre vs mean 23.5, range 12.8—52.3). At 1 year after the study, serum 25-OHD concentrations, every patients had a level above 12.5 nmol/litre	Likely to be applicable to the UK population in regions of similar latitude and sunlight hours	This study was conducted in 1981. Method of randomisation and allocation concealment not reported Small sample size No intention-to-treat analysis

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
				No adverse effects documented		
(Cockburn, Belton, and Purvis 1980)[974] Edinburgh (55.6° N), UK Non-RCT Evidence level: 2+	Pregnant women living in Edinburgh Both groups comparable for social class, parity and age (no information on ethnicity status) No information on whether 25-OHD levels were similar in the 2 groups 1139 women and their infants Vitamin D supp (*n* = 506) Placebo (*n* = 633)	Study Question: Is vitamin D supplementation during pregnancy beneficial to mothers and their infants? Statistical Analysis: Comparative analysis between a treatment group and a placebo group	Daily vitamin D 400 IU (10 micrograms) from 12th week of pregnancy (given during the months of September to May) till delivery vs. placebo	Maternal plasma 25-OHD (nmol/litre; values cubed of mean cube root) At 24 weeks: Vitamin D group: 39 (*n* = 82) Placebo group; 32.5 (*n* = 82) (*P* < 0.01) At 34 weeks: Vitamin D group: 44.5 (*n* = 80) Placebo group; 38.5(*n* = 80) (*P* < 0.05) At delivery: Vitamin D group: 42.8 (*n* = 80) Placebo group; 32.5 (*n* = 84) (*P* < 0.001) Infant plasma 25-OHD (nmol/litre; values cubed of mean cube root) At day 6 Vitamin D group: 34.5 (*n* = 54) Placebo group; 20.3 (*n* = 86) (*P* < 0.001) At day 6 Vitamin D group: Breastfed: 25.2 (*n* = 12) Artificial milk fed: 34.4 (*n* = 41) (*P* < 0.01) Placebo group: Breastfed: 15.4 (*n* = 22) Artificial milk fed: 20.1 (*n* = 57) (*P* < 0.01) Estimated dietary vitamin D intake based on recall at 34 weeks (*n* = 84): 91 IU (2.3 micrograms) /day Significant correlation between maternal and infant plasma 25-OHD (*r* = 0.71) In both groups, values of plasma 25-OHD 'peaked' during July and August	Maybe applicable to UK populations and setting depending on latitude of regions	This study was conducted in 1980. A non-RCT – subject to sampling bias and confounders (e.g., ethnicity status of the groups was not reported, self-report of dietary vitamin D intake, compliance)

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
				No adverse effects documented		
(Pietrek *et al.*. 1976)[982] Glasgow (55.9° N), UK Non-RCT Evidence level: 2−	Asian families living in Glasgow 66 members (20 adults and 46 children) of 14 Asian family in 3 groups Group 1: 16 members (4 families) Group 2: 18 members (4 families) Group 3: 32 members (6 families) No sig diff in baseline serum 25-OHD concentration between the 3 groups	Study Question: What are the effects of vitamin D fortified chupatty flour and weekly vitamin D in reducing the incidence of rickets and osteomalacia in the Asian community? Statistical Analysis: Comparative analysis between treatment groups and the control group	Group 1: no vitamin D supp, no vitamin D fortified chupatty flour (control) vs. Group 2: weekly vitamin D supp 3000 units (administered by health visitor to 3 families, I family self-administered) vs. Group 3: vitamin D fortified chupatty flour (6000 units /kg flour) for 6 months	Serum 25-OHD concentrations: At baseline (Dec) Group 1 (control): 4.7 ± 0.5 ng/ml Group 2 (weekly vitamin D supp): 6.8 ± 1.1 ng/ml Group 3 (vitamin D fortified flour): 4.0 ± 0.5 ng/ml (Group 2 vs Group 1: WMD 2.10, 95% CI 1.54 to 2.66)(Group 3 vs Group 1: WMD —0.70, 95% CI —1.00 to —0.40) At 3 months (March) Group 1 (control): 3.8 ± 0.5 ng/ml Group 2 (weekly vitamin D supp): 15.5 ± 2.3 ng/ml Group 3 (vitamin D fortified flour): 18.0 ± 1.2 ng/ml (Group 2 vs Group 1: WMD 11.70, 95% CI 10.61 to 12.79)(Group 3 vs Group 1: WMD 14.20, 95% CI 13.72 to 14.68) At 6 months (June) Group 1 (control): 5.1 ± 0.8 ng/ml Group 2 (weekly vitamin D supp): 18.1 ± 2.9 ng/ml Group 3 (vitamin D fortified flour): 19.5 ± 1.2 ng/ml (Group 2 vs Group 1: WMD 13.00, 95% CI 11.60 to 14.40)(Group 3 vs Group 1: WMD 14.40, 95% CI 13.83 to 14.97) Biochemical abnormalities suggestive of rickets: At 6 months Group 1: 2 members Group 2: 1 member Group 3: 0 2 individuals were followed up for 2 years, the serum 25-OHD levels had fallen to pre-study levels (data not available) No adverse events documented	Likely to be applicable in regions of similar latitude in the UK. However, in 1978, the Working Party at COMA concluded that mandatory fortification of any flour, milk or butter with vitaminamin D was not a practical solution	A non-RCT conducted in 1973 Small sample size Confounders: sampling bias unequal serum 25-OHD concentrations between the 3 groups at baseline attrition compliance
(Datta *et al.*. 2002)[975] Cardiff (51.5° N), UK	Asian women living in Wales (African, Afro-Caribbean, Asian, Far Eastern, Middle-Eastern) in the third trimester of pregnancy	Study Question: Is prenatal vitamin D supplementation effective in treating vitamin D deficiency in	Vitamin D supplement 800 IU/day or 1600 IU/day depending on serum 25-OHD levels at first	80/120 (50%) women had vitamin D levels < 8 ng/ml and were given vitamin D supplementation Subnormal vitamin D levels found in:	Likely to be applicable in the UK populations and settings	Possible seasonal variation in sunlight exposure but vitamin D status.

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
		Asian women?	antenatal clinic	50% of women who had been in the UK for > 3 years 25% of women who have lived in the UK for 3 years 25% of women who were born in the UK		
Before–after study. Evidence level: 2+	160 women	Statistical Analysis: Before and after treatment comparison	A vitamin D level of < 8 ng/ml(< 20 nmol/litre) taken as the cut-off value for commencing calciferol 800 IU/day	Maternal serum 25-OHD concentrations (micrograms/ml): At booking (*n* = 58): 5.79 ± 0.91 Post-delivery (*n* = 58): 11.24 ± 6.34 Vitamin D not affected by religion fluency in English or dressing habit		
(Mallet *et al*.. 1986)[976] Rouen (49.4° N), France RCT Evidence level: 1+	White pregnant women living in Rouen 77 women Vitamin D supp 1000 IU/day (*n* = 21) Single dose of 5 mg (*n* = 27) control (*n* = 29) No significant difference between the 3 groups in age, parity, frequency of outings, calcium intake	Study Question: What are the effects of daily vitamin D supp compared with one single dose of vitamin D or no vitamin D on serum 25-OHD in pregnant women? Statistical Analysis: Comparative analysis between treatment group and placebo group	Vitamin D supplement 1000 IU/day (25 micrograms/day) given during the third trimester vs. Single dose of vitamin D 5 mg (200 000 IU) given at 7th month vs. No vitamin D supplement	Women at delivery Mean serum 25-OHD levels Daily vitamin D: 25.3 ± 7.7 nmol/litre Control: 9.4 ± 4.9 nmol/litre (WMD 15.90, 95% CI 12.15 to 19.65) Single does vitamin D: 26.0 ± 6.4 nmol/litre Control: 9.4 ± 4.9 nmol/litre (WMD 16.60, 95% CI 13.60 to 19.60) Infants (born in February-March): Mean birthweight Daily vitamin D:3370 ± 376 g Control: 3460 ± 377 g (WMD —90.00 g, 95% CI —298.48 to 118.48) Single doe of vitamin D: 3210 ± 468 g Control:3460 ± 377 g ((WMD —250.00 g, 95% CI —492.68 to —732) No report of adverse events	May not be applicable to Caucasian women living in the UK which has a different latitude than the study region (NW France), also different food fortification policy of the 2 countries	This RCT was conducted in winter (Feb -March) 1986 Small sample size Randomisation generated by using a table of random numbers – no further details Method of allocation concealment not reported Dairy products not fortified in France. No power calculation.
(Delvin *et al*.. 1986)[977] Lyon (45.7° N), France	Pregnant women (ethnicity unknown) in the third trimester 40 women Data available for:	Study Question: What are the effects of maternal vitamin D nutritional status during the last trimester of pregnancy on maternal	Vitamin D supplement 1000 IU/day (25 micrograms/day) initiated at the third trimester	Serum 25-OHD concentrations (ng/ml) Maternal at delivery (June) Vitamin D: 26 ± 7SD (*n* = 40) Control: 13 ± 8 SD (*n* = 40)	Unlikely to be applicable to UK populations: milk and dairy products enriched with vitamin D in the UK, also latitudinal	Neither milk nor dairy products are enriched with vitamin D in France Drop outs:

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
	Vitamin D group (*n* = 20) no vitamin D group (*n* = 20) All selections in December and all deliveries in June Both groups comparable in maternal and gestational age, parity and infant birthweight (no data given) Biochemical parameters similar in both groups of women before initiation All infants singletons, breastfed from 6th hour after birth	and neonatal perinatal vitamin D levels? Statistical Analysis: Comparative analysis between treatment group and control group	vs. no vitamin D supplement Compliance verified by weekly visit by a midwife	(WMD 13.70, 95% CI 10.41 to 16.99) (unclear if SD or SEM used Cord blood Vitamin D: 18 ± 2 sem (*n* = 14 pairs) Control: 7 ± 1 sem (*n* = 13 pairs) (WMD 11.0, 95% CI 6.78 to 15.22) Infants (at day 4): Vitamin D: 13 ± 1 sem (*n* = 14 pairs) Control: 5 ± 1 sem (*n* = 12 pairs) (WMD 8.0, 95% CI5.23 to 10.77) Significant correlation between maternal and venous cord blood calcium and 25-OHD in both groups (0< 0.005)	variation in sunlight availability	Vitamin D group: 5 Control group: 1 Degree of exposure to sunlight and ethnicity of mothers not known
(Ala-Houhala 1985)[984] Tempere, Finland (61° N) RCT Evidence level: 1−	Breastfeeding mother–infant pairs Healthy term infants 92 mother–infant pairs (breastfed) Studied in winter (*n* = 47) Studied in summer (*n* = 45) Group 1 Maternal vitamin D (1000 IU/day [25 micrograms/day]after delivery)/no infant vitamin D (*n* = 17 in winter, *n* = 15 in summer) Group 2 No maternal vitamin D/infant vitamin D 400 IU/day (*n* = 15 in winter, *n* = 16 in summer) Group 3 No maternal vitamin D/infant vitamin D 1000 IU/day (*n* = 15 in winter, *n* = 14 in summer)	Study Question: What are the effects of vitamin D supp (with or without in mothers and infants) on serum 25-OHD levels during winter and summer? Statistical Analysis: Comparative analysis between treatment groups	Maternal vitamin D/no infant vitamin D vs. No maternal vitamin D/infant vitamin D 400 vs No maternal vitamin D/infant vitamin D 1000	Serum 25-OHD concentrations Maternal data (absolute data presented graphically) At delivery Sig higher 25-OHD in summer than in winter in all 3 groups of mothers (*P* < 0.001 in Groups 1 and 2; *P* < 0.01 in Group 3) At 8 weeks (in winter) Sig higher in Group 1 than in Group 2 and 3 (*P* < 0.001) In summer No sig diff between Group 1 and 3 In winter groups (*n* = 47) 12/47(26%) of Groups 1, 2 and 3 at delivery or at 8 weeks had levels < 5 ng/ml and 16/36(44%) of Groups 2 and 3 at 8 weeks had levels < 5 ng/ml but not at 20 weeks after delivery when it was spring No signs of clinical or biochemical rickets seen in the infants with 25-OHD levels In summer group (*n* = 45) Groups 2 and 3	May not be applicable to UK population due to different regional latitudes, amount of sunlight and food fortification policy	Study conducted in 1985 Different maternal vitamin D supp during pregnancy Small sample size. No power calculation. Applicability uncertain.

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
				No women of Groups 1, 2 and 3 at delivery had levels < 5 ng/ml at delivery or at 8 weeks 2/29(7%) of Groups 2 and 3 had levels < 5 ng/ml at 20 weeks when winter beginning (December)		
	Half of mothers received no vitamin D supp during pregnancy One-fourth received vitamin D supp 500 IU/day during middle pregnancy One-fourth received vitamin D 500 IU/day during entire pregnancy			Infant data (absolute data presented graphically)		
				25-OHD levels sig higher in all summer groups than in all winter groups ($P < 0.001$)		
	25-OHD levels comparable in all infants at beginning of study			In winter no sig diff in levels between the 3 groups in winter (at delivery)		
				In summer, sig lower levels in Group 3 than in Group 1 ($P < 0.05$)		
				In winter At 8 weeks: levels sig lower in Group 1 than Group 2 and Group 3 ($P < 0.001$) 10/18(56%) in Group 1 had levels below risk limit for rickets At 20 weeks (Spring) 2/17 (12%) of Group 1 had levels below risk limit for rickets		
				In summer No sig diff in levels between Group 1 and Group 2 Levels sig lower in Group 1 than in Group 3 ($P < 0.001$)		
				1 infants in Group 1 had levels below risk limit for rickets at 20 weeks when it was December		
				No signs of clinical or biochemical rickets seen in the infant with 25-OHD levels below risk limit for rickets		
				No adverse events documented		
(Greer and Marshall 1989)[978] Massachusetts	White infants born at term and exclusively breastfed for 6 months (Women received supplemental vitamin D during pregnancy -	Study Question: What are the effects of vitamin D supp in breastfed white infants on bone mineral content, serum	Vitamin D supplements 400 IU/day (10 micrograms/day) within the first week of	Total serum 25-OHD concentrations (ng/ml) At 6 weeks Group 1: 30.25 ± 9.54 Group 2: 15.76 ± 9.81	May not be applicable to UK population due to difference in regional latitudes: Britain (50–61° N) Massachusetts	83% infants completed the study There were more babies born in winter (33) than in summer

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
(42.4° N), USA	dose unknown)	vitamin D metabolite levels and association of sunlight exposure?	birth vs.	Group 3: 30.21 ± 6.08	(42° N)	(13)
	58 infants		daily placebo	At 3 months		Small no of babies were given vitamin D-free formula during the study.
RCT	Vitamin D sup (*n* = 22) Group 1	Statistical Analysis: Comparative analysis of treatment group and placebo group and an additional convenience control group not subjected to randomisation	(vs a convenience sample of formula-fed infants)	Group 1: 38.89 ± 10.34		
Evidence level: 1+	Placebo (*n* = 24) Group 2			Group 2: 15.72 ± 11.25		
	Control group (*n* = 12) Group 3			Group 3: 37.24 ± 6.08		Two fathers of infants were non-Caucasian
	13 infants born in summer		Vitamin D free formula given to mothers for emergency situations	At 6 months		
	33 infants born in winter			Group 1: 39.96 ± 11.86		
	Additional 12 full-term healthy and exclusively formula-fed infants used as a comparison group (no randomisation process)			Group 2: 23.53 ± 9.94		
				Group 3: 37.57 ± 8.54		
	No difference between the groups in sex, gestational age, birthweight and serum 25-OHD levels at start of study. Free from major congenital anomalies, neurologic disorders or gastrointestinal disease			Winter-born infants vs summer-born infants At 6 months Group 1: Winter-born: 36.7 ± 12.9 (*n* = 12) Summer-born: 37.4 ± 10.9 (*n* = 7) (NS)		
				Group 2: Winter-born: 25.1 ± 10.2 (*n* = 13) Summer-born: 20.2 ± 9.3 (*n* = 6)(NS)		
				Group 2 winter-born infants 13 ± 7.1 at 6 weeks vs. 25.1 ± 10.2 (*P* < 0.01)		
				Summer-born infants No significant changes in Group 1 and 2 between 6 weeks and 6 months		
				Bone mineral content (measured by photon absorptiometry of the distal radius)(mg/cm) All 3 groups had an increase in BMC during the study		
				At 6 months Group 1: 89.5 ± 12.5 Group 2: 101.0 ± 17.9 (*P* < 0.05)		

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
				Group 2: 101.0 ± 17.9 Group 3: 107.4 ± 10.6 ($P < 0.02$) (Change in BMC for Group 3 sig higher than the combined change in BMC for both Groups 1 and 2 [$P < 0.02$) Mean body weight (g) Group 1: 7570 ± 858 Group 2: 7752 ± 1182 Group 3: 7633 ± 1002 (NS) Maternal mean vitamin D intake (IU/day) of Groups 1 and 2: 701 ± 242 at 6 weeks 652 ± 181 at 6 months Mean weekly UVB exposure: No sig diff between the 3 groups No adverse events documented		
(Greer, Searcy and Levin 1981)[979] Ohio (40.1° N), USA RCT Evidence level 1+ Associated reference (Greer 1982)	Breastfed infants born at term, healthy and of appropriate gestational age (38–40 weeks) 18 infants vitamin D supplement ($n = 9$) placebo ($n = 9$) Additional comparison with a formula-fed control group ($n = 12$) No sig diff in their gestational age, birthweight or sunlight exposure between the 2 groups 16 infants born in summer (2 in November) 17 Caucasian (1 Asian-Indian) For bone mineral content: Additional control group: term, healthy, exclusively formula-fed infants	Study Question: What are the effects of supplemental vitamin D on bone mineralisation and serum 25-OHD levels? Statistical Analysis: Comparative analysis of treatment and control groups	Vitamin D supplementation400 I U/day vs. placebo (vs a convenience sample of formula-fed infants) Compliance estimated by regular enquiries of intake, record of refills, maintained by physicians who dispensed the supp and the placebo	Bone mineral content (absolute results reported graphically) At 6 weeks Vitamin D supplement vs placebo (NS) Vitamin D supplement vs formula-fed (sig higher, $P < 0.03$) At 12 weeks Vitamin D supplement vs placebo (sig higher, $P < 0.003$) Vitamin D supplement vs formula-fed (NS) Serum 25-OHD (ng/ml) At 12 weeks Vitamin D supplement: 38 placebo: 20 ($P < 0.003$) No signs of clinical rickets Mean maternal vitamin D intakes by dietary recall were similar in the two groups during the study (561 IU/day). Maternal sunshine exposure did not differ in the two groups. Estimated compliance: 85%	May not be applicable to UK populations and settings due to difference in regional latitude and food fortification policy	Published in 1982 Double blind (mothers and investigators) RCT Small sample size Data details reported graphically Accuracy of BMC scanning

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
(Greer *et al*. 1982)[980] Ohio (40.1° N), USA RCT Evidence level: 1+ Associated reference (Greer 1981)	Breastfed infants born at term, healthy and of appropriate gestational age (38–40 weeks) 13 infants vitamin D supplement (*n* = 6) placebo (*n* = 7) No sig diff in the gestational age, birthweight or sunlight exposure between the 2 groups At 6 months, the study was unblinded to the mothers of the infants and all infants were allowed solid foods and the placebo group was given daily vitamin D supplement of 400 IU	Study Question: What are the effects of supplemental vitamin D on bone mineralisation and serum 25-OHD levels? A follow-up study at 1 year Statistical Analysis: Comparative analysis between treatment and control groups	Vitamin D supplementation 400 IU/day vs. placebo	Bone mineral content At 26 weeks Vitamin D supp group (*n* = 6) vs placebo group (*n* = 7) (NS) Serum 25-OHD concentrations (ng/ml) At 26 weeks Vitamin D supp: 32.7 placebo: 12.9 At 52 weeks Vitamin D supp vs placebo (NS) None of the infants had clinical signs of rickets No adverse events documented	May not be applicable to UK populations and settings (latitude variation) and food fortification policy	Published in 1982 Small sample size Data details reported graphically

Interventions to promote uptake of vitamin D supplements

Authors Year Country Study Design Quality	Study Population	Research Question	Intervention	Main Results	Applicability to UK populations and settings	Confounders and Comments
(Box 1983)[971] London (51.5° N), UK Quasi-RCT: women allocated by alternation Evidence level 1—	20 pregnant Asian women (Hindu, Muslim and Sikh) No significant difference in vitamin D intake (2.3 to 2.5 mg/day) and serum 25-OHD (2.5 to 4.0 ng/ml, taken in January-February) between the two groups before intervention Counselled by health visitor (*n* = 11 [4 vegetarians]) Non-counselled (*n* = 9 [8 vegetarian women])	What are the effects of health education and counselling on dietary vitamin D intake and serum 25-OHD levels? Statistical Analysis Comparative analysis between a treatment and a control group	Counselled by health visitor vs. Non-counselled Counselling by health visitor at 6/8 weeks and at 2/4 months of pregnancy Components of the intervention: 1. Setting: antenatal clinic 2. Advice given: At first visit (6/8 weeks) Food sources rich in vitamin D Reinforce message with samples of food and proprietary brands Maximise exposure to sunlight Serum 25-OHD levels measured At second/third visit (2/4 months) Women questioned about understanding of advice previously given Advice reinforced Serum 25-OHD levels measured at third visit 3. Strategy Women encouraged to bring their mothers-in-law to clinic, as the latter usually make decision about the family's diet Use of Hindu, Muslim and Sikh-speaking receptionists as interpreters	Mean reported dietary vitamin D intake (mg/day) At 2 months Counselled: 2.8 ± 1.2 Non-counselled: 2.0 ± 0.8 (NS) At 4 months Counselled: 4.1 ± 1.5 Non-counselled: 2.7 ± 0.8 ($P < 0.05$) Mean serum 25-OHD levels (ng/ml) At 4 months (May-June) Counselled: 5.1 ± 1.5 Non-counselled: 4.9 ± 0.8 (NS) Difference between first and second sample Counselled: 0.07 ± 0.06 Non-counselled: 0.15 ± 0.07 (P~0.02)	Likely to be applicable and generalisable to UK populations depending on regional latitudes and exposure to sunlight	Quasi-RCT: women allocated by alternation at clinic Published in 1983 Small sample Amount of sunlight exposure and body coverage as confounders

Clinical question: What is the minimum level of alcohol intake associated with fetal alcohol syndrome and other baby outcomes?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gray, 2006	707	10 outcomes with low-to-moderate consumption of alcohol. A total of 11 separate studies examined the effect of binge drinking on the 10 outcomes above.	Determine whether an intake of up to six drinks a week was associated with more risk than total abstention and whether binge drinking by low-to-moderate drinkers is associated with harm. They also aimed to evaluate a 'safe level'. Two definitions were used in the review:	Fetal effects of low-to-moderate prenatal alcohol exposure and binge drinking	Miscarriage: A total of 8 studies looked at the effects of low-to-moderate alcohol consumption on miscarriage. 5 of these reported a significant effect: 2 had significant limitations, one had significant results among heavy smokers and the remaining 2 were of borderline statistical significance. The highest reported risk was a relative risk of 3.79 (95% CI 1.18 to 12.17) associated with consuming up to 10 units (equivalent to 6.7 drinks). Stillbirth: 5 studies examined stillbirth as the outcome and only one study reported significantly increased rates of stillbirth in babies of women who drank up to 25–60 g per week in pregnancy. Three studies reported higher rates of stillbirth in women who abstained but these were not statistically significant differences and were unadjusted for potential confounders. APH: One study included antepartum haemorrhage (APH) as an outcome and found no increase in risk of APH with low-to-moderate level of alcohol consumption. FGR: 7 studies examined intrauterine growth restriction as an outcome and only one study found a significant association but it was unadjusted for potential confounders. Three studies found low-to-moderate alcohol consumption to be mildly protective but, although of borderline statistical significance, two may have been subject to recall bias. Birthweight: 20 studies included birthweight as an outcome but only one reported a significant increase in the risk of low birthweight with consumption of < 0.1 oz alcohol per day (adjusted RR 3.20, 95% CI 1.87 to 5.46). However, at 0.1 – 0.25 oz per day, the RR was lower at 1.36 (95% CI 0.48 to 3.88). This result was inconsistent as higher levels were not associated with increased risk. It appeared that small amounts of alcohol exerted a mildly protective effect. Preterm birth: One out of a total of 16 studies that examined preterm birth as an outcome reported a significantly increased risk of preterm birth (RR of 2.11 and 2.15 in women consuming < 0.1 oz and 0.1–0.25 oz respectively of absolute alcohol per day at 7 months of gestation). This study suffered from residual confounding as it was unadjusted for socio-economic status. Malformation: None of the 6 studies that examined malformations as the outcome reported a significant association with low-to-moderate alcohol consumption although a trend in that direction was apparent in some studies. HC and birth length: A total of 5 studies looked at head circumference and birth length as the outcome and only one found a higher proportion of low birthweight babies among those whose mothers drank low-to-moderate amounts in pregnancy.		Systematic review	2++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					However, this study suffered from lack of adjustment for potential confounders. None of the other studies reported any differences at these levels of consumption. Postnatal growth: 2 studies that examined the association between alcohol exposure and postnatal growth differed in their results. One of these studies, which followed children up to age 14, found that children of women who drank small amounts in pregnancy were consistently lighter. However, the other study found that children of abstainers tended to be lighter. Neither of the results was significant. Neurodevelopmental outcome: 7 studies looked at neurodevelopmental outcomes; one was conducted at birth as compared to others that were later in childhood. 1 study found a poorer result in children of low-to-moderate drinkers, however this idinot reach statisticl significance and the analysis was not adjusted for potential confounders. Out of these 4 studies looked at neurodevelopmental outcomes and showed consistently poorer results in children exposed to binge drinking in pregnancy. The effects although quite small, included an increase in 'disinhibited behaviour', a reduction in verbal IQ and increase in delinquent behaviour, and more learning problems and poorer performance. The studies suffered from a possible overlap between binge drinkers who otherwise drink little and binge drinkers who generally drink substantial amounts. These studies represent the most consistent evidence suggesting that binge drinking in pregnancy may be associated with poor neurodevelopmental outcomes.			
Mariscal, 2006	[708]	Cases (*n* = 552) were mothers delivering a single newborn weighing < 2500 g and controls (*n* = 1451) were selected randomly from all delivering women.	Influence of alcohol drinking during pregnancy. Personal interviews, clinical charts, and prenatal care records were used for obtaining information.	low birthweight	Alcohol consumption of less than 6 g/day decreased the risk for low birthweight (adjusted OR 0.64, 95% CI 0.46–0.88). A similar result was obtained for moderate drinkers (< 12 g/day) on weekends only. The opposite relationship was observed between alcohol consumption on weekdays of 12 g/day or greater (adjusted OR 2.67, 95% CI 1.39–5.12), not observed in those drinking on weekends only.	Alcohol consumption of 12 g/day or greater increased the risk for low birthweight, whereas lower consumption during weekends showed the opposite effect (mainly in nonsmokers).	case–control study	2+
Weatherhead, 2007	[709]	555 cases, women (mean age 31 years, range 16–43) who delivered SGA babies and 1966 controls, women (mean age 31 years, range 14–43) who gave birth at term (> or =37 weeks of gestation) to healthy infants of normal weight at the hospitals where cases had been identified were included in the study.		Effect of alcohol intake on the risk of SGA birth, preterm or at term, and the potential interaction between alcohol consumption and risk factors for SGA birth	No increase in the risk of SGA birth observed in women drinking one or two drinks/day in pregnancy. The Odds ratios of 3 or more drink per day were 3.2 (1.7–6.2) for ≥ 3 drinks during the first trimester, 2.7 (1.4–5.3) during the second and 2.9 (1.5–5.7) during the third.	an increased risk of SGA births in mothers who drink ≥ 3 units/day of alcohol in pregnancy	case–control study	2+

