Appendix H Evidence tables

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?

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Martins 2009[31] Country: Brazil Study design: Prospective cohort Study dates: No details reported Aim of study: *Primary*: To examine whether fetal volume (FV) and crown-rump length (CRL) are different in singleton and twin	Population: N = 40 fetuses 20 twin and 20 singleton fetuses with gestational age 52 – 73 days Inclusion criteria: In vitro fertilisation and embryo transfer with a positive pregnancy test, maternal age ≤ 35 years, maternal BMI ≤30kg/m^2, acceptance to join research Exclusion criteria: Absence from one or more of four evaluation dates Other details: Gestational age determined	Investigation : CRL in twin fetuses Comparison: CRL in singleton fetuses Methods described adequately? Yes 3-D ultrasound (US) scans performed weekly from 52 days to 73 days and for each fetus in a twin pregnancy CRL measured using the longitudinal plane of the fetus in the 3-D US multiplanar view Equipment details reported Details of charts used not reported	1) Crown-rump length (mm) CRL at 52 days Twins = 11.48 ± 0.22 P = 0.45 Singletons = 11.74 ± 0.27 CRL at 59 days Twins = 19.36 ± 0.31 P = 0.85 Singletons = 19.26 ± 0.43 CRL at 66 days Twins = 26.51 ± 0.33 P = 0.91 Singletons = 26.44 ± 0.57 CRL at 73 days Twins = 35.87 ± 0.54 P = 0.76 Singletons = 36.19 ± 0.90 2) Weekly relative increase in CRL (mm) CRL at 5 –59 days Twins = 0.69 ± 0.03 P = 0.33 Singletons = 0.69 ± 0.02 CRL at 59 – 66 days Twins = 0.37 ± 0.02 P = 0.90 Singletons = 0.38 ± 0.02	Funding: No details reported Limitations: Main bias will arise from operator and equipment, and a small sample size N=10 twin pregnancies in which both fetuses measured (not independent) Categorical analysis in small blocks of gestational age, rather than unified analysis of repeated measurements Confidence intervals for estimated effect size not reported

Study details	Participants	Investigation	Outcome measures and results	Comments
pregnancies *Secondary :* To evaluate the comparative accuracy of FV and CRL to determine gestational age	by adding 14 days to the number of days between oocyte retrieval and date of the ultrasound scan All twins were dichorionic Details of maternal ethnicity not reported	Operator number/experience: A single operator performed all scans	CRL at 66 – 73 days Twins = 0.35 ± 0.02 P = 0.90 Singletons = 0.37 ± 0.02 All data reported as mean ± standard error (SE)*	* Results reported by authors as mean ± SD but actually mean ± SE Probably the same participants as in Martins 2008[32] but at earlier gestational age
First author, year: Martins 2008[32] Country: Brazil Study design: Prospective cohort Study dates: No details reported Aim of study: To compare crown-rump length (CRL) and fetal head and trunk (HT) volume between singletons and twins conceived after in vitro fertilisation (IVF)	Population: N = 40 fetuses 20 twin and 20 singleton fetuses with gestational age 73 – 101 days Inclusion criteria: In vitro fertilisation and embryo transfer with a positive pregnancy test performed 2 weeks after transfer, maternal age ≤ 35 years, maternal BMI ≤25kg/m^2, first IVF cycle, absence of uterine pathologies and acceptance to join research Exclusion criteria: None specified Other details: Gestational age determined by adding 14 days to the number of days between oocyte retrieval and date of the ultrasound scan No details of maternal	Investigation: CRL in twin fetuses Comparison: CRL in singleton fetuses Methods described adequately? Yes 3-D ultrasound (US) scans performed weekly from 73-101 days; for twins, a scan was performed for each fetus CRL measured using the longitudinal plane of the fetus in the 3-D US multiplanar view Equipment details reported Details of charts used not reported Operator number/experience A single operator performed all scans	1) Crown-rump length (mm) CRL at 73 days Twins = 35.9 ± 2.4 P = 0.76 Singletons = 36.2 ± 4.0 CRL at 80 days Twins = 50.8 ± 2.8 P = 0.62 Singletons = 50.4 ± 3.0 CRL at 87 days Twins = 63.4 ± 2.3 P = 0.19 Singletons = 64.4 ± 2.3 CRL at 94 days Twins = 75.4 ± 2.5 P = 0.41 Singletons = 74.7 ± 2.7 CRL at 101 days Twins = 85.2 ± 5.5 P = 0.83 Singletons = 85.6 ± 5.5 2) Weekly relative increase in CRL (mm) CRL at 73 – 80 days Twins = 0.42 ± 0.11 P = 0.57 Singletons = 0.40 ± 0.11 CRL at 80 – 87 days Twins = 0.25 ± 0.06 P = 0.11 Singletons = 0.28 ± 0.06 CRL at 87 – 94 days Twins = 0.19 ± 0.05 P = 0.06 Singletons = 0.19 ± 0.04 CRL at 94 – 101 days	Funding: No details reported Limitations: Main bias will arise from operator and equipment, and a small sample size Confidence intervals for estimated effect size not reported Probably the same participants as in Martins 2009[31] but at later gestational age

Study details	Participants	Investigation	Outcome measures and results	Comments
	ethnicity or chorionicity of twins reported		Twins = 0.13 ± 0.05 P = 0.31 Singletons = 0.15 ± 0.05 All data reported as mean ± SD	
First author, year: Gardosi 1997[30] Country: UK Study design: Retrospective (regression analysis) Study dates: Database of consecutive singleton and twin pregnancies resulting from assisted reproduction techniques (ART) in 1994 and 1995 was studied Aim of study: To investigate the size of singleton versus twin pregnancies at the time of a second trimester dating scan	Population: N = 86 fetuses Fetuses were from 63 pregnancies resulting from ART, comprising 40 singletons and 46 twins Inclusion criteria: Pregnancy achieved by ART in 1994 and 1995 in the Nottingham University Research and Treatment Unit in Reproduction, mid-trimester ultrasound results from all 25 booking hospitals, written maternal consent to analyse data Exclusion criteria: Pregnancies with missing data Other details: Gestational age calculated by adding 14 days to the conceptual age at scan which was the interval between the day of fertilisation (or frozen embryo replacement) and the day of the ultrasound scan No details of maternal	Investigation: Common regression line derived for 85 datapoints for biparietal diameter (BPD) (39 in singletons, 46 in twins) between 111 and 173 days' gestation, and residuals calculated for singletons and twins Methods described adequately? Yes Ultrasound biometry was conducted as part of routine mid-trimester scans in 25 different hospitals by ultrasonographers who were unaware of conception dates In pregnancies where more than one second trimester scan had been performed, the measurements at the time of the detailed structural scan were taken for analysis Details of charts used not reported	Comparison of difference in actual and estimated BPD (from regression line) in twins and singletons Twins: N = 46 Mean residual = –0.12 mm SD = 2.07 mm Singletons: N = 39 Mean residual = 0.14 mm SD = 2.21 mm Difference between means = 0.26 mm Standard Error = 0.46 mm P = 0.57 95% CI -0.66 to 1.18	Funding: No details reported Limitations: Main bias will arise because this is a retrospective study analysing data from a database Also, as data were obtained from 25 different hospitals, bias may arise in measurements from different operators of differing experience using different equipment Sample size may also be an issue

Study details	Participants	Investigation	Outcome measures and results	Comments
	ethnicity or chorionicity of twins reported			
First author, year: Chervenak 1998[35] Country: USA Study design: Retrospective (regression analysis) Study dates: *Singletons:* January 1993 - June 1996 *Twins and triplets:* July 1990 - December 1994 Aim of study: To analyse accuracy of fetal biometry (biparietal diameter [BPD], head circumference, abdominal circumference and femur length) at 14-22 weeks for prediction of gestational age in singleton, twin, and triplet pregnancies resulting from in vitro fertilisation (IVF)	Population: N = 238 women 152 singleton, 67 twin and 19 triplet gestations Inclusion criteria: IVF conception, initial second-trimester ultrasound (US) scan performed 14-22 weeks' gestation based on menstrual age (day of egg retrieval and fertilisation plus 14 days) For singletons, delivery at > 37 weeks, birthweight >2500 g with no congenital abnormalities For multiple pregnancies, delivery at > 24 weeks, alive at birth with no congenital abnormalities Exclusion criteria: Not reported Other details: No details of maternal ethnicity or chorionicity of twins/triplets reported	Investigation : Stepwise multiple regression used to derive a dating formula in singleton pregnancies using BPD, femur length, head circumference and abdominal circumference* Formula was compared with 38 previously published formulae, and then applied to twin and triplet populations Methods described adequately? Yes Ultrasound biometry conducted in a single ultrasound unit as part of routine mid-trimester examination (14-22 weeks) Equipment details reported Details of charts not reported Operator number/experience: All scans were performed by one of five sonographers (under supervision of a sonologist) **Best fitting model for estimated gestational age = [51.68 + 2.324* head circumference + 2.092 * abdominal circumference + 5.18 * femur length]*	Differences in dating of twins and triplets Mean difference in dating of twins versus singletons i) using the prediction formula and applying the maximum of each biometric parameter in the formula = 0.8 days ii) using the prediction formula and applying the minimum of each biometric parameter in the formula = −1.3 days iii) using the prediction formula and applying the average of maximum and minimum of each biometric parameter in the formula = −0.3 days Mean difference in dating of triplets versus singletons i) using the prediction formula and applying the maximum of each biometric parameter in the formula = 0.8 days ii) using the prediction formula and applying the minimum of each biometric parameter in the formula = −3.4 days iii) using the prediction formula and applying the average of maximum and minimum of each biometric parameter in the formula = −1.3 days	Funding: No details reported Limitations: Main limitation is that it is a cross-sectional study Bias may also arise from different operators with differing experience and different equipment Study does not use conventional ultrasound formulae to assess gestational age when comparing singleton and multiple pregnancies

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Wennerholm 1998[36] Country: Sweden Study design: Retrospective cohort study (reviewing delivery records) Study dates: January 1990 - December 1996 Aim of study: To compare the gestational age calculated from day of oocyte retrieval to that from ultrasound (US) measurements (biparietal diameter [BPD with or without femur length) in the second trimester of pregnancies resulting from in vitro fertilisation (IVF)	Population: N = 337 pregnancies 253 singleton pregnancies and 84 twin pregnancies (168 twins) Inclusion criteria: Women with IVF singleton and twin pregnancies who received antenatal care and were delivered at Sahlgrenska University Hospital between 1990 and 1996 All women had at least one first-trimester US scan Exclusion criteria: Women with fetuses with congenital malformations, unobtainable femur length, presence of more than one gestational sac at first trimester scan Other details: Gestational age was calculated from the day of oocyte retrieval and converted into menstrual age by adding 14 days All participants were healthy Swedish women; no details of chorionicity reported for twin pregnancies	Investigation: Gestational age calculated from formula* based on BPD in twins Comparison: Gestational age calculated from formula* based on BPD in singletons Methods described adequately? Yes US measurements performed using modern, commercially available real-time scanners For each parameter, the average of three measurements was used Details of charts not reported Operator number/experience: US measurements performed by specially trained midwives * Gestational age (days) = [BPD × 2.10 + 39.1]	Difference in dating of twins versus singletons - gestational age (GA) calculated using formula based on biparietal diameter measurements Twins: Mean GA = 116.8 days SD = 6.1 days Singletons: Mean GA = 118.9 days SD = 9.0 days Difference between means stated by the authors to be not statistically significant; no p-values or confidence intervals reported Difference in dating of twins versus singletons - gestational age (GA) calculated using day of oocyte retrieval Twins: Mean GA = 120.9 days SD = 8.6 days Singletons: Mean GA = 118.2 days SD = 5.3 days Difference between means stated by the authors to be not statistically significant; no p-values or confidence intervals reported	Funding: Study supported by Göteborg Medical Society and the Swedish Medical Research Council Limitations: Main limitation is the retrospective nature of the study Bias may also arise from different operators with differing experience and different equipment

