Appendix E Review protocols

Chapter 4 Determining gestational age and chorionicity

Gestational age

Review question

What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?

a) Are the measurements and charts (crown–rump length, biparietal diameter and head circumference) used for dating singletons equally effective for twins or are there systematic errors introduced from using these charts?

	Details	Additional comments
Review question	What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?	
Subquestion	a) Are the measurements and charts (crown–rump length, biparietal diameter and head circumference) used for dating singletons equally effective for twins or are there systematic errors introduced from using these charts?	
Objectives	To determine whether ultrasound measurements and charts used to determine gestational age in singleton pregnancies are accurate when used in multiple pregnancies	
Language	English	
Study design	Randomised controlled trials (RCTs) Diagnostic accuracy studies Other comparative studies	
Status	Published papers	
Population	All pregnancies (singleton and multiple) resulting from *in vitro* fertilisation (IVF) or other assisted reproduction techniques	IVF/assisted reproduction used because this gives more accurate information about date of conception than does spontaneous pregnancy
Intervention	Dating by crown–rump length in multiple pregnancies Dating by biparietal diameter in multiple pregnancies Dating by head circumference in multiple pregnancies Oocyte retrieval or embryo transfer dates in multiple pregnancies	
Comparator	Dating by crown–rump length in singleton pregnancies Dating by bipareietal diameter in singleton	

	Details	Additional comments
	pregnancies	
	Dating by head circumference in singleton pregnancies	
	Oocyte retrieval or embryo transfer dates in singleton pregnancies	
Outcomes	Differences in dating or size of singleton versus multiple pregnancies	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies	
	Exclude quadruplet or higher-order pregnancies	
	Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	

Review question

What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?

b) Which fetus should be used for estimating gestational age in multiple pregnancies?

	Details	Additional comments
Review question	What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?	
Subquestion	b) Which fetus should be used for estimating gestational age in multiple pregnancies?	Should we date by the larger (largest) fetus, smaller (smallest) fetus or average fetal size?
Objectives	To assess the optimal strategy for dating multiple pregnancies	
Language	English	
Study design	Diagnostic accuracy studies	
	Other comparative studies	
Status	Published papers	
Population	All multiple pregnancies	
Intervention	Dating using ultrasound measurements (crown–rump length, biparietal diameter or head circumference) from the larger twin	If studies based on triplets are identified then comparisons between the triplets may be considered
Comparator	Dating using ultrasound measurements from the smaller twin (crown–rump length, biparietal diameter,	If studies based on triplets are identified then com-

	Details	Additional comments
	or head circumference) Dating using average ultrasound measurements (crown–rump length, biparietal diameter, or head circumference)	parisons between the triplets may be considered
Outcomes	1. Prediction of fetal growth restriction 2. Prediction of growth discordance 3. Prediction of twin complications/anomalies 4. Accuracy of dating	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Chorionicity

Review question

What is the optimal method to determine chorionicity in multiple pregnancies?

	Details	Additional comments
Review question	What is the optimal method to determine chorionicity in multiple pregnancies?	
Objectives	To establish the optimal ultrasound method of determining chorionicity in multiple pregnancies	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of classification strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Index test	1. Membrane thickness 2. Lambda (twin peak sign) 3. T-sign 4. Number of membrane layers 5. Number of placental sites 6. Other tests, including composite measures	Include all forms of trans-abdominal and transvaginal ultrasound scan (such as 3-D)

	Details	Additional comments
Reference standard	Postpartum examination of the placenta (gold standard for reference)	
Outcomes	Diagnostic test accuracy measures including sensitivity (detection rate), specificity, positive and negative predictive values, positive and negative likelihood ratios, and false positive rate	
	Effect of classification strategies on clinical outcomes if reported	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies	
	Exclude quadruplet and higher-order pregnancies	
	Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	

Chapter 5 General care

Information and emotional support

Review question

Is there benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period?