8 Screening for haematological problems

8.3 Screening for haemoglobinopathies (sickle cell disease and thalassaemia)

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in identifying clinically significant thalassaemia and thalassaemia carrier status (trait): history; family origin, full blood count; Hb electrophoresis; ferritin; mean cell volume?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rogers *et al.*, 1995	[714]	Pregnant women Sample *n* = 857	Comparison of mean corpuscular volume (MCV) < 85 fl vs mean corpuscular haemoglobin < 27 pg as cut-off points for thalassaemia screening.	β thalassaemia status	Of 857 women, 606 had both an MCV < 85 fl and an MCH < 27 pg. 56 of these women (6.5%) were β thalassaemia carriers. At a cut-off of MCH < 27 pg would have identified all cases of β thalassaemia carrier status (trait).	UK study	Diagnostic case–control study	III
Bain, 1988	[715]	Pregnant women Sample *n* = 696	Comparison of mean corpuscular volume < 83 fl vs mean corpuscular haemoglobin (MCH) < 27.1 pg as cut-off points for thalassaemia screening.	β thalassaemia status	Of 696 women with an MCV at booking of less than 83 fl. 96 (13.8%) were found to have abnormal haemoglobin. In the other 600 women a HbA_2 estimation indicated a further 56 women with β thalassaemia carrier status (trait) (8% of total group screened). All MCH values for women with β thalassaemia carrier status (trait) fell below the cut-off point of 27.1 pg.	UK study	Case series	III
Sirichotiyakul, 2005	[716]	Pregnant women Sample *n* = 439	Diagnostic accuracy of mean corpuscular volume < 80 fl as cut-off point for thalassaemia screening.	α thalassaemia-1 and β thalassaemia status	Sensitivity 92.9% (39/42) [95% CI 83.7 to 96.4%]. Specificity 83.9% (333/397) [95% CI 80.8 to 87.6%]. Positive predictive value 37.9% (39/103) [95% CI 33.8 to 42.7%] . Negative predictive value 99.1% (333/336) [95% CI 98.2 to 99.9%].	Thailand	Diagnostic accuracy	III
Ghosh *et al.*, 1985	[717]	Pregnant women at gestation < 24 weeks. Sample *n* = 299	Diagnostic value of mean corpuscular volume followed by HbA_2 estimation compared with that of mean corpuscular volume plus ferritin and haemoglobin level followed by HbA_2 estimation. HbA_2 > 4.5% was taken to be diagnostic of β thalassaemia carrier status (trait). 8 ng/ml was taken as the lower limit for a	α thalassaemia-1 and β thalassaemia status	18 women (6%) had HbA_2 levels > 4.5% and were diagnosed to be carrying β thalassaemia. All of these 18 women had an MCV < 75 fl (in 15 the MCV was < 70 fl). 49 women had an MCV < 80 fl, of these women 18 had low ferritin levels (< 8 ng/ml). 2 of these women had HbA_2 levels over 4.5% and were diagnosed to be carrying β thalassaemia with iron deficiency.	Hong Kong	Diagnostic case–control study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			normal ferritin level. Mean corpuscular volume cut-off point was 80 fl.		37 women were found to have Hb levels < 10 g/100 ml. They included 9 β thalassaemia carriers, 19 women with iron deficiency and 9 presumed α thalassaemia carriers. At a cut-off level MCV < 80 fl all β thalassaemia carriers were detected; false positive rate 63%. At a cut-off level of MCV 75 fl the detection rate remained 100%; false positive rate 47%. At a cut-off of 70 fl the specificity of the test increased to 97% with a sensitivity of 83% and false negative rate of 16%. The study was repeated with a larger sample (*n* = 1166), with similar findings. 61 β thalassaemia carriers were identified (5.2%), all with an MCV < 75 fl.			
Name	[718]	Pregnant women at booking Sample *n* = 5834	Diagnostic value of mean corpuscular volume <= 75 fl as cut-off point for thalassaemia screening.	Thalassaemia status	At a cut-off of MCV < 75 fl 1859 thalassaemia carriers were identified, plus 57 women carrying other haemoglobin variants (86% of those identified by screening test). The number of false positives was 313/2229 (14%).	Hong Kong	Descriptive study (large case-series)	III
Name	[719]	Pregnant women at booking Sample *n* = 3696	Diagnostic value of mean corpuscular volume <= 80 fl as cut-off point for thalassaemia screening.	Thalassaemia status	A cut-off of MCV < 80 fl identified 494/3696 (13.4%) women. Of these women, 56 (11.3%) and 23 (4.7%) were confirmed to be carrying thalassaemia and HbE respectively, giving a false positive rate of 84%.	Singapore	Descriptive study (large case-series)	III
Modell *et al.*, 2001	[720]	Women pregnant with a baby affected by β thalassaemia major Sample *n* = 136 records	Women's care regarding screening for β thalassaemia assessed against a minimum standard.	(a) Risk identification and offer of prenatal diagnosis before 23 weeks of a first pregnancy. (b) Offer of prenatal diagnosis in the first trimester in subsequent pregnancies.	50% of at-risk couples were identified and informed of their risk in time for an offer of prenatal diagnosis in the first pregnancy. Risk was identified too late in 11% of pregnancies and not at all in 38% pregnancies. 28% of couples discovered their risk through diagnosis of an affected child.	UK	Retrospective audit	3Ahmed *et al.*, 2005
Ahmed *et al.*, 2006	[721]	Pregnant Pakistani women Sample *n* = 43	Exploration of Pakistani women's views.	Pakistani women's views towards antenatal diagnosis for thalassaemia and termination of pregnancy for β thalassaemia major.	Most women would opt for diagnosis because they would want 'to know', not because they would consider termination of pregnancy. Women's attitudes towards termination of pregnancy for an affected baby did not seem to relate to the woman's carrier status and were influenced by, but not solely dependant upon,	UK	Qualitative interview study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					their religious viewpoint (all women were Muslim). Women's responses suggested that the more severe the perception of thalassaemia major, the more likely the woman was to be in favour of antenatal diagnosis and termination of pregnancy. Some women also expressed the view that termination of pregnancy was only acceptable early in pregnancy.			
Ahmed *et al.*, 2005	[722]	Pregnant Pakistani women Sample *n* = 146: 110 women who were not carriers for thalassaemia plus 36 women identified as carriers.	Exploration of Pakistani women's attitudes to issues surrounding antenatal thalassaemia carrier status testing.	Pakistani women's attitudes towards informed consent for carrier status testing and perceived pre-test information needs.	113/146 women (77.4%) had not been told about thalassaemia carrier testing, and 97 of these (85.8%) said they would have wanted to have been told before the screening was carried out. Some women mentioned the increased anxiety associated with receiving information prior to screening, most saw this as inevitable part of being pregnant. Women who went on to discover they were thalassaemia carriers felt that prior information would have helped them prepare for this news. Women expressed a desire to know about the condition itself, when the results would be available, the meaning of positive and negative results and possible action following a positive result. This was not universal however, and carrier status affected women's responses with non-carriers being less likely to say they wanted detailed pre-screening information	UK	Qualitative study – questionnaires and interviews.	3

Women's views and experiences of thalassaemia screening in pregnancy

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Modell *et al.*, 2001	720	Women pregnant with a baby affected by β thalassaemia major Sample *n* = 136 records	Women's care regarding screening for β thalassaemia assessed against a minimum standard.	(a) Risk identification and offer of prenatal diagnosis before 23 weeks of a first pregnancy. (b) Offer of prenatal diagnosis in the first trimester in subsequent pregnancies.	50% of at-risk couples were identified and informed of their risk in time for an offer of prenatal diagnosis in the first pregnancy. Risk was identified too late in 11% of pregnancies and not at all in 38% pregnancies. 28% of couples discovered their risk through diagnosis of an affected child.	UK	Retrospective audit	3Ahmed *et al.*, 2005
Ahmed *et al.*, 2006	721	Pregnant Pakistani women Sample *n* = 43	Exploration of Pakistani women's views.	Pakistani women's views towards antenatal diagnosis for thalassaemia and termination of pregnancy for β thalassaemia major.	Most women would opt for diagnosis because they would want 'to know', not because they would consider termination of pregnancy. Women's attitudes towards termination of pregnancy for an affected baby did not seem to relate to the woman's carrier status and were influenced by, but not solely dependant upon, their religious viewpoint (all women were Muslim). Women's responses suggested that the more severe the perception of thalassaemia major, the more likely the woman was to be in favour of antenatal diagnosis and termination of pregnancy. Some women also expressed the view that termination of pregnancy was only acceptable early in pregnancy.	UK	Qualitative interview study	3
Ahmed *et al.*, 2005	722	Pregnant Pakistani women Sample *n* = 146: 110 women who were not carriers for thalassaemia plus 36 women identified as carriers.	Exploration of Pakistani women's attitudes to issues surrounding antenatal thalassaemia carrier status testing.	Pakistani women's attitudes towards informed consent for carrier status testing and perceived pre-test information needs.	113/146 women (77.4%) had not been told about thalassaemia carrier testing, and 97 of these (85.8%) said they would have wanted to have been told before the screening was carried out. Some women mentioned the increased anxiety associated with receiving information prior to screening, most saw this as inevitable part of being pregnant. Women who went on to discover they were thalassaemia carriers felt that prior information would have helped them prepare for this news. Women expressed a desire to know about the condition itself, when the results would be available, the meaning of positive and negative results and possible action following a positive result. This was not universal however, and carrier status affected women's responses with non-carriers being less likely to say they wanted detailed pre-screening information	UK	Qualitative study – questionnaires and interviews.	3

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in identifying clinically important genotypes of sickle cell disease and sickle cell carrier status (trait) including: history taking; family origin; full blood count: Hb electrophoresis; ferritin; mean cell volume; high performance liquid chromatography; sickle solubility testing (Sickledex)?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Chasen *et al.*, 1999	[711]	Pregnant women Sample *n* = 631	Diagnostic accuracy of Hb electrophoresis with selective use of Hb electrophoresis following sickle cell solubility testing and investigation of red blood cell indices.	Sickle cell disease	Sensitivity 88.9% (32/36) and specificity 79.4% (473/595) for the selective screening model. Positive predictive value = 20.8% Negative predictive value = 99.2%.	USA	Diagnostic accuracy	III

Women's views and experiences of antenatal screening for sickle cell disease/trait

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Durosinmi *et al.*, 1997	[723]	Well-educated, city-dwelling Nigerians, aged 15–50 years. Sample *n* = 433 (*n* = 204 males)	Investigation of views of antenatal diagnosis.	Acceptability of antenatal diagnosis of sickle cell disease.	78% of respondents felt antenatal sickle cell diagnosis should be available. 45% reported that they would decide to terminate a baby affected with sickle cell disease. Cross-tabulations showed that neither religion nor educational level significantly affected a person's decision whether or not to terminate an affected pregnancy.	Nigeria	Interview-based descriptive study.	3

Joint screening for sickle cell disease and thalassaemia

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Dyson *et al.*, 2006	[724]	Pregnant women at booking Sample *n* = 4559	Comparison of 2 family origins screening questions: Question A: classification question plus a 'tick all that apply' subsidiary section to record mixed heritage. Question B: 2 parts. Part One: binary question to identify women with ancestors outside the British Isles. Part Two: 5 free text boxes for addition of information regarding ancestry.	Test–retest reliability and proportion of carriers missed.	Question A: 3.2% cases were missing or uninterpretable. Question B: 4.7% cases were missing or uninterpretable. Test–retest error rate for reliability: Question A 4.3% vs Question B 9.5% (CI -8.5% to -1.8%; $P = 0.003$). Carriers of clinically relevant haemoglobinopathies missed: Question A 7/122 (5.74%). Question B 10/103 (9.7%) ($P = 0.026$ using a χ^2 test (χ^2 value not reported)).	UK	RCT	1+
Greengross *et al.*, 1999	[725]	All women found to be positive for haemoglobinopathy carrier state or disease at universal testing in one tertiary hospital from 1986 to 1995. Sample *n* = 1444 women referred in 1688 pregnancies	Comparison of unselected laboratory-based antenatal screening for sickle cell trait with antenatal unselected laboratory-based screening for thalassaemia trait.	Gestation at booking Attendance for counselling Partner attendance at counselling Take-up of antenatal diagnosis Take-up of partner testing	Women found to be carrying sickle cell disease booked 2.7 weeks [95% CI 0.14 to 5.1] later in pregnancy than women who were carrying thalassaemia. Women carrying sickle cell disease less likely to choose to receive counselling (83% vs 93%, RR 0.89 [95% CI 0.85 to 0.94]); their partners were less likely to be tested (77% vs 95%, RR 0.81 [95% CI 0.77 to 0.83]); and they were less likely to choose prenatal diagnosis (22% vs 90%, RR 0.37 [95% CI 0.24 to 0.57]) compared with women carrying thalassaemia. Of the tertiary referrals over 99% of women attended counselling and had their partners tested. There was no difference in acceptance of prenatal diagnosis between those at risk of sickle cell disease and those at risk of thalassaemia.	UK	Retrospective descriptive study	3
Thomas *et al.*, 2005	[726]	Pregnant women at first screening for haemoglobinopathy Sample total *n* = 648: *n* = 241 women from 6 general practices *n* = 276 from 2 hospital antenatal booking clinics *n* = 131 women from community midwife clinics	Evaluation of screening for sickle cell and thalassaemia in early pregnancy in UK general practice	Gestation at screening Stakeholder views of screening system and its implementation	General practices that already had a screening system in place were able to screen a high proportion of women (63% – 86%). However, 3 practices without an existing system only managed to screen between 3% and 26% of women. Women who were screened in general practices were screened at an earlier gestation than those screened at their first hospital booking visit (4.05 weeks [95% CI 3.41 to 4.68], $P < 0.001$) or at midwifery clinics (2.9 weeks [95% CI 2.1 to 3.7], $P < 0.001$).	UK	Participatory action research	3

9 Screening for fetal anomalies

9.1 Screening for structural anomalies

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in identifying serious structural anomalies?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Chitty 1991 Reported in: Bricker L et al, (HTA) 2000	297	1988–1989 UK (Luton), District general hospital Unselected *n* = 8785 (Multiple pregnancies not mentioned)	US done by Radiographers Number of scans not mentioned Scanned at 18–20 weeks Soft markers: yes	Diagnostic test characteristics at < 24 weeks	Prevalence of anomalous fetuses: 1.50% (130 fetuses) but anomalies not reported. Sensitivity: 71.5% Specificity: 99.98% LR+ 3095.83 LR− 0.44	Study reported in systematic review	Retrospective	II
Shirley 1991 Reported in: Bricker L et al, (HTA) 2000	297	1989–1990 UK (Hillingdon), District general hospital Unselected *n* = 6412 (73 multiple pregnancies)	By Radiographers Number of scans not mentioned Scanned at 19 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 1.40% (89 fetuses), but anomalies not reported False-positive: 1 Sensitivity: 57.3% Specificity: 99.97%	Study reported in systematic review	Retrospective	II
Levi 1991 Reported in: Bricker L et al, (HTA) 2000	297	1984–1989 Belgium (Brussels) 5 hospitals Unselected *n* = 15 654 (? 240 multiple pregnancies)	By obstetricians, technicians and sonographers Scanned at first trimester, 16–20 weeks and third trimester Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks taking only those defects exposed to scan at 12–24 weeks	Prevalence of Anomalous fetuses: 2.30% (381 fetuses) and Anomalies: 2.66% (417 anomalies) At < 24 weeks Sensitivity: 21.0% Specificity: 100.00% At > 24 weeks	Study reported in systematic review	Prospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: (37.2%) Specificity: ? <u>Overall detection</u> False-positive: 8 Sensitivity: 40.4% Specificity: 99.94%			
Luck 1992 Reported in: Bricker L et al, (HTA) 2000	297	1988–1991 UK (Ascot), District general hospital Unselected *n* = 8844	By radiographers Scanned at 12–14 weeks and 19 weeks Soft markers: yes	Diagnostic test characteristics at < 24 weeks with results based on number of anomalies	Prevalence of Anomalous fetuses: Not reported Anomalies: 1.90% (164 anomalies) False-positive: 3 Sensitivity: 85.3% Specificity: 99.90%	Study reported in systematic review	Prospective	II
Crane 1994 Reported in: Bricker L et al, (HTA) 2000	297	1987–1991 USA (RADIUS) Low-risk primary plus 28 laboratories *n* = 7575 (Multiple pregnancies not mentioned)	By technicians, physicians, sonologists and radiologists Scanned at 15–22 weeks and 31–35 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks	Prevalence of Anomalous fetuses: 2.30% (187 fetuses) and Anomalies: (232 anomalies) <u>At < 24 weeks</u> Sensitivity: 16.6% Specificity: 99.90% <u>At > 24 weeks</u> Sensitivity: 18.2% Specificity: ? <u>Overall detection</u> False-positive: 7 Sensitivity: 34.8% Specificity: 99.90%	Study reported in systematic review	RCT	II
Levi 1995 Reported in: Bricker L et al, (HTA) 2000	297	1990–1992 Belgium (Brussels) 5 hospitals Unselected *n* = 9601 (? 209 multiple pregnancies)	By obstetricians, technicians, sonographers Scanned at first trimester, 16–20 weeks, and third trimester Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks, with results based on number of anomalies given in brackets	Prevalence of Anomalous fetuses: 2.45% (235 fetuses) and Anomalies: 2.81% (270 anomalies) <u>At < 24 weeks</u> Sensitivity: (25.6%) Specificity: Not reported <u>At > 24 weeks</u> Sensitivity: (40.4%) Specificity: Not reported	Study reported in systematic review	Prospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Overall detection False-positive: 9 Sensitivity: 51.0% (65.9%) Specificity: 99.90%			
Skupski 1996 Reported in: Bricker L et al, (HTA) 2000	297	1990–1994 USA (Texas) Tertiary hospital, single centre Low risk *n* = 860 (6 twins)	By experienced sonographers Scanned at 18–20 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 1.16% (20 fetuses) but Anomalies not reported False-positive: 1 Sensitivity: 15.0% Specificity: 99.80%	Study reported in systematic review	Retrospective	II
Magriples 1998 Reported in: Bricker L et al, (HTA) 2000	297	? 18 months USA (Connecticut) Tertiary centre, single centre Low risk *n* = 911 (10 twins)	By sonographers Scanned at 16–19 weeks and third trimester Soft markers: yes	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 3.07% (28 fetuses), and Anomalies: 40 anomalies False-positive: 5 Sensitivity: 71.4% Specificity: 99.40%	Study reported in systematic review	Retrospective	II
Lee 1998 Reported in: Bricker L et al, (HTA) 2000	297	1990–1994 Korea Tertiary hospital, single centre Low risk *n* = 3004 (twins excluded)	By trained obstetric fellow Scanned at 18–20 weeks and 32–34 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks with results based on number of anomalies given in brackets	Prevalence of Anomalous fetuses: 0.76% (23 fetuses) and Anomalies: (37 anomalies) At < 24 weeks Sensitivity: 13.5% (13.5%) Specificity: 100.00% At > 24 weeks Sensitivity: 21.7% (16.2%) Specificity: 100.00% Overall detection False-positive: 0 Sensitivity: 34.8% (29.7%) Specificity: 100.00%	Study reported in systematic review	Retrospective	II
Van Dorsten 1998 Reported in:	297	1993–1996 USA (S.Carolina)	By registered diagnostic medical sonographers	Diagnostic test characteristics at	Prevalence of Anomalous fetuses: 1.30% (21 fetuses), and Anomalies:	Study reported in systematic review	Prospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Bricker L et al, (HTA) 2000		Mixed population from two sites Unselected *n* = 1611 (Twins excluded)	Scanned at 15–22 weeks Soft markers: no	< 24 weeks	(29 anomalies) False-positive: 1 Sensitivity: 47.6% Specificity: 99.90%			
Boyd 1998 Reported in: Bricker L et al, (HTA) 2000	297	1991–1996 UK (Oxford) Tertiary single centre Unselected *n* = 33 376 (Twins not specified)	Sonographers not mentioned Scanned at 18–22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 2.17% (725 fetuses) but Anomalies not reported False-positive: 15 Sensitivity: 41.1% Specificity: 99.90%	Study reported in systematic review	Retrospective	II
Whitelow 1999	300, 743	Not known UK (London) Single university hospital Unselected *n* = 6443 (77 twins; 4 triplets)	Sonographers: 6 different clinicians Scanned at 11–14 weeks either trasnabdominally or transvaginally Soft markers: yes	Diagnostic test characteristics at < 15 weeks and < 24 weeks	Prevalence of anomalous fetuses: 1.4% (92 fetuses), but anomalies: not reported <u>At < 15 weeks</u> Sensitivity: 58.7% Specificity: 99.90% <u>At < 24 weeks</u> Sensitivity: 81.0% Specificity: no data		Prospective	II
Eurenius 1999	727	1990–1992 Sweden (Uppsala) Tertiary hospital, single centre Unselected *n* = 8324 (111 twins, 3 triplets)	By trained midwife Scanned at 15–22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 0.74% (145 fetuses) Anomalies: not reported False-positive: 20 Sensitivity: 22.1% Specificity: 99.80%		Prospective	II
Stefos 1999	728	1990–1996 Greece (Ioannina) Tertiary, single centre Unselected	By experienced obstetricians Scanned at 18–22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 2.24% (162 fetuses) Anomalies: not reported		Prospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		n = 7326 (86 twins)			False-positive: 8 Sensitivity: 80.25% Specificity: 99.88%			
Taipale 2004	729	1994–1996 Finland (Helsinki) Tertiary hospital, single centre Low risk *n* = 4855 (multiples excluded)	By obstetrician and trained midwives Scanned at 13–14 weeks transvaginally and 18–22 weeks transabdominally	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 0.7% (33 fetuses) Anomalies: not reported False-positive: 2 Sensitivity: 48.5% Specificity: 99.96%		Prospective	II
Nakling 2005	730	1989–1999 Norway (Oppland), District general hospitals Unselected *n* = 18 181 (? Multiples)	By trained midwives and obstetricians Scanned at 13–24 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 1.47% (267 fetuses), but Anomalies: not reported False-positive: 11 Sensitivity: 39.0% Specificity: 99.94%		Prospective	II
Souka 2006	731	2002 Greece (Athens) Unselected Tertiary, single hospital *n* = 1148 (? Multiples)	By obstetricians Scanned at 11–14 weeks on Nuchal translucency measurement and at 22–24 weeks Soft markers: yes	Diagnostic test characteristics at < 24 weeks and overall detection rate	Anomalous fetuses: 1.21% (14 fetuses), but Anomalies: Not reported <u>At < 24 weeks</u> Sensitivity: 85.7% <u>Overall detection</u> False-positive: 3 Sensitivity: 92.9% Specificity: 99.74%		Prospective	II
Nikkila 2006	732	1984–1999 Denmark (Malmohus) 5 hospitals Unselected *n* = 141 240	Sonographers not mentioned Scanned at 18 weeks, some had scan at 33 weeks, as well Soft markers: yes	Diagnostic test characteristics at < 24 weeks and overall detection rate	Anomalous fetuses: 2.56% (3614 fetuses) Anomalies: not reported <u>At < 24 weeks</u>		Retrospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 38.9% Specificity: Not obtained <u>Overall</u> False-positive: 265 Sensitivity: 28.4% Specificity: 99.81%			
Rustico 1995 Reported in Randall P et al, 2005	749	Italy Tertiary referral centre Low-risk women *n* = 7024 Prevalence of congenital heart disease: 9.3 per 1000	20–22 weeks Four-chamber view plus outflow tracts 5/3.5 MHz Results confirmed by neonatal and paediatric examination, autopsy postnatally (neonatal echo and ECG, 24 month follow up)	Diagnostic accuracy results for cardiac defects – major, minor, and all defects. Results for non-structural defects or arrhythmias not reported	<u>Sensitivity</u> Major defects: 84.6% [95% CI 54.6 to 98.1] Minor defects 23.1% [95% CI 12.5 to 36.8] All defects 35.4% [95% CI 23.9 to 48.2] <u>Specificity</u> Major defects: 99.9% [95% CI 99.9 to 100] Minor defects 99.9% [95% CI 99.9 to 100] All defects 99.9% [95% CI 99.8 to 99.9]	Reported in systematic review	Prospective	
Anandakumar 2002 Reported in Randall P et al, 2005	749	Singapore Tertiary referral centre Unselected women *n* = 39 808 Prevalence of congenital heart disease: 7.6 per 1000	21–22 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination (6 months follow up)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects.	<u>Sensitivity</u> Major defects: 94.0% [95% CI 84.4 to 98.5] Minor defects 82.1% [95% CI 76.5 to 86.9] Non-structural defects/ arrhythmias 95.2% [95% CI 76.2 to 99.9] All defects 85.4% [95% CI 80.9 to 89.2] <u>Specificity</u> Major defects: 100.0% [95% CI 99.9 to 100] Minor defects	Reported in systematic review	Retrospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					99.9% [95% CI 99.9 to 99.9] Non-structural defects/ arrhythmias 99.9% [95% CI 99.9 to 99.9] All defects 99.9% [95% CI 99.9 to 99.9]			
Hafner 1998 Reported in Randall P et al, 2005	749	Austria District general hospital Low-risk women *n* = 6541 Prevalence of congenital heart disease: 13.6 per 1000	22 and 34 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected Results confirmed by neonatal examination (neonatal echo)		<u>Sensitivity</u> Major defects: 87.5% [95% CI 65.1 to 97.9] Minor defects 32.4% [95% CI 21.5 to 44.8] Non-structural defects/ arrhythmias 83.3% [95% CI 17.7 to 19.9] All defects 46.1% [95% CI 35.4 to 57.0] <u>Specificity</u> Major defects: 99.9% [95% CI 99.9 to 100] Minor defects 99.9% [95% CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95% CI 99.9 to 100] All defects 99.6% [95% CI 99.5 to 99.8]	Reported in systematic review	Prospective	
Achiron 1992 Reported in Randall P et al, 2005	749	Israel Tertiary referral centre Low-risk women *n* = 5347 Prevalence of congenital heart disease: 4.3 per 1000	18–24 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects	<u>Sensitivity</u> Major defects: 83.3% [95% CI 55.6 to 97.1] Minor defects 50.0% [95% CI 11.8 to 88.2] Non-structural defects/ arrhythmias 87.5% [95% CI 28.4 to 99.9] All defects 78.3% [95% CI 56.3 to 92.5] <u>Specificity</u> Major defects:	Reported in systematic review	Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					99.9% [95% CI 99.9 to 100] Minor defects 99.9% [95% CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95% CI 99.9 to 100] All defects 99.9% [95% CI 99.9 to 100]			
Stumpflen 1996 Reported in Randall P et al, 2005	749	Austria Tertiary referral centre Low-risk women *n* = 2181 Prevalence of congenital heart disease: 7.8 per 1000	18–28 weeks Four-chamber view plus outflow tracts and Doppler colour-flow mapping 3.5MHz Results confirmed by neonatal examination and autopsy (diagnostic investigations)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects Results for major, minor, and non-structural / arrhythmias not reported	<u>For All defects only</u> Sensitivity: 86.1% [95% CI 61.9 to 97.6] Specificity: 99.9% [95% CI 99.8 to 100]	Reported in systematic review	Prospective	
Buskens 1996	750	Netherlands Tertiary referral centre Low-risk women *n* = 5319 Prevalence of congenital heart disease: 8.3 per 1000	16–24 weeks Four-chamber view plus outflow tracts 3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Diagnostic accuracy results for all cardiac defects only. Diagnostic accuracy results reported for major and all cardiac defects only.	<u>Major defects</u> Sensitivity: 16.7% [95% CI 2.1 to 48.4] Specificity: Not reported <u>All defects</u> Sensitivity: 4.5% [95% CI 0.6 to 15.0] Specificity: 99.9% [95% CI 99.8 to 100]		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Tegnander 2006	751	Norway Tertiary referral centre Unselected women *n* = 29 460 Prevalence of congenital heart disease: 14.6 per 1000	16–22 weeks Four-chamber view plus outflow tracts for first 5 years, then four-chamber view plus outflow tract plus venous return for next 5 years 5/3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Results reported for Sensitivities for major, minor and all cardiac defects only.	Sensitivity Major defects: 56.7% [95% CI 46.9 to 66.5] Minor defects 3.6% [95% CI 3.4 to 3.8] All defects 15.6% [95% CI 12.1 to 19.0]		Prospective	
Bilardo 1998 Reported in Makrydimas, 2003	754	*n* = 1590 Excluded chromosomal abnormalities=50	US done at 10–14 weeks	Diagnostic accuracy results for NT threshold of 3.0 mm or greater	Sensitivity: 50% Specificity: 97.2%	Reported in systematic review	Prospective	
Hafner 1998 Reported in Makrydimas, 2003	754	*n* = 4214 Excluded chromosomal abnormalities=19	US done at 10–13 weeks	Diagnostic accuracy results for NT threshold of 2.5 mm or greater	Sensitivity: 28.6% Specificity: 98.6%	Reported in systematic review	Prospective	
Josefsson 1998 Reported in Makrydimas, 2003	754	*n* = 1460 Excluded chromosomal abnormalities=0	US done at gestational age of CRL 31–84 mm	Diagnostic accuracy results for NT threshold of 2.5 mm or greater, and 3.5 mm or greater	NT > 2.5 mm Sensitivity: 38.5% Specificity: 91.1% NT > 3.5 mm Sensitivity: 0% Specificity: 99.6%	Reported in systematic review	Prospective	
Hyett 1999 Also reported in Makrydimas, 2003	754,763	*n* = 29 154 Excluded chromosomal abnormalities=323	US done at 10–14 weeks	Diagnostic accuracy results for two thresholds – NT greater than 95th centile or greater than 3.5 mm	NT > 95th centile Sensitivity: 56.0% Specificity: 93.8% NT > 3.5 mm Sensitivity: 40.0% Specificity: 99.0%	Also reported in systematic review	Prospective	
Schwarzler 1999 Also reported in Makrydimas, 2003	754,764	*n* = 4474 Excluded chromosomal abnormalities=23	US done at 10–14 weeks	Diagnostic accuracy results for NT threshold of 2.5 mm or greater	Sensitivity: 11.1% Specificity: 97.3%	Also reported in systematic review	Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Michailidis 2001 Also reported in Makrydimas, 2003	754,765	*n* = 6606 Excluded chromosomal abnormalities=44	US done at 12–13 weeks	Diagnostic accuracy results for two thresholds – NT greater than 95th centile or greater than 99th centile	NT > 95th centile Sensitivity: 36.4% Specificity: 96.5% NT > 99th centile Sensitivity: 27.3% Specificity: 98.9%	Also reported in systematic review	Retrospective	
Marides 2001 Also reported in Makrydimas, 2003	754,766	*n* = 7339 Excluded chromosomal abnormalities, not defined	US done at 10–14 weeks	Diagnostic accuracy results for NT threshold of 2.5 mm or greater, and 3.5 mm or greater	NT > 2.5 mm Sensitivity: 15.4% Specificity: 96.5% NT > 3.5 mm Sensitivity: 11.5% Specificity: 99.2%	Also reported in systematic review	Prospective	
Orvos 2002 Reported in Makrydimas, 2003	754	*n* = 3655 Excluded chromosomal abnormalities=15	US done at 10–13 weeks	Diagnostic accuracy results for NT threshold of 3.0 mm or greater	Sensitivity: 51.4% Specificity: 97.7%		Retrospective	
Atzei 2005	756	*n* = 6921 Chromosomal abnormalities excluded (no number obtained)	US done at 11–13 weeks	Diagnostic accuracy results for four thresholds – NT greater than 95th centile, 3.5 mm or greater, 4.5 mm or greater, and 5.5 mm or greater.	NT > 95th centile Sensitivity: 79.5% Specificity: 50.9% NT > 3.5 mm Sensitivity: 48.5.0% Specificity: 85.1% NT > 4.5 mm Sensitivity: 31.1% Specificity: 94.4% NT > 5.5 mm Sensitivity: 21.2% Specificity: 97.2%		Prospective	
Bahado-Singh 2005	755	*n* = 8167 Excluded chromosomal	US done at 10–13 weeks	Diagnostic accuracy results for three thresholds	NT > 2.0 mm Sensitivity: 38.1%		Retrospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		abnormalities=101		– NT equal to or greater than 2.0 mm, 2.5 mm, and 3.5 mm	Specificity: 82.8% <u>NT > 2.5 mm</u> Sensitivity: 14.3% Specificity: 95.4% <u>NT > 3.5 mm</u> Sensitivity: 4.8% Specificity: 99.5%			
Westin 2006	757	*n* = 16 383 Excluded chromosomal abnormalities=80	US done at 12–14 weeks	Diagnostic accuracy results for three thresholds – NT greater than 95th centile, 3.0 mm or greater, and 3.5 mm or greater	<u>NT > 2.0 MoM</u> Sensitivity: 15.4% Specificity: 98.4% <u>NT > 2.5 MoM</u> Sensitivity: 13.5% Specificity: 99.4% <u>NT > 3.0 MoM</u> Sensitivity: 9.6% Specificity: 99.7%		Retrospective	
Simpson 2007	758	*n* = 34 266 Excluded chromosomal abnormalities=104	US done at 10 $^{3/7}$ to 13 $^{6/7\ weeks}$	Diagnostic accuracy results for three thresholds – NT value 2.0 MoM (98.3rd centile) or greater, 2.5 MoM (99.4TH centile) or greater, and 3.0 MoM (99.7TH centile) or greater	<u>NT > 2.0 MoM</u> Sensitivity: 15.4% Specificity: 98.4% <u>NT > 2.5 MoM</u> Sensitivity: 13.5% Specificity: 99.4% <u>NT > 3.0 MoM</u> Sensitivity: 9.6% Specificity: 99.7%		Retrospective	