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Dias 2010[33] Country: UK Study design: Retrospective cohort study Study dates: June 1997 - October 2009 Aim of study: To assess the performance of validated singleton crown-rump length (CRL) formulae in dating twin pregnancies at 11-14 weeks of pregnancy	Population: N = 376 pregnancies 266 singleton pregnancies and 110 twin pregnancies Inclusion criteria: Dichorionic twin and singleton pregnancies resulting from IVF or intracytoplasmic sperm injection (ICSI), seen for routine obstetric care between June 1997 and October 2009; only scans done between 11 and 14 weeks of pregnancy were included Exclusion criteria: Monochorionic twin pregnancies Other details: Gestational age was calculated by using the embryo transfer date as a proxy for the date of conception. IVF/ICSI singleton pregnancies were used for comparison to control for any variation in dating between and/or early fetal growth that might occur in pregnancies achieved by ART	Investigation: Mean differences between actual gestational ages and gestational ages estimated from CRL measurements were derived for singletons and twins. Three different CRL-based dating formulae* were used to estimate gestational age Methods described adequately? Yes A single CRL measurement was taken with the fetus in a neutral position. For each foetus, the gestational age calculated from the date of conception was compared with the estimated gestational age from foetal size (CRL) using three different formulae Operator number/experience: Scans were only carried out by sonographers who were certified for first-trimester ultrasound assessment * 1. Robinson: GA = 8.052 * √(CRL * 1.037) + 23.73 2. Rossavik: GA = 49.5 + 0.6 * CRL 3. Von Kaisenberg: GA = 49.1115 + 0.5954 * CRL	Mean difference between actual gestational age and estimated gestational age using Robinson's formula Singleton: 1.41 (1.15 to 1.68) days Bigger twin: 2.4 (2.4 to 2.6) days Smaller twin: 0.91 (0.55 to 1.30) days using Rossavik's formula Singleton: 0.14 (0.01 to 0.28) days Bigger twin: 1.27 (1.05 to 1.5) days Smaller twin: -0.51 (-0.30 to -0.72)days using Von Kaisenberg's formula Singleton: -0.54 (-0.41 to -0.67) days Bigger twin: 0.58 (0.36 to 0.8) days Smaller twin: -1.18 (-0.97 to -1.4) days Mean difference between actual CRL measurement and CRL estimated from date of conception (i.e. from IVF history) using Robinson's formula Singleton: 2.72 (2.49 to 2.95) mm Bigger twin: 4.7 (4.4 to 5.1) mm Smaller twin: 1.77 (1.4 to 2.1) mm using Rossavik's formula Singleton: 0.24 (1.8 to 2.5) mm Bigger twin: 2.1 (0.01 to 0.46) mm Smaller twin: −0.86 (−0.5 to −1.2) mm using Von Kaisenberg's formula Singleton: −0.91 (−0.7 to −1.13) mm Bigger twin: 0.98 (0.6 to 1.35) mm Smaller twin: −2.0 (−1.6 to −2.4) mm	Funding: There was no funding for the study Limitations: Main limitation is the retrospective nature of the study A further limitation may be the fact that the ultrasonographers had prior knowledge of the dates of conception
First author, year: Dias 2010[34]	Population: N = 376 pregnancies	Investigation: Observed fetal biometry for	Difference in mean biometry z-scores	Funding: Not reported

Study details	Participants	Investigation	Outcome measures and results	Comments
Country: UK Study design: Retrospective case control study Study dates: June 1999 – March 2010 Aim of study: To determine whether singleton head circumference formulae can be used to accurately date twin pregnancy	269 singleton pregnancies and 119 twin pregnancies Inclusion criteria: Non-anomalous dichorionic twins and singletons with a second trimester ultrasound between 16 and 26 weeks. Pregnancies conceived by IVF or intracytoplasmic sperm injection. Women seen in routine obstetric setting between June 1999 and March 2010 Exclusion criteria: Monochorionic twin pregnancies (n= 8) Other details: Expected age was calculated by using the embryo transfer date as a proxy for the date of conception (day 14) Mean gestational age at inclusion: Singletons: 21.7 ±1.1 weeks Twins: 21.4 ±1.2 weeks P=0.56	different head circumference, femur length and TCD were compared with expected fetal size for gestational age Mean differences between actual gestational ages and gestational ages estimated from measurements were derived for singletons and twins. Three different measurement formulae for head circumference and femur length were used to estimate gestational age (Chitty et al, Verburg et al, Salomon et al) Operator number/experience: Scans were only carried out by trained sonographers Expected age was calculated by using the embryo transfer date as a proxy for the date of conception (day 14)	Head circumference formulae: Singleton vs. bigger twin p=0.01 Singleton vs. smaller twin p< 0.005 Singleton vs. average twin size p=1 Femur length formulae: Singleton vs. bigger twin p=0.7 Singleton vs. smaller twin p<0.005 Singleton vs. average twin size p=1	Limitations: Potential overlap with other Dias 2010 study[33] Main limitation is the retrospective nature of the study

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?

Study Details	Participants	Investigation	Outcome Measures and Results	Comments
First author, year: Salomon 2005[37] Country: UK Study design: Prospective cohort Study dates: June 2001 to Feb 2004 Aim of study: To clarify the incidence and outcome of intertwin growth discrepancy in relation to pregnancy dating and other biometric parameters	Population: N = 182 twin pregnancies 47 pregnancies resulted from assisted reproduction techniques (ART) Inclusion Criteria: Twins conceived spontaneously or following ART, fetuses with crown–rump length 45−84 mm at first trimester ultrasound, oral informed consent obtained from parents Exclusion Criteria: Fetuses with crown–rump length less than 45 mm or greater than 84mm at first trimester ultrasound scan Other Details: Twins (conceived spontaneously or following ART) were evaluated at 11-14 weeks' gestation and onwards at 2-4 week intervals Of the 182 pregnancies, 20 (11%) were monochorionic and 162 (89%) dichorionic; details of chorionicity of the	Investigation : Gestational age was calculated individually for each fetus Among ART pregnancies, the correlation between actual gestational age (determined by date of oocyte retrieval) and that calculated from the crown–rump lengths of the longer and shorter twins, respectively, were analysed Methods described adequately? Yes Measurements obtained using transabdominal ultrasound (US) examination except when technical difficulties indicated transvaginal US examination Crown–rump length measured to nearest mm in a sagittal section with head of the fetus in a neutral position Equipment details reported Details of charts not reported	Prediction of growth discordance between the larger and smaller twin based on crown–rump length measurement Mean difference between larger and smaller twins = 3.4 mm SD = 3.18 mm Median difference = 3 mm Maximum difference = 17.3 mm 90th percentile = 8 mm 95th percentile = 9.8 mm Accuracy of dating among twins from ART pregnancies based on dating by crown–rump length measurement compared to actual gestational age using the longer twin Mean difference using the larger twin = 1.45 days SD = 2.17 days $P < 10^{-4}$ Accuracy of dating among twins from ART pregnancies based on dating by crown–rump length measurement compared to actual gestational age using the shorter twin Mean Difference = 0.06 days SD = 2.21 days P = 0.84	Funding: No details reported Limitations: Main limitation is the small sample size

Study Details	Participants	Investigation	Outcome Measures and Results	Comments
	47 ART pregnancies or ethnicity of all mothers not reported			
First author, year: Chervenak 1998[35] Country: USA Study design: Retrospective (regression analysis) Study dates: Singletons: January 1993 - June 1996 Twins and triplets: July 1990 - December 1994 Aim of study: To analyse accuracy of fetal biometry (biparietal diameter [BPD], head circumference, abdominal circumference and femur length) at 14-22 weeks for prediction of gestational age in singleton, twin, and triplet pregnancies resulting from in vitro	Population: N = 238 women 152 singleton, 67 twin and 19 triplet gestations Inclusion Criteria: IVF conception, initial second-trimester ultrasound (US) scan performed 14-22 weeks' gestation based on menstrual age (day of egg retrieval and fertilisation plus 14 days) For singletons, delivery at > 37 weeks, birthweight >2500 g with no congenital abnormalities For multiple pregnancies, delivery at > 24 weeks, alive at birth with no congenital abnormalities Exclusion Criteria: Not reported Other Details: No details of fetal chorionicity or maternal ethnicity reported	Investigation : Stepwise multiple regression used to derive a dating formula in singleton pregnancies using BPD, femur length, head circumference and abdominal circumference* Formula was compared with 38 previously published formulae, and then applied to twin and triplet populations Accuracy of new formula calculated using root-mean-square deviation (RMSD) between the true and estimated gestational ages Methods described adequately? Yes Ultrasound biometry conducted in a single ultrasound unit as part of routine mid-trimester examination (14-22 weeks) Equipment details reported Details of charts not reported Operator number/experience: All scans were performed by one of five sonographers (under supervision of a sonologist) *Best fitting model for estimated gestational age = [51.68 +	Comparison of accuracy* of estimated gestational age (using formula based on femur length, head and abdominal circumference) among twins and triplets Twins Using the larger twin (days): Mean = 0.8, SD = 4.1, RMSD = 4.17** Using the smaller twin (days): Mean = -1.3, SD = 3.9, RMSD = 4.11** Using average of twin sizes (days): Mean = -0.3, SD = 3.9, RMSD = 3.91** Triplets Using the largest triplet (days): Mean = 0.8, SD = 4.0, RMSD = 4.07** Using the smallest triplet (days): Mean = -3.4, SD = 3.5, RMSD = 4.87** Using average of triplet sizes (days): Mean = -1.3, SD = 3.5, RMSD = 3.73** * Accuracy defined in paper as root mean squared deviation (RMSD) = $\sqrt{(\text{systematic error}^2 + \text{random error}^2)}$ Systematic error defined as mean difference between estimated and true gestational ages Random error is the standard deviation between estimated and true gestational ages ** Calculated by NCC-WCH using data reported in the article	Funding: No details reported Limitations: Main limitation is that it is a cross-sectional study Bias may also arise from different operators with differing experience and different equipment Study does not use conventional ultrasound formulae to assess gestational age when comparing singleton and multiple pregnancies

Study Details	Participants	Investigation	Outcome Measures and Results	Comments
fertilisation (IVF)		2.324* head circumference + 2.092 * abdominal circumference + 5.18 * femur length]		
First author, year: Dias 2010[33] Country: UK Study design: Retrospective cohort study Study dates: June 1997 - October 2009 Aim of study: To determine the accuracy of singleton crown-rump length (CRL) formulae in dating twin pregnancies from the smaller, larger or mean twin CRL	Population: N = 376 pregnancies 266 singleton pregnancies and 110 twin pregnancies Inclusion Criteria: Dichorionic twin and singleton pregnancies resulting from IVF or intracytoplasmic sperm injection (ICSI), seen for routine obstetric care between June 1997 and October 2009; only scans done between 11 and 14 weeks of pregnancy were included Exclusion Criteria: Monochorionic twin pregnancies Other Details: Gestational age was calculated using the embryo transfer date. IVF/ICSI singleton pregnancies were used to control for any variation in dating between and/or early fetal growth that might occur in pregnancies achieved by ART.	Investigation: Mean differences between actual CRL measurements and CRL measurements estimated from the date of conception were derived for singleton, bigger and smaller twin, and mean twin size. Three different dating charts* were used for comparison Methods described adequately? Yes A single CRL measurement was taken with the fetus in a neutral position Details reported Operator number/experience: Scans were only carried out by sonographers who were certified for first-trimester ultrasound assessment * 1. Robinson: GA = 8.052 * √(CRL * 1.037) + 23.73 2. Rossavik: GA = 49.5 + 0.6 * CRL 3. Von Kaisenberg: GA = 49.1115 + 0.5954 * CRL	Mean difference between actual CRL measurement and CRL estimated from date of conception (i.e. from IVF history) using Robinson's formula Singleton: 2.72 (2.49 to 2.95) mm Bigger twin: 4.7 (4.4 to 5.1) mm Smaller twin: 1.77 (1.4 to 2.1) mm Mean twin size: 2.84 (2.5 to 0.63) mm using Rossavik's formula Singleton: 0.24 (1.8 to 2.5) mm Bigger twin: 2.1 (0.01 to 0.46) mm Smaller twin: −0.86 (−0.5 to −1.2) mm Mean twin size: 0.63 (0.3 to 1.0) mm using Von Kaisenberg's formula Singleton: −0.91 (−0.7 to −1.13) mm Bigger twin: 0.98 (0.6 to 1.35) mm Smaller twin: −2.0 (−1.6 to −2.4) mm Mean twin size: 0.5 (−0.8 to −1.7) mm	Funding: There was no funding for the study Limitations: Main limitation is the retrospective nature of the study A further limitation may be the fact that the ultrasonographers had prior knowledge of the dates of conception