	Details	Additional comments
Review question	Is there benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period?	
Objectives	To critically appraise the benefit of providing additional information and emotional support to women with multiple pregnancies during the antenatal period	The emphasis in this question is on support, although information may also be offered
Language	English	
Study design	RCTs	
	Cohort studies	
	Case–control studies	
	Qualitative studies (observational, grounded theory, phenomenological studies)	
Status	Published papers	
Population	Twin and triplet pregnancies	
Intervention	1. Special antenatal classes	5. This could include: referral

	Details	Additional comments
	2. Educational support provided antenatally 3. Home visiting 4. Designated midwives 5. Offering additional referrals to other healthcare professionals 6. Breastfeeding support 7. Peer mentoring (matching women with others who have had multiple pregnancies for advice and support) 8. Specific interventions such as literature, graphics, cartoons, video loops	to a physiotherapist, dietitian, perinatal mental health team, health visitor or community midwife; mention of a multi-disciplinary team approach; or protocols for providing ante-natal care with a dedicated midwife, consultant obste-trician and ultrasonographer
Comparator	1. No intervention 2. Head-to-head comparisons of interventions	
Outcomes	1. Maternal morbidity (including anxiety and depression) 2. Perinatal and neonatal mortality 3. Perinatal and neonatal morbidity (including preterm delivery) 4. Breastfeeding 5. Maternal satisfaction 6. Maternal mortality	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Nutritional supplements

Review question

What additional (or different) dietary supplements are effective in improving maternal health and wellbeing (for example, reducing the risk of anaemia) in women with multiple pregnancy?

	Details	Additional comments
Review question	What additional (or different) dietary supplements are effective in improving maternal health and wellbeing (for example, reducing the risk of anaemia) in women with multiple pregnancy?	Additional or different refers to the comparison with women with singleton pregnancies and covered in the routine antenatal care guideline: see 'Antenatal care' (NICE clinical guideline 62)[1]
Objectives	To assess the effectiveness of dietary supplements used to improve maternal health and wellbeing in women with multiple pregnancies	
Language	English	
Study design	RCTs Cohort studies Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Intervention	1. Any dietary supplement containing calories, proteins, or micronutrients 2. Iron supplements 3. Vitamins (for example, vitamin D) 4. Folic acid 5. Calcium supplements 6. Homeopathic/herbal supplements 7. Magnesium supplements 8. Fish oil supplements	
Comparator	1. No intervention 2. Head-to-head comparisons of interventions	
Outcomes	1. Birthweight centile 2. Preterm delivery 3. Maternal anaemia 4. Pre-eclampsia 5. Nausea, vomiting, heartburn, or constipation in pregnancy 6. Maternal weight gain or loss 7. Maternal satisfaction (level of energy/tiredness) 8. Maternal stress levels, mood swings, anxiety, depression	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies	

	Details	Additional comments
	Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Diet and lifestyle advice

Review question

Is nutritional advice specific to multiple pregnancies effective in improving maternal and fetal health and wellbeing?

	Details	Additional comments
Review question	Is nutritional advice specific to multiple pregnancies effective in improving maternal and fetal health and wellbeing?	
Objectives	To assess the effectiveness of nutritional advice specific to twins and triplet pregnancies in improving the maternal and fetal health and wellbeing	
Language	English	
Study design	RCTs Cohort studies Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Intervention	1. Nutritional advice programme 2. Dietary information and education	
Comparator	No intervention (routine nutritional advice in antenatal care)	
Outcomes	1. Birthweight centile 2. Preterm delivery 3. Maternal anaemia 4. Pre-eclampsia 5. Nausea, vomiting, heartburn or constipation in pregnancy 6. Maternal weight gain or loss 7. Maternal satisfaction (level of energy/tiredness)	

	Details	Additional comments
	8. Maternal stress levels, mood swings, anxiety, depression	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies	
	Exclude quadruplet or higher-order pregnancies	
	Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
	Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	

Specialist care

Review question

Do specialist multiple pregnancy clinics improve outcomes in twin and triplet pregnancies?