9.2 Screening for Down's syndrome

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in identifying babies with Down's Syndrome: bood tests; nuchal translucency; maternal age; ultrasound – soft markers (choroid plexus cyst, thickened nuchal fold, echogenic echocardiac focus, echogenic bowel, renal pylectasis, humeral and femoral shortening); ultrasound – nasal bone. Different timings include: first trimester; second trimester; integrated. First-trimester screening for Down's syndrome and other chromosomal anomalies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Nicolaides *et al.*, 2005	[768]	1998 – 2003 6 hospitals, 1 fetal medicine unit UK Sample size 75 821 (96.7% of study population) Unselected (booked for maternity care) Maternal age: Median – 31 (Range 13 to 49) Exclusions: adequately described	Combined (NT + β-HCG + PAPP-A) Validated reference standard: Yes (prenatal karyotype, pregnancy records) Risk cut-off ≥ 1 in 300 for all	Diagnostic test characteristics	Number of cases (prevalence in %) DS 325 (0.43) T 18/13 122 (0.16) Others 97 (0.13) Estimated Detection Rate for FPR 5.2% DS 92.6 T 18/13 88.5 Others 85.6		Cohort study	Ib
Wapner *et al.*, 2003	[769]	Unspecified period. 12 prenatal diagnostic centres USA Sample size 8216 (93.2% of study population) Selected (12 diagnostic centres)(small sample) Maternal age: Mean – 34.5 (SD 4.6) Exclusions: adequately described	Combined Validated reference standard: Yes (karyotype – pre/postnatal, pregnancy records) Risk cut-off 1 : 270 for DS, 1 : 150 for T 18	Diagnostic test characteristics	Number of cases (prevalence in %) DS 61 (0.74) T 18 11 (0.13) Observed Detection Rate and FPR (with 95% CI) DS 85.2 (73.8 to 93.0) with FPR 9.4% (8.8 to 10.1) T 18 90.9 (58.7 to 99.8) with FPR 2% (1.7 to 2.3)		Cohort study	II
Stenhouse *et al.*, 2004	[770]	3 years ANC clinic of 1 hospital UK Sample size 5000 (98.3 %of study population) Selected (75% screening uptake, 27% ≥ 35 years) Maternal age: Median 31.5 (Range 14 to 45) Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records) Risk cut-off ≥ 1 : 250 for all	Diagnostic test characteristics	Number of cases (prevalence in %) DS 15 (0.3) All 26 (0.52) Observed Detection Rate DS 93 at FPR 5.9% All 96 at FPR 6.3%		Cohort study	II
Malone *et al.*, 2005	[771]	8 months 15 specialist centres USA	Fetal nasal bone (NB)	Diagnostic test	Number of cases (prevalence in		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Sample size 6228 (98.5%of study population) Selected (small sample) Maternal age: Mean 30.1 SD 5.7 Range 16 to 47 Exclusions: adequately described	Validated reference: Yes (prenatal karyotype, pregnancy records)	characteristics	%) DS 11 (0.18) T 18 2 (0.03) All 13 (0.21) Observed detection rate and FPR (with 95% CI) DS 0 (no case detected) All 7.7 (0.2 to 36) with FPR 0.3 (0.2 to 0.5)			
Cicero *et al.*, 2006	[772]	2001 to 2004 1 fetal medicine unit UK 20 418 (96.9% of study population) Selected (Single Centre) Maternal age: 35 Range 18 to 50 Exclusions: adequately described	Combined ± NB Validated reference: Yes (karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 140 (0.68) T 18 40 (0.13) Others 73 (0.36) Estimated detection rate FOR DS CASES ONLY Combined 90 with 5% FPR Combined + NB 93.6 with 5% FPR		Cohort study	II
Prefumo *et al.*, 2006	[773]	2001 to 2003 1 fetal medicine unit UK 7626 (100% of study population) Selected 6.7% Unselected 93.3% (Routine ANC and referrals) Maternal age: Median 31.6 Range 14.5 to 50.2 Exclusions: adequately described	Fetal Nasal Bone (NB) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 35 (0.5) *Selected* 23 (4.5) *Unselected* 12 (0.2) All 64 (0.8) Observed performance (with 95% CI) FOR DS CASES ONLY *Selected* Sensit. 47.6 (25.7 – 70.2) Specif. 95.3 (92.9 – 97.1) PPV 33.3 (17.3 – 52.8) NPV 97.4 (95.3 – 98.7) *Unselected* Sensit. 16.7 (2.1 – 48.4)		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specif. 97.3 (96.9 – 97.7) PPV 1.1 (0.1 – 4.1) NPV 99.8 (99.7 – 99.9)			
Weingertner *et al.*, 2006	779	2002 to 2004 1 reference centre France 2044 (91.5% of study population) Selected – 33% Unselected 67% (Single reference centre) Maternal age: Median 32 Range 16 to 47 Exclusions: adequately described	NT ± NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (Prevalence in %) DS 30 (1.47) T 18 14 (0.68) Others 35 (1.71) i) Observed performance for DS Risk 1 : 250 (NT), ≤ 0.60 MoM (NB) NT NT + NB ST 88 (86–90) 100 FPR 23 (21–26) 5 (3–6) ii) Performance of only NB ST 32 FPR 10 LR+ 4.4 (2.0 – 9.4)		Cohort study	III
Ramos-Corpas *et al.*, 2006	774	2003 to 2004 1 fetal medicine unit Spain 1800 (45% of population) Selected (Single centre, only 45% participated) Maternal age: Mean 30.09, SD 5.37 Range 15 to 46 Exclusions: Not described	Fetal nasal bone (NB) Validated reference: Yes (karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 7 (0.39) Others 3 (0.17) Observed performance of NB for DS ST 33.3 (4.3 – 77.7) FPR 1.13 SP 98.9 (98.5 – 99.4) PPV 9.5 (1.2 – 30.4) NPV 99.7 (99.4 – 99.9)		Cohort study	III
Orlandi *et al.*, 2005	780	Unspecified period. 1 fetal medicine unit Italy 2411 (unspecified % of population) Selected (details not specified) Maternal age: 30.5 SD 4.115 Exclusions: Not described	Combined ± NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 15 (0.62) i) Observed performance of NB for DS ST 53.3 (26.6 – 78.7)		Cohort study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					SP 99.5 (99.3 – 99.8) PPV 47.1 (23.3 – 70.8) LR+ 142 (63 – 318) LR− 0.47 (0.27 – 0.80) ii) Estimated performance (Risk 1 : 250) *Comb.* *Comb.* + *NB* DR 87 90 FPR 4.3 2.5			
Kozlowski *et al.*, 2006	965	2002 to 2004 1 prenatal centre Germany 2973 (92.4 % of study population) Selected (single centre, 46% > 35 years) Maternal age: 34 Range 14 to 46 Exclusions: adequately described	Combined ± NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 18 (0.60) Others 22 (0.74) Estimated performance for DS Risk cut-off 1 : 300 *Comb.* *Comb.* + NB DR 94.4 77.8 FPR 5.5 2.8		Cohort study	III
Zoppi *et al.*, 2003	776	2001 to 2002 1 prenatal diagnosis unit Italy 3503 (64.6% of study population) Selected (single study centre) Maternal age: Median 32 Range 15 to 48 Exclusions: adequately described	Fetal nasal bone (NB) Validated reference standard: Incomplete info. For 35% of study population	Diagnostic test characteristics	Number of cases (prevalence in %) DS 27 (0.77) Others 13 (0.37) Observed performance of NB for DS DR 70 FPR ??		Cohort study	III
Viora *et al.*, 2003	777	2001 to 2002 1 prenatal diagnosis unit Italy 1906 (unspecified % of study population) Selected (referred women) Maternal age: 32.2 Range 18 to 47 Exclusions: adequately described	Fetal Nasal Bone (NB) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 10 (0.57) Others 9 (0.51) Observed performance of NB for DS DR 60 FPR 1.4		Cohort study	III

First-trimester screening for Down's syndrome only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rozenberg *et al*., 2006	778	2001 to 2002 10 perinatal units France 14 380 (96.3% of study population) Unselected (in a health authority) Materrnal age: Median 30.7 25th to 75th centile – 28 to 33.9 Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 51 (0.34) Observed results (95% CI) Detection rate (%) 79.6 FPR (%) 2.7 Risk cut-off 1 : 250		Cohort study	Ib
Avgidou *et al*., 2005	781	1999 – 2001 1 hospital, 1 fetal medicine unit UK 30 564 (95.8% of study population) Selected (48.5% ≥ 35 years) Maternal age: Median 34 Range 15 to 49 Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 196 (0.64) Estimated results: Detection rate (%) 90.3 FPR (%) 5 (fixed) Risk cut-off 1 : 250		Cohort study	II
Crossley *et al*., 2002	767	2 years 15 maternity units UK 17 229 (100% of study population) Unselected (for routine ANC care) Maternal age: Median 29.9 Range 15 to 49 Exclusions: not applicable (100% follow up)	Combined Validated reference: Yes (prenatal karyotype, pregnancy records	Diagnostic test characteristics	Number of DS cases (prevalence in %) 45 (0.57) Observed results: Detection rate (%) 82 (65 – 93) with 34 cases FPR (%) 5 Risk cut-off 1 : 250		Cohort study	II

Second-trimester screening for Down's syndrome and other chromosomal anomalies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Jaques, 2006	782	1998 – 2000 3 databases Australia 19 143 (99.2% of study population) Sample size for analysis of Down's and T 18 – 16 607 (86.7%) Sample size for analysis of Neural tube defects – 17 288 (90.3%) Maternal age: Mean 30.3 (range 14–51) 20.1% > 35 years	Quadruple test	Diagnostic test characteristics	Number of cases (prevalence in %) DS 27 (0.16) T 18 8 (0.05) NTD 14 (0.08) Observed results: *For DS* Quadruple test (Risk ≥ 1 : 250) DR 85 (72 – 99) FPR 6.8 PPV 2		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Quadruple test (FPR fixed at 5%) DR 78 FPR 5.0 PPV 2.5 *For T 18* Quadruple test (Risk ≥ 1 : 200) DR 44 (12 – 77) FPR 0.5 PPV 4.7 *For NTD (AFP ≥ 2.5 MoM)* All NTD DR 73 FPR 1.1 PPV 5.6 Spina bifida DR 50 FPR 1.1 PPV 2.1 Anencephaly DR 100 FPR 1.1 PPV 3.1			

Second-trimester screening for Down's only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Smith-Bindman, 2001	315	56 english language studies taken from MEDLINE 1980 – 1999 132 295 Exclusion criteria well defined	Ultrasound (US) Validated reference Yes (karyotyping in 53 of the 56 studies)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 1930 (1.5) Results: Summary measures (with 95% CI) for US markers when seen individually Thickened Nuchal fold ST 0.04 (0.02 – 0.01) SP 0.99 (0.99 – 0.99) LR+ 17 (8 – 38) LR− 0.97 (0.94 – 1.00) Fetal loss per case 0.6 Choroid plexus cyst ST 0.01 (0 – 0.03) SP 0.99 (0.97 – 1.00) LR+ 1.00 (0.12 – 9.4) LR− 1.00 (0.97 – 1.00) Fetal loss per case 4.3 Femur length ST 0.16 (0.05 – 0.40) SP 0.96 (0.94 – 0.98) LR+ 2.7 (1.2 – 6.0) LR− 0.87 (0.67 – 1.1) Fetal loss per case 1.2 Humerus length ST 0.09 (0 – 0.60) SP 0.97 (0.91 – 0.99) LR+ 7.5 (4.7 – 12) LR− 0.87 (0.67 – 1.1) Fetal loss per case 1.9		Meta-analysis	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Echogenic bowel ST 0.04 (0.01 – 0.24) SP 0.99 (0.97 – 1.00) LR+ 6.1 (3.0 – 12.6) LR− 1.00 (0.98 – 1.00) Fetal loss per case 1.0 Echogenic intracardiac focus ST 0.11 (0.06 – 0.18) SP 0.96 (0.94 – 0.97) LR+ 2.8 (1.5 – 5.5) LR− 0.95 (0.89 – 1.00) Fetal loss per case 2.0 Renal pyelectasis ST 0.02 (0.01 – 0.06) SP 0.99 (0.98 – 1.00) LR+ 1.9 (0.7 – 5.1) LR− 1.00 (1.00 – 1.00) Fetal loss per case 2.6			
Conde-Agudelo, 1998	320	20 cohort studies taken from MEDLINE search from 1966 – November 1996 (English, French or German language) 194 326 Maternal age: Mean varied between 24.5 and 33.5 Inclusion and exclusion criteria well defined	Triple marker screen for DS Validated reference: – 4 studies obtained fetal karyotypes. In other studies CVS or amniocentesis was offered to screen-positive women. Proportion of women accepting prenatal diagnostic testing ranged from 67 to 92. Follow-up information on pregnancy outcome incomplete in 8 studies	Diagnostic test characteristics	Results Cut-offs 1 : 190 – 200 Maternal age (MA) ≥ 35 years ST (Range) 89 (78 – 100) FPR (Range) 25 (20 – 29) All ages ST 67 (48 – 91) FPR 4 (3 – 7) Cut-offs 1 : 250 – 295 MA ≥ 35 ST 80 (75 – 100) FPR 21 (20 – 21) MA < 35 ST 57 (53 – 58) FPR 4 (3 – 6) All ages ST 71 (48 – 80) FPR 6 (4 – 7)		Meta-analysis	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Cut-offs 1 : 350 – 380 All ages ST 73 (70 – 80) FPR 8 (7 – 13)			
Sotiriadis, 2003	783	11 studies taken from MEDLINE and EMBASE between 1985 to August 2002 (English, French and German language) 51 831 Maternal age: Mean ranged between 29 – 35 years	Intracardiac echogenic foci	Diagnostic test characteristics	Data included 51 831 fetuses with 333 Down's syndrome cases ('combined': 27 360 with 321 Down's syndrome cases, 'isolated' – 39 360 with 130 Down's syndrome cases). Results: Random effects model (REM) 'Combined Setting' ST 0.26 (0.19 – 0.35) SP 0.963 (0.937 – 0.979) 'Isolated setting ST 0.22 (0.14 – 0.33) SP 0.959 (0.910 – 0.982) All ST 0.26 (0.19 – 0.34) SP 0.958 (0.922 – 0.978) Fixed effects model (FEM) 'Combined setting' ST 0.30 (0.25 – 0.36) SP 0.927 (0.924 – 0.931) 'Isolated setting' ST 0.22 (0.15 – 0.30) SP 0.964 (0.961 – 0.966) All ST 0.30 (0.25 – 0.36) SP 0.940 (0.937 – 0.942) Further it was estimated that the probability of DS (assuming LR+ of 6.2) after an intracardiac echogenic foci has been detected would be 0.44% in a population with prevalence of 1 : 1400, 0.62% with prevalence of 1 : 1000, and 1.03% with prevalence of 1 : 600		Meta-analysis	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Coco, 2005	784	1998 – 2002 single medical centre Italy 12 672 (77.8% of study population) Maternal age: Mean 27.2 ± 5.5 years	US detection of Fetal pyelectasis as a screening test. Validated reference: Yes (karyotyping, postnatal records, information from mother)	Diagnostic tests characteristics	Number of cases (prevalence in %) DS 11 (0.09) Pyelectasis 367 (2.9%) Only one case of Down's syndrome identified with pyelectasis. Results: Isolated pyelectasis ST 9.1 (1.62 – 37.4) SP 97.6 (97.32 – 97.85) PPV 0.33 NPV 99.9 LR+ 3.8 (0.58 – 24.61) LR− 0.9 (0.77 – 11.2) Pylectasis + other markers ST 9.1 SP 99.5 PPV 1.6 NPV 99.9 LR+ 19.2		Cohort study	II

First- and second-trimester screening for Down's syndrome only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Malone *et al*., 2005	785	1999 – 2002 15 medical centres USA 33 547 (82% of study population) with complete data from both trimesters Unselected Maternal age: Mean 30.1 SD 5.8 Exclusions: adequately described	All serum tests with NT (Combined, Quadruple, integrated and Serum integrated) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 92 (0.27) Results: Detection rate at fixed FPR 5% (95% CI) Combined (11 weeks) – 87 (82 – 92) Quadruple (15–17 weeks) – 81 (70 – 86) Serum integrated – 88 (81 – 92) Fully integrated – 96 (92 – 97)		Cohort study	Ib
Wald *et al*., 2003	316	1996 – 2001 25 maternity centres UK and Austria 43 712 (92% of study population). 98 cases, 490 controls for screening performance. 600 controls added for statistical power Unselected Unspecified maternal age	All serum and urine biochemical markers with NT Validated reference: yes (karyotype – pre/postnatal pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 101 (0.23) Results: Estimated Detection Rate at fixed FPR 5% first trimester (10 – 13 week) PAPP-A + NT 76 Combined 84 Combined + inhibin A 87 second trimester (15 – 20) Double 71 Triple 77 Quadruple 83 Integrated screening (both first and second trimester) NT (10 weeks) + Quadruple 90 Serum integrated 90 Integrated 93		Nested Case–control (within a cohort)	II
Knight *et al*., 2005	786	2001 – 2003 229/260 prenatal care practitioners USA 8773 (78.6% of study population) Selected (61% enrolled for study) Maternal age: Mean – 27.8 SD 5.5	Integrated serum screening Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 16 (0.18) Results: Observed screening performance with 95% CI		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Triple Risk 1 : 270 DR 67 (43 – 84) FPR 6.4 (5.9 – 6.9) Quadruple Risk 1 : 150 DR 56 (33 – 76) FPR 3.3 (2.9 – 3.7) Serum integrated Risk 1 : 100 DR 79 (55 – 92) FPR 3.2 (2.8 – 3.6)			
Platt *et al*., 2004	787	Unspecified period 122 prenatal diagnostic centres USA 4325 *first-trimester screen positive* 180 (52.7% of study population) *first-trimester screen-negative* 4145 Selected (low uptake of second-trimester screening) (small sample) Maternal age: Mean 34.5 SD – 4.6	Sequential screening using Triple marker after first-trimester Combined test Validated reference: Yes (karyotype – prenatal pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 13 (0.30) Results: Observed screening performance with 95% CI among first-trimester screen-negative women Risk 1 : 270 DR 85.7 (42.1 -99.6) FPR 8.9 (8.0 – 9.8)		Cohort study	II

Modelling studies for comparing different Down's syndrome screening tests

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Wright, 2006	789		'Contingent screening', the protocol involves measuring free β-hCG and PAPP-A in all pregnant women at 10 weeks in the first stage. Those with low risk were screened negative at this stage, the remainder underwent NT measurement in the second stage and the risk reassessed (for combined test). After the second stage, those with low risk were screened negative and those with very high risk were offered diagnostic tests. In the third stage, women with intermediate risk received second-trimester quadruple test. Risk was reassessed according to the integrated test and high-risk women were offered diagnosis.	Potential value of three-stage sequential screening for Down's syndrome	With full adherence to a three stage policy, an overall detection rate of nearly 90% and a false positive rate of below 2% can be achieved. About two-thirds of the women can be screened on the basis of first-trimester biochemistry alone and about 80% by the combined test. The DR for first-trimester screening is about 60%. This protocol allows most of the Down's syndrome pregnancies to be detected in the first trimester.		Modelling	III
Wald, 2006	790		compared the integrated test in three policies for screening – i) integrated screening for all women ii) Sequential screening (based on first-trimester tests, high-risk pregnancies to be diagnosed and remaining to undergo integrated test) iii) Contingent screening. Detection and false positive rates were estimated based on the data from a large cohort (nested case–control study) done in the UK.		integrated screening had the best screening performance. As the first-trimester test FPR was decreased, the performance of other two policies approached that of the integrated screen. Setting the first-trimester risk cut-off to $\geq$ 1 in 300 with a fixed DR of 90%, sequential and contingent screening gave overall FPR's of 2.3% and 2.4% respectively, and 66% of affected pregnancies were detected by the first-trimester tests. The integrated test on all women gave a FPR of 2.2%.	If pregnancies with a first-trimester risk of $\leq$ 1 in 2000 are classified screen negative and receive no further testing, then 99.5% of women with sequential screening or 30% with contingent screening would proceed to integrated screening.	Modelling	III

Effectiveness of different Down's syndrome screening tests

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Saltvedt, 2005	791	8 Swedish Hospitals 39 572 (19 796 in 12 weeks, 19 776 in 18 weeks)	Comparison of routine ultrasound scan at 12–14 weeks by nuchal translucency *versus* routine ultrasound at 15–20 weeks by maternal age. Validated reference: yes (karyotyping, pregnancy outcome)	Screening test effectiveness	Number of DS cases (prevalence in %) 98 (0.25) Results: Outcome 12 week group 18 week group *P* value Prevalence rate 55/19 796 (0.28) 43/19 776 (0.22) 0.18 Rate of liveborn DS babies (at > 22 weeks) 10/19 796 (0.05) 16/19 776 (0.08) 0.25 Antenatal detection rate (< 22 weeks in living fetus) 42/55 (76) 25/41* (61) 0.12 Antenatal detection rate (if karyotyping performed only for defined policy) 39/55 (71) 21/41* (51) 0.06 Detection rate (other chromosomal anomalies) 20/35 (57) 25/35 (71) 0.32 Terminations done for DS		RCT	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					39/19 796 (0.20) 24/19 776 (0.12) 0.08 Fetal loss rate in DS fetuses (terminations and miscarriages) 45/19 796 (0.23) 27/19 776 (0.14) 0.04 Rate of invasive tests (for karyotyping) 1593/19 796 (8) 2118/19 776 (0.14) < 0.001 Spontaneous fetal loss rate after invasive tests in normal fetuses 14/1507 (0.9) 15/2041 (0.7) 0.58 No. of invasive tests per one case of DS detected (< 22 weeks)(if karyotyping performed only for defined policy) 16 89 * of the 43 cases of DS, diagnosis was made in one case by amniocentesis at < 22 weeks but pregnancy continued, and in other diagnosis made at 35 weeks – leaving 41 cases for calculating DR			
Wald, 2003	316	See Table III	Safety in terms of number of unaffected fetal losses per 100 000 women screened and number of DS pregnancies detected for each procedure related unaffected fetal loss	Screening test effectiveness	Results: FPR (5%) Combined 6.1 Double 13.1 Triple 9.3 Quadruple 6.2 Serum integrated 2.7 Integrated 1.2		Nested case–control	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Unaffected fetal losses per 100 000 women Combined 44 Double 94 Triple 67 Quadruple 45 Serum integrated 19 Integrated 9 DS cases detected for each procedure related fetal loss Combined 3.9 Double 1.8 Triple 2.6 Quadruple 3.8 Serum integrated 9.1 Integrated 19.2			
Biggio, 2004	792	Hypothetical cohort of 1 000 000 women < 35 years	Comparison of 5 screening strategies (1) first-trimester combined screen (2) second-trimester quadruple screen (3) second-trimester triple screen (4) integrated screen (5) sequential screen.	Screening test effectiveness	Prevalence of Down's syndrome at 10 weeks of gestation was estimated as 1 in 595 pregnancies, and baseline live birth rate 1 of 1030 Results: No screening Cost of programme (million US$) 662 DS cases detected (n) 0 DS live births averted (n) 0 Euploid loss due to procedure 0 Triple screen, no sonogram Cost of programme (million US$) 497 DS cases detected (n) 529 DS live births averted (n) 366 Euploid loss due to procedure 311 Triple screen, with sonogram Cost of programme (million US$) 566 DS cases detected (n) 365 DS live births averted (n) 253 Euploid loss due to procedure 25 Quadruple screen, no sonogram		Decision analysis model	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Cost of programme (million US$) 472 DS cases detected (n) 618 DS live births averted (n) 427 Euploid loss due to procedure 311 Quadruple screen, with sonogram Cost of programme (million US$) 554 DS cases detected (n) 426 DS live births averted (n) 295 Euploid loss due to procedure 25 Combined screen Cost of programme (million US$) 486 DS cases detected (n) 941 DS live births averted (n) 490 Euploid loss due to procedure 559 Integrated screen Cost of programme (million US$) 521 DS cases detected (n) 750 DS live births averted (n) 520 Euploid loss due to procedure 62 Sequential screen Cost of programme (million US$) 455 DS cases detected (n) 1213 DS live births averted (n) 678 Euploid loss due to procedure 859			
Smith-Bindman, 2001	315	For details see Table II B	See table II B	Screening test effectiveness	See table II B	See table II B	See table II B	See table II B
Comstock CH, 2006	793	Analysis of multicentre prospective trial in the USA (FASTER trial) 36 120 Maternal age: ≥ 16 Exclusions: well defined	Determine whether there is a NT measurement above which immediate invasive testing should be offered without waiting for serum testing and computerised aneuploidy risk assessment	Screening test effectiveness	Results (in %) ≥ 2 mm 10 weeks 2.0 11 weeks 1.5 12 weeks 2.5 13 weeks 5.1 Total 3.0			2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					≥ 3 mm 10 weeks 0.4 11 weeks 0.5 12 weeks 0.3 13 weeks 0.4 Total 0.4 ≥ 4 mm 10 weeks 0.16 11 weeks 0.1 12 weeks 0.1 13 weeks 0.05 Total 0.09 ≥ 5 mm 10 weeks 0 11 weeks 0.04 12 weeks 0.09 13 weeks 0 Total 0.05 On comparison of outcome of pregnancies based on the various nuchal translucencies cut-offs, the following results were observed: ≥ 2 mm Number (%) 1081 (3.0) Aneuploidy 51 T21 39 T 18 5 ≥ 3 mm Number (%) 128 (0.4) Aneuploidy 22 T21 17 T 18 4 ≥ 4 mm Number (%) 32 (0.09)			

Study	Ref.	Population	Intervention	Outcomes	Results		Comments	Study type	EL
					Aneuploidy	10			
					T21	6			
					T 18	4			