Chorionicity

Review question

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

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
First author, year: Barss 1985[50] Aim of study: To investigate sonographic criteria for distinguishing chorionicity of twin pregnancies antenatally Setting: Not reported clearly, although the study authors were based at a hospital in the USA Study design: Prospective	Population: N= 33 twin pregnancies Inclusion criteria: Suspected twin pregnancies with multiple indications, e.g. size greater than expected for gestational age, twin discordance, genetic amniocentesis, fetal abnormalities Gestational age at scan: 7-38 weeks	Index test: Ultrasound - Composite of membrane thickness and number of placental masses Reference test: Postpartum histological evaluation of the placenta	Composite of number of placental masses and thin/thick membrane	9	0	0	23	100* (66 to 100*)	100* (85 to 100*)	100* (66 to 100*)	100* (85 to 100*)	500* (2.93 to 711)	0.00* (0.00 to 0.76)	One dichorionic triplet pregnancy was reported in this study but has not been included here, as it cannot be entered into a 2x2 table with the twin data, and there were not enough triplet data to allow separate statistics for triplet pregnancies to be calculated There were four cases of feto-fetal transfusion syndrome

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
diagnostic accuracy study Quality: High - no limitations	Trimester of first scan: First n= 5 Second n= 16 Third n= 13													Blinding of the clinicians undertaking the reference test was not reported No clinical outcomes were reported in this study Where this study was conducted was not reported, but the study authors were based in the USA No sources of funding were cited
First author, year: Bracero 2003[42]	Population: N= 44 twin pregnancies Inclusion	Index test: Transab-dominal ultrasound - Membrane	Membrane thickness (≥2.0mm) for monochor-ionicity:	5*	5*	2*	32*	76 (29 to 96*)	86 (71 to 95*)	50* (19 to 81*)	94* (86 to 100*)	5.29* (2.06 to 13.53 *)	0.33* (0.10 to 1.07*)	Unclear whether the pathologist was blind to the scan results

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
Aim of study: To assess the value of ultrasound measurement of twin dividing membrane thickness in predicting chorionicity and perinatal outcome Secondary objective to compare magnified and unmagnified images, and measurements taken with dividing membranes parallel and perpendicular to the ultrasound beam	criteria: Twin pregnancies Median gestational age at scan= 26 weeks (IQR 12-40 weeks)	thickness Reference test: Postpartum histological evaluation of the placenta												No clinical outcomes were reported in this study This study was conducted in the USA No sources of funding were cited

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
Setting: Two medical centres in the USA Study design: Prospective diagnostic accuracy study Quality: Moderate - some limitations														
First author, year: Carroll 2002[39] Aim of study: To examine the accuracy of sonographic determination of chorionicity in twin pregnancies at 10-14 weeks' gestation	Population: N= 150 twin pregnancies Inclusion criteria: Twin pregnancies Exclusion criteria: Pregnancies with placentae unsuitable for	Index Test: Transab-dominal (first choice) or transvaginal (if transabdom-inal image was suboptimal, small number of cases) ultrasound	Reference test results (n= 150): Monochorion ic= 34 (23%) Dichorionic= 116 (77%) Median thickness of inter-twin membrane: Monochor-ionic=											Pathologists were blind to scan results No clinical outcomes were reported in this study This study was conducted in the UK Funding was

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
<u>Setting:</u> Fetal medicine or ultrasound department in two hospitals in the UK <u>Study design:</u> Prospective diagnostic accuracy study <u>Quality:</u> Low - serious limitations	examination due to autolysis or damage to the amnion (n= 5), no follow-up details (n= 2), terminated pregnancies (n= 1) Median gestational age at scan= 12 weeks (IQR 10-14 weeks)	- Lambda/T-sign (n= 150) - Membrane thickness (n= 140, 10 not entered into database due to oversight) <u>Reference test:</u> Postpartum histological evaluation of the placenta (n= 111) or fetal sex (n= 39)	0.9mm (IQR 0.6 to 1.2mm) Dichorionic= 2.2mm (IQR 0.7 to 4.1mm) P<0.001										received from the Medical Research Committee of the Special Trustees for United Bristol Hospitals
			T and/or membrane thickness (<1.5mm) for monochord-ionicity (n= 140): Predictive accuracy= 94%	32*	9*	0*	99*	100 (89 to 100*)	92 (85 to 96*)	78 (65 to 91*)	100 (96 to 100)	12.00* (6.42 to 22.43*)	0.00* (NC)	
			T for monochorionicity (n= 150): Predictive accuracy= 99%	34*	2*	0*	114*	100 (90 to 100*)	98 (94 to 100*)	94	100	58.0*	0.00*	
			Membrane thickness (<1.5mm) for	32*	7*	0*	101*	100 (89 to 100*)	94 (89 to 98*)	82 (70 to 94*)	100 (96 to 100)	15.43* (7.54	0.00* (NC)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
			monochorio-nicity (n= 140): Predictive accuracy= 94%									to 31.58 *)		
			Lambda or separate placentae and/or membrane thickness (≥ 1.5mm) (n= 140): Predictive accuracy for dichorionicity = 99%	31*	0*	1*	108*	99 (84 to 100*)	100 (97 to 100*)	100 (97 to 100*)	99* (97 to 100*)	NC*	0.03* (0.00 to 0.22*)	
			Lambda or separate placentae (n= 150): Accuracy= 98%	33*	0*	1*	116*	97	100	100	92	NC*	0.03*	
			Membrane thickness (≥ 1.5mm) (n=140):	30*	0*	2*	108*	93	100	100	80	NC*	0.06*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
			Accuracy for dichorionicity = 94%											
			Absence of lambda or one/fused placenta	34	3	0	113	100* (90 to 100*)	97* (93 to 99*)	92*	100*	38.67 *	0.00*	
First author, year: Copperman 1995[51] Aim of study: To determine whether chorionicity could be predicted accurately using early first-trimester transvaginal ultrasound Setting: A hospital in the USA Study design:	Population: N= 47 twin pregnancies Scans performed 41 days after embryo transfer	Index test: Transvaginal ultrasound - Composite of number of gestational sacs and fetal poles; number of placental sites; membrane presence and thickness; and lambda sign Reference test: Postpartum histological	Composite for monochor-ionicity	3	0	0	44	100 (29 to 100*)	100 (92 to 100*)	100* (29 to 100*)	100* (92 to 100*)	>1000 * (4.88 to 1271*)	0.00* (0.01 to 1.69*)	Pathologists were blind to antenatal scan results No clinical outcomes were reported in this study This study was conducted in the USA No source of funding was cited
			All antenatal diagnoses of a single gestational sac were confirmed as monochor-ionic All antenatal diagnoses of dichorionicity were confirmed as											

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
Prospective diagnostic accuracy study <u>Quality:</u> High - no limitations		evaluation of the placenta	dichorionic Diagnostic accuracy= 100% It was not reported whether other methods or a composite method for determining monochor-ionicity were accurate											
<u>First author, Year:</u> D'Alton 1988[48] <u>Aim of study:</u> To determine whether the number of layers in the dividing membrane is an accurate	<u>Population:</u> N= 69 twin pregnancies Gestational age at scan: 16 to 27 weeks n=62 28 to 31 weeks n= 6 32 to 34 weeks n= 1	<u>Index test:</u> Ultrasound - Number of membrane layers (2 layers for monochorion icity, 3 or 4 for dichorioni-city)	Accuracy= 98.5%											If the membrane was not visualised satisfactorily, repeat ultrasono-graphic examinations were carried out until a definitive assessment of chorionicity
			Number of membrane layers	17	1	0	51	100* (90 to 100*)	98* (90 to 100*)	94* (84 to 100*)	100* (93 to 100*)	52.00* (7.46 to 362.24*)	0.00* (NC)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
method for prediction of chorionicity in twin pregnancies Setting: A hospital in Canada Study design: Prospective diagnostic accuracy study Quality: High - no limitations	Average 1.2 scans per pregnancy Inclusion criteria: Consecutive women with twin pregnancies Exclusion criteria: Not reported	Reference test: Postpartum histological evaluation												could be made Pathologists were blind to antenatal classification of chorionicity No clinical outcomes were reported in this study This study was conducted in Canada No source of funding was cited
First author, year: Devlieger 2001[45] Aim of study: To evaluate the accuracy of a composite	Population: N= 82 twin pregnancies Exclusion criteria: Lost to follow up (n= 3), miscarriage	Index test: Transabdominal or transvaginal ultrasound (choice depending on preference	Index test results: Septum: ≥ 2mm= 65/76 (85.5%) < 2mm= 11/76 (14.5%)											Unclear whether the pathologist was blind to the scan results No clinical outcomes were reported in this study

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
of the most commonly suggested ultrasound markers for detection of chorionicity and amnionicity in a clinical setting where ultrasound examination is performed by physicians with different levels of experience Setting: A hospital in Belgium Study design: Prospective diagnostic accuracy study	(n= 2) Mean gestational age at scan= 10.1 weeks (95% CI 5.5 to 26.0 weeks)	of physician or GA or patient characteris-tics) - Membrane thickness - Lambda/T sign Reference test: Postpartum histological evaluation of the placenta	Lambda sign present= 31/82 (37.8%) Single placenta= 18/69 (26.1%)										This study was conducted in Belgium No sources of funding were cited
			Inter-twin membrane <2mm for monochorion icity (n= 76)	7	4	0*	65*	100 (59 to 100*)	94 (86 to 98*)	64 (35 to 92*)	100 (94 to 100*)	17.25 * (6.66 to 44.66 *)	0.00* (NC)	
			Lambda sign (n= 82)	10*	41*	0	31	100 (69 to 100*)	44 (32 to 55*)	20 (9 to 31*)	100 (89 to 100*)	1.76* (1.44 to 2.15*)	0.00* (NC)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
Quality: Moderate - some limitations														
First author, year: Guilherme 2009[44] Aim of study: To assess diagnostic accuracy and prognostic influence of ultrasonographic criteria in triplet pregnancies Setting: A tertiary care referral centre in France Study design: Prospective diagnostic accuracy	Population: N= 50 triplet pregnancies Inclusion criteria: Every set of triplets in which at least one baby (live or stillborn) weighed ≥500g, and gestational age at delivery >22 weeks Mean GA at scan= 17 weeks Exclusion criteria: Quadruplet pregnancy	Index test: Ultrasound - Lambda/T sign - Membrane thickness ≥2mm Reference test: Postpartum histological evaluation of the placenta	Composite of lambda/t-sign, number of placental masses, fetal sex, membrane thickness with 2mm cut-off	17*	2*	1*	30*	94* (84 to 100*)	94* (85 to 100*)	89* (76 to 100*)	97* (91 to 100*)	15.11* (3.93 to 58.09*)	0.06* (0.0 to 0.15*)	This study did not include twins. To analyse the data in a 2x2 table, monochorionic and dichorionic pregnancies were combined and compared to the trichorionic group. The true positive data, therefore, incorporated monochorionic and dichorionic triplet pregnancies that were correctly classified. The false positive

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
study <u>Quality:</u> High – no limitations	reduced to triplet pregnancy (n= 1), cases without full ultrasound data available (n= 1)													data represented pregnancies that were classified as monochorionic or dichorionic on the ultrasound scan but were found to be trichorionic using the reference test. False negative data represented pregnancies that were classified as trichorionic based on ultrasound scan, but were found to be monochorionic or dichorionic using the reference test.