	Details	Additional comments
Review question	Do specialist multiple pregnancy clinics improve outcomes in twin and triplet pregnancies?	
Objectives	To assess the effectiveness of specialist multiple pregnancy clinics in improving the outcomes (for example decreased morbidity and mortality) of twin and triplet pregnancies	
Language	English	
Study design	RCTs	
	Cohort studies	
	Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Intervention	Specialist clinics/care	
Comparator	Routine antenatal care	
Outcomes	1. Maternal morbidity (including anxiety and depression)	
	2. Perinatal and neonatal mortality	
	3. Perinatal and neonatal morbidity including preterm delivery	
	4. Breastfeeding	

	5. Maternal satisfaction 6. Maternal mortality	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Chapter 6 Fetal complications

Screening for chromosomal abnormalities

Review question

When and how should screening be used to identify chromosomal abnormalities in multiple pregnancy?

	Details	Additional comments
Review question	When and how should screening be used to identify chromosomal abnormalities in multiple pregnancies?	
Objectives	To determine what is the most accurate screening strategy for identifying chromosomal abnormalities in multiple pregnancy	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Index test	Ultrasound markers at 11–13^{+6} weeks: – nuchal translucency (alone or in combination with others) As part of a combination test: – nasal bone – tricuspid regurgitation – ductus venosus Doppler – combined test (first trimester): nuchal translucency, hCG, PAPP-A	Fetal Medicine Foundation (FMF): each twin has its own risk Wolfson: combined risk for whole pregnancy
	Maternal serum screening at 16–20 weeks:	The double and triple tests will be excluded as they have

	Details	Additional comments
	– quadruple (hCG, uE3, aFP, inhibin A) – integrated (11–14 weeks combined test +16–20 weeks aFP, UE3, inhibin A)	not been shown to be sufficiently accurate in singletons so are unlikely to have higher accuracy in multiple pregnancy
Reference standard	Karyotype, PCR or fluorescent in situ hybridisation (FISH) obtained by: • amniocentesis or chorionic villus sampling or fetal blood sample • postnatal blood sample or postmortem blood or skin sample	
Outcomes	1. Diagnostic accuracy of different screening techniques including: sensitivity (detection rate), specificity, positive and negative likelihood ratios and false positive and false negative rates, screen positive rate Report single pregnancy or individual fetal risk (and Wolfson/FMF criteria) 2. Maternal satisfaction/acceptability	National Screening Committee statement
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order multiple pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study size < 5 Exclude studies considering normal variants (at 18^{+0} to 20^{+6} weeks) only (choroid plexus cyst, dilated cisterna magna, echogenic foci in the heart, two vessel cord)	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Screening for structural abnormalities

Review question

When and how should screening be used to identify structural abnormalities in multiple pregnancies?

	Details	Additional comments
Review question	When and how should screening be used to identify structural abnormalities in multiple pregnancy?	
Objectives	To determine what is the most accurate screening strategy for identifying structural anomalies in multiple	

	Details	Additional comments
	pregnancy	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies	
Index test	Routine screening: Ultrasound scans at 11^{+0} to13^{+6} weeks Ultrasound scans at 18^{+0} to 20^{+6} weeks Ultrasound scans at 21^{+0} to 23^{+6} weeks Fetal echocardiogram (first and second trimester) Nuchal translucency at ultrasound scan at 11^{+0} to 13^{+6} weeks to identify risk of cardiac anomaly	
Reference standard	Postnatal clinical examination, postnatal ultrasound scan, CT scan, MRI scan, postnatal surgery or postmortem examination	This will include data from congenital anomaly registers if reported in published studies
Outcomes	1. Diagnostic accuracy of different screening techniques, including sensitivity (detection rate), specificity, positive and negative likelihood ratios for fetal structural and cardiac anomaly, overall and according to RCOG and NHS FASP* categories of anomaly Diagnostic accuracy for different anomalies will be reported as subgroups according to chorionicity where possible 2. Failure rate (including number of scans repeated) 3. Maternal satisfaction/acceptability	As in the routine antenatal care guideline – see 'Antenatal care' (NICE clinical guideline 62)[1]
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order multiple pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study size < 5 fetuses Exclude studies published before 1995	Consider sensitivity analysis comparing studies by date of publication Due to advances in ultrasound technology studies published before 1995 are unlikely to be clinically comparable to more recent studies
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual	

	Details	Additional comments
	(January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

* FASP: Fetal Anomaly Screening Programme

Monitoring for feto-fetal transfusion syndrome

Review question

When and how should screening be used to identify feto-fetal transfusion syndrome in multiple pregnancy?