Women's Views of ultrasound screening for fetal anomalies and Down's Syndrome

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Green, 2004	794	Any genetic screening programme aimed at pregnant women or newborn babies was included. Both comparative and descriptive studies which reported data collected directly from pregnant women or parents were included. There were no geographical or methodological limits except that studies asking hypothetical questions, case reviews and those where US was done to detect structural anomalies only (and not include chromosomal anomalies) were excluded.	5 broad questions concerned with i) knowledge ii) anxiety iii) other emotional aspects iv) factors associated with participation in the programmes and v) long-term sequelae of the results.	Psychosocial aspects of genetic screening of pregnant women and newborns	Knowledge and understanding of screening for DS – 30 studies were selected: 7 used pre-test measures only, 6 employed both before and after test measures (ideal for comparing), and 17 employed after test measures only. Eight areas of information as specified in RCOG 1993 professional guidelines were used as a 'validated/gold standard questionnaire' for evaluating knowledge in the selected studies. 30 studies related to knowledge were reviewed, but owing to disparate research aims, poorly operationalised measures for evaluation, and variation in timing of assessment, it was concluded that none of the study evaluated all the 8 areas and hence knowledge was inadequately assessed by all of them. Influence on anxiety in prenatal screening for DS – Of the 24 studies measuring anxiety, 13 used a validated scale (mainly State-Trait Anxiety Inventory). Most studies were carried out in the UK. As knowledge influences anxiety and attitudes, the findings from studies represents the feelings and views of many people who are in fact not well informed about the topic under discussion. Understanding decision making about screening – Of the 52 studies included, 34 were concerned with DS screening and 11 of them compared differences in those screened with those not screened. Most studies employed questionnaire or interview survey methods.		Systematic review	2++
Rowe HJ, 2006	795	4 antenatal clinics in Australia. pregnant women between 8 and 14 weeks attending at their first prenatal visit	A validated measure, and to compare anxiety levels in women who are well informed versus poorly informed. Written and oral information was provided to all participants as per the existing hospital policy. Informed choice was measured by Multidimensional Measure of Informed Choice (MMIC), a validated measure of informed choice which assesses knowledge and attitude dimensions and also confirms whether woman's participation in screening test matches her attitude. The Hospital Anxiety and Depression Scale (HADS) were used to measure anxiety and this scale specifically distinguishes between anxiety	Assess informed choice in pregnant women to participate in second-trimester serum screening	134 recruited women completing the first assessment in the second study, 63.9% returned the second questionnaire and 57.8% the third. The mean age of the sample was 29.1 ± 4.7 years and 89.6% were married. Using MMIC, 48.1% of women were classified as having 'good knowledge' and 87.2% having a 'positive attitude' to screening. Overall only 37.3% of decisions to participate in screening were informed; those who participated in screening were more than twice as likely to have made an informed choice than those who did not participate (47% versus 20%, $P = 0.01$). Informed decisions were not significantly associated with participant's age, gravidity, country of birth, or whether pregnancy was unwelcome or unexpected. No significant association was found between the knowledge levels and attitude to the test ($P = 0.27$). Some important misconceptions were revealed about further testing; 31% did not know that miscarriage was a possible consequence of diagnostic testing subsequent to an increased risk screening result, and only 62% correctly identified that termination of pregnancy would be offered if Down's syndrome was diagnosed. Regarding anxiety, no		Prospective cohort	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			and depression. Both the scales were administered at the booking visit and HADS was repeated at 20 weeks (after participation in the test) and at 30 weeks using postal questionnaires		significant difference was found between the informed and not informed group in psychological outcomes at any of the three assessments, even after adjusting for repeated measures on individual participants.			
Georgsson, 2004	796		The 12 week group was the intervention group and 18 week group acted as the control. The State-Trait Anxiety Inventory (validated tool for evaluating general anxiety) and Edinburgh Postnatal Depression Scale (validated for evaluating anxiety in antenatal/postnatal period) were also used. Information was collected at 3 different timings – first questionnaire was filled at the antenatal clinic, second was sent at 24 weeks of gestation (mid-pregnancy), and the last was posted 2 months after delivery. Same instruments were used for all the three questionnaires.	Women's worries about the 'possibility of something being wrong with the baby' was measured by the Swedish version of Cambridge Worry Scale questionnaire including 16 items of common concerns during pregnancy.	82.7% (854/1030) women in 12 week group, and 84.1% (837/996) in the 18 week group respectively who responded to all 3 questionnaires. The demographic characteristics of the two groups were similar. Emotional wellbeing at baseline in early pregnancy was also similar. In the early pregnancy 39.1% of women in 12 week group and 36.0% in 18 week group were worried about something being wrong with the baby, but the difference was not statistically significant. The prevalence decreased to 29.2% versus 27.8% during mid-pregnancy, and finally to 5.2% versus 6.6% at 2 months after delivery in the 2 groups. No statistically significant difference was found between the 2 groups during these periods also. Within both trial groups, there was statistically significant decrease in the levels of major worry about baby's health from early to mid-pregnancy ($P < 0.001$), and from mid-pregnancy to 2 months after delivery ($P < 0.001$).		Qualitative	3
Lawson, 2006	797	Participants included high-risk pregnant women (maternal age > 35 years) who opted for MSS or amniocentesis or did not opt for any testing.	Investigate the relationship between maternal serum screening (MSS) use and maternal attachment to pregnancy following the receipt of favourable results (i.e lowered risk ratio). Informational posters were placed at various places (physician offices, laboratories, maternity stores), and interested women who met the eligibility criteria were enrolled. The instrument used to collect information was a self-administered questionnaire by mail, and prenatal attachment was measured by 21-item Prenatal Attachment Inventory (construct validity and reliability of this scale were established). The three groups were		One-way ANOVA indicated that attachment levels for MSS group (mean 51.7, SD 9.4) were significantly lower than those reported by amniocentesis group (mean 58.5, SD 10.7) and no test group (mean 57.0, SD 8.3) [$t(68) = 0.68$, $P = 0.02$]. Moreover amniocentesis group did not differ in bonding levels compared to the no testing group [$t(67) = 0.66$, $P = 0.51$], thereby proving both the hypothesis. This difference persisted even after removing the influence of maternal age and attitude towards abortion. There was no significant interaction between testing status of the 3 groups and timing of conducting survey (second or third trimester) when they were used as independent variables with PAI as the dependant variable.		Cross-sectional survey	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			compared using ANOVA and ANCOVA for statistical analysis.					
Rowe, 2004	798		Studies were assessed in terms of a) utilisation – number of women screened as a proportion of those eligible b) offer – number of women offered screening as a proportion of those eligible, and c) uptake – number of women screened as a proportion of those offered screening	non participation rate and whether the distinction between utilisation, offer and uptake was	these suggested that compared to White women, utilisation of testing was lower in Asian women, two others indicated that both utilisation and uptake was lower, and fourth study found both acceptance and uptake of amniocentesis lower in women from Asia. In the remaining 5 studies, no statistically significant association was found between socio-demographic factors and test utilisation. Four studies reported on the offer of screening or diagnosis for DS. Two of these suggested that Asian women were less likely to be offered amniocentesis, while in the third study fewer Bangladeshi than White women were offered screening, although this result was not statistically significant. The fourth study did not analyse the results according to the social class or ethnic group.		Systematic review	2+
Dormandy, 2005	799	two UK district hospitals	Attitudes towards undergoing the test were assessed by women's responses to a structured question with 4 items. Knowledge about the test was assessed using an 8 item questionnaire deemed important in professional guidelines for informed consent in screening. Choices were classified as 'informed' depending on the consistency between test uptake, women's attitude towards the test, and their knowledge about it.	Reasons for lower uptake of screening tests in women from minority ethnic groups and socio-economically (SE) disadvantaged sections of society. Screening uptake was evaluated from hospital records	a) Screening uptake – overall uptake was 49% (95% CI 47–52). Uptake was higher in white and SE advantaged women. b) Knowledge – Overall the mean knowledge score was above the midpoint of the scale. Knowledge was higher for white, SE advantaged and older women. c) Attitudes towards test: The mean overall score was above the scale midpoint, that is, overall women had positive attitude towards the test. No difference in attitudes was found related to ethnicity, SE status or parity; but older women had more positive attitude than younger ones. d) Uptake-attitude consistency – In women with positive attitudes, white and SE advantaged women were more likely to act in line with their attitudes (76% white women had test compared to 45% South Asian women, $P < 0.001$) and (78% SE advantaged women had test compared with 63% SE disadvantaged women, $P < 0.001$). In women with negative attitude, no difference was found between ethnic or social groups. e) Informed choice – rates of informed choice were higher for white women (56% vs 20% South Asian, $P < 0.001$) and SE advantaged women (59% vs 14% for SE disadavantaged, $P < 0.001$). After controlling for confounding variables (ethnicity, age, SE status, and hospital attended), it was found that both South Asian women and SE disadvantaged women with positive attitudes were less likely to act consistently with their attitudes compared to white and SE advantaged women (OR 0.22, 95% CI 0.10–0.45 for South Asian vs white) and (OR 0.62, 95% CI 0.41–0.93 for social groups).		Qualitative	3
Spencer, 2004	800	6 UK maternity units (3 in	Pregnant women attending	To ascertain by	75% of women selected first-trimester screening (option 1		Cross-	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Scotland, 3 in England)	antenatal clinics were asked to put in order of preference four different approaches for screening (all with FPR of 5%) – (1) first-trimester testing – 90% detection with results available in 1 hour (2) first-trimester testing – 90% detection with results within 2–3 days (combined test) (3) first-trimester plus second-trimester detection, 93% detection and results within 2–3 days of second test (integrated test) (4) second-trimester testing, 75% detection and results available within 2–3 days.	means of a structured questionnaire women's preference for type of screening test	or option 2) as their first choice, with 68.2 % preferring results within 1 hour (option 1) and 6.8% preferring combined test. 24% opted for integrated test and just 1% opted for second-trimester testing as their first choice.		sectional survey	

10 Screening for infections

10.3 *Chlamydia trachomatis*

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in identifying genital Chlamydia: age; uring testing testing; endocervical swab; serum antibody testing; history?

Diagnostic accuracy studies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Smith *et al* , 1987	[805]	Pregnant (*n* = 231) and non-pregnant women (*n* = 827) below the age of 35 years attending an obstetrics and gynecology clinic in the USA. Prevalence 12.1% in pregnant women	Comparison of ELISA and DFA with culture (blind passage) of the endocervical swabs.	Diagnostic accuracy results for pregnant women only. Reference standard – positive by initial or repeat culture Threshold for positive EIA – optical density 0.100 greater than mean optical density of 3 negative controls Threshold for positive DFA – greater than 10 elementary bodies per slide	EIA (*n* = 231) Sensitivity: 85.7% Specificity: 95.6% PPV: 72.7% NPV: 98.0% DFA (*n* = 144) Sensitivity: 84.6% Specificity: 96.6% PPV: 84.6% NPV: 96.6% First culture with blind passage Sensitivity: 82.1% NPV: 98.8% First culture without blind passage Sensitivity: 60.7% NPV: 94.7%	Specimens collected randomly Blinding of technicians Test described adequately	CH	I b
Binns *et al*., 1988	[966]	Consecutive asymptomatic pregnant women opting for abortion and attending a counselling clinic in Canada	Comparison of ELISA and DFA with culture of the endocervical swabs	Diagnostic accuracy results for two different reference standards– positive culture without blind passage or positive results for any two of the three	Positive culture as reference standard EIA (*n* = 462) Sensitivity: 96% Specificity: 95%	Blinding not specified Tests not described in details	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		(*n* = 531). Prevalence 10.8%		tests	PPV: 69% NPV: 99.5% DFA (*n* = 462) Sensitivity: 89% Specificity: 99% PPV: 78% NPV: 99% Any two positive tests as reference standard Culture (*n* = 462) Sensitivity: 80% Specificity: 99.8% PPV: 98% NPV: 97% EIA (*n* = 462) Sensitivity: 98% Specificity: 98% PPV: 87% NPV: 99.8% DFA (*n* = 462) Sensitivity: 93% Specificity: 100% PPV: 100% NPV: 99%			
Baselski *et al.*, 1987	[806]	Indigent pregnant women (*n* = 255) at high risk of chlamydia and attending a regional medical centre in the USA. Prevalence 21.2%	Comparison of ELISA and DFA of cervical swabs with culture.	Diagnostic accuracy Reference standard – positive cell culture Threshold for positive EIA – absorbance > mean value of negative controls plus 0.1 Threshold for positive DFA – presence of one or more typical inclusion bodies	EIA (*n* = 250) Sensitivity: 96.3% Specificity: 92.9% PPV: 78.8% NPV: 98.9% DFA (*n* = 247) Sensitivity: 98.1% Specificity: 95.4%	High-risk population Blinding of technicians Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					PPV: 85.0% NPV: 99.5%			
Stamm *et al.*, 1984	[807]	A multicentre study in the USA recruited symptomatic men (*n* = 576) and women (*n* = 595) from sexually transmitted disease clinics, and asymptomatic pregnant women attending abortion clinic or prenatal clinic (*n* = 225). Prevalence in asymptomatic women 13.0%	Comparison of DFA cervical swab with culture	Diagnostic accuracy Reference standard – positive cell culture on one occasion (done twice) Threshold for positive DFA – two or more elementary bodies.	DFA (*n* = 225) Sensitivity: 86.2% Specificity: 99.0% PPV: 92.6% NPV: 98.0%	Blinding of technicians Test described adequately	CH	I b
Garland *et al.*, 2000	[808]	Consecutive pregnant women going for legal termination of pregnancy at a tertiary hospital in Australia (*n* = 1245) Prevalence 2.8%	Comparison of PCR (endocervical swab, urine, tampon), LCR (endocervical swab, urine, tampon), and cell culture (endocervical swab only)	Diagnostic accuracy Reference standard – positive culture and/or at least one other specimen positive by PCR and LCR	Sensitivity for endocervical swab Culture – 45.5% PCR – 81.8% LCR – 87.9% Culture endocervical swab vs PCR and LCR (*n* = 1175) *P* < 0.0005 for both PCR vs LCR (*n* = 1175) For urine *P*=0.25 For tampon *P*=0.5 For endocervical swab *P*=0.5	Representative population Blinding of technicians Test described adequately	CH	I b
Andrews *et al.*, 1997	[809]	Unmarried, publicly funded pregnant women with many having risk factors for Chlamydia infection (*n* = 478, mean age 22.9 ± 5.6 years) Prevalence 20.1%	Comparison of LCR (urine, endocervical swab) with culture endocervical swab	Diagnostic accuracy Reference standard – positive culture or negative culture with positive LCR confirmed by further testing with DFA or MOMP-LCR	Culture endocervix Sensitivity: 30.1% Specificity: 100% LCR endocervix Sensitivity: 90.3% Specificity: 100% LCR urine	High-risk population Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 83.9% Specificity: 99.5%			
Thejls *et al.*, 1994	[810]	Consecutive pregnant women seeking abortion at 3 hospitals in Sweden during a 6 month period (*n* = 419, 41.8 % women < 24 years) Prevalence 4.3%	Comparison of culture, DFA, EIA and PCR of endocervical specimens	Diagnostic accuracy Reference standard – positive culture (first time or reculturing) or at least two positive non-culture tests. Threshold for positive DFA – ten or more elementary bodies per slide	Culture (*n* = 419) Sensitivity: 66.7% Specificity: 100% PPV: 100% NPV: 98.5% DFA (*n* = 419) Sensitivity: 61.1% Specificity: 99.8% PPV: 91.7% NPV: 98.3% EIA (*n* = 419) Sensitivity: 64.7% Specificity: 100% PPV: 100% NPV: 98.5% PCR (*n* = 381) Sensitivity: 71.4% Specificity: 100% PPV: 100% NPV: 98.9%	Blinding not specified Test described adequately	CH	II
MacMillan *et al.*, 2003	[811]	Consecutive women less than 25 years of age attending abortion, family planning, and antenatal clinics in the UK. Pregnant women 204/303 and prevalence in them 10.8%	Comparison of EIA endocervical swab, LCRs for first void urine sample, vaginal swab and endocervical swab	Diagnostic accuracy Positive EIA confirmed further by DFA, while positive LCR by MOMP-LCR Reference standard – one or more specimens positive by two independent tests	EIA Sensitivity: 82% Specificity: 100% LCR endocervix Sensitivity: 82% Specificity: 100% LCR vagina	Single blinded Test adequately described	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 100% Specificity: 100% LCR urine Sensitivity: 91% Specificity: 100%			
Renton *et al*., 2006	[812]	Pregnant women presenting for termination of pregnancy at a family planning clinic in the UK (*n* = 863) Prevalence 8.5%	Comparison of LCR and DFA of cervical swab, vaginal swab, and urine	Diagnostic accuracy Reference standard – positive test result from any site or positive LCR	Sensitivity with positive test result from any site as reference standard LCR cervical swab 97.0% LCR vaginal swab 94.0% LCR urine 83.0% DFA cervical swab 93.0% DFA vaginal swab 92.0% DFA urine 78.0% Positive LCR as reference standard DFA cervical swab Sensitivity: 93.8% Specificity: 99.9% DFA vaginal swab Sensitivity: 92.1% Specificity: 99.5%	Blinding not specified Test described adequately	CH	II
Hosein *et al*., 1992	[813]	Consecutive low-income pregnant women attending a university medical centre in the USA (*n* = 322).	Comparison of DNA probe test with culture	Diagnostic accuracy Reference standard – positive culture Threshold for positive DNA probe test – one or more fluorescing inclusion	DNA probe test (*n* = 246) Sensitivity: 93.9% Specificity: 99.1% PPV: 93.9%	Blinding of technicians Test described adequately Drop out rate > 20%	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Prevalence 13.4%		bodies	NPV: 99.1%			
Yang *et al.*, 1991	[814]	Asymptomatic pregnant women attending for routine prenatal care (*n* = 257), and women with symptoms of lower genital tract infection or history of STD (*n* = 169) in the USA Prevalence in pregnant women 8.6%	Comparison of DNA probe test with culture	Diagnostic accuracy In case of discrepant results, probe competition assays performed. Reference standard – positive culture or negative culture with positive two non-culture tests.	Culture (*n* = 257) Sensitivity: 95.4% Specificity: 100% PPV: 100% NPV: 99.6% DNA probe test (*n* = 257) Sensitivity: 86.4% Specificity: 100% PPV: 100% NPV: 98.7% Diagnostic accuracy of DNA probe test with positive culture as reference standard Sensitivity: 85.7% Specificity: 99.6% PPV: 94.7% NPV: 98.7%	Blinding not specified Test described adequately	CH	II
Asbill *et al.*, 2000	[815]	Pregnant women at their initial visit to an obstetric clinic or at 36 weeks of gestation in the USA (*n* = 519, 63% women < 24 years of age) Prevalence 6.8%	Comparison of Gram stain (cervical mucous) with DNA probe test	Diagnostic accuracy Reference standard – positive DNA probe test Threshold for a positive gram stain – 10 or more polymorphonuclear leucocytes per high power field	Sensitivity: 91.0% Specificity: 18.0% PPV: 7.5% NPV: 96.7%	Blinding of technicians Test described adequately	CH	I b
Spence *et al.*, 1986	[816]	Unselected pregnant women seeking first- or second-trimester termination of pregnancy at a tertiary hospital in the USA (*n* = 300, mean age 21.4 years) Prevalence 14.3%	Comparison of Pap smear with culture	Diagnostic accuracy Reference standard – positive culture Threshold of positive Pap smear findings – inflammation, consistent with Chlamydia infection, others or negative	Pap smear findings consistent with Chlamydia infection as threshold Sensitivity: 2.3% Specificity: 98.1% Pap smear findings consistent with Chlamydia infection plus inflammation as threshold	Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 60.5% Specificity: 56.4%			

Effectiveness studies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Martin *et al.*, 1997	817	Pregnant women at 23–29 weeks with Chlamydia isolated from endocervical specimens by culture and successfully completing a one week placebo run-in (*n* = 414). Population selected from on-going multicentre trial in the USA looking at vaginal infections and premature births.	Treatment with erythromycin base 333 g TDS for 7 days (*n* = 205) compared to placebo (*n* = 209). Repeat cultures obtained 2–4 weeks after starting treatment, and outcomes stratified by study sites for placebo group into high clearance group (repeat culture negative) and low clearance group (repeat culture positive)	Pregnancy outcomes: mean birthweight in g, low birthweight (< 2500 g), preterm delivery (< 37 weeks), PROM, stillbirth, neonatal death	Mean birthweight ± SD (in grams) 3192 ± 524 vs 3146 ± 552 *P* > 0.05 Low birthweight 17/201 (8%) vs 22/199 (11%) *P* > 0.05 Preterm delivery 27/202 (13%) vs 30/203 (15%) *P* > 0.05 PROM 21/196 (11%) vs 25/193 (13%) *P* > 0.05 Stillbirth 2/202 (1%) vs 1/203 (0.5%) *P* > 0.05 Neonatal death 1/202 (0.5%) vs 0/203 *P* > 0.05 Low clearance groups Low birthweight 9/114 (8%) vs 18/105 (17%) *P* = 0.04	Adequate randomisation Concealment of allocation Groups compared Double blinded Intention-to-treat analysis	RCT	1++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Preterm delivery 15/115 (13%) vs 18/105 (17%) *P* = 0.4 High clearance groups Low birthweight 8/87 (9%) vs 4/94 (4%) *P* = 0.18 Preterm delivery 12/87 (14%) vs 12/98 (12%) *P* = 0.75			
Ryan *et al.*, 1990	818	Consecutive new obstetric patients (*n* = 11 544) in a regional medical centre, USA. Population predominantly urban, black, lower socio-economic status. Group 1 – untreated (*n* = 1110), Group 2 – treated (*n* = 1323) and Group 3 – culture negative (*n* = 9111)	Initially no treatment given to culture positive group, but after 16 months of starting study, erythromycin 500/250 mg QID for 7 days, or sulfisoxazole 1 g QID for 7 days given	PROM (rupture of membranes more than 1 hour before birth), low birthweight infants (< 2500 g), newborn survival (those who left the hospital alive or alive after 28 days of hospitalisation). Confounding variables controlled by logistic regression for PROM and newborn survival	<u>Group 1 vs Group 2</u> PROM 5.2% vs 2.9% *P* < 0.001 low birthweight 19.6% vs 11.0% *P* < 0.0001 newborn survival 97.6% vs 99.4% *P* < 0.001 *After adjustment* PROM OR 0.56 (0.37–0.85) *P* < 0.01 newborn survival OR 2.21 (0.89–5.49) *P* < 0.08 <u>Group 1 vs Group 3</u> PROM 5.2% vs 2.7% *P* < 0.001	Confounders controlled Blinding not specified Population representative	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					low birthweight 19.6% vs 11.7% *P* < 0.0001 newborn survival 97.6% vs 98.5% *P* < 0.05 *After adjustment* PROM OR 2.12 (1.57–2.86) *P*< 0.001 newborn survival *P* > 0.05 <u>Group 2 vs Group 3</u> PROM 2.9% vs 2.7% *P* = 0.556 low birthweight 11.0% vs 11.7% *P* = 0.42 newborn survival 99.4% vs 98.5% *P* < 0.01 *After adjustment* PROM *P* > 0.05 newborn survival *P* > 0.05			
Cohen *et al.*, 1990	819	low income, indigent, and urban pregnant women considered at high risk for infection with Chlamydia	Treatment with erythromycin 500 mg QID for 7 days, and repeat culture after	PROM (rupture of membranes before onset of labour), Preterm delivery (labour < 37 weeks), Premature contractions, Small-for gestational age	<u>Group 1 vs Group 2</u> Premature delivery	Groups comparable Blinding not specified Confounders partially	Retrospective	2−

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		trachomatis in the USA (*n* = 567) Group 1 – successfully treated (*n* = 244), Group 2 – treated but remained chlamydia positive during pregnancy (*n* = 79), and Group 3 – Chlamydia negative matched controls (*n* = 244) Matching done for age, race, gravidity, parity, marital status, SE status and health habits	delivery.	(SGA), Stillbirth, Antepartum hemorrhage (APH), Vaginal delivery, Caesarean section, Postpartum endometritis, mean fetal weight, mean gestational age	2.9% vs 13.9% *P* = 0.00002 PROM 7.4% vs 20.2% *P* = 0.02 Premature contractions 4.1% vs 24.0% *P* = 0.00001 SGA 13.1% vs 25.3% *P* = 0.001 Stillbirth 0.4% vs 0 *P* > 0.05 APH 1.2% vs 2.5% *P* > 0.05 Vaginal delivery 88.9% vs 82.3% *P* > 0.05 Caesarean section 11.1% vs 17.7% *P* > 0.05 Postpartum endometritis 2.9% vs 2.5% *P* > 0.05 Gestational age (mean ± SD) 39.35 ± 2.25 vs 38.76 ± 2.97 *P* > 0.05	controlled		

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Fetal weight (mean ± SD) 3202.6 ± 508.6 vs 3002.1 ± 626.5 *P* = 0.004 <u>Group 1 vs Group 3</u> Premature delivery 2.9% vs 11.9% *P* = 0.0001 PROM 7.4% vs 7.4% *P* > 0.05 Premature contractions 4.1% vs 1.6% *P* > 0.05 SGA 13.1% vs 11.9% *P* > 0.05 Stillbirth 0.4% vs 0 *P* > 0.05 APH 1.2% vs 0% *P* > 0.05 Vaginal delivery 88.9% vs 84.4% *P* > 0.05 Caesarean section 11.1% vs 15.6% *P* > 0.05			

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Postpartum endometritis 2.9% vs 2.1% *P* > 0.05 Gestational age (mean ± SD) 39.35 ± 2.25 vs 38.93 ± 2.42 *P* = 0.05 Fetal weight (mean ± SD) 3202.6 ± 508.6 vs 3095.1 ± 577.1 *P* = 0.03			
Black-Payne *et al.*, 1990	820	Asymptomatic pregnant women with estimated gestational age 28–32 weeks attending a medical centre in the USA (*n* = 199) Chlamydiazyme-positive group (*n* = 52), Chlamydiazyme-negative group (*n* = 126)	To determine if rapid EIA test (Chlamydiazyme) can be used reliably for screening programme by comparing perinatal and neonatal outcomes between two groups. Test positive women treated with erythromycin 500 mg QID for 7 days	Perinatal – ROM, preterm delivery (< 37 weeks), cesarean section rate, postpartum endometritis Neonatal – respiratory tract infections, conjunctivitis in first 6–8 weeks of life	Rupture of membranes < 6 hours, 6–12 hours, and > 12 hours 73% vs 69% 19% vs 27% 8% vs 4% *P* > 0.05 for all Preterm birth 3% vs 6% *P* > 0.05 Cesarean section 20% vs 15% *P* > 0.05 Postpartum endometritis 5% vs 12% *P* > 0.05 Incidence of neonatal respiratory tract infections and conjunctivitis *P* > 0.05 for both	Groups compared Chance of bias	CH	2−
Rivlin *et al.*, 1997	821	Pregnant women registering consecutively at university	Women with positive DFA test treated with	Maternal complications – abortion, PROM, preterm delivery,	*P* > 0.05 for all maternal, neonatal and infant complications between the two	Groups compared Clinicians blinded to	Retrospective	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		medical centre in the USA (*n* = 1350), but for this study, only women with positive Chlamydia culture taken. Treated group (*n* = 23) Untreated group (*n* = 58)	erythromycin 800 mg QID for 7 days, and those with negative test not treated.	chorioamnionitis, endomyometritis, mastitis. Neonatal complications – stillbirth, premature, RDS, tachypnoea, sepsis Infant complications – conjunctivitis, pneumonia, otitis, URI, bronchitis, diarrhea.	groups	culture results		
McMillan *et al*., 1985	822	Pregnant women with positive chlamydia culture at 32–36 weeks cared for in 3 obstetrical clinics in a university hospital in the USA (*n* = 85/1082). Infants of treated group (*n* = 16) Infants of untreated group (*n* = 21)	Women in treated group received erythromycin 500 mg BD for 10 days	Nasopharyngeal or conjunctival culture with episodes of conjunctivitis and pneumonia,	Positive nasopharyngeal or conjunctival culture and symptomatic for neonatal conjunctivitis and pneumonia 0% vs 23% *P* < 0.04	Groups not compared Blinding not specified High risk of bias	CH	2−