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
														True negative data represented pregnancies that were correctly classified as trichorionic Feto-fetal transfusion syndrome was diagnosed in two dichorionic triplets Blinding was not reported The method of ultrasound (transvaginal/transabdominal) was not reported The gestational age at which chorionicity was

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
														established was significantly different depending on the methods used: - Lambda= 12.5 weeks (95% CI 12-13) - Membrane thickness= 19 weeks (95% CI 12-30) p<0.001 The study was conducted in France No source of funding was cited
First author, year: Hertzberg 1986[46] Aim of study: To determine	Population: N= 54 twin pregnancies Inclusion criteria: Twin	Index test: Ultrasound scan - Membrane thickness Reference	Membrane thickness >1mm	3	4	9	38	25* (5 to 57*)	90* (77 to 97*)	43* (6 to 80*)	81* (70 to 92*)	2.63* (0.68 to 10.15 *)	0.82* (0.59 to 1.17*)	Accuracy of seeing thick membrane: First trimester= 100% Second trimester= 89%

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
if dichorionic and monochorionic twin gestations could be distinguished from each other by analysing membrane thickness between fetuses using sonography Setting: A hospital in the USA Study design: Prospective diagnostic accuracy study Quality: High - no limitations	pregnancies Average of 2.2 scans for each pregnancy	test: "Clinical or pathological information"												Third trimester= 36% All ultrasound scans were reviewed without knowledge of the amnionicity or chorionicity, fetal sex or number of placental sites No clinical outcomes were reported in this study This study was conducted in the USA No source of funding was cited
First author,	Population:	Index test:	Membrane	NC*	NC*	1	4	NC*	NC*	NC*	NC*	NC*	NC*	Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
year: Kurtz 1992[38] Aim of study: To evaluate a twin pregnancies of known chorionicity and amnionicity to determine overall predictive accuracy of ultrasound in the first trimester Setting: Not reported, although all study authors were based in the USA Study design: Prospective diagnostic	N= 105 twin pregnancies Inclusion criteria: Twin pregnancies Scans performed at gestational age: 9 weeks n= 39 10 weeks n = 30 11 weeks n= 26 12 weeks n= 10	Transabdominal ultrasound - Membrane thickness - Lambda sign Reference test: Postpartum histological evaluation of the placenta and fetal sex	thickness 1-2mm											whether pathologists were blind to the ultrasound results No clinical outcomes were reported in this study Unclear where this study was conducted, but the study authors were from the USA No source of funding was cited
			Lambda sign for predicting monochorionicity	18	79	2	6	90* (68 to 99*)	7* (3 to 15*)	19*	75*	0.97*	1.42*	
			Membrane thickness (<1mm)	19	3	1*	82*	95* (75 to 100*)	96* (90 to 99*)	88 (72 to 100*)	99* (96 to 100*)	26.92* (8.82 to 82.17*)	0.05* (0.01 to 0.35*)	
			Membrane thickness (≥2mm)	20*	7*	0	78	100* (83 to 100*)	92* (84 to 97*)	74* (58 to 91*)	100* (95 to 100)	12.14* (5.97 to 24.69*)	0.00* (NC)	
			Membrane thickness and placental number	NC*	NC*	NC*	NC*	NC*	NC*	96	NC*	NC*	NC*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
accuracy study Quality: High - no limitations													
First author, year: Lee 2006[40] Aim of study: To assess the accuracy of using placental location(s), lambda/T-sign and/or fetal gender for determining chorionicity Setting: A tertiary care centre in the USA Study design: Retrospective diagnostic	Population: N= 410 consecutive twin pregnancies Inclusion criteria: Consecutive women with twin pregnancies Mean gestational age at scan=not reported Mean maternal age= not reported Exclusion criteria:	Index test: Transvaginal and transabdom-inal ultrasound -Placental location(s), presence of lambda or T-sign, and/or fetal gender(s) Reference test: Postpartum histological evaluation of inter-twin placental membranes	Composite of placental location(s), lambda/T-sign and or fetal gender - Scans from all GAs (1st and 2nd trimester)	88	7	11	304	88.9 (81 to 94*)	97.7 (95 to 99*)	92.6	96.5	39.49 *	0.11*	Unclear whether the pathologist was blind to the scan results Clinical outcomes were reported for this study: Of the 18 cases of antenatal-postnatal discordant chorionicities, 2 affected patient counselling (single fetal demise in incorrectly diagnosed monochorionic twins caused concern for a potential
			Placental location(s), lambda/T-sign - 1st trimester scans	44	1	5	197	89.8 (81.3 to 98*)	99.5 (99.0 to 100*)	97.8	97.5	177.80*	0.10*	
			Composite of placental location(s), lambda/T-sign and or fetal gender	44	6	6	107	88.0 (79.0 to 97.0*)	94.7 (90.6 to 98.8*)	88.0 (79 to 97*)	94.7 (91 to 99*)	16.57 * (7.56 to 36.35 *)	0.13* (0.06 to 0.27*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
accuracy study Quality: High – no limitations	No placental pathology, chorionicity indeterminable by histologic exam, no scan before GA 24 weeks		- 2nd trimester scans											adverse neurologic outcome) or were associated with adverse outcomes (polyhydram-nios and a 'stuck' appearance) This study was conducted in the USA No sources of funding were cited
First author, year: Mahoney 1985[43] Aim of study: To determine if antenatal sonography	Population: N= 66 twin pregnancies Mean menstrual age= 22.4 weeks (range 9-36 weeks)	Index test: Ultrasound - Number of placental sites Reference test: Postpartum	One placental site for monochorionicity	26	27	0	13	100 (87 to 100*)	33* (19 to 49*)	49 (36 to 63*)	100* (75 to 100*)	1.48* (1.19 to 1.84*)	0.00* (NC)	Blinding of pathologists was not reported No clinical outcomes were reported in this study

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
alone gives an accurate assessment of amnionicity and chorionicity in twin pregnancies Setting: Not reported clearly, although the study authors were based in a university hospital in the USA Study design: Prospective diagnostic accuracy study Quality: Moderate - some limitations	Inclusion criteria: Clinical follow-up and pathological examination data available Exclusion criteria: Not reported	histological evaluation of the placenta												This study was conducted in the USA No source of funding was cited

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
First author, year: Stenhouse 2002[41] Aim of study: To determine the accuracy of antenatal prediction of chorionicity in twin pregnancies Setting: An obstetrics and	Population: N= 138 twin pregnancies Inclusion criteria: All twin pregnancies Median maternal age: 30 years (IQR 15-40 years) Median gestational age at scan= 12	Index test: Transab-dominal ultrasound findings -Composite of the number of placental masses, twin peak sign and fetal sex Reference test: the Baby's sex determined	Scans at all gestational ages for monochorion icity	31	4	3	100	91 (76 to 98*)	96 (90 to 99*)	89	97	23.07 *	0.1*	Unclear whether the pathologist (when involved) was blind to the scan results No clinical outcomes were reported in this study This study was conducted in the UK No sources of funding were
			Scan at gestational age <14 weeks for monochorion icity	21	1	0	74	100 (84 to 100*)	99 (96 to 100*)	95 (87 to 100)	100 (95 to 100)	75.00 * (10.70 to 525.51*)	0.00* (NC)	
			Scan at gestational age ≥14 weeks for monochorion icity	10	3	3	26	77* (54 to 100*)	90 (79 to 100*)	77* (54 to 100*)	90 (79 to 100*)	7.44* (2.45 to 22.61*)	0.90* (0.79 to 1.00*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
gynaecology hospital department in the UK Study design: Prospective diagnostic accuracy study Quality: Moderate - some limitations	(IQR 7-28 weeks)	at delivery. If concordant, chorionicity determined by postpartum histological evaluation of the placenta	Agreement between tests: Monochor-ionic= 31/34 (91%) Dichorionic= 100/104 (96%) Overall= 131/138 (95%)											cited
First author, year: Townsend 1998[47]	Population: N= 75 twin pregnancies	Index Test: Ultrasound - Membrane thickness	Thin membrane for monochor-	23	5	8	39	74* (55 to 88*)	89 (75 to 96*)	83 (68 to 96*)	83 (72 to 94*)	6.53* (2.79 to 15.29	0.29* (0.16 to 0.53*)	When multiple images of the membrane were available, the

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
<u>Aim of study:</u> To evaluate accuracy of prediction of chorionicity and amnionicity based on membrane thickness <u>Setting:</u> Not reported, although all study authors were based in the USA <u>Study design:</u> Prospective diagnostic accuracy study <u>Quality:</u> High - no limitations	<u>Inclusion criteria:</u> Twin pregnancies with ultrasound scans performed; and records of delivery and placental pathology available Date of scan: First trimester n= 6 Second trimester n= 49 Third trimester n= 20 <u>Exclusion criteria:</u> None reported	<u>Reference Test:</u> Records of delivery - Number of placentae - The baby's sex determined after the birth	ionicity									*)		predominant appearance of the membrane was judged. The earliest sonogram available in each pregnancy was used to predict chorionicity Method of ultrasound (transabdominal /transvaginal) not reported Clinicians analysing scans were blind to results of index and reference tests 100% intraobserver concordance and 91%
			Thick membrane for dichorioni-city, third trimester scans only	NC*	NC*	NC*	NC*	52	NC*	NC*	NC*	NC*	NC*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
														interobserver concordance were reported (based on 23 scan images) No clinical outcomes were reported in this study Not clear where this study was conducted, although all study authors were based in the USA No sources of funding were cited
First author, year: Wood 1996[49] Aim of study: To assess the	Population: N= 45 twin pregnancies Inclusion criteria:	Index test: Ultrasound - Number of placental masses and Lambda sign	Composite	8	2	1	34	89* (52 to 100*)	94 (81 to 99*)	80* (55 to 100*)	97* (92 to 100*)	16.00* (4.08 to 62.75*)	0.12* (0.02 to 0.75*)	In this study, lambda sign is referred to as either lambda or 'twin peak sign'

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
diagnostic accuracy of ultrasound assessment, using the twin peak or lambda sign, in determining chorionicity in multiple pregnancies Setting: A hospital in Canada Study design: Prospective diagnostic accuracy study Quality: High - no limitations	Consecutive twin pregnancies Exclusion criteria: Gestational age >28 weeks, delivery records or placental pathology reports not available (n= 7), lost to follow up (n= 3), terminated pregnancy (n= 1) Gestational age range: 12-40 weeks	(referred to as either lambda or 'twin peak sign' by the study authors) Reference test: Postpartum histological evaluation of the placenta and the baby's sex determined after the birth	Composite for monochorionicity, second trimester scans only	NC*	NC*	NC*	NC*	NC*	NC*	100	NC*	NC*	NC*	Blinding of assessors was not reported No clinical outcomes were reported in this study This study was conducted in Canada No sources of funding were cited

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?

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Luke, 2003[54] Country: USA Study design: Prospective cohort Study dates: 1996 to 2002 Aim of study: To evaluate the effect of antenatal nutrition and education programme on twin pregnancy, neonatal and early childhood outcomes	Population: N= 529 twin pregnancies All dichorionic Inclusion criteria : All twins births at the University of Michigan Health Systems delivered between 1996 and 2002 Exclusion criteria: Monochorionic pregnancies Women with emergencies pregnancy complications Fetal death or major congenital anomalies of one or both twins	Investigation : Programme pregnancies N=190 Comparison: Non-programme pregnancies N=339 Methods Women were either self-referred to the programme or referred by any member of the healthcare team All antenatal care for twin pregnancies was given by resident physician, including generalists and maternal fetal medicine specialist Women in both groups (programme and non-programme) had regular antenatal visits with primary care physician. Education for both programme and non-programme mothers were included discussion of environment and work hazards, physical activity, travel and sign of preterm labour. In addition to the above women in the	Programme mothers were older (p<0.0001), tended to have private health insurance; n=92/80 (p=.002) and less likely to be smokers; n=2/10 (p<0.001) The two groups were similar on all other maternal demographic variables (parity, infertility treatment, gestational diabetes, bleeding >20 weeks, BMI, height, week of first antenatal visits ,pre-existing medical condition) Entry to the programme began at 16 ± 0.4 weeks' gestation. Number of programme visits averaged 6 ± 0.2 Perinatal and maternal morbidity Preeclampsia Programme= 15/190* (8%) Non-programme= 58/339* (17%) AOR 0.41 (95% CI 0.23-0.75) p=0.004 Preterm labour Programme= 44/190 (23%) Non-programme= 142/339 (42%) AOR 0.45 (95% CI 0.30 to 0.68) P<0.0001 Premature rupture of membranes Programme= 19/190 (10%) Non-programme= 85/339 (25%) AOR 0.35 (95% CI 0.20-0.60)	Funding: Sponsored by grants from the Office of the Vice President for Research, University of Michigan, the Gerber Foundation Limitations: Lack of random assignment to the programme. Significant demographic and smoking differences between the two groups (favouring the programme women) No attempt to distinguish the components of care in the two groups which may have influenced outcome (education, support, clinical care etc)

Study details	Participants	Investigation	Outcome measures and results	Comments
		programme group also had: twice monthly antenatal visits with a registered dietitian and nurse practitioner in addition to regular antenatal visits with women's primary care physician additional maternal education (advice on diet, signs and symptoms of preeclamsia, fetal growth and exploration of any problems) modification of maternal activity (work leave was recommended by 24 weeks' gestation or sooner with antenatal complications, decreasing stair climbing, lifting and carrying, walking and swimming) individualised dietary prescription (dietary assessment and advice in each antenatal visit) multimineral supplementation (daily mineral supplement of calcium and magnesium with zinc plus multivitamins) serial monitoring of nutritional status (adherence and use of correct dosage of supplements) Ultrasonic measures of fetal growth were obtained at 18 to 20 weeks' gestation and again at 24, 28 and 32 weeks'	p<0.0001 Neonatal Outcomes <u>Major neonatal morbidity</u> (retinopathy of prematurity, necrotising enterocolititis, ventilator support, intravenous haemorrhage) Programme= 32/190 (17%) Non-programme= 108/339 (32%) AOR 0.44 95% CI 0.31-0.62 p< 0.0001 <u>Premature birth</u> Birth <36 weeks Programme= 78/190 (41%) Non-programme= 180/339 (53%) AOR 0.62 95% CI 0.43-0.89 p=0.01 Birth <32 weeks Programme= 13/190(7%) Non-programme= 71/339 (21%) AOR 0.27 (95% CI 0.15-0.51) p<0.001 Birth <30 weeks Programme= 6/190 (3%) Non-programme= 31/339 (9%) AOR 0.29 95% CI 0.11-0.76 p=0.01 <u>Very low birthweight</u> Programme= 10/190 (5%) Non-programme= 54/339 (16%) AOR 0.30 95% CI 0.15-0.61 p=0.001	