	Details	Additional comments
Review question	When and how should screening be used to identify feto-fetal transfusion syndrome in multiple pregnancy?	Also known as twin-to-twin transfusion syndrome (TTTS) in twin pregnancy
Objectives	To determine what is the most accurate screening strategy for feto-fetal transfusion syndrome in twin and triplet pregnancies	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Monochorionic twin pregnancies and triplet pregnancies containing a monochorionic twin pair	
Index test	Ultrasound scan at 11–13^{+6} weeks: • discrepant crown–rump length • discrepant nuchal translucency • abnormal ductus venosus Doppler (in combination or individually)	
	Ultrasound scan at 11–26 weeks: • growth discordancy (fetal biometry including head circumference, abdominal circumference, femur length and estimated fetal weight) • amniotic fluid discordancy (amniotic fluid index or maximum pool depth) • Doppler studies (umbilical artery Doppler, ductus venosus Doppler) • placental anastomoses • tricuspid regurgitation • absent visualisation of donor bladder • intertwining/infolding of the membrane The optimum frequency and gestational age of ultrasound scans should be assessed	Upper limit of 26 weeks to detect feto-fetal transfusion syndrome (not severe if detected after this). Monitoring after 26 weeks will be considered in review question on screening to detect IUGR

	Details	Additional comments
	The above tests in isolation or combination will be considered	
Reference standard	Ultrasound diagnosis according to Quintero criteria or the need for treatment for feto-fetal transfusion syndrome, pregnancy loss due to feto-fetal transfusion syndrome, or neonatal evidence of feto-fetal transfusion syndrome	Optimum timing and frequency of diagnostic scans
Outcomes	1. Diagnostic accuracy of different screening techniques including sensitivity (detection rate), specificity, positive and negative likelihood ratios and false positive rate 2. Subsequent midtrimester loss rate in population	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order multiple pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study size < 5 pregnancies	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Monitoring for intrauterine growth restriction

Review question

What is the optimal screening programme to detect intrauterine growth restriction in multiple pregnancies?

	Details	Additional comments
Review question	What is the optimal screening programme to detect IUGR in multiple pregnancies?	
Objectives	To determine what is the most accurate screening strategy for IUGR in multiple pregnancy	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies including monochorionic and dichorionic twin pregnancy and triplet pregnancy	
Index test	Abdominal palpation and symphysio-fundal height	

	Details	Additional comments
	measurement Ultrasound scan measurement of fetal biometry including any of the following alone or in combination/ratio: • abdominal circumference • head circumference • femur length • biparietal diameter Estimated fetal weight based on formulae combining two or more of the above (including difference in estimated fetal weight of each twin ≥ 15%) Plotting symphysio-fundal height, estimated fetal weight and fetal biometric measurements on standard population or customised growth charts, twin-specific charts, individual measurements or growth velocity Amniotic fluid volume: • amniotic fluid index • maximum pool depth • discordancy between twins in amniotic fluid volume Doppler studies: • umbilical artery and vein • middle cerebral artery • ductus venosus Timing and frequency of ultrasound scanning Composite screening strategies	
Reference standard	Recognised reference standard for SGA or IUGR* including birthweight centiles by gestational age as reported in studies, standard deviation score (according to population or customised or twin specific growth charts) Ponderal index, skin fold thickness, head circum-ference/abdominal circumference Intertwin weight discordance (any reported > 15%)	
Outcomes	Diagnostic accuracy of different screening techniques including sensitivity (detection rate), specificity, positive and negative likelihood ratios and false positive rate. Maternal satisfaction/acceptability including anxiety/depression	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order multiple pregnancies Exclude studies that do not report results specifically	

	Details	Additional comments
	for twin and/or triplet pregnancies Exclude study size < 5 pregnancies Exclude feto-fetal transfusion cases Exclude the following biometric measurements when used as an index test: abdominal diameter, trunk area, thigh circumference Exclude studies reporting absolute weights where percentage difference or centiles cannot be calculated Exclude studies that do not correct for gestational age	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

SGA: small for gestational age; IUGR: intrauterine growth restriction

Chapter 7 Maternal complications

Hypertension

Review question

What is the optimal screening programme to detect hypertension in multiple pregnancy in the antenatal period?