11 Screening for clinical problems

11.1 Gestational diabetes

Clinical question: What is the diagnostic value and effectiveness of screening tests to identify women at risk of diabetes in pregnancy?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gribble, 1995	494	Pregnant women with at least 2 urinalysis tests during first 2 trimesters were included Women with preexisting DM, multiple gestation excluded Sample size 2965	All women were screened with 50 g GCT at 24–28 weeks. Positive screens (cut-off 7.78 mmol/litre (140 mg/100 ml)) started a 3 day CHO load, and fasting 100 g GTT. Categorised into 2 groups, negative or positive glycosuria groups Threshold 2 or more ≥ fasting 105; 1 hour 190; 2 hour 165 and 3 hour 8.1 mmol/litre (145 mg/100 ml) Negative screens comparison of the 2 glycosuria groups in terms of outcomes	Prediction of gestational diabetes	Higher incidence of GDM in women with positive glycosuria in the first two trimesters (12.8% vs 2.9% for negative screens). Sensitivity of glycosuria in first trimester as a predictor of GD was 7.1% Specificity 98.5% PPV 12.8% NPV 97.1%	Routine dipstick urinalysis for glucose can identify pregnant women at increased risk for GD and diagnose them earlier than 24–28 weeks.	Retrospective observational study	II
Watson, 1990	493	Pregnant women, Military dependants, unrestricted access to medical care without monetary cost Those with previous DM excluded Sample size 500	All women given random urinalysis for glucose at each antenatal visit (mean 10.8, SD 2.6). Diagnosis glycosuria if trace, 1+, 2+ or 3+ found on at least 2 visits. Severe glycosuria if ≥ 2+ on two visits At 28 weeks (no range given) 50 g GCT without regard to ingestion state. Threshold ≥ 7.78 mmol/litre (140 mg/100 ml) Diagnostic test fasting 100 g GTT, after 3 days high CHO diet Thresholds 2 or more values: fasting 105; 1 hour 190; 2 hour 165 and 3 hour 8.1 mmol/litre (145 mg/100 ml	Prediction of gestational diabetes	22 (4.4%) incidence of GD 85 (17%) showed glycosuria and 19 (3.8%) severe glycosuria 10 patients with glycosuria with GD (6 glycosuria, 4 severe glycosuria)	Routine random urine testing is a poor screening method but recommend that those classed as severe glycosuria before 24 weeks should have an earlier 50 g GCT	Non randomised population-based study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ostlund, 2004	837	All pregnant women without diabetes Sample size 3616	Random blood glucose (proposed every 4–6 weeks) and Risk factors (family history of diabetes, obesity, a prior LGA infant or prior GD) assessed. All were offered diagnostic test, 75 g OGTT between 28–32 weeks of gestation	Diagnostic value	61/3616 or 1.7% had GD At a cut-off level of ≥ 8 mmol/litre Sensitivity: 47.5% Specificity: 97%	RBG measurement has the same sensitivity for detecting GD as using traditional risk factors, but reduces the need to carry out the OGTT from 15.8% to 3.8% of the population Traditional risk factors have poor sensitivity for GD.	Prospective population-based study	II
Nasrat, 1988	838	Healthy pregnant women Sample size 250	Random plasma glucose determined in 276 women and 250/276 women given a standard 75 g OGTT	Diagnostic value	3/250 or 1.2% had GD Using Lind and Anderson threshold (7.0 mmol/litre < 2 hour 6.4 mmol/litre > 2 hours) for random plasma glucose Sens: 16% Spec: 96% PPV: 47% Using 90th percentile of study group Sens: 29% Spec: 89% PPV: 38%	Random plasma glucose has limited predictive value	Prospective study	II
Seshiah, 2004	840	Consecutive pregnant women Sample size 1251	1 hour 50 g GCT, 2 hour 75 g OGTT, given to all during second and third trimesters	Diagnostic value	Positive screens 891 168/891 or 18.9% had GD Sens: 79.8%, Spec: 42.7%, PPV: 24.5%, NPV: 90.1%	Using 2 hour plasma glucose ≥ 7.78 mmol/litre (140 mg/100 ml) as once step procedure is simple and economical for countries more prone to GD	Prospective consecutive population-based study	II
Perucchini, 1999	499	All pregnant women with singleton pregnancy giving birth after 28 weeks of gestation Exclusion criteria: pre-existing diabetes mellitus, lack of examination before 24 weeks of gestation. 772 eligible 558 consented 520 completed study	FPG, 50 g GCT, 3 hour 100 g OGTT, given to all	Diagnostic value	52/520 or 10.2% had GD FPG at 4.8 mmol/litre, 50 g GCT 7.8 mmol/litre Sens: FPG 81%, 50 g GCT 59% Spec: FPG 76%, 50 g GCT 91%	Sample representative of general population. Measuring FPG is easier than 50 g GCT and allows 70% of women to avoid the GCT.	Prospective population based observational study	
Cetin and Cetin, 1997	841	Pregnant women included if examined < 20 weeks of gestation Exclusion criteria: pre-existing diabetes mellitus, multiple	1 hour 50 g GCT, 100 g OGTT, given to all between 24–28 weeks of gestation	Diagnostic value	17/274 or 6.2% had GD Sens: < 2 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 75%, cut-off 8.22 mmol/litre	Sample too small. Standard cut-off 7.78 mmol/litre (140 mg/100 ml) Sens 65% Spec 88% PPV 27% Suggested cut-off Sens 59% spec 92% PPV 32%.	Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		pregnancy, preterm premature rupture of membranes, pre-eclampsia, birth ≤ 28 weeks, regular ingestion of any drug. 291/344 eligible, 274/291 completed study			(148 mg/100 ml) 63% 2–3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 60%, cut-off 7.89 mmol/litre (142 mg/100 ml) 60% > 3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 50%, cut-off 8.33 mmol/litre (150 mg/100 ml) 50% Spec: < 2 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 86%, cut-off 8.22 mmol/litre (148 mg/100 ml) 91% 2–3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 89% cut-off 7.89 mmol/litre (142 mg/100 ml) 92% > 3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 89%, cut-off 8.33 mmol/litre (150 mg/100 ml) 92% PPV: < 2 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 27%, cut-off 8.22 mmol/litre (148 mg/100 ml) 33% 2–3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 30% cut-off 7.89 mmol/litre (142 mg/100 ml) 30% > 3 hour cut-off 7.78 mmol/litre (140 mg/100 ml) 25%, cut-off 8.33 mmol/litre (150 mg/100 ml) 33%			
O'Sullivan, 1973	842	Prenatal women 752/ 986 (76%) eligible	1 hour 50 g GCT, 3 hour OGTT given to all Weeks of gestation not reported	Diagnostic value	1 hour 50 g GCT ≥ 130 mg/100 ml cut-off Sens: 78.9% Spec: 87.2% PPV: 13.8%	Timing of testing in relation to stage of pregnancy not reported No quantity of glucose stated for GTT	Cohort study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					NPV: 99.4%	Sample collected between 1956 and 1957		
Buhling, 2003	843	Pregnant women Sample size 193	Comparison of 50 g GCT with five portable meters	Diagnostic value of 5 portable meters	Sens: Accu-Chek 84% EuroFlash 100% GlucoTouch 98% HemoCue 57% OneTouch 92% Precision Plus 90% Spec: Accu-Chek 98% EuroFlash 79% GlucoTouch 86% HemoCue 100% OneTouch 92% Precision Plus 91%	The accuracy of Accu-Chek, GlucoTouch, OneTouch and precision was acceptable for use in GD screening.	Prospective study	II
Murphy, 1994	844	Pregnant women No other data given Sample size 124	3 groups, no control Tested at 24–28 weeks Non-fasting screening test: Group 1: 50 g glucose polymer Group 2: standard 50 g glucose solution Group 3: milk chocolate bar 50 g Blood test at 1 h Diagnostic test: 3 hour 100 g GTT	Serum glucose response, side effects and women's subjective acceptance of the polymer or a candy bar (3 Musketeers, Mars) to the standard d-glucose solution	5/108 or 4.6% diagnosed with GD. Glucose ≥ 7.5 mmol/litre Sens: overall 60% standard glucose 33.3% polymer 100% Spec: overall 84% standard glucose 73.6% polymer 92.8% PPV: overall 16% standard glucose 9% polymer 49%	The polymer is an inexpensive and well tolerated but the use of candy bar needs further research.	Randomised trial with no control	II
Court, 1985	845	Pregnant women Sample size: 100 women randomised to glucose screening test (48) and glucose polymer test (52) glucose polymer test given to additional 178 women so total 230 women received polymer test.	100 g glucose screening test and 100 g glucose polymer screening test, No cut-off value used, Diagnostic test: 3 hour 100 g OGTT	Improvement of screening of GD with the use of glucose polymer rather than glucose	12/230 or 5.2% diagnosed with GD 8 mmol/litre or 144 mg/100 ml, For glucose polymer Sens: 89% Spec: 81% PPV:	The glucose polymer is preferable to glucose for CHO loading in pregnancy because of lower rates of nausea, better reproducibility of test results.	RCT	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					29%			
Reichelt, 1998	498	Inclusion criteria: women aged ≥ 20 years, with no diagnosis of DM and between 21 and 28 weeks on enrolment Sample size 5,579, 5,010 remaining in the study	FPG Diagnostic test given to all, 2 hour 75 g OGTT	Diagnostic value	379/5,010 or 7.6% diagnosed with GD At cut-off value of 81 mg/100 ml or 4.5 mmol/litre Sens: 94% Spec: 51% PPV: 0.6 NPV: 100 At cut-off value of 85 mg/100 ml or 4.7 mmol/litre Sens: 94% Spec: 66% PPV: 0.9 NPV: 100 At cut-off value of 89 mg/100 ml or 4.9 mmol/litre Sens: 88% Spec: 78% PPV: 1.3 NPV: 100	FPG is a useful screening test for GD, a threshold of 4.94 mmol/litre or 89 mg/100 ml maximises sensitivity and specificity.	Cohort study	II
Fadl, 2006	846	Pregnant women Sample size 3616	Fasting plasma glucose Diagnostic test given to all 2 hour 75 g OGTT between 28–32 weeks	Diagnostic value	55/3616 or 1.52% diagnosed with GD FPG Cut-off values between 4.0 and 5.0 mmol/litre, Sensitivity 87% to 47% Specificity 51% and 96%. LR+ and LR− best at ≥ 5.0 mmol/litre.	Fasting plasma glucose was found to be an acceptable and useful screening test for gestational diabetes	Cross-sectional population based study	II
Lamar, 1999	847	Pregnant women Women with diabetes mellitus were excluded Sample size 160, 136 completed the study	Jelly beans vs standard glucose (randomisation done), Blood glucose ≥ 7.78 mmol/litre (140 mg/100 ml) 3 hour 100 g fasting GTT used as diagnostic test	Diagnostic value using jelly beans	5/136 or 3.7% diagnosed with GD Using cut-off 7.78 mmol/litre (140 mg/100 ml), standard glucose: Sens: 80% Spec: 82% PPV: 15% NPV: 99% Jelly beans:	There is no significant difference in screening performance for jelly beans and the standard glucose. Patients report fewer side effects after a jelly bean challenge than after a 50 g glucose beverage test. So jelly beans may be used an alternative to the 50 g glucose	Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sens: 40% Spec: 85% PPV: 9% NPV: 97%	beverage test.		
Boyd, 1995	848	Pregnant women Exclusion criteria: Insulin dependent diabetics, women with a history of insulin usage for GD in a prior pregnancy and previously diagnosed gestational diabetics Sample size 157	Cola beverage vs Jelly beans, Diagnostic test given to all participants 3 hour 100 g GTT used as diagnostic test	Diagnostic value using jelly beans	13/157 or 8.3% diagnosed with GD Using cut-off 7.78 mmol/litre (140 mg/100 ml for cola beverage Sens: 46% Spec: 81% PPV: 18% Using cut-off 6.67 mmol/litre (120 mg/100 ml) for jelly beans Sens: 54% Spec: 81% PPV: 20%	Patient tolerance was greater for jelly beans as compared with the 50 g cola beverage. Jelly beans may serve as an alternative to a cola beverage containing 50 g of glucose.	Prospective study	II
Griffin, 2000	832	Pregnant women Risk factor group has one or more risk factors for GD	The risk factor group had a 3 hour 100 g OGTT at 32 weeks if any risk factor for GD was present. The universal group had a 50 g GCT and if their plasma glucose at 1 hour was ≥ 7.8 mmol/litre, a formal 3 hour 100 g OGTT was then performed.	Spontaneous vaginal delivery, macrosomia, caesarean section, prematurity, pre-eclampsia and admission to neonatal intensive care unit	Universal screening detected a GD prevalence of 2.7%, significantly 1.45% more than in the risk factor screened group. Universal screening group had higher rates of spontaneous vaginal delivery at term, lower rates of macrosomia, caesarean section, prematurity, pre-eclampsia and admission to neonatal intensive care unit.	Universal screening for GD was found to be superior to risk factor based screening as it detected more cases, facilitated early diagnosis and is associated with improved pregnancy outcomes.	RCT	2+
Schytte, 2004	833	Pregnant women who accepted screening for GD Sample size 1392	Capillary fasting blood glucose measurements between 20 and 32 weeks of gestation If levels ≥ 4.1 mmol/litre and < 6.7 mmol/litre a 3 hour 75 g OGTT was offered	Clinical outcome of pregnant women in relation to separate components of the pre-screening procedure, presence of GD and the capillary blood glucose 120 minutes after glucose load ($cBG_{120\ min}$) concentration after a 75 g glucose load	Screening cFBG of 4.1 mmol/litre unable to predict GD and adverse outcome Best predictor of complicated delivery was a high BMI. Best predictor of fetal adverse outcome was $cBG_{120\ min}$ ≥ 9.0 mmol/litre after a 75 g glucose load Identical fraction complications were present in GD and non-GD.	Screening procedure for GD needs to be refined	Retrospective study	2−
Weijers, 2006	834	Pregnant women	The following data were collected for all	Diagnostic value of antepartum clinical	11/168 or 6.6% of women	Early postpartum diabetes is rare	Cross-sectional	2−

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Sample size 2031	women: age and gestational age at entry into the study; pre-pregnancy body mass index (BMI); ethnicity; obstetric and clinical history, including the onset of early postpartum diabetes; pregnancy outcome; level of fasting C-peptide; and glycemic parameters of 50 g 1 hour glucose challenge test and 100 g 3 hour oral glucose tolerance test (diagnostic OGTT)	characteristics	developed early postpartum diabetes. Family history of diabetes showed association with early postpartum diabetes. ROC curve analysis identified all three glucose challenge-test parameters, including fasting glucose concentration, as poor diagnostic tests, with a PPV of 22%, whereas PPV associated with the area under the diagnostic OGTT curve increased progressively over monitoring time from 20.6% to 100%. Using a 3 hour OGTT glucose area threshold of 35.7 mmol·h/l resulted in 100% sensitivity and 100% specificity, identifying the 11 women who developed early postpartum diabetes.	in GD women (6.5%), and that the clinical usefulness of the total area under the diagnostic 3 hour OGTT is superior to all other glycemic parameters for detecting early postpartum diabetes.	study	
Rajab, 1998	849	Pregnant women Sample size 3400	Screening test used was blood glucose 1 hour after 50 g glucose load (GCT) given in fasting state between 28 and 32 weeks. If blood glucose was ≥ 7.7 mmol/litre then 3 hour GTT was given	Pregnancy outcomes were compared for the following groups: A. GCT > 7.7 and < 8.3 mmol/litre (194 women) B. GCT ≥ 8.3 mmol/litre (194 women) C. GCT < 7.7 mmol/litre (194 women matched for age, parity and weight with group B)	197/3400 or 5.8% of women were considered to have abnormal GTT plus 199/3400 or 5.8% had impaired glucose tolerance. There was no significant difference in pregnancy-induced hypertension between groups. Preterm delivery was significantly more in group B. Birthweight > 4.5 kg was 4% in group C, 6% in group A and 9% in group B. The APGAR > 6 at 1 minute found no significant differences between groups.	Study was on a small scale but it suggests that it is possible to raise the cut-off level requiring full GTT from 7.7 to 8.3 mmol/litre without a serious adverse effect on pregnancy outcome	Prospective cohort study	2+
Yogev, 2005	850	Pregnant women Sample size 6854	A 50 g GCT was performed at 24–28 weeks of gestation and a screening value of ≥ 7.22 mmol/litre (130 mg/100 ml) was followed by a 100 g OGTT	Women were categorised by pre-pregnancy BMI and by different GCT thresholds. Maternal outcome was defined by rate of pre-eclampsia, gestational age at delivery, cesarean section (CS) rate and the need for labor induction. Neonatal outcome was defined by fetal size (macrosomia/LGA), arterial cord pH, respiratory complications and neonatal	A positive GCT result (GCT ≥ 7.22 mmol/litre (130 mg/100 ml)) was identified in 2541/6854 or 37% of women. 464/6854 or 6.8% of women were diagnosed with GD. In both groups of screening results (> 7.22 mmol/litre (130 mg/100 ml) and < 7.22 mmol/litre	Fetal size and cesarean section are associated with the degree of carbohydrate intolerance. Obesity remains the main contributor impacting fetal size.	Prospective cohort study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				intensive care unit (NICU) admission.	(130 mg/100 ml)), the obese women were significantly older, gained more weight during pregnancy and had a lower rate of nulliparity in comparison with the non obese women. The obese women had higher rates of macrosomia, LGA and induction of labor. No difference was found in mean birthweight, the total rate of cesarean section, preterm delivery, 5 minute Apgar score ≤ 7, mean arterial cord pH, NICU admission and a need for respiratory support in comparison with non obese women in both groups of screening results. A gradual increase in the rate of macrosomia, LGA and cesarean section was identified in both obese and non-obese women in relation to increasing GCT severity categories.			
Dietrich, 1987	851	Middle-class, healthy, Caucasian pregnant women Sample size 2000	Screening test involved a 50 g GCT followed by a 3 hour OGTT if necessary	Compared the value of routine versus selective diabetes screening1. Those to undergo routine screening between 24 and 28 weeks of gestation 2. Those to be tested selectively in the presence of standard risk factors.	Incidence of GD in the selectively screened group was twice (19/453, 4.2%) that in routinely screened group (21/1000, 2.1%). Glucose intolerance without a risk factor was found in only one case (1/1000, 0.1%) in the routinely screened group.	This assessment has allowed clinical practice to safely eliminate the need for diabetes screening in more than half of their private patients, which reduces office time, patient inconvenience, and expense.	Prospective study	2+
Sun, 1995	852	Pregnant women, no history of diabetes mellitus before pregnancy Sample size 622	50 g GCT and a 75 g OGTT was performed if screening tests value was ≥ 7.78 mmol/litre	Relationship between the 50 g GCT and pregnancy outcomes	103/622 or 16.56% of women underwent the diagnostic test, among whom, 32 were identified as having gestational impaired glucose tolerance (GIGT) and 12 as GD. The sensitivity of 50 gGCT was 42.72% (44/103). The incidences of edema-proteinuria-hypertension syndrome (EPH-syndrome), premature rupture of membranes, fetal macrosomia, operative	50 gGCT is an ideal method of screening for GD and should be performed on all pregnant women.	Prospective randomised study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					deliveries and perinatal morbidity were higher in women with GIGT/GD than in women without GIGT/GD.			
Rumbold, 2002	853	Total of 158 women participated in the study whereas 51 women participated after being screened	They tested the hypothesis that women with a positive result on the screen test will experience a reduction in quality of life, their health and that of their baby when compared with women with a normal screening result	Women's experiences of being screened for GD A Spielberger State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale and Short Form 36 Item Health Survey were used to study the main outcome measures: anxiety, depression, health status, concerns about the health of the baby and perceived health	No differences in the levels of anxiety, depression or the women's concerns about the health of their babies. When positively screened women for GD were compared with negatively screened women, the positively screened group had significantly lower health perceptions, were significantly less likely to rate their health as 'much better than one year ago' and were significantly more likely to rate their health as 'fair' rather than 'very good' or 'excellent'.	There is a negative impact on the health perceptions in women screened positive for GD.	Prospective survey	2−
Kerbel, 1997	854	Women between 12 and 14 weeks of gestation with no previous history of diabetes mellitus or GD were included 809 women completed questionnaires at baseline, 32 weeks, and 36 weeks of gestation	50 g glucose challenge test	Whether false positive results of 50 g glucose challenge test for GD are associated with adverse psychological effects.	At 32 weeks, 20% of women with false positive GCT results significantly perceived their health as excellent as compared to 38% of women with negative results or not tested. These results were sustained at 36 weeks. The study showed no significant association between false positive test result and anxiety levels, depression or woman's concern for health of baby. These results were neither significant between baseline and 32 weeks nor at 36 weeks.	False positive screening for GD is associated with a decreased perception of maternal health persisting at 36 weeks of gestation and this should be taken into account when setting a policy of screening all pregnant women for GD.	Prospective cohort study	2+
Naylor, 1997	855	Pregnant women Sample size 3131	3131 women randomly divided into two groups – a derivation group and a validation group. The screening strategies were derived from the derivation group data which were then tested in the validation group by comparing the effectiveness and efficiency with those of usual care. The strategies used were; no screening for low-risk women, usual care for intermediate-risk women, and universal screening with lower thresholds – plasma glucose values of 130 mg per deciliter (7.2 mmol per liter) or 128 mg per	Using clinical characteristics for assessing women's risks of gestational diabetes could enhance the efficiency of screening	There was a 34.6% reduction (95% CI 32.3 to 37.0) in the number of screening tests performed after using the new strategies. The detection rate of gestational diabetes with new strategies was 81.2 to 82.6 % compared with the 78.3% detected through usual care. There was a significant reduction in the percentage of false positive screening tests	The consideration of women's clinical characteristics allows efficient selective screening for gestational diabetes.	Prospective study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			deciliter (7.1 mmol per liter) – for high-risk women.		from 17.9 % with usual care to 16.0 % or 15.4 % (*P*< 0.001) with the new strategies, depending on the threshold values for high-risk women.			
Scott, 2002	483				Risk factors for gestational diabetes included obesity, advanced maternal age advanced maternal age, family history of diabetes, minority ethnic background, increased weight gain in early adulthood and current smoker.		Systematic review	2+
Dornhorst, 1992	829			frequency of gestational diabetes according age, BMI, parity and ethnic origin in women without known pre-existing diabetes mellitus and to analyse the influence of risk factors separately for each ethnic group	170/11 205 (1.5%) women were diagnosed with gestational diabetes. Women with gestational diabetes were significantly older (32.3 versus 28.3 years; *P* < 0.001) had higher BMI (27.7 versus 23.8; *P* < 0.001) and more likely to be from an ethnic minority (55.4% versus 15.3%; *P* < 0.0001). Rates of gestational diabetes by ethnicity were: white 0.4% (26/6135), Black 1.5% (29/1977); South East Asian 3.5% (20/572); Indian 4.4% (54/1218). After adjusting for age, BMI and parity the RR (with white as the reference category) was as follows: Black 3.1 (95% CI 1.8 – 5.5); South East Asian 7.6 (95% CI 4.1 – 14.1); Indian 11.3 (95% CI 6.8–18.8).		Retrospective study	2−
Moses, 1995	830			the proportion of women with gestational diabetes missed if testing was confined to risk factors	Women without GD were significantly younger (26.4:28.1, *P* < 0.02) and had a lower BMI (24.2:25.9, *P* < 0.05) than women with GD. 31 women (39.2%) with		Observational study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					GD had no historical risk factors and would have been missed if only selective testing undertaken.			
Ostlund, 2003	835		Traditional risk factors used were family history of diabetes (first-degree relative), obesity (≥ 90 kg), prior large for gestational age baby (≥ 4500 g) or prior GD		Women who did not take the OGTT were more likely to be multiparous and of non-nordic origin but were less likely to have a family history of diabetes, prior macrosomic baby or prior gestational diabetes. 1.7% of women who were given OGTT were diagnosed with gestational diabetes. The risk factors with the strongest association were prior gestational diabetes (12/61, OR 23.6, 95% CI 11.6–48.0) and prior macrosomic baby (9/61, OR 5.59, 95% CI 2.68–11.7). Other risk factors were family history of diabetes (13/61, OR 2.74, CI 1.47–5.11) non-nordic origin (13/61, OR 2.19, 95% CI 1.18–4.08) weight (≥ 90 kg: 8/61, OR 3.33, 95% CI 1.56–7.13) BMI (≥ 30: 11/61, OR 2.65, 95% CI 1.36–5.14) and age (≥ 25: 55/61, OR 3.37, 95% CI 1.45–7.85).		Prospective population-based study	2+
Kim, 2007	836	13 studies were included		Recurrence rates and risk factors for gestational diabetes	The recurrence rate of glucose intolerance during subsequent pregnancies varied markedly across studies. The most consistent predictor of future recurrence appeared to be nonwhite race/ethnicity, although the racial breakdowns within a study were not always clearly described. The recurrence rates varied between 30 and 84% after the index pregnancy. The recurrence rates were higher in the		Systematic review	2++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					minority populations (52–69%) as compared to lower rates found in non-Hispanic white populations (30–37%). No other risk factors were consistently associated with recurrence of GD across studies. Other risk factors, such as maternal age, parity, BMI, OGTT levels, and insulin use inconsistently predicted development of recurrent GD across studies.			