Study details	Participants	Investigation	Outcome measures and results	Comments
		gestation Neonatal development of both programme and non-programme mothers were followed at 8 months, 18 months and 3 years of age <u>Data analysis</u> Differences between continuous variables were compared with Student's t- test. Differences in categorical variables were preformed with the χ2 test and Fisher's exact test. Logistic regression analysis was used to obtain odds ratios. Adjusted for confounding factors	(no definition for very low birthweight reported) <u>NICU admission</u> Programme= 82/190 (43%) Non-programme=210/339 (63%) AOR 0.48 95% CI 0.36-0.64 p<0.001 <u>Apnea, bradycardia or cyanosis</u> Programme= 13/109 (7%) Non-programme= 78/339 (23%) AOR 0.27 (95% CI 0.17 to 0.44) p<0.0001 <u>Anaemia</u> Programme= 8/190 (4%) Non-programme= 44/339 (13%) AOR 0.31 (95% CI 0.17 to 0.56) p<0.0001 <u>Hyperbilirubinaemia</u> Programme= 36/190 (19%) Non-programme= 98/339 (29%) AOR 0.56 (95% CI 0.40 to 0.79) p=0.001 <u>Patent ductus arteriosus</u> Programme= 4/190 (2%) Non-programme= 17/339 (5%) AOR 0.37 (95% CI 0.15 to 0.88) p=0.02 <u>Retinopathy of prematurity</u> Programme= 2/190 (1%) Non-programme= 24/339 (7%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			AOR 0.19 (95% CI 0.07 to 0.50) p=0.001 <u>Necrotising enterocolitis</u> Programme = 2/190 (1%) Non-programme = 10/339 (3%) AOR 0.21 (95% CI 0.05 to 0.95) p=0.04 <u>Intravenous fluids</u> Programme= 72/190 (38%) Non-programme= 200/339 (59%) AOR 0.43 (95% CI 0.32 to 0.57) p<0.0001 <u>Antibiotics</u> Programme= 80/190 (42%) Non-programme= 203/339 (60%) AOR 0.50 (95% CI 0.37 to 0.67) p<0.0001 <u>Supplemental oxygen</u> Programme = 53/190 (28%) Non-programme = 153/339 (45%) AOR 0.49 (95% CI 0.36 to 0.67) p<0.0001 <u>Mechanical ventilation</u> Programme= 29/190 (15%) Non-programme= 102/339 (30%) AOR 0.41 (95% CI 0.28 to 0.59) p<0.0001 <u>Phototherapy</u> Programme= 30/190 (16%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Non-programme= 125/339 (37%) AOR 0.34 (95% CI 0.24 to 0.49) p<0.0001 Parenteral nutrition Programme= 25/190 (13%) Non-programme= 105/339 (31%) AOR 0.32 (95% CI 0.22 to 0.46) p<0.0001 Respiratory distress syndrome Programme= 34/109 (18%) Non-programme= 105/339 (31%) AOR 0.49 (95% CI 0.35 to 0.69) p<0.0001	
First author, year: Ellings, 1993[52] Country: USA Study design: Prospective cohort Study dates: 1998 to 1993 Aim of study: To evaluate the success of a specialised, multidisciplinary antenatal twin clinic	Population: N= 140 twin pregnancies Inclusion criteria : Twin pairs followed in the twin clinic since 1988 were compared with 51 twin pairs who did not attend the clinic Exclusion criteria: Not reported Other details: Using the Medical university of South Carolina Perinatal Information Network, the outcomes of n=89 twins pairs followed in the twin clinic in 1988 compared with n=51 other twin pairs delivered	Investigation : Twin clinic n=89 twin pregnancies Comparison: High risk obstetric clinic n= 51 twin pregnancies Methods The twin clinic was established at Medical University of South Carolina as a special antenatal clinic for multiple pregnancies. The care was provided by a multidisciplinary team Monthly ultrasound evaluation preformed by a certified technologist. Nutritional status was monitored weekly by assessing weight gain and laboratory evaluation. Dietary	The two groups were similar on all maternal demographic variables (age, black race, gravity, parity, marriage, school education, public fund, month antenatal care began, and median number of antenatal visits) Maternal Outcomes Premature rupture of membranes Twin clinic= 11/89 (12%) High risk clinic= 13/51 (25%) Not significant (p value not reported) Bleeding ≥20 weeks Twin clinic= 2/89 (2%) High risk clinic= 4/51 (8%) Not significant (p value not reported) Anaemia (Hgb<10 mg/dl) Twin clinic= 17/89 (19%) High risk clinic= 11/51 (22%)	Funding: Not reported Limitations: Small study with selection bias. Many of the women in the control group were not referred to the twin clinic because of transportation or other logistic difficulties No attempt to distinguish the components of care in the two groups which may have influenced outcome (education, support, clinical care etc)

Study details	Participants	Investigation	Outcome measures and results	Comments
	since 1988 who met the inclusion criteria but did not attend the twin clinic (control)	counselling provided by a nutritional consultant was reinforced at each clinic visit by the certified nurse-midwife. Social service evaluation was conducted early in pregnancy to develop support and assistance as needed. A board-certified specialist in maternal fetal medicine provided obstetric consultation and oversees all the clinic activities Women were educated in the individualised teaching session about signs and symptoms of preterm labour and self-palpation of uterine contractions. A cervical examination was performed at each visit after 20 weeks' gestation <u>Control group</u> All women in the control group attended the high risk obstetric clinic. Antenatal care provided by the obstetric faculty and resident staff. Some women in the control group were private patients of university-based faculty <u>Data analysis</u> Data were obtained using the medical University of South	Not significant (p value not reported) <u>Pre-eclampsia</u> Twin clinic= 10/89 (11%) High risk clinic= 4/51 (8%) Not significant (p value not reported) <u>Gestational diabetes</u> Twin clinic= 6/89 (7%) High risk clinic= 1/51 (2%) Not significant (p value not reported) <u>Urinary tract infection</u> Twin clinic= 4/89 (4%) High risk clinic= 3/51 (6%) Not significant (p value not reported) <u>Caesarean section rate</u> Twin clinic= 29/89 (33%) High risk clinic= 15/51 (29%) Not significant (p value not reported) Neonatal Outcomes <u>Preterm Birth (< 37 weeks)</u> Twin clinic= 69/89 (78%) Contemporary control= 37/51 (73%) P=NS <u>Birth <30 weeks</u> Twin clinic= 2/89 (2.2%) Contemporary control= 9/51 (17.6%) P=0.003 <u>Very low birthweight (<1500 g)</u> Twin clinic= 10/178 (6%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
		Carolina Perinatal Information Network. Differences between the two groups were compared using Student's t test for nominal variables and the χ2 test for differences among categorical variables	Contemporary control= 27/102 (26%) P<0.0001 NICU admission Twin clinic= 24/178 (13%) Contemporary control= 39/102 (38%) P<0.0001 Perinatal mortality Twin clinic= 1/178 (1%) Contemporary control= 8/102 (8%) P<0.0002	
First author, year: Ruiz, 2001[53] Country: USA Study design: Retrospective cohort study Study dates: 1995 to 1997 Aim of study: To examine the effectiveness of a twin clinic to increase the gestational age of twins, increase the birth weights, decrease the length of hospital stays and	Population: N=71 twin pregnancies Inclusion criteria: Newborn of women who received care from the twin clinic Exclusion criteria: Women receiving antenatal care after 30 weeks Other details: The number of women who came to the clinic during initial 18 months of the protocol determined the sample size for special care group (twin clinic) The standard care group received care from January 1995 to February 1996	Investigation: Maternal and neonatal outcomes in women who received care in the twin clinic (n=30 twin pregnancies) Comparison: Maternal and neonatal outcomes in women who received standard care and had given birth 1 year before (n=41 twin pregnancies) Methods In the specialised care group (twin clinic) the participants received their primary care from a nurse practitioner, with a weekly consultation and review by a perinatalogis On entry to twin clinic, visits were scheduled every other	The two groups were similar on all maternal demographic variables (age, race, gravity, parity, marriage, insurance status, number of antenatal visits) Maternal outcomes Anaemia: Twin clinic= 5/30 (16%) Standard care= 7/41 (16%) Not significant (p value not reported) Gestational hypertension Twin clinic= 5/30 (16%) Standard care= 6/41 (14%) Not significant (p value not reported) Gestational diabetes Twin clinic= 1/30 (3%) Standard care= 0/41 Not significant (p value not reported) Urinary tract infection	Funding: Not reported Limitations: The women in the control group received their care prior to the intervention group – some of the improvements attributed to the specialist clinics may have resulted from changes in practice during this time No attempt to distinguish the components of care in the two groups which may have influenced outcome (education, support, clinical care etc)

Study details	Participants	Investigation	Outcome measures and results	Comments
measure the economic impact		week until 24 weeks' gestation. From 24 weeks' gestation visits were weekly A nutritionist, social workers, and genetic counsellor were available as support Participants received a preterm labour risk assessment, psychological and nutrition assessment preformed by the nurse practitioner Between 20-24 weeks, the nurse practitioner made a home visits to assess the problems and perform a general environment and stress assessment. Women were also provided with leaflets and information regarding signs and symptoms of preterm labour at the home visit In each antenatal visit symptoms of preterm labour were assessed, a cervical examination preformed and recommendation to modify activity based on the specified risk of preterm delivery was given Work leave was encouraged after 24 weeks' gestation, frequent testing for bacterial vaginosis was preformed by wet smear. Social workers were used to obtain emergency	Twin clinic= 2/30 (7%) Standard care= 4/41 (9%) Not significant (p value not reported) <u>Caesarean section rate</u> Twin clinic= 12/30 (40%) Standard care= 19/41 (44%) Not significant (p value not reported) Neonatal outcomes <u>Birth <36 weeks</u> Twin clinic= 19/30 (32.1%) Standard care= 34/41 (41%) P<0.08 <u>Birth <30 weeks</u> Twin clinic= 0/30 Standard care= 12/41 P<0.01 <u>Mean birthweight (g)</u> Twin clinic= 2,413 (±77) CI 2,259 to 3,005 Standard care= 2,164 (±78) CI 2008 to 2320.6 P<0.03 <u>Very low birthweight (<1500 g)</u> Twin clinic= 5/30 Standard care= 16/41 P<0.08 <u>Mean NICU stay (days)</u> Twin clinic 7.8 (±1.7) CI: 4.4, 14.3 Standard care 17 (±3.21) CI: 10.6, 23.4 P<0.007	

Study details	Participants	Investigation	Outcome measures and results	Comments
		financial aid in the absence of funds resulting from work leave <u>Control group</u> Women had no consistent care provider and no specialised protocols were followed Women were seen by residents or faculty member at 1-3 week intervals, they received no special teaching on premature labour signs and symptoms, no home visits, and were given inconsistent work leave recommendation and nutritional interventions Consultation with maternal fetal medicine specialist was available for both groups. Residents and obstetrics faculty attended all the deliveries for both comparison and the specialised care group <u>Data analysis</u> Data were extracted from review of medical records SPSS was used. Differences between the two groups were compared using Student's t test for nominal variable and the $\chi 2$ test for differences among categorical variables	<u>Perinatal mortality</u> Twin clinic= 1/30 Standard care= 2/41 P=NS	

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?