	Details	Additional comments
Review question	What is the optimal screening programme to detect hypertension in multiple pregnancy in the antenatal period?	
Objectives	To determine what is the most accurate strategy for screening and detection of hypertensive disorders in multiple pregnancy	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies including monochorionic and dichorionic twin pregnancy and triplet pregnancy	
Index test	History: • nulliparous • age 40 years or older • personal or family history of pre-eclampsia • BMI ≥ 35 (at booking)	Evidence in relation to history may include but will not be limited to the items listed and may involve different thresholds (thresholds shown are those used in routine antenatal care – see 'Antenatal care' (NICE

	Details	Additional comments
	• preexisting vascular disease • time interval between pregnancies Blood pressure at booking Maternal blood tests: • alpha feto-protein (aFP) • fetal DNA • B-human hCG • serum fibronectin (total and cellular) • haemoglobin/haematocrit • oestriol • uric acid • biomarkers, such as vascular endothelial growth factor (VEGF), soluble fms-like tyrosine kinase 1 (sFlt-1), placenta protein 13 (pp-13), soluble endoglin Maternal urine tests: • urinary calcium excretion • urine calcium:creatinine ratio • urinary protein (24-hour/spot tests for total proteinuria, albuminuria, albumin:creatinine ratio. Kallikrein, sodium docecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) proteins) Maternal ultrasound: • uterine artery Doppler (notching-unilateral, bilateral, pulsatility index, resistance index, other ratios) in first or second trimester Integrated test: • Doppler plus serum markers Strategies for measuring blood pressure: • booking blood pressure • frequency of blood pressure measurements • ambulatory versus conventional • pregnant woman home monitoring versus conventional Composite screening strategies	clinical guideline 62)[1] Ensure consistency with 'Hypertension in pregnancy' (NICE clinical guideline 107)[2] in terms of definitions of hypertensive disorders in pregnancy
Reference standard	Pre-eclampsia: hypertension ≥ 140/90 mmHg with proteinuria (total protein ≥ 300mg in 24-hour urine collection, ≥ 30 mg/dl single sample or ≥ +1 on dipstick, arising for the first time after 20 weeks' gestation with or without generalised oedema) Gestational hypertension	

	Details	Additional comments
Outcomes	1. Diagnostic accuracy of different screening techniques including sensitivity (detection rate), specificity, positive and negative likelihood ratios and false positive rate 2. Effect of different screening techniques on clinical outcomes if reported	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher order multiple pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study size < 5 pregnancies	
Search strategies	See Appendix F	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Chapter 8 Preterm birth

Predicting the risk of preterm birth

Review question

What is the optimal screening programme to predict the risks of spontaneous preterm delivery?

	Details	Additional comments
Review question	What is the optimal screening programme to predict the risks of spontaneous preterm delivery?	
Objectives	To establish the optimal screening programme (screening methods and their frequency) performed routinely in women with multiple pregnancy to predict the risks of spontaneous preterm delivery	
Language	English	
Study design	Diagnostic accuracy studies including RCTs of screening strategies, cohort studies	
Status	Published papers	
Population	Twin and triplet pregnancies (not symptomatic, not in labour) • All twin pregnancies (monochorionic and dichorionic) • All triplet pregnancies	
Index test or	Screening methods:	Screening based on fundal height and relaxin will not be

	Details	Additional comments
intervention	• cervical length measurement • fibronectin test • ambulatory uterine activity monitoring • previous obstetric history (previous preterm labour [< 37 completed weeks], cervical surgery, midtrimester loss [< 24 weeks]) Interventions: • additional antenatal care contacts Composites of screening methods, for example combined fibronectin test and cervical length measurements	considered
Reference standard/comparator	Reference standard: preterm delivery Comparator: no intervention (routine antenatal care)	
Outcomes	Diagnostic test accuracy measures including sensitivity (detection rate), specificity, positive and negative predictive values, positive and negative likelihood ratios, and false positive rate.) 1. Prediction of spontaneous preterm birth 2. Prediction of spontaneous preterm labour Effect of screening strategies on clinical outcomes if reported. 1. Level of maternal anxiety/stress 2. Hospital admission/transfer after screening	Compare methods/head-to-head comparisons
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude studies that involve women in labour or requiring imminent birth	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Preventing preterm birth

Review question

What interventions are effective in preventing spontaneous preterm delivery in multiple pregnancy, including bed rest, progesterone and cervical cerclage?