11.2 Pre-eclampsia

Clinical question: What is the diagnostic value of different screening methods in identifying women at risk of developing pre-eclampsia?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Yaron, 1999	857	Sample size 60 040 Exclusion criteria: structural or chromosomal anomalies Age not reported 14–22 weeks	Reference standard: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; presence of proteinuria Index cut-off: Competitive RIA (Sanofi Diagnostics) 2.5 MoM	Diagnostic value of AFP screening test	Incidence of pre-eclampsia 3.2% Sens: 4.3% Spec: 97.4%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy	Prospective cohort study	II
Pouta, 1998	858	Sample size 637, Inclusion criteria: nulliparas Exclusion criteria: multiple pregnancies, fetal defects 27.7 ± 4.5 years 15–19 weeks	Reference standard: BP ≥ 140/90 mmHg 6 hours apart or rise 30/15 mmHg; Prot. ≥ 300 mg/24 hours Index cut-off: time resolved FIA (Wallac) 2.0 MoM	Diagnostic value of AFP screening test	Incidence of pre-eclampsia 5.3% Sens: 3% Spec: 98%	AFP not helpful in predicting pre-eclampsia	Population-based cohort study	II
Cotter, 2004	859	Sample size 264 (88 cases and 176 controls) Inclusion criteria: Normotensive non-proteinuric women, male fetuses Exclusion criteria: aneuploid fetuses 26.1 ± 5.9 years, 15.7 ± 3.6 weeks	Reference standard: BP ≥ 140/90 mmHg; Prot. ≥ 0.3 g/ 24 hours or 1+/2+ dipstick Index cut-off: fDNA Real-time PCR TaqMan SRY < 10,000 copies/ml < 50,000 > 50,000	Diagnostic value of Fetal DNA screening test	SRY copies/ml < 10,000 Sens: 94.32% Spec: 32.39% LR+: 1.39 < 50,000 Sens: 81.82% Spec: 64.77% LR+: 2.32	Increased fetal DNA is present in the maternal circulation in early pregnancy in women who subsequently develop pre-eclampsia and there appears to be a graded response between the quantity of fetal DNA and the risk of developing pre-eclampsia.	Case–control study (nested and matched)	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					> 50,000 Sens: 38.64% Spec: 90.34% LR+: 4.00			
Leung, 2001	860	Sample size: 51 (18 cases and 33 controls), Inclusion criteria: singleton pregnancies, male fetuses Age n.r. 11–22 weeks	Reference standard: DBP ≥ 90 mmHg 2x ≥ 4 hours apart or DBP ≥ 110 mmHg; Prot. ≥ 0.3 g/ 24 hours or 2+ dipstick 2x ≥ 4 hours apart, Incidence n.r. Index cut-off: fDNA Real-time PCR TaqMan SRY ≥ 33.5 Geq/ml	Diagnostic value of Fetal DNA screening test	SRY ≥ 33.5 Geq/ml Sens: 67% Spec: 82% (cant calculate LRs)	Maternal plasma fetal DNA might be used as a marker for predicting pre-eclampsia.	Case–control study (nested and matched)	II
Yaron,1999	857	Sample size: 45 565, Exclusion criteria: structural or chromosomal anomalies Age n.r. 14–22 weeks	Reference standard: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; presence of proteinuria Index cut-off: β-hCG IRMA 2.5 MoM	Diagnostic value of β-hCG screening test	Incidence of pre-eclampsia 3.0% Sens: 5.5% Spec: 96%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy	Prospective cohort study	II
Lambert-Messerlian , 2000	861	Sample size: 359 (60 cases, 299 controls) IN: singleton pregnancies EX: chronic hypertension, diabetes; 26.9 ± 7.3 years 15–21 weeks	Reference standard: BP> 140/90 mmHg; Prot. > 300 mg/24 hours or ≥ 2+ dipstick, Index cut-off: Total hCG (Serono MAIO Clone) 2.3 MoM	Diagnostic value of β-hCG screening test	Incidence of pre-eclampsia 16.7% With 95% specificity a modeled sensitivity of 15% (cant calculate LRs)	second-trimester serum levels of hCG is a modest predictor of later onset pre-eclampsia.	Case–control study	II
Ashour, 1997	862	Sample size: 6138, IN: singleton pregnancies EX: fetal/ chromosomal abnormalities, diabetes, chronic hypertension 28.1 ± 5.3 years 15–22 weeks	Reference standard: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg 2x 6 hours apart; Prot. > 300 mg/24 hours or ≥ 1+ dipstick 2x 6 hours apart Index cut-off: β-hCG (IMx Abbott) 2.0 MoM	Diagnostic value of β-hCG screening test	Incidence of pre-eclampsia 3.2%	The utility of an elevated second-trimester β-hCG level as a screening test for pre-eclampsia is limited.	Prospective cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Sanchez-Ramos, 1991	863	Sample size: 99, Inclusion criteria: Normotensive nulliparas Exclusion criteria: diabetes mellitus, renal disease, chronic hypertension, other chronic medical illnesses 18.7 ± 0.5 years, 10–24 weeks	Reference standard: BP ≥ 140/90 mmHg twice ≥ 6 hours apart or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg Prot. ≥ 0.3 g/ 24 hours or ≥ 1+ dipstick Index cut-off: Colorimetric/ colorimetric autoanalyser ≤ 195 mg/24 hours	Diagnostic value of urinary calcium excretion screening test	Incidence of pre-eclampsia 8.1% Sens: 86% Spec: 84% PPV: 46% NPV: 98%	The study suggests a pathophysiologic role for altered urinary calcium excretion in women with pre-eclampsia that may contribute to early identification of patients at risk for the disease.	Prospective longitudinal study	II
Baker, 1994	864	Sample size: 500, Inclusion criteria: Normotensive nulliparas Exclusion criteria: renal disease, chronic hypertension Median 27 years (range 24–31), 18–19 weeks	Reference standard: DBP ≥ 90 mmHg twice ≥ 4 hours apart Prot. ≥ 0.3 g/ 24 hours Index cut-off: Perspective analyser (colorimetric)/ Monarch centrifugal analyser (kinetic) n.r.	Diagnostic value of urinary calcium excretion screening test	Incidence of pre-eclampsia: 2.6% Sens: 31% Spec: 72% (correctly predicted 71%)		Prospective, non-interventional study	II
Rogers, 1994	865	Sample size: 199, Inclusion criteria: normotensive primigravidas, singleton pregnancies Exclusion criteria: congenital malformations 27.1 ± 3.8 years, 18–26 weeks	Reference standard: BP ≥ 140/90 mmHg ≥ twice Prot. ≥ 0.3 g/l Index cut-off: Cresolphtalein method (American Monitor)/ Beckman Astra-8 analyser 0.3	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 4.0% Sens: 49% Spec: 90%		Cohort study	II
Conde, 1994	866	Sample size: 387 women, Inclusion criteria: normotensive nulliparas, singleton pregnancies Exlcusion criteria: diabetes mellitus, renal disease, proteinuria, chronic hypertension, other chronic medical illnesses 23.8 ± 5.7 years, 20 weeks	Reference standard: SBP ≥ 140 or DBP ≥ 90 mmHg twice ≥ 6 hours apart Prot. ≥ 0.3 g/l Index cut-off: Colorimetric (direct)/ picrato alcalino method 0.07	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 3.4% Sens: 33% Spec: 78% PPV: 5% NPV: 97%	Poor predictive values suggest that changes in the biochemical and hematologic tests occur only when pre-eclampsia has been established.	Prospective cohort study	II
Kazerooni, 2003	867	Sample size: 102, Inclusion criteria: nulliparas (18–35 years) Exclusion criteria: renal disease, diabetes mellitus, proteinuria, chronic hypertension, other chronic medical illnesses	Reference standard: BP ≥ 140/90 mmHg or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg twice ≥ 6 hours apart Prot. ≥ 0.3 g/ 24 hours or ≥ 1+ dipstick Index cut-off:	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 7.8% Sens: 75% Spec: 77.7% PPV: 20.7% NPV: 97%	Single urine calcium to creatinine ratio may be an effective method for screening women at the greatest risk of pre-eclampsia.	Prospective cross-sectional study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		22.8 ± 4.5 years, 20–24 weeks	n.r. ≤ 0.01 mmol/litre:mmol/litre (0.229 (mg/100 ml:mg/100 ml)					
Baker, 1994	864	Sample size: 500, Inclusion criteria: Normotensive nulliparas Exclusion criteria: renal disease, chronic hypertension Median 27 years (range 24–31), 18–19 weeks	Reference standard: DBP ≥ 90 mmHg twice ≥ 4 hours apart Prot. ≥ 0.3 g/ 24 hours Index cut-off Perspective analyser (colorimetric)/ Monarch centrifugal analyser (kinetic) n.r.	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 2.6% Sens: 31% Spec: 55% (correctly predicted 71%)		Prospective, non-interventional study	II
Papageorghiou, 2001	868	Sample size: 7851, Inclusion criteria: singleton pregnancies, routine antenatal care. Exclusion criteria: fetal abnormalities 29.7 (16–47) yrs, 22–24 weeks	Reference standard: DBP≥ 90 mmHg twice > 4 hours apart, prot. ≥ 0.3 g/24 hours or ≥ 2+ dipstick twice if no 24 hour collection available Index cut-off: CD+PW, transvaginal Acuson SP-10, Aloka 5000, Aloka 17000, ATL HDI 3000, ATL Hdi 3500, Hitachi, Toshiba, Siemens	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 1.4% Sens: 25.4% Spec: 90.9% PPV: 2.5% NPV: 99.3% LR+: 8.87 LR−: 0.62		Cohort study	II
Harrington, 1997	869	Sample size: 626, Inclusion criteria: Singleton pregnancies, unselected 15–49 years, 12–16 weeks	Reference standard: SBP≥ 140 or DBP≥ 90 mmHg, prot > 0.3 g/24 hours Index cut-off: CD+PW, transvaginal Acuson 128	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 4.8% Sens: 92.9% Spec: 85.1% PPV: 23.6% NPV: 99.5%		Cohort study	II
Marchesoni, 2003	870	895 (177 cases and 718 controls) Unselected women 31.7 ± 5.3 years, 20 weeks, 24 weeks	Reference standard: BP> 140/90 mmHg, prot. > 0.3 g/24 hours Index cut-off: CD Acuson Sequoia	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 2.9% Sens: 72% Spec: 94% PPV: 26% NPV: 99%		Case–control study	II
Schwarze, 2005	871	Sample size: 346 women (19–22 weeks: 215 women) (23–26 weeks-131 women), Exclusion criteria: essential hypertension, DM, autoimmune disorders, history of PE, FGR, IUD, placental abruption; multiple	Reference standard: RR≥ 140/90 mmHg, prot. ≥ 0.3 g/24 hours, no UTI Index cut-off: CD Elegra (Siemens), Acuson 128 XP10	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 4.9% 19–22 weeks vs 23–26 weeks Sens: 40% vs 67% Spec: 82% vs 84% PPV: 10% vs 17%	The predictive value of uterine artery Doppler for adverse pregnancy outcome in a low-risk population is of limited diagnostic value. Performing uterine artery Doppler studies at 23–	Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		pregnancies, fetal abnormalities 31.4 (17–46) yrs, 19–22 weeks, 23–26 weeks			NPV: 97% vs 98%	26 weeks of gestation increases the predictive value for adverse pregnancy outcomes.		
Emine,2005	872	Sample size: 178, Exclusion criteria: multiple pregnancies, hypertension before 26 weeks, diabetes or pregnancy with prenatal and postnatal diagnosis of a chromosomal/ structural abnormality, previous pregnancy complicated by pre-eclampsia, 28.8 ± 5.1 30.6 ± 4.3, 16–18 weeks 24–26 weeks	Reference standard: BP≥ 140/90 mmHg and first D_X after 20 weeks, proteinuria ≥ 300 mg/24 hour Index cut-off: Two site enzyme immunoassays, immunometric assays, two site chemiluminescent immunometric assay, ultrasound machines	Diagnostic value of integrated Doppler screening test	Incidence of pre-eclampsia 7.9% Bilateral notch Sens:85.7% Spec: 97.6% Bilateral notch + serum activin Sens: 78.6% Spec: 100% Bilateral notch+ serum inhibin A Sens: 71.4% Spec: 100% Bilateral notch OR serum activin Sens: 100% Spec: 86%	Maternal serum inhibin A and activin A levels and uterine artery Doppler appear to be uselful screening tests during the second trimester for pre-eclampsia. However the addition of these hormonal markers to Doppler velocimetry only slightly improves the predictive efficacy.	Prospective study	II
Audibert, 2005	873	Sample size: 2615, EX: multiple pregnancies, without ultrasound between 10–14 weeks, women refered for nuchal translucency, structural anomalies, chromosomal abnormalities, 30.9 ± 4.5 years, 14–18 weeks 18–26 weeks	Reference standard: SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg twice, proteinuria > 0.3 g/24 hour or at least 2+ protein on urine dipstick Index cut-off: Amerlite kit	Diagnostic value of integrated Doppler screening test	Prevalence of PE 1.95% Bilateral notch Sens: 21.56% Spec: 95.94% History of pre-eclampsia or bilateral notch or hCG> 2.5 MoM Sens: 41.17% Spec: 91.61%	Combination of serum markers and abnormal uterine Doppler ultrasound improves the identification of women at risk for subsequent pregnancy complications. The care providers should be encouraged to perform a uterine Doppler ultrasound when serum markers are abnormal. However, the sensitivity of these tests is too low to provide an efficient generalised screening.	Cohort study	II
Skjaerven *et al*., 2002	531	Sample size: 551,478 women who had 2 or more singleton deliveries and 209,423 women who had 3 or more	A large registry used in Norway to evaluate the effects on the risk of pre-eclampsia of both the interbirth interval	Time interval between pregnancies	Risk in a second or third pregnancy was directly related to the time elapsed since the previous delivery.	The protective effect of previous pregnancy against pre-eclampsia is	Prospective study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		singleton deliveries were studied	and a change of partner		The association between risk of pre-eclampsia and interval was more significant than the association between risk and change of partner. When the interval was 10 years or more the risk of pre-eclampsia was about the same as that in nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the probability of pre-eclampsia was increased by 1.12 for each year increase in the interval (odds ratio 1.12, 1.11 to 1.13).	transient.		
Conde-Agudelo *et al*., 2000	874	456,889 parous women delivering singleton infants	Impact of interpregnancy interval	Maternal morbidity and mortality	women with more than 59 months between pregnancies had significantly increased risks of pre-eclampsia (RR 1.83, 1.72 to 1.94) compared with women with intervals of 18–23 months	interpregnancy intervals < 6 months and > 59 months are associated with an increased risk of adverse maternal outcomes.	Retrospective cross-sectional study	3
Basso *et al*., 2001	875	Danish women with pre-eclampsia in the previous birth (8,401 women) all women with pre-eclampsia in second (but not first) birth together with a sample of women with two births (26,596 women)	Interpregnancy interval	Interpregnancy interval may confound or modify the paternal effect on pre-eclampsia	a long interval between pregnancies was associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia had not been present in the first pregnancy and paternity had not changed	The interval between births should be taken into consideration when studying the effect of changing partner on pre-eclampsia.	cohort study	2+
Reiss *et al*., 1987	876	30 patients met their criteria for pre-eclampsia and were matched for age, race, and parity with normotensive control subjects	Reviewed the outpatient charts of all patients with pre-eclampsia who received prenatal care at their clinics during the past 3 years	Blood pressure at booking	Both systolic and diastolic blood pressures were significantly higher ($P < 0.05$) in the first trimester for women with pre-eclampsia than for normal control subjects beginning in the first trimester.	This difference persisted throughout pregnancy and was also present at the 6 week postpartum visit ($P < 0.025$).	Retrospective study	2−
Sibai *et al*., 1995	877	2947 healthy women with a single fetus were prospectively followed up from randomisation at 13 to 27 weeks of gestation to the end of pregnancy	Determine whether any maternal demographic or clinical characteristics are predictive of pre-eclampsia	Blood pressure at booking	Higher systolic and diastolic blood pressures at the first visit were associated with an increased incidence of pre-eclampsia (3.8% in women with diastolic blood pressure of < 55 mmHg, 7.4% in those with diastolic blood pressure 70–84 mmHg). However, their recruitment was limited to women with a first blood pressure reading of ≤ 135/85 mmHg.	Risk factors should be of value to practitioners counselling women regarding pre-eclampsia.	Clinical trial	1+
Odegard *et al*., 2000	878	323 cases of pre-eclampsia and 650 healthy controls were selected	Studied the associations between established risk factors for pre-eclampsia	Clinical manifestations of disease	a systolic blood pressure ≥ 130 mmHg compared with	Nulliparity and hypertension increased	Population based nested case–	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			and different clinical manifestations of the disease		< 110 mmHg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (adjusted OR 3.6 [2.0 to 6.6]). The association with a diastolic pressure ≥ 80 mmHg compared with < 60 mmHg was similar but not significant (adjusted OR 1.8 [0.7 to 4.6]).	the risk for each subgroup of pre-eclampsia, but high maternal weight, previous pre-eclampsia and smoking were not consistently associated with each clinical subtype	control	
Stamilio *et al*., 2000	530	Cases with severe pre-eclampsia were compared with control subjects with respect to clinical data and multiple-marker screening test results. Patients were assigned a predictive score according to the presence or absence of predictive factors	To develop a clinical prediction rule for severe pre-eclampsia that was based on clinical risk factors and biochemical factors.		The only variables that remained significantly associated with severe pre-eclampsia were nulliparity (RR 3.8, 95% CI, 1.7–8.3), history of pre-eclampsia (RR 5.0, 95% CI, 1.7–17.2), elevated screening mean arterial pressure (RR 3.5, 95% CI, 1.7–7.2), and low unconjugated estriol concentration (RR 1.7, 95% CI, 0.9–3.4). This predictive model for severe pre-eclampsia, which included only these 4 variables, had a sensitivity of 76% and a specificity of 46%.	Even after incorporation of the strongest risk factors, the predictive model had only modest sensitivity and specificity for discrimination of patients at risk for development of severe pre-eclampsia.	Retrospective cohort study	2−
Stettler *et al*., 1992	879	65 pregnancies in 53 women with the following criteria: proteinuria exceeding 500 mg per day, no previously known renal disease, no reversible renal dysfunction, and no evidence for pre-eclampsia at discovery were studied.	Evaluated varying degrees of chronic proteinuria as a predictor of pregnancy outcome. Determined the significance of otherwise 'asymptomatic' proteinuria identified during pregnancy	Perinatal outcomes	58% of the women with proteinuria combined with renal insufficiency developed pre-eclampsia. 100% of women with preteinuria combined with chronic hypertension developed pre-eclampsia whereas 77% of women with with all three together developed pre-eclampsia	'Asymptomatic' proteinuria is associated with a number of adverse pregnancy outcomes and serious long-term maternal morbidity.	Retrospective study	2−