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Dubois 1991[55] Country: Canada Study design: Retrospective cohort study Study dates: 1974 to 1988 Aim of study: To evaluate the impact of the Higgins Nutrition Intervention Program on twin-pregnancy outcome The Higgins method was created at the Montreal Diet Dispensary to help compensate for the effect of the risk factors for adverse pregnancy outcome that are frequently observed in socially	Population: N = 520 women with twin pregnancies (1040 twins) 177 women (354 twins) were treated with the Higgins method and 343 women (686 twins) were not Inclusion criteria: Women with twin pregnancies that resulted in live births of both twins, identified from records of 18 hospitals in Montreal, Canada. Exclusion criteria: Women with miscarriage of one or both foetuses; women lost to follow up; women with missing data; women first admitted to other hospitals outside the Montreal area. Other details: 50% of mothers in the intervention group and 13% in the comparison group were non-white (statistically significant). Details of chorionicity not	Investigation: Higgins Nutrition Intervention Program Comparison: Normal antenatal care Methods described adequately? Yes A review of medical charts was undertaken; the intervention group consisted of women with twin pregnancies who were treated with the Higgins programme at the Montreal Diet Dispensary between 1974 and 1988 and whose twins were born at 18 Montreal-area hospitals; the comparison group was a randomly selected subgroup of all women with twin pregnancies that were not treated with the Higgins programme but whose babies were born at the same hospitals. Under the Higgins programme, women with twin pregnancies were prescribed with an additional daily intake	Pregnancy-induced hypertension Higgins Nutrition group = 21*/177 (12%) Normal antenatal care group = 52*/343 (15%) P = not stated; not significant Maternal weight gain (mean ± SD) Higgins Nutrition Intervention group = 18 ± 7 kg Normal antenatal care group = 16 ± 6 kg P <0.05 Preterm birth (<37 weeks) Higgins Nutrition group = 142*/354 (40%) Normal antenatal care group= 322*/686 (47%) Test for statistical significance not reported Very preterm birth (<34 weeks) Higgins Nutrition group = 64*/354 (18%) Normal antenatal care group = 110*/686 (16%) Test for statistical significance not reported Birth weight (mean ± SD) Higgins Nutrition group = 2468 ± 559 g Normal antenatal care group = 2378 ± 620 g Test for statistical significance not reported Results of multivariable analysis (adjusted for pregravid weight, socioeconomic status, previous obstetric history, smoking, underlying medical conditions, infant sex, hospital and year of delivery): Adjusted birthweight difference between groups (mean ± SD)= 80 ± 42 g; P = <0.06 Adjusted odds ratio for preterm delivery = 0.68 (0.51 to 0.92) Adjusted odds ratio for very preterm delivery =	Funding: Not reported Limitations: Main limitation is the retrospective nature of the study There were significant differences between women in the intervention and comparison groups with regards to race, marital and socioeconomic status.

Study details	Participants	Investigation	Outcome measures and results	Comments
disadvantaged women	reported	of 1000 kilocalories and 50g protein, after the 20th week of pregnancy. Details reported. Descriptive data on maternal and neonatal outcomes were presented. Multivariable analyses adjusted for effects of key confounding variables were also reported	0.96 (0.64 to 1.44) Adjusted odds ratio for low birth weight = 0.73 (0.54 to 0.99) Adjusted odds ratio for very low birth weight = 0.53 (0.29 to 0.97) * Calculations carried out by the NCC-WCH technical team	
First author, year: Villar 2009[56] Study design: Multicentre, placebo-controlled, double-blind RCT Countries: India, Peru, South Africa & Viet Nam Study dates: October 2004 to December 2006 Aim of study: To determine if Vitamin C and E supplementation in high-risk pregnant women with low nutritional status	Population: N = 181 women with twin pregnancies The trial recruited a total of 1365 pregnant women with risk factors for pre-eclampsia but only data for twin pregnancies were extracted 81 of the women with twin pregnancies were randomised to receive vitamins and 100 received placebo Inclusion criteria: Pregnant women considered high risk for pre-eclampsia Exclusion criteria: Women on vitamin supplements containing ≥200 mg of vitamin C and/or ≥50 IU of vitamin	Investigation: Daily supplementation with Vitamins C and E Comparison: No supplementation (placebo) Methods described adequately? Yes Tablets and capsules were packaged as sealed blister strips of a one-week supply. The active and placebo tablets/capsules for each vitamin were identical in form, colour and taste and were provided in boxes containing four blister packs, each marked Monday to Sunday The women were instructed to take one tablet and one capsule daily and to leave unused tablets or capsules in	Pre-eclampsia in women with twin pregnancy Daily vitamins C and E group = 23/81 (28.4%) No supplementation group = 23/100 (23.0%) Relative risk = 1.2 (0.7 to 2.0)	Funding: Study supported by UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, World Health Organization The Cape Town, South Africa, study site was supported by funds provided by the United Kingdom authors Limitation: Study population is not immediately comparable to that of the UK Unequal numbers in the intervention and control groups

Study details	Participants	Investigation	Outcome measures and results	Comments
reduces pre-eclampsia The trial recruited all women with risk factors for pre-eclampsia but only data for twin pregnancies were extracted for the guidelinereview	E; women on warfarin therapy; women unable to give informed consent Other details: Eligible women, between 14 and 22 weeks pregnant, were randomly assigned to take vitamins C and E or placebo, from enrolment to delivery Vitamins were provided as tablets (1000 mg Vitamin C) or capsules (400 IU Vitamin E); identical tablets or capsules contained microcrystalline cellulose or sunflower oil, respectively Details of ethnicity or chorionicity not reported	the blister and to return the blisters at the subsequent trial visit, regardless of whether all tablets and capsules had been taken Block randomisation was used and copies of the randomisation sequence were provided to the packaging /delivery company and to those in charge of data management Data, recorded on specifically designed forms, were then transferred to an internet-based data system All data were collected and used within the context of the UK Data Protection Act; details provided		
First author, year: Olsen 2000[57] Study design: Multicentre randomised controlled trial Countries: Denmark, Scotland, Sweden, England, Italy, The Netherlands, Norway, Belgium and Russia	Population: N = 579 women with twin pregnancies The trial recruited a total of 1619 women with high-risk pregnancies but only data for twin pregnancies were extracted Of the 579 women with twin pregnancies, 289 were randomised to the fish oil group and 290 to the olive oil (placebo) group	Investigation: Daily supplementation with fish oil (Pikasol) Comparison: Daily supplementation with olive oil (placebo) Methods described adequately? Yes Both oils were provided in 1 g identical-looking, but not identical tasting, gelatine capsules. Women with twin	Pre-eclampsia Fish oil group = 14/246 (5.7%) Olive oil group = 6/251 (2.4%) Odds ratio = 2.46 (0.93 to 6.52) Preterm birth (<37 weeks) Fish oil group = 129/286 (45.1%) Olive oil group = 127/283 (44.9%) Odds ratio = 1.01 (0.73 to 1.40) Early preterm birth (<34 weeks) Fish oil group = 37/286 (12.9%) Olive oil group = 44/283 (15.5%) Odds ratio = 0.81 (0.50 to 1.29) Birthweight (mean ± SD) Fish oil group = 2512 ± 626.6 g Olive oil group = 2498 ± 598.5 g	Funding: Study was funded and supported by Concerted Action and PECO programmes of the European Commission, and the Danish National Research Foundation Fish oil and olive oil capsules were provided by Lube Ltd

Study details	Participants	Investigation	Outcome measures and results	Comments
Aim of study: To test the postulated preventive effects of dietary n-3 fatty acids (found in fish oil) on preterm delivery, intrauterine growth restriction (IUGR) and hypertension in pregnancy (PIH). The trial recruited several subsets of women but only data for women with twin pregnancies were extracted for the guideline review	Inclusion criteria: Women with an uncomplicated high risk pregnancy (previous preterm birth, IUGR, or PIH; twin pregnancy; current pre-eclampsia, suspected IUGR) of more than 16 weeks duration Exclusion criteria: Diabetes in or before pregnancy; severe fetal malformation or hydrops; suspected or previous abruptio placentae; drug or alcohol abuse; regular intake of fish oil or NSAIDs or other drugs with an effect on thrombocyte function or eicosanoid metabolism; allergy to fish products; high probability of birth soon after randomisation Other details: Details of ethnicity or chorionicity not reported.	pregnancies received four capsules of either oil per day, amounting to 2.7 g of fish oil for those randomised to fish oil. Packages with capsules were identified by a hidden number, the code of which was known only by the data manager Restricted blockwise computer generated randomisation (1:1, individual-based) was employed within strata defined by cross tabulating clinical centres against the subsets of women. Randomisation identified a package number at the relevant centre, where packages were ordered in a random way as to oil type. The packages contained enough capsules to cover the whole trial period for each woman Details of data management, sample size considerations, analytic strategy and data monitoring reported	Mean difference = 13.4 (−85.2 to 58.4) g Adjusted mean difference = 8.2 (-52.8 to 36.5) g Low birthweight (<2500 g) Fish oil group = 238/556 (42.8%) Olive oil group = 242/566 (42.8%) Odds ratio = 1.00 (0.79 to 1.27)	

Diet and lifestyle advice

Review question

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

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Luke 2003[54] Country: USA Study design: Non-randomised intervention study Study dates: 1996 to 2002 Aim of study: To evaluate the effectiveness of the University of Michigan Multiples Clinic The University of Michigan Multiples Clinic was a comprehensive antenatal regimen designed to maximise the health and nutritional status of mothers, facilitate optimal fetal growth and reduce maternal	Population: N = 529 women with dichorionic twin pregnancies 190 women took part in the programme and 339 women who did not, underwent normal antenatal care Inclusion criteria: All women with twin pregnancies that resulted in live birth of both twins at the University of Michigan Health Systems Exclusion criteria: Women with emergency transfer from outlying hospitals due to complications at the time of birth; monochorionic twin pregnancies; pregnancies with fetal death or major congenital anomalies of one or both twins Other details: 85% of participants were White, 9% African American, 2% Asian and 4% Other. The corresponding figures for non-participants were 87%, 9%, 3% and 1%, respectively	Investigation: Antenatal nutritional and educational programme for women with twin pregnancies Comparison: Normal antenatal care Methods described adequately? Yes Women participated in the programme by way of referral from a member of the healthcare team, or by self-referral The programme included fortnightly visits to a registered dietitian/nurse practitioner in addition to antenatal visits to the doctor, advice on dietary and multimineral supplementation, and additional maternal education related to diet, modification of maternal activity, individualised dietary prescription, multimineral supplementation, and serial monitoring of nutritional status	Birthweight (mean ± SD) Nutritional advice group = 2467 ± 37 g No advice group = 2217 ± 36 g Mean difference = +220.3 g; P = <0.0001 Low birthweight (<2500 g) Nutritional advice group = 78*/190 (41%) No advice group = 217*/339 (64%) Adjusted Odds ratio = 0.42 (0.29 to 0.61) Very low birthweight (<1500 g) Nutritional advice group = 10*/190 (5%) No advice group = 54*/339 (16%) Adjusted Odds ratio = 0.30 (0.15 to 0.61) Pre-eclampsia Nutritional advice group = 15*/190 (8%) No advice group = 58*/339 (17%) Adjusted Odds ratio = 0.41 (0.23 to 0.75) Preterm birth <36 weeks Nutritional advice group = 78*/190 (41%) No advice group = 180*/339 (53%) Adjusted Odds ratio = 0.62 (0.43 to 0.89) Preterm birth <32 weeks Nutritional advice group = 13*/190 (7%) No advice group = 71*/339 (21%) Adjusted Odds ratio = 0.27 (0.15 to 0.51) Preterm birth <30 weeks Nutritional advice group = 6*/190 (3%) No advice group = 31*/339 (9%) Adjusted Odds ratio = 0.29 (0.11 to 0.76) * Calculations carried out by the NCC-WCH	Funding: Supported by grants from the Office of the Vice President for Research, University of Michigan, the Gerber Foundation, and Matria Healthcare, Inc Limitations: Non-randomised study The average age of the women in the programme group was significantly older than in the non-programme group (31.5 years versus 29.7 years). There were significantly more women in the nonprogram group than the program group on Medicaid (20% versus 8%) rather than private or HMO insurance (92% versus 80%)

Study details	Participants	Investigation	Outcome measures and results	Comments
and neonatal complications and acute care costs		Patient education for both groups included discussions of environmental and work hazards, physical activity, signs of preterm labour, and travel. Women on the program also had discussions on diet, signs and symptoms of pre-eclampsia, fetal growth and development, as well as exploration of any problems of symptoms Work leave was recommended by 24 weeks' gestation or sooner with stressful physical or mental work or antenatal complications, as well as decreasing stair climbing, strenuous lifting or carrying, and limiting recreational activities to walking or swimming (not clarified whether this was for both groups or just women in the programme) Women in the programme received a dietary assessment on entry to the programme. If necessary, recommendations were made to bring the diet to 3000 to 4000 kcal/day depending on prepregnancy BMI, consisting of 20% calories from protein, 40% calories from carbohydrate and 40% calories from fat. The dietary	technical team	