	Details	Additional comments
Review question	What interventions are effective in preventing spontaneous preterm delivery in multiple pregnancy, including bed rest, progesterone and cervical cerclage?	
Objectives	To assess the effectiveness in multiple pregnancy of interventions in general use to prevent spontaneous preterm birth	
Language	English	
Study design	RCTs Cohort studies Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies (not symptomatic, nor in labour, nor requiring imminent birth for maternal or fetal indications. • Twin pregnancies (monochorionic and dichorionic). • Triplet pregnancies	The focus is on preventing spontaneous labour in twins and triplets in women who are not in labour when they are treated
Interventions	1. Bed rest 2. Progesterone and progestagens 3. Cervical cerclage 4. Tocolytics – betamimetics – ritodrine – magnesium sulphate – nifedipine • Sexual abstinence	
Comparator	1. No intervention 2. Head-to-head comparisons of interventions	
Outcomes	Primary outcomes 1. Neonatal: – spontaneous preterm birth – gestational age at delivery – perinatal mortality and morbidity 2. Maternal: – length of stay – maternal side effects (infection, haemorrhage, drug effects, tachycardia, caesarean section) Secondary outcomes	Not interested in iatrogenic preterm birth (for example, babies born early because the woman had pre-eclampsia and required elective early delivery by induction of labour)

	Details	Additional comments
	1. Neonatal unit admission 2. Low birthweight and very low birthweight 3. Respiratory distress syndrome 4. Intraventricular haemorrhage 5. Necrotising enterocolitis 6. Neonatal length of stay 7. Maternal quality of life 8. Maternal satisfaction	Length of stay refers to length of stay in hospital (neonatal intensive care unit or other high dependency unit)
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies separately Exclude studies in which interventions are given to women in labour or women requiring imminent birth Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions	Include studies involving women with complications (for example hypertension or gestational diabetes) because healthcare professionals may still offer these interventions to such women and in RCTs they should balance out across treatment groups
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Untargeted corticosteroids

Review question

Is routine/elective antenatal corticosteroid prophylaxis effective in reducing perinatal morbidity, including neonatal respiratory distress syndrome, necrotising colitis and intraventricular haemorrhage, in multiple pregnancy?

	Details	Additional comments
Review question	Is routine/elective antenatal corticosteroid prophylaxis effective in reducing perinatal morbidity, including neonatal respiratory distress syndrome, necrotising colitis and intraventricular haemorrhage, in multiple pregnancy?	
Objectives	To assess the effectiveness of routine antenatal administration of corticosteroids to women with multiple pregnancies in reducing the incidence of complications of prematurity, such as respiratory distress syndrome, necrotising enterocolitis, and intraventricular haemorrhage	Routine refers to situations when imminent preterm birth is not planned or predicted
Language	English	

	Details	Additional comments
Study design	RCTs Cohort studies Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies where the women are not already in labour	
Intervention	Any corticosteroid	
Comparator	• No intervention • Targeted use • Different corticosteroids • Same corticosteroid (frequency of dose as well as length of course) • Timing of corticosteroid administration	Targeted use refers to use in women at high risk of preterm birth over and above having a multiple pregnancy but not in labour
Outcomes	1. Perinatal and neonatal mortality 2. Long-term neurodevelopmental outcomes 3. Respiratory distress syndrome 4. Intraventricular haemorrhage 5. Necrotising enterocolitis 6. Maternal hypertension and/or gestational diabetes 7. Maternal satisfaction 8. Neonatal length of stay 9. Birthweight for gestational age 10. Composite outcomes based on the above	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher-order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude studies in which corticosteroids were given to women in labour or to women requiring imminent birth	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

Chapter 9 Indications for referral to a tertiary level fetal medicine centre

Review question

What are the clinical indications for referral to subspecialist services?