11.3 Preterm birth

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Goldenberg *et al.*, 1998	880	Asymptomatic pregnant women with singleton pregnancies at 22–24 weeks in the USA who already had a dating scan (*n* = 2929). Mean age 23.7 ± 5.5 years, 63% Black, 42% nulliparaous	Predictive value, prevalence, and PAR. Reference standard – postnatal assessment of gestational age. Threshold of positive history – spontaneous previous birth at 20–37 weeks. Threshold for positive FFN test (single sample from posterior vaginal fornix at 24–26 weeks) – levels > 50 ng/ml. Threshold for short cervix on TVS at 24 and 28 weeks – length ≤ 25 mm	Spontaneous preterm delivery at < 32, < 35 and < 37 weeks	<u>For SPTB < 37 weeks</u> H/O previous SPTB (*n* = 1711) Sensitivity: 42% (35%, 49%) Specificity: 82% (80%, 83%) OR: 2.6 (1.9, 3.6) Positive FFN test (*n* = 2929) Sensitivity: 19% (14%, 23%) Specificity: 95% (94%, 95%) OR nullipara: 2.9 (1.5, 5.5) OR multipara: 3.4 (2.1, 5.4) Short cervix (*n* = 2929) Sensitivity: 24% (19%, 28%) Specificity: 93% (92%, 94%) OR nullipara: 4.6 (2.8, 7.5) OR multipara: 2.5 (1.6, 3.8)	Multicentre study Representative population Blinding of outcome assessors Tests described in details	CH	I b
Iams *et al.*, 1998	881	Asymptomatic parous women with singleton pregnancies at 22–24 weeks in the USA who already had a dating scan, and with H/O previous SPTB (*n* = 1282)	Estimation of risk of SPTB by H/O previous SPTB (from 18 to 37 weeks), positive FFN test (level > 50 ng/ml) and short cervical length (< 25 mm on TVS)	Spontaneous preterm delivery at < 35 weeks	<u>H/O previous SPTB at 18–26 weeks</u> RR (with short cervix): 0.25 (0.04, 0.72) RR (with short cervix + positive FFN): 0.64 (0.15, 0.95) <u>H/O previous SPTB at 27–31 weeks</u> Sensitivity: 33% (23%, 44%) Specificity: 88% (86%, 89%) RR (with short cervix): 0.25 (0.04, 0.72) RR (with short cervix + positive FFN): 0.64 (0.14, 0.95) <u>H/O previous SPTB at 32–36 weeks</u>	Multicentre study (retrospective analysis of data) Representative population Blinding of outcome assessors Tests described in details	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 67% (56%, 77%) Specificity: 73% (70%, 76%) RR (with short cervix): 0.25 (0.04, 0.70) RR (with short cervix + positive FFN): 0.63 (0.15, 0.94) <u>H/O previous SPTB at > 37 weeks</u> RR (with short cervix): 0.06 (0.01, 0.25) RR (with short cervix + positive FFN): 0.25 (0.04, 0.71)			
Kristensen *et al*., 1995	882	All women with permanent address in Denmark who gave birth to their first singleton infant in 1982 and a second in 1982–87. (*n* = 13 965). Information obtained from National Medical Birth Register and National Register of Hospital Discharges	Relationship between preterm delivery in first pregnancy (both idiopathic and indicated) and complications in second pregnancy.	Preterm delivery at < 37 weeks (both idiopathic and indicated)	<u>Diagnostic value for H/O idiopathic preterm delivery</u> Sensitivity: 19% (14%, 23%) Specificity: 97% (96%, 97%) <u>Relative risk for preterm delivery by conditions in first pregnancy</u> SGA: 2.7 (2.0, 3.7) LGA: 1.2 (0.6, 2.3) Birthweight < 2500 g: 4.7 (3.8, 5.6) Gest age < 32 weeks: 6.0 (4.1, 8.8) Gest age 32–36 weeks: 4.8 (3.9, 6.0)	Retrospective analysis of data Population representative Blinding not specified Test described in details	CH	II
Iams *et al*., 2002	883	Asymptomatic nulli and multiparous women with singleton pregnancies at 22–24 weeks in the USA who already had a dating scan, and with no H/O previous SPTB (*n* = 2107)	To assess FFN levels (positive test if levels > 50 ng/ml), Bishop score ($\geq$ 4 as threshold, digital examination done 4 times before 35 weeks) and short cervix ($\leq$ 25 mm by TVS) as predictor of preterm delivery	Predictive value for spontaneous preterm delivery at < 35 weeks	<u>Bishop score</u> Sensitivity: 23.4% Specificity: 92.6% PPV: 9.1% NPV: 97.5% RR: 3.6 (2.1, 6.3) <u>Short cervix</u> Sensitivity: 39.1%	Multicentre study (retrospective analysis of data) Representative population Blinding of outcome assessors Tests described in details	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 92.5% PPV: 14.0% NPV: 98.0% RR: 6.9 (4.3, 11.1) <u>Positive FFN test</u> Sensitivity: 23.4% Specificity: 97.0% PPV: 19.7% NPV: 98.0% RR: 8.2 (4.8, 13.9)			
Blondel *et al.*, 1990	884	Women with single pregnancies attending two teaching hospitals in France (*n* = 7641)	Clinical examination done at 25–28 and 29–31 weeks for 5 signs – (1 cm internal os dilatation, short cervix $\leq$ 1 cm, mid position of cervix, soft or firm cervix, expansion of lower uterine segment). Two risk scores compared – Score 1 with maternal characteristics and symptoms, Score 2 with maternal characteristics, symptoms and vaginal examination.	Predictive value for spontaneous preterm delivery at < 35 weeks for clinical examination findings, and the two scores	<u>At 25–28 weeks for nulliparaous</u> 1) Cervical dilatation Sensitivity: 13% (8%, 19%) Specificity: 98% (98%, 99%) 2) Short cervix Sensitivity: 14% (9%, 20%) Specificity: 95% (94%, 96%) 3) Score 1 Sensitivity: 45.6% Specificity: 68.4% 3) Score 2 Sensitivity: 53.7% Specificity: 66.4% <u>At 25–28 weeks for multiparaous</u> 1) Cervical dilatation Sensitivity: 15% (9%, 23%) Specificity: 97% (96%, 98%) 2) Short cervix Sensitivity: 11% (6%, 17%) Specificity: 95% (94%, 96%) 3) Score 1 Sensitivity: 48.1% Specificity: 70.8% 3) Score 2 Sensitivity: 57.5% Specificity: 68.5%	Multicentre study Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					At 29–31 weeks for nulliparaous 1) Score 1 Sensitivity: 55.0% Specificity: 66.0% 2) Score 2 Sensitivity: 63.3% Specificity: 62.7% At 29–31 weeks for multiparaous 1) Score 1 Sensitivity: 52.1% Specificity: 71.3% 2) Score 2 Sensitivity: 54.9% Specificity: 71.8%			
Chambers *et al.*, 1990	885	Women with singleton pregnancies and with at least 2 visits to a hospital in France at < 28 weeks of gestation (*n* = 5758)	Clinical examination done once in two weeks. Threshold for short cervix – length $\leq$ 1 cm before 28 weeks Threshold for cervical dilatation – length $\geq$ 1 cm before 37 weeks.	Diagnostic accuracy results and risk for spontaneous preterm delivery < 37 weeks	Short cervix only Sensitivity: 21% (15%, 28%) Specificity: 89% (88%, 90%) RR: 2.15 Cervical dilatation Sensitivity: 37% (30%, 45%) Specificity: 83% (82%, 84%) RR: 2.73 Both together Sensitivity: 21.6% Specificity: 96.5% RR: 6.54	Population not representative Blinding not specified Test described adequately	CH	II
Parikh and Mehta, 1961	886	Singleton pregnancies attending antenatal clinic of a government hospital in India at 21 weeks or more (*n* = 655)	Vaginal examination done every 2 weeks from 21–36 weeks Threshold for open os – admit examining finger	Spontaneous preterm delivery < 37 weeks. Outcome of pregnancy also correlated with parity, character of internal os, and duration of gestation	Sensitivity: 49% (36%, 63%) Specificity: 57% (52%, 62%)	Population not representative. Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Leveno *et al.*, 1986	887	Low-risk singleton pregnancies enrolled consecutively in a medical centre in the USA (*n* = 185)	Single vaginal examination done at 26–30 weeks. Threshold for cervical dilatation – os > 2cm dilated	Spontaneous preterm delivery < 34 weeks.	Sensitivity: 57% (18%, 90%) Specificity: 94% (89%, 98%)	Population not representative Blinding of outcome assessors Test described adequately	CH	II
Heath *et al.*, 2000	888	Women with singleton pregnancies attending a fetal medicine unit in the UK for routine second-trimester anomaly scan (*n* = 5146)	Risk ascertained for preterm delivery < 33 weeks for maternal characteristics (smoking, previous delivery at 24–33 weeks), FFN positivity (≥ 50 ng/ml) and cervical length (≤ 15 mm) by TVS. Two swabs taken from posterior vaginal fornix at 22–24 weeks.	Diagnostic value for predicting spontaneous preterm delivery < 34 weeks.	<u>Positive FFN test</u> Sensitivity: 32.6% Specificity: 96.9% PPV: 8.1% NPV: 99.4% <u>Short cervical length</u> Sensitivity: 27.9% Specificity: 99.5% PPV: 30.8% NPV: 99.4% <u>Maternal smoking</u> Sensitivity: 32.6% Specificity: 85.4% PPV: 1.9% NPV: 99.3% <u>Previous delivery at 24–33 weeks</u> Sensitivity: 9.3% Specificity: 98.6% PPV: 5.5% NPV: 99.2%	Representative population Blinding for FFN levels, not for cervical length Test described adequately	CH	I b
Chang *et al.*, 1997	889	Asymptomatic women at 28 weeks with no risk factors for preterm labour attending an out-patient clinic in Singapore (*n* = 240)	To evaluate usefulness of FFN as a screening test. Single Dacron swab taken from posterior vaginal fornix at 22–25 weeks. Threshold ≥ 50 ng/ml for a positive test	Spontaneous preterm delivery < 34 and < 37 weeks.	<u>For delivery < 37 weeks</u> Sensitivity: 16.7% Specificity: 99.1% PPV: 60.0% NPV: 93.4% <u>For delivery < 34 weeks</u> Sensitivity: 50.0%	Representative population Blinding of technicians Test described adequately.	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 99.1% PPV: 60.0% NPV: 98.7%			
Faron *et al.*, 1997	890	Consecutive pregnant women attending antenatal clinic of a hospital in Belgium for routine care with known gestational age (*n* = 170)	To assess accuracy of single FFN test for predicting preterm delivery. Single swab taken from posterior vaginal fornix at 24–33 weeks. Threshold ≥ 50 ng/ml for a positive test	Spontaneous preterm delivery < 37 weeks	Positive FFN test Sensitivity: 26.7% Specificity: 95.7% PPV: 40.0% NPV: 92.4% History of prior preterm delivery (*n* = 87) Sensitivity: 30% Specificity: 96% PPV: 50.0%	Population representative Blinding of technicians Test described adequately	CH	I b
Daskalakis *et al.*, 2006	891	Singleton pregnancies having anomaly scan at 22–25 weeks in a fetal medicine unit in Greece (*n* = 1287)	To evaluate incidence of bacterial vaginosis in a low-risk population at 22–25 weeks. Dacron swabs taken from posterior vaginal fornix for FFN levels (level ≥ 50 ng/ml for a positive test), bacterial vaginosis (Gram stain score by Nugent' criterion), and culture for Group B streptococcus colonisation. Cervical length was measured by TVS (≤ 20 mm as threshold). Threshold for funneling by TVS not defined.	Spontaneous preterm delivery < 37 weeks. Comparison of incidence of preterm delivery in women with and without the risk factors (in %), predictive accuracy, and risk association after controlling for confounding variables	FFN levels (*n* = 718) 13.3% vs 6.1% (*P* = 0.03) Sensitivity: 13% (5%, 23%) Specificity: 94% (92%, 96%) RR: 2.32 (1.00, 5.54) Bacterial vaginosis (*n* = 1197) 15.4% vs 7.2% (*P* = 0.003) Sensitivity: 15% (8%, 22%) Specificity: 93% (91%, 94%) RR: 2.19 (1.21, 3.98) GBS colonisation on culture (*n* = 1197) 5.8% vs 13.2% (*P* = 0.03) RR: 0.43 (0.19, 1.00) Short cervix (*n* = 1197) 4.8% vs 1.1% (*P* = 0.01) Sensitivity: 5% (1%, 9%) Specificity: 99% (98%, 99%) RR: 3.31 (1.04, 1.98)	Population representative Blinding of technicians for bacterial vaginosis, GBS culture and TVS measurements, not for FFN levels. Test described adequately	CH	I b II (for FFN)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Funneling (*n* = 1197) 8.6% vs 3.8% (*P* = 0.07) Sensitivity: 9% (3%, 14%) Specificity: 96% (95%, 97%) RR: 2.07 (0.94, 4.54)			
Crane *et al*., 1999	892	Singleton pregnancies at 20–24 weeks recruited from the perinatal centre of a maternity hospital in the USA (*n* = 238)	To evaluate combination of vaginal and cervical FFN, and preterm birth risk score. Threshold of positive FFN test for both cervical and vaginal swabs – levels ≥ 50 ng/ml For Nova Scotia preterm birth risk score – presence of one major or two minor factors	Spontaneous preterm delivery < 37 weeks	Preterm birth risk score (*n* = 140) Sensitivity: 77.8% Specificity: 80.2% PPV: 21.2% NPV: 98.1% Positive vaginal FFN levels (*n* = 140) Sensitivity: 55.6% Specificity: 83.2% PPV: 18.5% NPV: 96.5% Preterm birth risk score and positive vaginal FFN levels Sensitivity: 44.4% Specificity: 97.7% PPV: 57.1% NPV: 96.2% Preterm birth risk score or positive vaginal FFN levels Sensitivity: 88.9% Specificity: 65.7% PPV: 15.1% NPV: 98.9%	Population not representative Blinding of technicians Test described adequately	CH	II
Lockwood *et al*., 1994	893	Women with singleton pregnancies attending a single obstetric clinic in the USA (*n* = 161). Study group (*n* = 34) of	To determine if elevated IL-6 in vaginal and cervical secretions are associated with preterm delivery. Vaginal swabs were taken	Spontaneous preterm delivery < 37 weeks ROC curve used to establish cut-off values for cervical and vaginal IL-6,	Single value > 250 pg/ml as positive test Sensitivity: 50.0% Specificity: 85.0%	Nested case–control study Population not representative Blinding of technicians	CC	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		women delivering spontaneously before 37 weeks, and control group (*n* = 127) of consecutive women delivering at term.	serially every 3–4 weeks between 24 and 36 weeks of gestation. Levels > 125 and 250 pg/ml used as threshold using the ROC curve	and diagnostic values calculated. Characteristics of women with preterm deliveries and IL-6 > 250 pg/ml (*n* = 17) compared with those having lower levels (*n* = 17).	PPV: 47.2% NPV: 86.4% <u>Single value > 125 pg/ml as positive test</u> Sensitivity: 45.5% Specificity: 86.6% <u>Comparison of two groups</u> Gestational age at delivery (weeks) 34.2 ± 3.2 vs 35.0 ± 2.5 (*P* = 0.44) Time interval from sampling to delivery (weeks) 1.8 ± 1.3 vs 1.9 ± 0.9 (*P* = 0.70) Birthweight (g) 2341 ± 764 vs 2485 ± 576 (*P* = 0.54)	Test described adequately		
Inglis *et al.*, 1994	894	Singleton pregnancies between 15 to 40 years at < 37 weeks and with intact membranes attending a medical centre in the USA. Population included asymptomatic women (*n* = 73), and those with threatened preterm labour (*n* = 38).	To determine association of tumor necrosis factor, IL-6 and FFN identified in lower genital tract during pregnancy with preterm delivery. Vaginal swabs collected once at 20–36 weeks (levels > 50 pg/ml for positive IL-6 test, levels > 50 microg/ml for positive FFN test)	Spontaneous preterm delivery < 37 weeks. Risk of preterm delivery was evaluated for these 3 factors (preterm vs term delivery)	<u>Positive Tumor necrosis factor</u> (*n* = 73) 18.2% vs 16.1% RR: 1.13 (0.28, 4.46) <u>Positive IL-6 factor</u> (*n* = 73) 9.1% vs 16.1% RR: 0.56 (0.08, 3.97) <u>Positive FFN levels</u> (*n* = 73) 18.2% vs 17.7% RR: 1.02 (0.26, 4.01)	Population not representative Blinding of technicians Test described adequately	CH	II
Goepfert *et al.*, 2001	895	Cohort of asymptomatic pregnant women (*n* = 2929) with singleton pregnancies at 22–24 weeks in the USA	To evaluate association between cervical IL-6, FFN and preterm birth. Single vaginal swab taken	Spontaneous preterm delivery < 32 and < 35 weeks. Predictive accuracy	<u>For delivery < 35 weeks</u> IL-6 positive only Sensitivity: 20%	Case–control study nested within the multicentre prospective cohort study (data analysed	CC	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		and with a dating scan *Cases*: women with preterm delivery < 35 weeks and cervical specimen available for IL-6 assay (*n* = 125) *Controls*: women with term deliveries and matched for race, parity and centre (*n* = 125)	at 22–24 weeks. Levels > 305 pg/ml for positive IL-6 test, and > 50 ng/ml for positive FFN test.	calculated for < 29, < 32, and < 35 weeks.	Specificity: 90% FFN positive only Sensitivity: 23% Specificity: 97% Both IL-6 and FFN positive Sensitivity: 8% Specificity: 98% Either IL-6 or FFN positive Sensitivity: 35% Specificity: 90%	retrospectively) Population not representative Blinding of technicians Test described adequately		
Sakai *et al*., 2004	896	Singleton pregnancies who had perinatal care and delivery in 10 hospitals in Japan (*n* = 13 299)	Association between IL-8 and cervical length with preterm birth and preterm PROM. Swabs taken serially from cervical canal – once a month in 20–23 weeks and then once biweekly in 24–28 weeks. Levels > 360 ng/ml for a positive test for IL-8, and length < 25 mm for short cervix on TVS	Spontaneous preterm delivery < 32, < 34 and < 37 weeks Comparison of risk of preterm delivery between women with positive IL-8 test (*n* = 845) vs negative test (*n* = 3358), and those with short cervix (85) vs not short cervix (*n* = 4118).	<u>For IL-8 levels</u> < 32 weeks 0.9% vs 0.4% OR: 2.5 (1.0, 6.8) *P* = 0.037 < 34 weeks 1.5% vs 0.5% OR: 3.2 (1.5, 6.9) *P* = 0.0015 < 37 weeks 4.9% vs 3.3% OR: 1.5 (1.0, 2.2) *P* = 0.02 <u>For short cervix</u> < 32 weeks 5.9% vs 0.3% OR: 18.6 (11.1, 31.3) *P* < 0.0001 < 34 weeks 11.8% vs 0.4%	Population representative Blinding of technicians not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					OR: 28.5 (13.4, 60.4) *P* < 0.0001 < 37 weeks 43.5% vs 2.5% OR: 17.6 (12.9, 23.9) *P* < 0.0001			
Sakai *et al*., 2004	897	Women with single pregnancy receiving prenatal care in outpatient clinic of a university hospital in Japan (*n* = 501)	Relationship between vaginal pathogens and IL-8 in cervical mucus studied in relationship to preterm delivery. Single cervical specimen collected at 20–24 weeks. Threshold of a positive IL-8 test 377 ng/ml, and culture done for bacterial pathogens	Spontaneous preterm delivery < 37 weeks. Comparison of pathogens between high IL-8 group (*n* = 84) and normal IL-8 group (*n* = 417). Also risk of premature births compared for IL-8 levels and Lactobacillus presence/absence	<u>Comparison of pathogens</u> Lactobacillus 56.0% vs 84.7% *P* < 0.0001 Anaerobic 83.3% vs 43.9% *P* < 0.0001 Aerobic 47.6% vs 52.3% *P* = 0.43 Candida 17.9% vs 12.7% *P* = 0.21 <u>Premature birth rates</u> For IL-8 levels 13.1% vs 3.6% OR: 4.0 (1.78, 14.0) *P* = 0.0003 For Lactobacillus 11.9% vs 3.5% OR: 3.7 (1.66, 8.31) *P* = 0.0007	Population representative Blinding not done/specified Test described adequately	CH	II
Simpson *et al*., 1995	898	Singleton pregnancies attending a regional medical centre in the USA. Population mainly from lower socio-economic group, 80% black and 20%	To evaluate if second and third-trimester maternal serum AFP levels (taken at 15–20 and 24–36 weeks) predicts adverse pregnancy outcomes.	Detection rates (DR), false positive rates (FPR), and odds ratios for four pregnancy complications – preterm birth (< 37 weeks), preterm PROM, FGR (< 10th centile), and LBW (	AT 15–20 WEEKS (*n* = 650) <u>Preterm birth</u> DR: 19% FPR: 6.3%	Population representative Blinding of clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		white. (*n* = 753)	Threshold for a positive test – AFP level ≥ 2.0 MoM.	< 2500 g)	OR: 3.5 (1.4, 8.7) <u>Preterm PROM</u> DR: 40% FPR: 6.0% OR: 10.4 (3.6, 29.4) <u>FGR</u> DR: 16.7% FPR: 6.8% OR: 2.7 (0.8, 10.6) <u>LBW</u> DR: 14.7% FPR: 6.2% OR: 2.6 (1.1, 5.8)			
Dugoff *et al.*, 2005	899	Women ≥ 16 years age confirmed to have singleton pregnancies between 10–14 weeks gestational age, and attending one of the 14 study centres (*n* = 33 145)	To estimate predictive relationship between second-trimester levels (at 15–19 weeks) of AFP, HCG, unconjugated estriol (UE-3), and inhibin A, and obstetric complications. Threshold levels for AFP, HCG and inhibin A ≥ 2.0 MoM, and for UE-3 ≤ 0.5 MoM.	Comparison of incidence and association (OR after adjusting for confounding variables) of adverse complications – preterm delivery < 32 weeks, LBW < 10th centile, Fetal loss < 24 weeks, and Fetal demise > 24 weeks, between positive and negative serum levels	<u>Preterm delivery</u> AFP 3.4% vs 0.7% *P* < 0.001 OR: 1.76 (0.81, 3.84) HCG 1.5% vs 0.7% *P* < 0.001 OR: 0.83 (0.43, 1.58) UE-3 1.14% vs 0.8% *P* = 0.4 OR: 1.68 (0.61, 4.64) inhibin A 3.1% vs 0.65% *P* < 0.001 OR: 2.38 (1.4, 3.95)	Retrospective analysis of data from FASTER trial Population representative Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Morssink *et al.*, 1995	900	Singleton pregnancies who underwent screening for Down's or neural tube defects in Netherlands (*n* = 10 305)	To examine association between second-trimester AFP and HCG levels (at 15–20 weeks) and preterm delivery. Threshold for abnormal test – levels of AFP and HCG ≥ 2.5 MoM	Comparison of prevalence of outcomes (preterm delivery < 37 weeks, SGA < 10th centile) between elevated levels vs normal levels.	Preterm delivery (*n* = 7992) AFP levels 14.3% vs 5.9% *P* < 0.01 RR: 2.4 HCG levels 8.6% vs 5.9% *P* > 0.05 Both AFP and HCG levels raised 15.4% vs 6.0% *P* > 0.05	Retrospective analysis of data Population representative Blinding not done/specified Test described adequately	CH	II
Ong *et al.*, 2000	901	Singleton pregnancies without fetal and chromosomal anomalies attending antenatal clinics of two hospitals in the UK (*n* = 5548)	To evaluate first trimester (10–14 weeks) maternal HCG and PAPP-A as predictors pf pregnancy complications. Different thresholds – < 5th centile, < 10th centile, and < median values	Sensitivity of HCG and PAPP-A below 5th and 10th centile in the prediction of outcomes (spontaneous preterm delivery < 37 and < 34 weeks, birthweight < 10th centile, miscarriage).	Preterm delivery < 37 weeks (*n* = 5297) HCG < 5th centile Sensitivity: 5.7% Specificity: 95% PAPP-A < 5th centile Sensitivity: 7.8% Preterm delivery < 34 weeks HCG < 5th centile Sensitivity: 8.5% PAPP-A < 5th centile Sensitivity: 14.9%	Population representative Blinding not done/specified Test described adequately	CH	II
Yaron *et al.*, 2002	902	Consecutive singleton pregnancies undergoing first-trimester screening for Down's syndrome at prenatal diagnosis unit in Israel (*n* = 1722)	To evaluate whether abnormal HCG in first trimester (10–13 weeks) is predictive of abnormal pregnancy outcomes. Different levels of HCG used as cut-off (< 1.00, 1.01–2.00, 2.01–3.00,	Complication rates for outcomes – spontaneous preterm delivery < 37 weeks, birthweight < 5th centile, spontaneous miscarriage	For preterm delivery (*n* = 1622) HCG (threshold ≤ 2.0 MoM) Sensitivity: 73% (60%, 85%) Specificity: 21% (19%, 23%)	Population representative Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			3.01–4.00, 4.01–5.00, > 5.01 MoM)					
Hvilsom *et al.*, 2002	903	Pregnant women presenting for antenatal care at a university hospital in Denmark (*n* = 2846). *Cases*: women with idiopathic spontaneous preterm delivery < 37 weeks (*n* = 84) *Controls*: randomly selected women who had term delivery (*n* = 400)	To examine association between CRP levels and preterm delivery. Maternal CRP levels measured at 14–19 weeks (median 16.3 weeks). Threshold 7.6 ng/ml for a positive test.	Association (OR) between preterm delivery and CRP levels (cases vs controls) at various cut-off values.	CRP levels (5.6 mg/l) or cut-off 75th centile 7.35% vs 7.24% OR: 1.7 (1.0, 2.7) CRP levels (7.6 mg/l) or cut-off 85th centile 2.26% vs 8.14% OR: 2.0 (1.2, 3.5) CRP levels (16.4 mg/l) or cut-off 95th centile 5.9% vs 1.5% OR: 1.9 (0.8, 4.4)	Nested case–control study Population representative Blinding not done/specified Test described adequately	CC	III
Karinen *et al.*, 2005	904	Women with a history of at least 1 delivery and data available on first pregnancy from the Northern Finland 1966 Birth Cohort (*n* = 2309) *Cases*: women with idiopathic spontaneous preterm delivery < 37 weeks (*n* = 104) *Controls*: randomly selected women who had term delivery matched on age and parity (*n* = 402)	To evaluate association between Chlamydia trachomatis antibodies and CRP levels to preterm delivery. Serum samples collected at first trimester (mean age 10.4 weeks) obtained from serum bank. Threshold for positive CRP – levels > 4.3 ng/ml, and Chlamydia trachomatis IgG positive in 1 : 8 dilutions	Spontaneous preterm delivery < 37 weeks. Comparison of test results (OR) in cases vs controls for preterm delivery	Positive CRP only 20.2% vs 18.4% OR: 1.3 (0.7, 2.3) Positive Chlamydia trachomatis IgG levels only 14.4% vs 16.7% OR: 1.0 (0.5, 2.0) Both CRP and Chlamydia trachomatis IgG positive 14.4% vs 4.0% OR: 4.3 (2.0, 9.3)	Nested case–control study Population representative Blinding not done/specified Test described adequately	CC	III
Wren *et al.*, 1969	905	All pregnant women booking at an antenatal clinic in Australia (*n* = 3604)	To evaluate association between asymptomatic bacteriuria and pregnancy complications Mid-stream urine culture done at first visit, and repeated if positive.	Comparison of cases of untreated bacilluria (*n* = 90) and non-bacilluria controls (*n* = 3009) for pregnancy complications (abortion, birthweight < 2500 g, delivery < 37 weeks,	Abortion 6.7% vs 2.8% Birthweight < 2500 g 15.5% vs 4.6%	Population representative Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			Threshold not specified	stillbirths, neonatal death)	Delivery < 37 weeks 27.8% vs 6.8% Stillbirths 3.3% vs 0.4% Neonatal deaths 3.3% vs 1%			
Robertson *et al.*, 1969	906	All pregnant women attending the booking antenatal clinic in the UK (*n* = 8275) Treatment was initiated later in the study for women with positive urine culture.	Investigation into the incidence and consequences of asymptomatic bacteriuria. Mid-stream urine sample obtained during the booking visit, and cultured if initial modified nitrite test was positive. Count > 100,000 for a positive culture	Comparison of incidence of anemia (Hb < 10.gm%), hypertension (BP > 140/90 mmHg on two occasions), prematurity (gestational age < 36 weeks and birthweight < 2500 g) between untreated bacteriuria positive (*n* = 204) and control group (*n* = 1980)	Anemia 18.0% vs 8.0% Hypertension 7.0% vs 12.0% Prematurity (gestational age < 36 weeks) 6.0% vs 3.0% Prematurity (birthweight < 2500 g) 8.0% vs 6.0%	Population representative Blinding not done/specified Test described adequately	CH	II
Uncu *et al.*, 2001	907	All pregnant women up to 32 weeks seen at outpatient obstetrics clinic in Turkey (*n* = 247)	To determine incidence of asymptomatic bacteriuria and its relation to pregnancy complications. Midstream sample of morning urine obtained for culture, and colony growth > 100,000 bacteria/ml considered positive.	Comparison of incidence of premature labour, PROM, FGR, hypertension, anemia, and other complications between culture positive group (*n* = 23) and culture negative group (*n* = 163).	Premature labour 26.0% vs 9.8% PROM 4.3% vs 3.0% FGR 0 vs 0.6% Hypertension 4.3% vs 4.2% Anemia 26.0% vs 21.4%	Population representative Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Layton 1964	908	All pregnant women attending an antenatal clinic in the UK before 32 weeks of gestation (*n* = 1000)	To test the reliability of urine culture at first antenatal visit. Midstream urine sample collected and cultured at the booking visit and after 4 weeks of the first visit, and count over 100,000 regarded as significant.	Comparison between bacteriuric group (*n* = 67) and control group (*n* = 118) for outcomes – pre-eclamptic toxaemia (BP 140/90 + oedema), anaemia (Hb < 7.0 gm%), preterm delivery (< 37 weeks) and LBW (< 5.5 pounds)	Pre-eclamptic toxaemia 14.9% vs 9.3% Anemia 31.3% vs 19.5% Preterm delivery 6.3% vs 8.0% LBW 16.9% vs 8.9%	Population representative Blinding not done/specified Test described adequately	CH	II
Klebanoff *et al*., 2005	909	Pregnant women participating in a multicentre trial in the USA at 8–22 weeks gestational age and with no major medical or obstetric complications, no symptoms of UTI, and not received any antibiotics within past 14 days (*n* = 15 864)	To find association between timing of detection of BV and preterm delivery. Single vaginal swab taken at 8–22 weeks gestational age. Positive BV defined as vaginal Gram stain Nugent score ≥ 7 in conjunction with vaginal pH > 4.4.	Comparison of incidence of spontaneous preterm delivery < 37 weeks between BV positive (*n* = 4634) vs BV negative group (*n* = 8303) at different gestational age	At < 13 weeks 15.6% vs 14.0% At 13–14 weeks 15.3% vs 14.0% At 15–16 weeks 15.5% vs 11.7% At 17–18 weeks 13.3% vs 9.8% At 19–20 weeks 15.4% vs 10.0% At 21–22 weeks 13.2% vs 10.5%	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b
Hillier *et al*., 1995	910	Singleton pregnancies enrolled in one of seven medical centres in the USA for routine prenatal care and at 23–26 gestational age wks (*n* = 10 397)	To find association between BV and preterm delivery after adjusting for other known risk factors. Single posterior fornix swab taken at 23–26 weeks. Threshold for a positive test	Comparison (OR) of adverse outcomes – preterm delivery (< 37 weeks), LBW (< 2500 g), and PROM (rupture of membranes before regular uterine contractions) between	Mean birthweight (g) 3204 ± 618 vs 3294 ± 576 Preterm delivery 6.3% vs 4.2% OR: 1.5 (1.2, 1.9)	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			– vaginal PH above 4.5 and Gram staining score > 7.	women with positive BV vs those with negative BV	LBW 9.7% vs 6.6% OR: 1.5 (1.2, 1.9) PROM 3.1% vs 2.8% OR: 1.1 (0.8, 1.6)			
Purwar *et al*., 2001	911	Randomly selected asymptomatic low-risk pregnant women without vaginal discharge attending a government medical college in India (*n* = 1006)	To find association of BV with adverse pregnancy outcomes. Single vaginal swab taken at 16–28 weeks, and scored for BV according to Nugent's criterion.	Comparison of spontaneous preterm delivery (< 37 weeks), PROM (spontaneous rupture of membranes before onset of labour), preterm PROM (spontaneous rupture of membranes before onset of labour and before 37 weeks)	Preterm delivery 27.8% vs 4.9% RR: 5.7 (4.6, 8.3) *P* = 0.001 PROM 22.6% vs 3.4% RR: 6.6 (5.0, 10.0) *P* = 0.001 Preterm PROM 8.7% vs 0.7% RR: 11.9 (6.7, 32.4) *P* = 0.001	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b
Gratacos *et al*., 1998	358	Women with singleton pregnancies at a hospital clinic in Spain at less than 35 weeks gestational age (*n* = 688)	To evaluate influence of BV on pregnancy complications Sampling done twice from the posterior fornix at < 24 and then < 35 weeks. BV diagnosed on the basis of Nugent criteria	Comparison of preterm delivery (< 37 weeks), PROM (rupture of membranes before 37 weeks or at least 6 hours prior to onset of labour), premature labour (presence of regular contractions in woman with intact membranes)	Preterm delivery 15.2% vs 4.7% RR: 3.2 (1.8, 5.7) *P* < 0.0001 PROM 18.4% vs 5.4% RR: 3.3 (2.0, 5.6) *P* < 0.0001 Premature labour 16.0% vs 5.0% RR: 3.1 (1.8, 5.4)	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					$P < 0.0001$			
Taipale *et al.*, 1998	912	Consecutive singleton pregnancies screened for routine anomalies by ultrasonography at 18–22 weeks in a hospital in Finland ($n = 4206$)	To evaluate if TVS can predict preterm delivery. TVS done at 18–22 weeks by six different operators, but their prints checked by another operator. Different thresholds used but cervical length $\leq$ 29 mm was the best threshold identified using ROC curve	Spontaneous preterm delivery at < 35 and < 37 weeks. Diagnostic accuracy results and relative risk calculated for different thresholds.	Preterm delivery < 37 weeks ($n = 3694$) Cx length $\leq$ 25 mm Sensitivity: 6% Specificity: 100% PPV: 39% RR: 17 (8, 35) Cx length $\leq$ 27 mm Sensitivity: 8% Specificity: 99% PPV: 23% RR: 10 (5, 20) Cx length $\leq$ 29 mm Sensitivity: 16% Specificity: 97% PPV: 13% RR: 6 (4, 11) Cx length $\leq$ 35 mm Sensitivity: 35% Specificity: 73% PPV: 3% RR: 1.5 (1.0, 2.3)	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b
Leung *et al.*, 2005	913	Ethnic Chinese women with singleton pregnancies with ultrasound measurement at 18–22 weeks in a tertiary obstetric unit in Hong Kong ($n = 2952$)	To examine the predictive value of cervical length and funneling for spontaneous preterm delivery by mid-trimester TVS. Single TVS examination done at 18–22 weeks. Different thresholds used but cervical length	Diagnostic accuracy results for spontaneous preterm delivery at < 34 weeks. ROC curve used for prediction analysis for different percentiles/cut-offs for cervical length and funneling.	Cx length < 25 mm Sensitivity: 26.3% Specificity: 98.3% PPV: 9.4% NPV: 99.5% Cx length < 27 mm	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			≤ 27 mm identified using ROC curve as the best threshold. Funneling defined as protrusion of amniotic membranes > 5 mm into cervical canal.		Sensitivity: 36.8% Specificity: 96.2% PPV: 6.1% NPV: 99.6% <u>Cx length < 30 mm</u> Sensitivity: 36.8% Specificity: 96.2% PPV: 6.1% NPV: 99.6% <u>Funneling only</u> Sensitivity: 31.6% Specificity: 93.9% PPV: 3.3% NPV: 99.5% <u>Cx length < 27 mm + funneling</u> Sensitivity: 26.3% Specificity: 99.0% PPV: 14.7% NPV: 99.5% <u>Cx length < 27 mm or funneling</u> Sensitivity: 42.1% Specificity: 91.1% PPV: 3.1% NPV: 99.6%			
Fukami *et al.*, 2003	914	Women with singleton pregnancies scanned between 16–19 weeks at a medical school hospital in Japan (*n* = 3367)	To compare shortened cervical length and absence of new parameter 'cervical gland area (CGA)' for predicting preterm delivery. Threshold for shortened cervix – length ≤ 30 mm, and CGA defined as sonographically hyper/hypoechoic zone surrounding the cervical	Predictive accuracy calculated for spontaneous preterm delivery < 32 weeks and at 32–36 weeks	<u>For 32–36 weeks</u> (*n* = 3030) Short cervix Sensitivity: 18.2% Specificity: 98.9% PPV: 33.3% NPV: 97.6% Absence of CGA Sensitivity: 2.3%	Population representative Blinding not done/ not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			canal.		Specificity: 99.7% PPV: 18.2% NPV: 97.2% Short cervix and absence of CGA Sensitivity: 2.3% Specificity: 99.7% PPV: 20.0% NPV: 97.2%			
To *et al.*, 2001	915	Women with singleton pregnancies attending for routine ANC in a UK hospital, and undergoing 22–24 week cervical assessment using ultrasound scan. (*n* = 6819)	To establish relationship of cervical length with preterm delivery. Single TVS was done at 22–24 weeks and threshold for funneling was dilatation of internal os ≥ 5 mm in width.	Regression analysis used to calculate relationship between cervical length and risk of spontaneous preterm delivery < 33 weeks.	Funneling group (*n* = 231) vs no funneling group (*n* = 6103) Preterm delivery 6.9% vs 0.7% *P* < 0.0001 Risk of preterm delivery Short cervix OR: 24.9 (*P* < 0.0001) Funneling OR: 1.8 *P*=0.40	Population representative Blinding not done/ not specified Test described adequately	CH	II

12 Fetal growth and wellbeing

Clinical question: What is the diagnostic value and effectiveness of the following screening methods in determining fetal growth: symphisis-fundal height (SFH) measurement; ultrasound scanning; use of customised growth charts with SFH measurement; use of customised growth charts with ultrasound scanning; clinical judgement/abdominal palpation?