Study details	Participants	Investigation	Outcome measures and results	Comments
		assessment was repeated at each visit and additional recommendations were made as needed. The diet consisted of three meals and three snacks per day Women in the program were advised to take 3g calcium carbonate, 1.2g magnesium oxide, and 45mg zinc oxide in three equal doses each day, as well as a multivitamin containing 100% of the non-pregnancy Recommended Daily Allowances (200% after 20 weeks' gestation). Participants were questioned regarding compliance and use of correct dosage at each visit Multiple logistic regression models, adjusted for maternal age, insurance status and smoking, were used to estimate odds ratios Details of study variables, power and statistical analyses reported		

Specialist clinics

Review question

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

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Luke, 2003[54] Country: USA Study design: Prospective cohort study Study dates: 1996 to 2002 Aim of study: To evaluate the effect of antenatal nutrition and education programme on twin pregnancy, neonatal and early childhood outcomes	Population: N= 529 twin pregnancies All dichorionic Inclusion criteria : All twin births at the University of Michigan Health Systems between 1996 and 2002 Exclusion criteria: Monochorionic pregnancies, pregnancies that were transferred to the hospital as an emergency, pregnancies with fetal death or major congenital abnormalities in one or both twins Maternal age (years): Study group=31.5±0.4 Control group= 29.7±0.3 P<0.0001 Entry to the programme began at average of 16 ± 0.4 weeks (range 12 to 24 weeks) Significant differences	Investigation : Twice monthly specialist clinics with a registered dietitian and nurse practitioner, additional maternal education (diet, symptoms and signs of pre-eclampsia, fetal growth), modification of maternal activity (work leave by 24 weeks' gestation; decreased stair climbing, lifting, carrying, walking and swimming), individualised dietary prescription, multimineral supplements, serial monitoring of nutritional status (n= 190) Number of programme visits averaged 6 ± 0.2 (range 3 to 9) Comparison: Standard antenatal care (n=339) Methods Women were either self-referred to the programme or referred by a member of the healthcare team All antenatal care for twin pregnancies was given by	Maternal Pre-eclampsia: Twin clinic= 15/190 (8%) Standard care= 58/339 (17%) P=0.004 Adjusted OR (AOR) 0.41 (95% CI 0.23 to 0.75) Pre-term labour: Twin clinic= 44/190 (23%) Standard care= 142/339 (42%) P<0.0001 AOR 0.45 (95% CI 0.30 to 0.68) Premature rupture of membranes: Twin clinic= 19/190 (10%) Standard care= 85/339 (25%) P<0.0001 AOR 0.35 (95% CI 0.20 to 0.60) Fetal/neonatal Delivery <36 weeks: Twin clinic=78/190 (41%) Standard care= 180/339 (53%) P=0.01 AOR 0.62 (95% CI 0.43 to 0.89) Delivery <32 weeks: Twin clinic= 13/190 (7%) Standard care= 71/339 (21%) P<0.0001	Funding: Grants from the Office of the Vice President for Research (University of Michigan), the Gerber Foundation and Matria Healthcare Inc Limitations: Women were not randomly assigned to groups. Women were either referred by a member of the healthcare team (there may have been complications that led to their referral) or self-referred to the programme There were significantly more smokers in the control group than the study group (p=0.001), which may be a confounding variable, for example, for low birthweight Pregnancies resulting in fetal death or major abnormalities were excluded

Study details	Participants	Investigation	Outcome measures and results	Comments
	between the control and study groups for private health insurance (p=0.002) and smoking (p=0.001)	resident physician, including generalists and maternal fetal medicine specialist Women in both groups (programme and non-programme) had regular antenatal visits with primary care physician. Education for both programme and non-programme mothers included discussion of environment and work hazards, physical activity, travel and sign of preterm labour Ultrasonic measures of fetal growth were obtained at 18 to 20 weeks' gestation and again at 24, 28 and 32 weeks' gestation Neonatal development in both programme and non-programme groups was followed at 8 months, 18 months and three years of age	AOR 0.27 (0.15 to 0.51) Delivery <30 weeks: Twin clinic= 6/190 (3%) Standard care= 31/339 (9%) P= 0.01 AOR 0.29 (0.11 to 0.76) Delivery ≥36 weeks: Twin clinic= 112/190 (59%) Standard care=159/339 (47%) P= 0.01 AOR 1.62 (95% CI 1.12 to 2.34) Low birthweight: Twin clinic= 78/190 (41%) Standard care=217/339 (64%) P<0.0001 AOR 0.42 (95% CI 0.29 to 0.61) Very low birthweight: Twin clinic=10/190 (5%) Standard care= 54/339 (16%) P=0.001 AOR 0.30 (95% CI 0.15 to 0.61) Non-low birthweight: Twin clinic= 112/190 (59%) Standard care= 122.339 (36%) P<0.0001 AOR 2.40 (95% CI 1.65 to 3.48) NICU admissions: Twin clinic= 82/190 (43%) Standard care= 210/339 (62%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			P<0.0001 AOR 0.48 (95% CI 0.36 to 0.64) Intravenous fluids: Twin clinic= 72/190 (38%) Standard care= 200/339 (59%) P<0.0001 AOR 0.43 (95% CI 0.32 to 0.57) Antibiotics: Twin clinic= 80/190 (42%) Standard care= 203/339 (60%) P<0.0001 AOR 0.50 (95% CI 0.37 to 0.67) Supplemental oxygen: Twin clinic= 53/190 (28%) Standard care= 153/339 (45%) P<0.0001 AOR 0.49 (95% CI 0.36 to 0.67) Mechanical ventilation: Twin clinic= 29/190 (15%) Standard care= 102/339 (30%) P<0.0001 AOR 0.41 (95% CI 0.28 to 0.59) Phototherapy: Twin clinic= 30/190 (16%) Standard care= 125/339 (37%) P<0.0001 AOR 0.34 (95% CI 0.24 to 0.49) Parenteral nutrition: Twin clinic= 25/190 (13%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Standard care= 105/339 (31%) P<0.0001 AOR 0.32 (95% CI 0.22 to 0.46) Respiratory distress syndrome: Twin clinic= 34/109 (18%) Standard care= 105/339 (31%) P<0.0001 AOR 0.49 (95% CI 0.35 to 0.69) Apnea, bradycardia or cyanosis: Twin clinic= 13/109 (7%) Standard care= 78/339 (23%) P<0.0001 AOR 0.27 (95% CI 0.17 to 0.44) Anaemia: Twin clinic= 8/190 (4%) Standard care= 44/339 (13%) P<0.0001 AOR 0.31 (95% CI 0.17 to 0.56) Hyperbilirubinaemia: Twin clinic= 36/190 (19%) Standard care= 98/339 (29%) P=0.001 AOR 0.56 (95% CI 0.40 to 0.79) Patent ductus arteriosus: Twin clinic= 4/190 (2%) Standard care= 17/339 (5%) P=0.02 AOR 0.37 (95% CI 0.15 to 0.88) Retinopathy of prematurity:	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Twin clinic= 2/190 (1%) Standard care= 24/339 (7%) P=0.001 AOR 0.19 (95% CI 0.07 to 0.50) Necrotising enterocolitis: Twin clinic= 2/190 (1%) Standard care= 10/339 (3%) P=0.04 AOR 0.21 (95% CI 0.05 to 0.95) Major morbidity (retinopathy of prematurity, necrotising enterocolitis, ventilator support, or intraventricular haemorrhage): Twin clinic= 32/190 (17%) Standard care= 108/339 (32%) P<0.0001 AOR 0.44 (95% CI 0.31 to 0.62)	
First author, year: Ellings, 1993[52] Country: USA Study design: Prospective cohort Study dates: 1988 to 1993 Aim of study: To determine whether a specialised twin clinic is successful	Population: N= 140 twin pregnancies Chorionicity not reported Inclusion criteria : Twins followed in the clinic and twins not in the clinic between 1988 and 1993 No patient selection process was used for the twin clinic Exclusion criteria: Not reported Groups were similar on all	Investigation : Twin clinic (n=89 twin pregnancies) Comparison: Standard 'high risk' antenatal care (n= 51 twin pregnancies) Methods Twin clinic: Care was provided by a multidisciplinary team Monthly ultrasound evaluation preformed by a certified technologist	Maternal outcomes Premature rupture of membranes: Twin clinic= 11/89 (12%) High risk clinic= 13/51 (25%) Not significant (p value not reported) Bleeding ≥20 weeks: Twin clinic= 2/89 (2%) High risk clinic= 4/51 (8%) Not significant (p value not reported) Anemia (Hgb<10 mg/dl): Twin clinic= 17/89 (19%) High risk clinic= 11/51 (22%) Not significant (p value not reported) Pre-eclampsia:	Funding: Not reported Limitations: Not randomised allocation. Many of the women in the control group were not referred to the twin clinic because of transportation or other logistic difficulties (although there were no significant differences in demographic information) A few women were found to have a multiple pregnancy late in pregnancy and were unlikely to benefit from twin clinic (and

Study details	Participants	Investigation	Outcome measures and results	Comments
	maternal demographic variables (age, black race, gravity, parity, marriage, school education, public fund, month antenatal care began, and median number of antenatal visits)	Nutritional status was monitored weekly by assessing weight gain and laboratory evaluation Dietary counselling provided by a nutritional consultant was reinforced at each clinic visit by the certified nurse-midwife Social service evaluation was conducted early in pregnancy to develop support and assistance as needed A board-certified specialist in maternal fetal medicine provided obstetric consultation and oversaw all the clinic activities Women were educated in the individualised teaching session about signs and symptoms of preterm labour and self-palpation of uterine contractions Digital cervical examination at each visit after 20 weeks' gestation Control group: Attended the high risk obstetric clinic by the obstetric faculty	Twin clinic= 10/89 (11%) High risk clinic= 4/51 (8%) Not significant (p value not reported) Gestational diabetes: Twin clinic= 6/89 (7%) High risk clinic= 1/51 (2%) Not significant (p value not reported) Urinary tract infection: Twin clinic= 4/89 (4%) High risk clinic= 3/51 (6%) Not significant (p value not reported) Caesarean section rate: Twin clinic= 29/89 (33%) High risk clinic= 15/51 (29%) Not significant (p value not reported) <u>Neonatal outcomes</u> Preterm Birth (<37 weeks): Twin clinic= 138/178 (78%) High risk clinic= 74/102 (73%) Not significant (p value not reported) Preterm Birth (<30 weeks): Twin clinic= 4/178 (2.2%) High risk clinic= 18/102 (17.6%) P= 0.003 Very low birthweight (<1500g): Twin clinic= 10/178 (6%) High risk clinic= 27/102 (26%) P<0.0001	therefore not referred to the specialist clinic) There are a relatively small number of cases for each outcome, e.g. preterm birth <30 weeks The study dates span a five year period, during which neonatal outcomes could have improved with better standards of healthcare The results for perinatal mortality could have been affected by preterm birth rates

Study details	Participants	Investigation	Outcome measures and results	Comments
		and resident staff	NICU admission: Twin clinic= 24/178 (13%) High risk clinic= 39/102 (38%) P<0.0001 Perinatal mortality: Twin clinic= 1/178 (1%) High risk clinic= 8/102 (8%) P<0.0002	
First author, year: Ruiz, 2001[53] Country: USA Study design: Retrospective cohort study Study dates: 1995 to 1997 Aim of study: To determine the effectiveness of a twin clinic and its economic impact	Population: N= 71 twin pregnancies Chorionicity not reported Inclusion criteria: Newborn babies of women who received care from a twin clinic Exclusion criteria: Women receiving antenatal care after 30 weeks The standard care group received care from January 1995 to February 1996 The two groups were similar on all maternal demographic variables (age, race, gravity, parity, marriage, insurance status, number of antenatal visits)	Investigation: Maternal and neonatal outcomes in those who received care in a twin clinic (n=30 twin pregnancies) Comparison: Maternal and neonatal outcomes in those who received standard care and had given birth 1 year before (n=41 twin pregnancies) Methods Twin clinic: Primary care from a nurse practitioner, with a weekly consultation and review by a perinatologist Visits scheduled every other week until 24 weeks. From 24 weeks visits were weekly A nutritionist, social workers, and genetic counsellor were	Maternal outcomes Anaemia: Twin clinic= 5/30 (16%) Standard care= 7/41 (16%) Not significant (p value not reported) Gestational hypertension: Twin clinic= 5/30 (16%) Standard care= 6/41 (14%) Not significant (p value not reported) Gestational diabetes: Twin clinic= 1/30 (3%) Standard care= 0/41 Not significant (p value not reported) Urinary tract infection: Twin clinic= 2/30 (7%) Standard care= 4/41 (9%) Not significant (p value not reported) Caesarean section rate: Twin clinic= 12/30 (40%) Standard care= 19/41 (44%) Not significant (p value not reported)	Funding: Not reported Limitations: Retrospective study where women were not randomly assigned to groups The women in the control group received their care prior to the intervention group – some of the improvements attributed to the specialist clinics may have resulted from changes in practice during this time Preterm birth results may have been affected by the different healthcare professionals involved – the standard care group saw different healthcare professionals at each visit, and so the decision to deliver early could have been made by any of them (especially as there were no standardised protocols