	Details	Additional comments
Review question	What are the clinical indications for referral to subspecialist services?	Include consideration of advice to subspecialist services about referring back to routine multiple pregnancy care Important to consider chorio-nicity for this question
Objectives	To determine whether discordant fetal growth, single fetal death, fetal anomaly, triplet pregnancy and monochorionic monoamniotic pregnancy are indications for referral to subspecialist services	Management of pregnancies with feto-fetal transfusion syndrome is outside the scope of the guideline
Language	English	
Study design	RCTs Cohort studies Case–control studies	
Status	Published papers	
Population	Twin and triplet pregnancies with single fetal death, discordant fetal anomaly, discordant fetal growth Monochorionic monoamniotic pregnancies	
Intervention	Referral for specialist care	
Comparator	No referral/intervention	
Outcomes	1. Stillbirth 2. Neonatal mortality 3. Neonatal morbidity (especially respiratory and neurological) 4. Admission to a neonatal unit 5. Maternal satisfaction, costs of travelling and so on 6. Maternal morbidity (such as postpartum haemorrhage requiring blood transfusion, hypertension) 7. Emergency caesarean section 8. Apgar score 9. Birthweight 10. Meconium-stained liquor 11. Maternal anxiety, depression, quality of life, pain 12. Breastfeeding	
Other criteria for inclusion/exclusion	Exclude non-human studies	

	Details	Additional comments
of studies	Exclude quadruplet or higher-order pregnancies	
	Exclude studies that do not report results specifically for twin and/or triplet pregnancies	
	Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009)	
	A list of excluded studies will be provided following weeding	
	Evidence tables and an evidence profile will be used to summarise the evidence	

Chapter 10 Timing of birth

Review question

What is the optimal timing of delivery in women with uncomplicated multiple pregnancies?

	Details	Additional comments
Review question	What is the optimal timing of delivery in women with uncomplicated multiple pregnancies?	GDG to consider what is meant by preterm birth in multiple pregnancies
		Need to consider mono-chorionic and dichorionic pregnancies separately
Objectives	To determine optimal timing of delivery in women with uncomplicated multiple pregnancies	Separate analyses to be presented for monochorionic and dichorionic twin pregnancies
Subquestions	a) What is the gestational age profile for spontaneous delivery in twin/triplet pregnancies?	All subquestions to be addressed through a single search for evidence
	b) What is the perinatal mortality and morbidity in spontaneous or uncomplicated delivery in twin/triplet pregnancies at different gestational ages?	
	c) What is the effectiveness of elective delivery in multiple pregnancy?	
Language	English	
Study design	RCTs	
	Cohort studies	
	Case–control studies	
	Cross-sectional studies	
Status	Published papers	

	Details	Additional comments
Population	Uncomplicated twin and triplet pregnancies (monochorionic and dichorionic)	
Intervention	Elective delivery by gestational age (for subquestion c only)	Document mode of delivery in each included study
Comparator	No elective delivery (for subquestion c only)	
Outcomes	1. Stillbirth and perinatal/neonatal mortality 2. Neonatal morbidity (such as respiratory problems, admission to a neonatal unit, neonatal encephalopathy, infection) 3. Maternal morbidity (such as postpartum haemorrhage requiring blood transfusion, hypertension, infection) 4. Operative delivery (caesarean section, instrumental delivery) **5.** Apgar score **6.** Birthweight	
Other criteria for inclusion/exclusion of studies	Exclude non-human studies Exclude quadruplet or higher order pregnancies Exclude studies that do not report results specifically for twin and/or triplet pregnancies Exclude study designs lower in the hierarchy of evidence if systematic reviews and/or RCTs are available for the same interventions Exclude pregnancies with any complications which would lead to elective preterm delivery (for example feto-fetal transfusion syndrome, IUGR, pre-eclampsia)	
Search strategies	See separate document	
Review strategies	Studies will be assessed for study quality according to the process described in the NICE guidelines manual (January 2009) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	

References

1. National Collaborating Centre for Women's and Children's Health. Antenatal care: routine care for the healthy pregnant woman. 2008. London, RCOG Press.

2. National Collaborating Centre for Women's and Children's Health. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2010. London, RCOG Press.