12.2 and 12.3 Diagnostic accuracy studies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Bais *et al.*, 2004	916	Retrospective analysis of database of a geographical cohort in Netherlands, and included all low-risk singleton pregnancies at 20 weeks GA confirmed by US (*n* = 6725)	To evaluate performance of abdominal palpation as a screening test to detect FGR, and US as diagnostic test for women referred with suspected FGR. Abdominal palpation done by midwives after 20 weeks till referral or delivery (frequency not specified, and Threshold by clinical judgement). US done by consulted obstetricians	Predictive performance of abdominal palpation and US calculated for SGA (BW < 10th centile)and severe SGA (BW < 2.3rd centile)	<u>Abdominal palpation (*n* = 6318)</u> For SGA Prevalence: 8.5% Sensitivity: 21.3% (17.8, 24.7) Specificity: 95.9% (95.4, 96.4) PPV: 32.6% (27.7, 37.5) NPV: 92.9% (92.3, 93.6) For severe SGA Prevalence: 1.5% Sensitivity: 27.9% (19.0, 37.0) Specificity: 94.8% (94.2, 95.4) PPV: 7.4% (4.7, 10.1) NPV: 98.9% (98.6, 99.1) <u>Abdominal palpation + US (*n* = 6318)</u> For SGA Prevalence: 8.5% Sensitivity: 15.1% (12.1, 18.1) Specificity: 98.9% (98.6, 99.1) PPV: 55.1% (47.1, 63.1)	Retrospective analysis of database of a geographical cohort Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					NPV: 92.6% (92.0, 93.3) For severe SGA Prevalence: 1.5% Sensitivity: 24.7% (15.9, 33.5) Specificity: 98.0% (97.7, 98.4) PPV: 15.6% (9.8, 21.5) NPV: 98.9% (98.6, 99.1)			
Secher *et al*., 1990	917	Randomly selected women with singleton pregnancies and confirmed GA by US at 16–18 weeks in a city in Denmark (*n* = 199)	To evaluate measurement of SFH alone and in combination with EFW to detect SGA. SFH measured once a week from 33–36 weeks, EFW calculated and EFW curve generated using modeling. Sample for this study – women with > 3 measurements.	Predictive accuracy and risk calculated for SGA defined as BW < 85% of expected for GA (or < 9.4th centile for GA).	Last EFW value < 10th centile Sensitivity: 45% Specificity: 91% PPV: 38% NPV: 94% RR: 6.2 EFW curve < 10th centile Sensitivity: 38% Specificity: 92% PPV: 33% NPV: 93% RR: 4.8 Last SFH value < 10th centile Sensitivity: 33% Specificity: 93% PPV: 35% NPV: 93% RR: 4.8 Last SFH and EFW value < 10th centile Sensitivity: 12% Specificity: 100% PPV: 100% NPV: 91%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	III
Persson *et al*., 1986	919	Consecutive singleton pregnancies with regular menstrual cycles and	To graphically illustrate progression of SFH in a sample of women, and use	Predictive accuracy of SFH calculated for BW < 10th centile for GA (SGA),	BW < 10th centile Sensitivity: 26.6%	Multicentre study Representative population	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		known LMP attending one of three hospitals in Sweden (*n* = 3197)	it to predict abnormal fetal size. SFH measured about 15 times during entire pregnancy and value < 2 SD of reference curve (generated from 1350 healthy pregnant women) used as threshold.	BW/length ratio below 2 SD, BW > 90th centile (LGA), and BW/length ratio above 2 SD.	Specificity: 88.0% PPV: 18.0% NPV: 92.4% <u>BW > 90th centile</u> Sensitivity: 37.5% Specificity: 87.9% PPV: 24.5% NPV: 93.1% <u>BW/length ratio < 2 SD</u> Sensitivity: 16.7% Specificity: 86.7% PPV: 1.8% NPV: 98.6% <u>BW/length ratio > 2 SD</u> Sensitivity: 31.8% Specificity: 85.7% PPV: 3.3% NPV: 98.8%	Blinding not done/specified Test described adequately Reference test validated		
Harding *et al.*, 1995	920	Randomly selected group of pregnant women who had approx. 5 scans between 18–38 weeks in a hospital in Australia (*n* = 1135). This cohort was selected from an ongoing RCT.	To find most appropriate cut-offs (using ROC curve) for detecting SGA at various gestational ages using SFH, AFI, and US measurement of FAC. SFH, AFI and US done 5 times at 18–20, 24, 28, 34, and 38 weeks. Threshold for SFH – single value < 10th centile or 28 cm (28 weeks), 33.5 cm (34 weeks) and 36 cm (38 weeks). For AFI and FAC – single value < 10th centile	BW < 10th centile using charts constructed from Western Australian population.	<u>At 28 weeks (*n* = 760)</u> For SFH Prevalence: 12.3% Sensitivity: 32% Specificity: 88% PPV: 28% NPV: 90% For AFI Prevalence: 12.6% Sensitivity: 21% Specificity: 93% PPV: 21% NPV: 93% <u>At 34 weeks (*n* = 914)</u> For SFH	Representative population but loss to follow up Blinding of technicians Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Prevalence: 11.8% Sensitivity: 31% Specificity: 87% PPV: 24% NPV: 90% For AFI Prevalence: 11.7% Sensitivity: 11% Specificity: 89% PPV: 12% NPV: 88%			
Rosenberg *et al.*, 1982	918	All women having singleton pregnancies with confirmed GA (by careful history or US) of < 26 weeks attending an antenatal clinic in the UK. (*n* = 761)	To evaluate efficacy of SFH in identification of growth retardation. SFH measured from 20 weeks till delivery. *Threshold*: Two consecutive or three isolated SFH values < 10th centile of Reference curve (generated from 478 healthy pregnant women).	Prediction of growth retardation (BW < 10th centile for GA) using different criterion for thresholds	SFH (*n* = 753) Sensitivity: 56% (42%, 70%) Specificity: 85% (82%, 87%) Threshold – 20% measurements < 10th centile Sensitivity: 62% False positive rate: 21% Threshold – 30% measurements < 10th centile Sensitivity: 52% False positive rate: 8%	Retrospective cohort study Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Grover *et al.*, 1991	921	Healthy singleton pregnancies with known GA and absence of obstetric complications attending a tertiary level hospital for antenatal care in India (*n* = 400)	To analyse usefulness of SFH measurement for predicting altered fetal growth. SFH recorded fortnightly till 30 weeks and then weekly till term. *Threshold*: SFH value < 1 SD of Reference curve generated from 200 healthy pregnant women.	Predictive accuracy calculated for Small-for-date (BW < 10th centile for GA) and LGA (BW > 90th centile for GA) babies	SFD (*n* = 350) Sensitivity: 80.8% Specificity: 93.5% PPV: 84% False positive rate: 16% False negative rate: 8% LGA (*n* = 350) Sensitivity: 79.2% Specificity: 95.2% PPV: 76% False positive rate: 24% False negative rate: 4%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rogers *et al*., 1985	922	Randomly selected pregnant women attending antenatal clinic of a hospital in the UK (*n* = 250).	To evaluate precision of SFH for predicting FGR. SFH measured in the third trimester, and single value < 3 cm below mean of the sample or 3 consecutive static or declining values taken as the threshold.	Diagnostic accuracy for predicting FGR (BW < 10th centile)	Sensitivity: 73.1% Specificity: 91.9% PPV: 51.3% NPV: 96.7%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Warsof *et al*., 1986	923	Consecutive women with ultrasonographically confirmed singleton pregnancies before 24 weeks attending a tertiary level hospital in the UK (*n* = 4527)	US done once in the third trimester at 28, 30, 32, 34 or 36 weeks. Threshold for BPD, HC and AC – values < 25th centile or < 10th centile for GA	Diagnostic accuracy for predicting FGR (BW < 10th centile)	<u>For values < 10th centile as threshold</u> Only BPD abnormal (*n* = 7385) Sensitivity: 25% Specificity: 93% PPV: 39% NPV: 87% Only HC abnormal (*n* = 3308) Sensitivity: 35% Specificity: 91% PPV: 49% NPV: 86% Only AC abnormal (*n* = 4893) Sensitivity: 48% Specificity: 93% PPV: 61% NPV: 89% Both BPD and AC abnormal (*n* = 4789) Sensitivity: 22% Specificity: 97% PPV: 64% NPV: 86% BPD or AC abnormal (*n* = 4789) Sensitivity: 54% Specificity: 85%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					PPV: 43% NPV: 90%			
Skovron *et al.*, 1991	924	Women with singleton gestation who had an US examination for fetal size determination in a medical centre in the USA	US done once between 26 and 34 weeks, and then repeated in some cases. Threshold values for AC and EFW (Shepard's formula) at < 10th and < 25th centile for GA.	Predictive performance calculated for SGA babies (BW < 10th centile for GA) by ROC curve	<u>Single US examination and < 10th centile as threshold</u> AC Sensitivity: 72% Specificity: 69% PPV: 19% EFW Sensitivity: 25% Specificity: 97% PPV: 47% <u>Single US examination and < 25th centile as threshold</u> AC Sensitivity: 83% Specificity: 56% PPV: 16% EFW Sensitivity: 51% Specificity: 80% PPV: 20% <u>Serial US and threshold < 10th centile for both AC measurement</u> Sensitivity: 62% Specificity: 81% PPV: 31%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Lin *et al.*, 1990	927	Records of all women with singleton pregnancies who had undergone obstetric US at a tertiary hospital in the USA (*n* = 463)	To determine if oligohydramnios increases the accuracy of prenatal diagnosis of FGR. US done (AC and AFI) twice in the third trimester at an interval of 2–4 weeks. Threshold for AC < 10th centile for GA, and vertical	FGR defined as BW < 10th centile for GA.	<u>For AC < 10th centile</u> Sensitivity: 87.5% Specificity: 77.2% PPV: 38.1% NPV: 97.5% <u>For AC < 5th centile</u>	Retrospective analysis of records Representative population Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			diameter < 2 cm for largest pocket for AFI.		Sensitivity: 50.0% Specificity: 90.0% PPV: 44.4% NPV: 91.8% <u>For AC < 10th centile and oligo</u> Sensitivity: 25.0% Specificity: 98.0% PPV: 66.7% NPV: 89.1%	Reference test validated		
Hedriana *et al*., 1994	926	Women with normal singleton pregnancy and known LMP confirmed by first-trimester physical examination (*n* = 302)	To determine if two or more US examination is superior to a single scan. Single scan (32–36 weeks) and serial scans (two to five times between 28–42 weeks) *Threshold*: Slope ± SD calculated for AC and EFW (Shepard's formula) centile using regression analysis.	Diagnostic accuracy of parameters calculated for predicting SGA (BW < 10th centile) and LGA (BW > 90th centile) babies	<u>Single examination for SGA (*n* = 249)</u> EFW Sensitivity: 100% Specificity: 76% PPV: 25% NPV: 100% AC Sensitivity: 68% Specificity: 88% PPV: 33% NPV: 97% <u>Serial examinations for SGA (*n* = 247)</u> EFW Sensitivity: 100% Specificity: 75% PPV: 25% NPV: 100% AC Sensitivity: 100% Specificity: 88% PPV: 40% NPV: 100% <u>Single examination for LGA (*n* = 249)</u>	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					EFW Sensitivity: 48% Specificity: 94% PPV: 63% NPV: 89% AC Sensitivity: 54% Specificity: 89% PPV: 53% NPV: 90% <u>Serial examinations for LGA (*n* = 247)</u> EFW Sensitivity: 62% Specificity: 100% PPV: 100% NPV: 92% AC Sensitivity: 84% Specificity: 100% PPV: 100% NPV: 97%			
Newnham *et al.*, 1990	925	Pregnant women with singleton gestation attending a public antenatal clinic of a tertiary hospital in Australia (*n* = 615)	To evaluate role for US and Doppler US in predicting perinatal complications. Both US performed at 18, 24, 28 and 34 weeks. Threshold for abnormal AC < 5th centile for gestational age, and for abnormal Doppler – S/D ratio > 95th centile for GA	Diagnostic accuracy results for FGR (BW < 10th centile for GA) and fetal hypoxia (operative delivery due to fetal hypoxia with umbilical artery ph < 7.20 or 5 minute Apgar score < 7	<u>FGR at 28 weeks</u> Umb. artery S/D ratio (*n* = 470) Prevalence: 9.1% Sensitivity: 18.6% Specificity: 95.6% PPV: 29.6% NPV: 92.1% Fetal AC (*n* = 476) Prevalence: 9.2% Sensitivity: 27.3%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 96.1% PPV: 41.5% NPV: 92.8% <u>FGR at 34 weeks</u> Umb. artery S/D ratio (*n* = 445) Prevalence: 8.1% Sensitivity: 16.7% Specificity: 95.1% PPV: 23.1% NPV: 92.8% Fetal AC (*n* = 451) Prevalence: 8.2% Sensitivity: 48.7% Specificity: 94.0% PPV: 41.9% NPV: 95.3%			
Chauhan *et al.*, 1999	928	*Cases*: Singleton pregnancies, AFI ≤ 5 cm, reliable GA and no known anomalies (*n* = 162) *Controls*: Next pregnancy with same GA and AFI between 5.1 to 23.9 cm (*n* = 162)	To assess predictive accuracy of oligohydramnios for detecting fetal growth restriction. Third-trimester US done within 72 hours of delivery to evaluate for AFI (threshold ≤ 5 cm)	Diagnostic accuracy calculated for fetal growth restriction (BW < 10th centile for GA)	Sensitivity: 76% (56%, 89%) Specificity: 95% (90%, 98%) PPV: 78% (59%, 91%) NPV: 94% (89%, 98%)	Population not representative Blinding not done/specified Test described adequately Reference test validated	CH	III
Beattie *et al.*, 1989	929	Ultrasonically dated singleton pregnancies attending aa antenatal clinic in the UK within 7 days of their 28th gestational week (*n* = 2097)	To assess usefulness of Doppler US as a screening tool for detecting FGR. Doppler US done at 28, 34 and 38 weeks and FGR predicted using pulsatility index, systolic/diastolic ratio, and resistance parameter (threshold value > 90th centile for all)	FGR taken as BW < 5th centile for GA	<u>Pulsatility index at 28 weeks</u> Sensitivity: 28% Specificity: 89% PPV: 11% NPV: 97% <u>S/D ratio at 28 weeks</u> Sensitivity: 31% Specificity: 90% PPV: 12%	Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					NPV: 97% Pulsatility index at 34 weeks Sensitivity: 32% Specificity: 89% PPV: 12% NPV: 97% S/D ratio at 34 weeks Sensitivity: 40% Specificity: 84% PPV: 11% NPV: 97%			
Todros *et al.*, 1995	930	Singleton pregnancies with no obstetrical risk, pre-pegnancy pathological condition or anomaly attending out-patient clinics of six hospitals in Italy (*n* = 962).	To assess efficacy of Doppler examination of umbilical and uterine arteries as a screening test for FGR or PIH. Doppler US done twice at 19–24 and 26–31 weeks. *Threshold*: S/D ratio of 4.5 (at 19–24 weeks) and 3.5 (at 26–31 weeks) derived from ROC curve.	Diagnostic accuracy of Doppler Umbilical arteries for SGA (BW < 10th centile for GA) and PIH (BP > 140/90 mmHg at two measurements 4 hours apart for the first time after 20 weeks GA)	*n* = 916 for all SGA at 19–24 weeks Sensitivity: 46.1% Specificity: 74.1% PPV: 7.8% NPV: 96.7% SGA at 26–31 weeks Sensitivity: 43.2% Specificity: 80.5% PPV: 7.0% NPV: 96.8% PIH at 19–24 weeks Sensitivity: 37.9% Specificity: 73.9% PPV: 4.7% NPV: 97.2% PIH at 26–31 weeks Sensitivity: 37.5% Specificity: 80.2% PPV: 7.0% NPV: 96.9%	Multicentre study Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Sijmons *et al.*, 1989	931	Randomly selected singleton pregnancies from a university hospital population in Netherlands (*n* = 400).	To assess validity of umbilical artery Doppler as a screening tool at 28 and 34 weeks for predicting SGA infants. *Threshold*: Pulsatility index > 95th centile for GA in the study population.	Diagnostic accuracy of Doppler for predicting SGA (BW < 10th or 2.3rd centile) and low weight for length infants (ponderal index < 10th or 3rd centile)	SGA (BW < 10th centile) at 28 weeks (*n* = 394) Prevalence: 22.6% Sensitivity: 16.9% Specificity: 95.1% PPV: 50.1% NPV: 79.6% Low weight for length (ponderal index < 10th centile) at 28 weeks (*n* = 352) Prevalence: 10.2% Sensitivity: 19.4% Specificity: 94.9% PPV: 30.4% NPV: 91.2% SGA (BW < 10th centile) at 34 weeks (*n* = 368) Prevalence: 22.2% Sensitivity: 22.0% Specificity: 94.4% PPV: 52.9% NPV: 80.8% Low weight for length (ponderal index < 10th centile) at 34 weeks (*n* = 330) Prevalence: 8.8% Sensitivity: 24.1% Specificity: 92.7% PPV: 23.3% NPV: 92.7%	Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b
Atkinson *et al.*, 1994	932	Low-risk nulliparaous women with singleton pregnancies enrolled in a double-blind trial of low dose aspirin for pre-eclampsia prevention in the USA (*n* = 565)	To evaluate usefulness of umbilical artery Doppler for predicting FGR or pre-eclampsia at 20–26, 27–31, 32–36 and 37–42 weeks. *Threshold*: S/D ratio > 90th centile for GA in study population	Diagnostic accuracy for predicting SGA (BW < 10th centile for GA) and pre-eclampsia	SGA at 20–26 weeks (*n* = 490) Sensitivity: 18% Specificity: 91% PPV: 13% NPV: 94%	Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					SGA at 27–31 weeks (*n* = 475) Sensitivity: 20% Specificity: 91% PPV: 15% NPV: 93% SGA at 32–36 weeks (*n* = 439) Sensitivity: 24% Specificity: 91% PPV: 17% NPV: 94%			
Owens *et al.*, 2003	933	Women with singleton pregnancies and confirmed GA < 85 days in a hospital in the UK (*n* = 330)	To compare two methods of predicting FGR. Third-trimester US done at 2 weekly intervals to calculate EFW (using BPD, abd. area, FL) and the last EFW prior to delivery used to obtain customised fetal weight centile. *Threshold:* Centile < 5th and < 10th for estimated values.	FGR defined as ponderal index < 25th centile. Other outcomes - skinfold thickness < 10th centile and mid-arm to occipito-frontal circumference ratio < 1SD.	For customised EFW < 5th centile and ponderal index < 25th centile (*n* = 258) Sensitivity: 19% Specificity: 97% PPV: 54% NPV: 87% For customised EFW < 10th centile and ponderal index < 25th centile (*n* = 258) Sensitivity: 42% Specificity: 90% PPV: 41% NPV: 90%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Okonofua *et al.*, 1986	934	Singleton uncomplicated pregnancies attending a hospital antenatal clinic in the UK, and who were sure of their LMP (*n* = 100)	To compare SFH and US biometry in predicting SGA and LGA babies. SFH and US biometry done after 20 weeks in the third trimester. *Threshold*: Two consecutive values for SFH, BPD or AC > 90th centile of reference curve (generated from sample of 30 healthy uncomplicated singleton pregnancies)	SGA defined with BW < 10th centile, and LGA with BW > 90th centile	SGA by SFH Sensitivity: 71.4% Specificity: 85% PPV: 50% LGA by SFH Sensitivity: 33.3% Specificity: 85% PPV: 31.3% SGA by US biometry	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 85.7% Specificity: 95.4% PPV: 66.7% <u>LGA by US biometry</u> Sensitivity: 66.7% Specificity: 95.4% PPV: 75%			
Ott *et al*., 1984	935	Pregnant women undergoing US examination within 72 hours of delivery in a medical centre in the USA (*n* = 595)	To evaluate US biometry for detecting altered fetal growth. BPD and AC measured by US and EFW (Shepard's formula) calculated. *Threshold*: EFW > 1.5 SD for the reference curve.	Diagnostic accuracy results for predicting SGA (BW < 10th centile for GA) and LGA (BW > 90th centile for GA) babies	<u>For SGA</u> Sensitivity: 89.9% Specificity: 78.8% PPV: 63.2% <u>For LGA</u> Sensitivity: 73.5% Specificity: 78.8% PPV: 59.6%	Retrospective study, population not representative Blinding not done/specified Test described adequately Reference test validated	CH	III

Effectiveness studies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Neilson JP	566	Pregnant women around 14 weeks of pregnancy randomly allocated to the experimental or control group using sealed, opaque and unnumbered envelopes (*n* = 1639, 1 trial)	Tape measurement of SFH routinely measured after 28 weeks and plotted on a locally derived centile chart	Primary: complications associated with FGR or FGR (intrauterine death, asphyxia hypoglycaemia) complications associated with macrosomia (CPD, caesarean for failure to progress, shoulder dystocia) complications associated with multiple pregnancy (preterm delivery, perinatal mortality) Secondary: other indices of maternal and perinatal mortality and morbidity, and indices of obstetric care including admission to hospital.	Peto Odds ratio with 95% CI Perinatal mortality 1.25 (0.38 – 4.08) Apgar score < 4 at 1 minute 0.93 (0.38 – 2.31) Apgar score < 4 at 5 minutes 1.04 (0.26 – 4.17) Labour induction for FGR 0.84 (0.44 – 1.59) Caesarean section for FGR 0.72 (0.31 – 1.67) Birthweight < 10th centile 1.34 (0.91 – 1.98) Admission neonatal unit 1.07 (0.69 – 1.65)	Methodology explained in detail Only 1 trial included	SR	1+
Smith-Bindman *et al.*, 2002	936	Study population selected from a cohort of 1836 singleton pregnancies attending a medical centre in the USA, and included all those who underwent two or more US examinations 2–17 weeks apart during the study period (*n* = 321)	To determine if fetal growth measured at serial US examination can predict neonatal morbidity. Results of US fetal biometry measurements obtained from computerised database and EFW calculated using HC, AC and FL	Comparison of risk between FGR group (*n* = 24) and Normal FG (*n* = 212) for – LBW (BW < 2500 g, < 1500 g, < 5th centile and < 3rd centile for GA), preterm birth (< 37 weeks), long hospital stay (> 4 days), admission in neonatal intensive care unit, and assisted ventilation required at birth. Risk was also calculated after adjustment for confounding variables (maternal age, weight, height, race, parity, fetal sex, EFW)	LBW (BW < 2500 g) 63% vs 16% RR: 3.9 (2.5, 6.0) Adj. OR: 16.9 (4.2, 68.1) LBW (BW < 1500 g) 25% vs 3% RR: 8.8 (3.1, 25.2) Adj. OR: 17.6 (2.6, 122.0) LBW (BW < 5th centile) 25% vs 1% RR: 17.7 (4.7, 66.1) Adj. OR: 36.1 (3.9, 336.7)	Retrospective analysis of hospital database Blinding not specified Confounding variables controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Preterm birth 50% vs 22% RR: 2.3 (1.4, 3.7) Adj. OR: 4.1 (1.2, 14.1) Long hospital stay 50% vs 19% RR: 2.6 (1.6, 4.2) Adj. OR: 6.2 (1.7, 22.6) Admission in NICU 46% vs 13% RR: 3.6 (2.1, 6.3) Adj. OR: 5.7 (1.5, 21.9)			
Stratton *et al.*, 1995	937	Unselected mothers with singleton pregnancies and confirmed GA by a second-trimester scan referred for third-trimester US examination to a hospital in the UK (*n* = 285)	To compare outcomes in fetuses with US evidence of inadequate growth but born with BW > 10th centile for GA (Inadequate fetal growth group, *n* = 75) with infants with normal US for fetal growth (Adequate fetal growth group, *n* = 121).	Abnormal Doppler, induction of labour, meconium staining, need for intrapartum fetal blood sampling, operative vaginal delivery, caesarean section, Apgar score < 7 at 5 minutes and need for admission to neonatal ICU.	Meconium staining 23% vs 17% OR: 1.40 (0.64, 3.03) *P* = 0.36 Admission to neonatal ICU 20% vs 7% OR: 3.11 (1.19, 8.52) *P* < 0.05 Abnormal Doppler 7% vs 9% *P* > 0.05 Induction of labour 35% vs 34% *P* > 0.05 Cesarean section 16% vs 16% *P* > 0.05	Baseline characteristics of groups not compared Confounding variables not adjusted Blinding not done/specified	CH	2−
Zhang *et al.*, 2004	938	English speaking women more than 18 years of age with singleton pregnancy, known LMP and GA	To examine fetal growth and perinatal outcomes in pregnancies with isolated oligohydramnios (defined	Preterm delivery (< 37 weks), caesarean delivery, Apgar score < 7 at 1 and 5 minutes, Duration of	Group 1 Preterm delivery 24.4% vs 13.2%	Baseline characteristics of two groups similar Blinding of outcome assessor	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		< 18 weeks in the screening arm of the RADIUS trial (multicentre trial) in the USA, and who underwent US screening twice at 15–22 and 31–35 weeks (*n* = 7549)	as AFI ≤ 5 cm). Comparison made between OH and Normal AFI in two groups – Group 1 with associated maternal/fetal conditions like PROM, HT, DM, and Group 2 without such associated conditions	NICU stay, perinatal mortality, moderate and severe morbidity	RR: 1.9 (1.2, 3.1) Caesarean section 24% vs 29% RR: 0.9 (0.6, 1.3) Apgar < 7 at 5 minutes 7.7% vs 3.1% RR: 2.2 (1.1, 4.7) Perinatal mortality 5.1% vs 1.2% RR: 4.1 (1.3, 13.4) Severe morbidity 7.7% vs 5.3% RR: 1.5 (0.5, 3.8) Group 2 Preterm delivery 3.5% vs 4.1% RR: 0.9 (0.3, 2.7) Caesarean section 19% vs 14% RR: 1.4 (0.8, 2.4) Apgar < 7 at 5 minutes 1.2% vs 1.2% RR: 1.0 (0.1, 7.0) Perinatal mortality 0% vs 0.5% RR: 0 Severe morbidity 1.2% vs 0.8% RR: 1.4 (0.2, 10.3)	Confounding variables controlled		

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Biggio *et al.*, 1995	939	Review of all computerised records of a tertiary hospital in the USA (*n* = 40 065) *Cases*: pregnancies complicated by hydramnios after 20 weeks of gestation (*n* = 370) *Controls*: all singleton pregnancies having normal AF volume on US after 20 weeks (*n* = 36 425)	Hydramnios taken as AFI ≥ 25 cm or depth more than 8 cm measured in a single vertical pocket or sonographers subjective impression.	Comparison made for adverse perinatal outcomes (Perinatal mortality rate (PMR) per 1000 births, fetal anomalies, FGR, caesarean section, and diabetes), and confounding variables known to influence perinatal outcomes adjusted using regression model.	PMR (per 1000 births) 49 vs 14 RR: 3.4 (2.2, 5.4) Adj RR: 3.8 (1.9, 7.3) Fetal anomalies 8.4% vs 0.3% RR: 25.4 (17.4, 37.2) Adj. RR: 18.2 (8.7, 38.2) FGR 3.8% vs 6.7% RR: 0.6 (0.3, 0.9) Adj. RR: 0.5 (0.2, 1.1) Caesarean 47.0% vs 16.4% RR: 2.9 (2.6, 3.2)	Nested case–control Minimal chance of bias Blinding not specified Confounding variables controlled	CC	2+
Bricker and Neilson,	575	The review includes all randomised and quasi-randomised controlled trials where routine Doppler US of umbilical artery and/or uterine artery was done in both unselected and low-risk pregnant women (*n* = 14 338, 5 trials)	To assess the effectiveness of routine Doppler US on obstetric practice and pregnancy outcomes in unselected and low-risk pregnancies	Primary outcome measures were induction of labour, caesarean section, preterm delivery < 28 and < 34 weeks, all deaths (perinatal, neonatal, and infant), neurodevelopment at 2 years of age, and maternal psychological effects	Routine Doppler US vs no/concealed/selective Doppler US Meta-analysis (4 trials) – no differences between the two groups in antenatal admissions or other tests of fetal wellbeing, induction of labour, instrumental deliveries, caesarean section, neonatal interventions and perinatal mortality. 3 trials report perinatal mortality for fetuses/neonates without congenital anomalies, but there was heterogeneity of results (χ^2 10.44, P < 0.025) with one trial finding increased perinatal mortality in screened group (OR 3.31, 95% CI 1.37–2.53). Serial US and Doppler US versus selective US Single trial compared the two groups and no difference was found between them for all the primary outcomes. More babies in the screened group were of BW < 10th	Cochrane review Well addressed question and methodology explained in detail	SR	1++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					and < 3rd centile			
Gardosi and Francis, 1999	567	Two similar catchment areas (distance from hospital, ethnicity and socio-economic background of population, number of referrals per year) of a tertiary hospital in the UK served by separate and non-overlapping groups of community midwives and GP's. *Study group:* singleton pregnancies (*n* = 667) booked before 22 weeks GA and issued CFGC, *Control group:* consecutive singleton pregnancies (*n* = 605) booked before 22 weeks and delivered in the hospital	To evaluate the effect of a policy using serial SFH measurements plotted on CFGC (study group) compared with routine antenatal care policy of recording SFH against women's GA (control group)	Primary outcomes: number of SGA (< 10th centile) and LGA (> 90th centile) babies detected antenatally in each group. Secondary outcomes: total number of investigations performed in each group including referrals to US department/pregnancy assessment unit, and admissions to the ward.	Number of SGA detected antenatally 47.9% vs 29.2% OR: 2.23 (1.12, 4.45) Number of LGA detected antenatally 45.7% vs 24.2% OR: 2.63 (1.27, 5.45) Induction of labour 15.7% vs 16.7% OR: 0.93 (0.69, 1.26) Preterm birth 7.8% vs 6.4% OR: 1.23 (0.80, 1.88) Admissions to SCBU 3.3% vs 2.6% OR: 1.26 (0.65, 2.41) Resuscitation at birth 16.5% vs 14.4% OR: 1.18 (0.87, 1.56) Fetal abnormality 1.0% vs 1.5% OR: 0.70 (0.26, 1.90)	Non-RCT Incomplete data for calculating diagnostic accuracy Blinding not specified		1−
Clausson *et al*., 2001	940	Details of all the live births recorded in the Swedish Birth Register between 1992–1995 after excluding those with congenital malformations, unknown gestational age, and insufficient information for calculating customised birthweight centile. (*n* = 326,377)	To determine if CFGC improves detection of SGA babies and association with adverse perinatal outcomes. Two standards for estimating birthweight constructed from database – a population one based on gender and gestational length, and an individually customised one with adjustment for maternal	Risks of stillbirth, neonatal death and Apgar score < 4 at 5 minutes compared in infants classified as SGA by the two standards to that of non-SGA infants. SGA defined as the lowest 10%, 5% or 2.5% of birthweights in the population.	SGA (pop) vs non-SGA (cust.) Stillbirth OR: 1.2 (0.8, 1.9) Neonatal death OR: 0.9 (0.3, 2.3) Apgar < 4 at 5 minutes OR: 1.2 (0.9, 1.5)	Population based cohort Baseline characteristics of two groups similar Confounding variables not controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			height, weight, parity and ethnic group.		SGA (cust.) vs non-SGA (pop.) Stillbirth OR: 6.1 (5.0, 7.5) Neonatal death OR: 4.1 (2.5, 6.6) Apgar < 4 at 5 minutes OR: 2.2 (1.9, 2.7) SGA (cust.) vs SGA (pop.) Stillbirth OR: 5.1 (4.3, 5.9) Neonatal death OR: 3.4 (2.4, 4.8) Apgar < 4 at 5 minutes OR: 2.0 (1.7, 2.3)			
Zhang *et al*., 2007	941	All recorded births with complete data for a period of 10 years (1992–2001) in the Swedish Birth Register. Apart from excluding those with congenital malformations, unknown gestational age, and insufficient information for calculating customised birthweight centile (as in previous study), it also excluded births with GA < 28 weeks. (*n* = 782,303)	To critically examine potential biases and artifacts underlying the use of CFGC. All the births were classified as non-SGA (both standards), SGA (cust.), SGA (pop.), or SGA (both), using the same standards as the above study	Risks of stillbirth, neonatal death and Apgar score < 4 at 5 minutes compared in infants classified as SGA by the two standards to that of non-SGA infants after controlling for confounding variables (gestational age and pre-pregnancy BMI)	SGA (pop) vs non-SGA (cust.) Stillbirth OR: 1.4 (1.1, 1.9) Adj. OR: 1.8 (1.3, 2.4) Neonatal death OR: 1.3 (0.9, 2.0) Adj. OR: 1.6 (1.0, 2.4) SGA (cust.) vs non-SGA (pop.) Stillbirth OR: 7.8 (6.9, 8.9) Adj. OR: 2.3 (2.0, 2.6) Neonatal death OR: 6.7 (5.5, 8.1) Adj. OR: 2.0 (1.6, 2.5)	Retrospective analysis of data from the population based cohort Baseline characteristics of two groups similar Confounding variables controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					SGA (cust.) vs SGA (pop.) Stillbirth OR: 5.7 (5.2, 6.2) Adj. OR: 4.9 (4.4, 5.4) Neonatal death OR: 5.7 (4.9, 6.5) Adj. OR: 4.9 (4.3, 5.7)			

14 Antenatal assessment tool

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Nelson et al, 2007	2004	Pregnant women on a low income (95% defined as being below poverty level – US) Total number of pregnant women in 4 reported studies = 2026	To describe and compare different screening assessment tools used to identify intimate partner violence.	Detection rate of intimate partner violence (IPV) (one tool compared with another)	4 simple questionnaire=based screening tools gave similar results when used to detect women suffering IPV (3-item Abuse Assessment Screen; 30-item Index of Spouse Abuse; 19-item Conflict Tactic Scale and the Domestic Abuse Screen). The 5-item Abuse-Assessment Screen scored higher than social services interview. However a nurse conducted interview was found to be better at detecting IC than a 4-item questionnaire.	Review contained 4 studies where the population was pregnant women. Quality ratings for studies: one good, one fair and two poor. Country: US	Systematic review	III
Anderson, 2002	1008	Pregnant women Intervention group n=21 healthcare providers. Comparison group n=27 healthcare providers.	To compare detection of psychosocial risk factors using the Antenatal Psychosocial Health Assessment (ALPHA) with detection through usual antenatal consultations.	Detection of psychosocial problems.	ALPHA group health care providers identified 115 psychosocial problems in sub-sample of 98 women. Usual care providers identified 96 psychosocial problems in sub-sample of 129 women. OR 1.8, 95% CI 1.1 to 3.0). Providers in ALPHA group signif. more likely to express a high level of concern about psychosocial issues compared with providers in comparison group: 11.2% vs. 2.3%; p=0.0006).	Low response rate – 44% in intervention group and 56% in comparison group. Country: Canada	RCT	1-
McDonnell et al, 2006	1005	Pregnant women N=478	To determine the acceptability of antenatal enquiry about partner violence.	Women's views of acceptability	Most women (99.4%) found questions about IPV acceptable during antenatal consultations. 61 women (12.9%) reported experiencing IPV within the previous year.	Country: Eire	Cross-sectional survey	III
Webster and Holt, 2004	1007	Antenatal records N=937	Compare detection rate of IPV using 6-item self-completion Maternity Social Support Scale checklist and 4-item Domestic Violence Initiative form (questions asked by health care provider).	Detection of IPV	More partner violence was detected by the 6-item Maternity Social Support Scale checklist than by the Domestic Violence Initiative form. On 107 occassions partner violence was detected by the Maternity Social Support Scale and not by the Domestic Violence Initiative form.	Country: Australia	Retrospective audit of records	III
Lu et al, 2003	1001	Systematic review of 15 studies.	To investigate effectiveness and diagnostic accuaracy of antenatal risk assessment, health promotion and psychosocial interventions in preventing low birthweight.	Prevention and detection of low birthweight.	None of the risk assessments reviewed were able to identify more than two-thirds of women who went on to give birth pre-term. Most tools predicted less than 50% of pre-term births.	International	Systematic review	III

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					Findings for one of the most comprehensive risk assessment studies included in the review – the Cardiff Preterm Prediction Study: SSSensitivity: 24% and 18% (nulliparous women and multiparous women respectively) PPV: 29% and 33% (nulliparous women and multiparous women respectively)			
Carroli et al, 2001	1009	Systematic review of 7 studies.	To investigate the accuracy and effectiveness of antenatal risk assessment in preventing maternal mortality and serious morbidity.	Prediction of serious maternal morbidity.	Review of 5 studies of individual risk scoring showed that only 10-30% of women allocated to high risk groups experienced the adverse outcome that the risk assessment had identified. Review of 2 studies based on more complex scoring systems did not provide sufficient data to enable accuracy or effectiveness to be determined. Overall conclusion: scoring systems poor at discriminating between women at high risk and those at low risk.	Low income countries.	Systematic review	III
Gueorguieva et al, 2003	1002	Review of 166 372 medical records.	Evaluation of weighted risk scoring system in predicting very low birthweight babies compared with the Healthy Start screening tool.	Prediction of very low birthweight.	Positive likelihood ratio values for risk scoring sytems: 1,34 to 2.95.	Country: US	Retrospective cross-sectional study	III
Gomez and Young, 2002	1003	N=782 pregnant women	Evaluation of risk scoring system, the Risk Index, used at each AN visit.	Maternal and neonatal outcomes including: Low birthweight Caesarean section Low 5 minute Apgar score	Incidence of low birthweight: 13% in high-risk group vs. 1.4% in low-risk group; RR: 2.27, 95% CI 1.57 to 4.59. Sensitivity 40% Specificty 81% Caesarean section: 51% in high risk group vs. 23% in low-risk group; RR 2.2, 95% CI 1.77 to 2.70. Sensitivity 35% Specificity 86% Low Apgar score at 5 minutes: RR 4.1, 95% CI 1.2 to 13.9. Sensitivity: 50% Specificity: 81%	Country: US	Prospective evaluation	III
Stahl and Hundley, 2003	2010	N=111 pregnant women	To investigate the effect of being labelled as “high risk” on women’s psychological state during pregnancy.	Score on psychometric questionnaire to guage psychological state during pregnancy.	Group labelled as “high risk” significantly poorer psycholical scores than women labelled as “low risk” after adjusting for age difference: $R^2 = 0.07$, $F = 7.592$, 1 df, $p=0.007$.	Group labelled as “high risk” were significantly older than group labelled as “low risk”. Country:	Prospective cross-sectional study	III

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
						Germany		

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(2003 version)

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