Study details	Participants	Investigation	Outcome measures and results	Comments
		available as support Preterm labour risk assessment, psychological and nutrition assessment preformed by the nurse practitioner Between 20-24 weeks' gestation, the nurse practitioner made a home visit to assess problems and perform a general environment and stress assessment Women were also provided with leaflets and information regarding signs and symptoms of preterm labour at the home visit In each antenatal visit symptoms of preterm labour were assessed, a cervical examination preformed and recommendation to modify activity based on the specified risk of preterm delivery was given Work leave was encouraged after 24 weeks' gestation. Social workers were used to obtain emergency financial aid in the absence of funds resulting from work leave	<u>Neonatal outcomes</u> Preterm birth (<36 weeks): Twin clinic= 38/60 (32.1%) Standard care= 68/82 (41%) P<0.08 Preterm birth (<30 weeks): Twin clinic= 0/60 (0%) Standard care= 24/82 (29%) P<0.01 Mean birthweight (g): Twin clinic= 2,413 (±77; 95% CI 2,259 to 3,005) Standard care= 2,164 (±78; 95% CI 2008 to 2320.6) P<0.03 Very low birthweight (<1500 g): Twin clinic= 10/60 (17%) Standard care= 32/82 (39%) P<0.08 Mean NICU Stay (days): Twin clinic= 7.8 (±1.7; 95% CI 4.4 to 14.3) Standard care= 17 (±3.21; 95% CI 10.6 to 23.4) P<0.007 Perinatal mortality: Twin clinic= 2/60 (3%) Standard care= 4/82 (5%) Not significant (p value not reported)	to determine when to deliver). The twin clinic had a designated healthcare professional and the decision to deliver early was made by them (so they were less likely to be delivered early that the standard care group)

Study details	Participants	Investigation	Outcome measures and results	Comments
		Frequent testing for bacterial vaginosis was performed by wet smear Control group: No consistent care provider and no specialised protocols were followed Women were seen by residents or faculty member at 1 to 3 week intervals No special teaching on premature labour signs and symptoms, no home visits, were given, inconsistent work leave recommendation and nutritional interventions Consultation with maternal fetal medicine specialist was available for both groups. Residents and obstetrics faculty attended all the deliveries for both comparison and the specialised care group		
First author, year: Kogan, 2000[60] Country: USA Study design:	Population: N before exclusion= 1,479,862 twin pregnancies N after exclusion not reported, estimated to be around 811,505 twin pregnancies	Investigation and comparison : Level of antenatal care (intensive, adequate or less than adequate)	All twin pregnancies (1989 to 1997): Intensive= 165,120 Adequate= 425,876 Less than adequate= 220,509 Term or post-term birth (1989 to 1997, n= 404,260):	* data calculated from a small graph in the paper ** statistics calculated by NCC-WCH technical team Use of antenatal care measured by R-GINDEX – based on calculations of when

Study details	Participants	Investigation	Outcome measures and results	Comments
Retrospective cohort study Study dates: 1981 to 1997 Aim of study: The determine whether more aggressive management of twin pregnancies affects birth outcomes	 Inclusion criteria: Twin pregnancies Data from National Center for Health Statistics maternity files from 1981 to 1997 and the National Center for Health Statistics 1983 to 1984, 1989 to 1990 and 1995 to 1996 Exclusion criteria: Inconsistent or missing data on antenatal care or the length of gestation (excluded between 5% and 7% of records each year) Gestational age at delivery not reported Maternal age not reported		Intensive= 81,615/165,120 (49%) Adequate= 188,678/425,876 (44%) Less than adequate= 133,967/220,509 (61%) Significance levels not reported **OR of intensive versus. adequate= 1.12 (95% CI 1.10 to 1.13) **OR of adequate versus. less than adequate= 0.73 (95% CI 0.72 to 0.74) **OR of intensive versus less than adequate= 0.81 (95% CI 0.80 to 0.82) Infant mortality rates per 1000 live births by use of antenatal care (number of deaths) (1983 to 1984): Intensive= 27.6 (95% CI 24.6 to 30.5) (343) Adequate= 53.8 (95% CI 51.9 to 55.8) (3291) Less than adequate= 51.0 (95% CI 48.9 to 53.1) (2433) Overall infant mortality rate= 50.0 (95% CI 48.7 to 51.3) (5977) Significant z test score for intensive versus overall, and adequate versus overall groups (p value not reported) Infant mortality rates per 1000 live births by use of antenatal care (number of deaths) (1989 to 1990): Intensive= 22.1 (95% CI 20.5 to 23.7) (713) Adequate= 43.4 (95% CI 42.0 to 44.8) (3735) Less than adequate= 48.5 (95% CI 46.6 to 50.4) (2721) Overall infant mortality rate= 41.1 (95% CI 40.1 to 42.1) (7169) Significant z test score for intensive versus overall, adequate versus overall, and less	a woman began care and the number of visits she received, adjusted for the length of gestation at delivery Excessively large number of antenatal care visits= 1 standard deviation above the mean number of visits Preterm birth – delivery between 20 and 36 weeks Low birthweight – babies weighing less than 2500g Small for gestational age – 10th percentile of birthweight values of 1991 USA cohort From 1989 to 1997, clinical estimate of gestation age was used when the date of the last menstrual period was not reported, or where the date of the last menstrual period was inconsistent with birthweight Data reported for three groups (preterm and induced; preterm and first Caesarean delivery; preterm without procedures), but the authors did not report clearly whether the groups were mutually exclusive or whether they contained, for example, term births that were induced. These data are, therefore, not reported here Funding: One author supported in part

Study details	Participants	Investigation	Outcome measures and results	Comments
			intensive versus overall groups (p value not reported) Infant mortality rates per 1000 live births by use of antenatal care (number of deaths) (1995 to 1996): Intensive= 17.8 (95% CI 16.5 to 19.1) (726) Adequate= 33.0 (95% CI 31.9 to 34.1) (3350) Less than adequate= 32.8 (95% CI 31.0 to 34.5) (1410) Overall infant mortality rate= 29.2 (95% CI 28.4 to 30.0) (5486) Significant z test score for intensive versus overall, adequate vesus overall, and less intensive versus overall groups (p value not reported) Preterm small for gestational age rate per 100 twin births (1981): Intensive= 8.7 Adequate= 13.4 Less than adequate= 10.9 Significance level not reported Preterm small for gestational age rate per 100 twin births (1997): Intensive= 14.0 Adequate= 14.6 Less than adequate= 12.4 Significance level not reported Term small for gestational age rate per 100 twin births (1981): Intensive= 28.9 Adequate= 22.0	by DHHS, HRSA, MCHB grant MCJ-9040. Two other authors supported in part by DHHS, HRSA, MCHB grant MCJ-107 Limitations: The intensive group may have had more monitoring due to more complications, which would bias the results

Study details	Participants	Investigation	Outcome measures and results	Comments
			Less than adequate= 40.5 Significance level not reported Term small for gestational age rate per 100 twin births (1997): Intensive= 19.1 Adequate= 17.0 Less than adequate= 31.9 Significance level not reported *Preterm birth rate per 100 live births (1981): Intensive= 35 Adequate= 51 Less than adequate= 32 Significance level not reported *Preterm birth rate per 100 live births (1997): Intensive= 55 Adequate= 60 Less than adequate= 41 Significance level not reported	
First author, year: Dodd, 2009[61] Country: Australia Study design: Systematic review Study dates: Searches from Cochrane Pregnancy and Childbirth Group's Trial Register (Oct	Population: Women with multiple pregnancy Inclusion criteria: RCTs that compared outcomes in women and babies who received specialist antenatal care to those who received standard antenatal care Exclusion criteria: Not reported	Investigation: Specialist antenatal clinics Comparison: Standard antenatal care	No relevant studies were identified	This is a Cochrane review Funding: One author: Neil Hamilton Fairly Fellowship supported by the NHMRC (ID 399224)

Study details	Participants	Investigation	Outcome measures and results	Comments
1996), Cochrane Central register of Controlled Trials (2005, issue 4) and PubMed (Jan 1966 to Jan 2006) Aim of study: To assess the effectiveness of specialist multiple pregnancy clinics				

Chapter 6 Fetal complications

Screening for chromosomal abnormalities

Review question

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

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
First author, year: Gonce 2005[63] Aim of study: To evaluate the effectiveness of the addition of biochemistry to fetal nuchal translucency measure-ment in the combined test when screening for	Population: N= 100 twin pregnancies 12 pregnancies were monochor-ionic, 88 were dichorionic Attending department for antenatal care or referred for first trimester aneuploidy screening Mean maternal	Index test: Ultrasound between 11-14 weeks. CRL measured and NT thickness assessed using Fetal Medicine Foundation (FMF) guidelines. Larger of 2 CRLs used to estimate the overall gestational age of the pregnancy	NT + maternal age Risk > 1:250 All chorionicities	3	17	0	166	100* (29 to 100*)	91* (87 to 95*)	15* (0 to 31*)	100* (98 to 100*)	10.76* (6.85 to 16.93*)	0.00* (0.01 to 0.85*)	All TP cases of trisomy 21; 2 resulted from one monochorionic pregnancy The risk was calculated differently depending on when the women were enrolled in the study. It is not clear how many women had their risk calculated in a particular way
			Combined NT+ f-beta-hCG+ PAPP-A+ maternal age Risk > 1: 250 All chorionicities	3	7	0	190	100* (29 to 100)	96* (93 to 99)	30* (2 to 58*)	100* (98 to 100*)	23.1* (10.4 to 51.1)	0.13* (0.01 to 1.74)	
			NT + maternal age Risk > 1:250 In monochorionic pregnancies	2	2	0	20	100* (16 to 100*)	91* (79 to 100*)	50* (10 to 99*)	100* (83 to 100*)	11.00* (2.14 to 27*)	0.00* (0.01 to 2.36*)	
			Combined NT+ f-beta-hCG+ PAPP-A+ maternal age Risk > 1: 250	2	2	0	20	100* (16 to 100*)	91* (79 to 100*)	50* (10 to 99*)	100* (83 to 100*)	11.00* (2.14 to 27*)	0.00* (0.01 to 2.36*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
trisomy 21 in twin pregnancies Setting: Antenatal diagnosis unit, Barcelona, Spain July 2001-December 2003 Study design: Prospective cohort, however only NT results applied clinically, combined test calculated retrospect-	age 33.3years (range 23-42 years) 56 pregnancies resulted from assisted reproduction, 12 monochorionic Inclusion criteria: Both fetuses alive at 11-14 week scan Exclusion criteria: Lost to follow up (n=2) and where diagnostic procedure cancelled on death of affected fetus	Blood for free beta-hCG and PAPP-A taken at 8-12 weeks, values converted into multiples of the median (MoM) for the corresponding gestational age after correction for the presence of twins (as per Spencer 2000) High risk defined as greater than 1:250 Reference test: Karyotype for trisomy 21 offered to high-	In monochorionic pregnancies										It was not possible to calculate the diagnostic accuracy of the tests separately for monochorionic and dichorionic pregnancies as the number of false positives and false negatives were not reported separately CVS performed in 25 women, amniocentesis in 10. 10 procedures because of
			NT + maternal age Risk > 1:250 In dichorionic pregnancies	1*	15*	0*	160 *	100* (3 to 100*)	91* (87 to 96*)	6* (0 to 18*)	100* (98 to 100*)	11.67* (3.36 to 22*)	0.00* (0.02 to 3.02*)	
			Combined NT+ f-beta-hCG+ PAPP-A+ maternal age Risk > 1: 250 In dichorionic pregnancies	1*	5*	0*	170 *	100* (3 to 100*)	97* (95 to 99.6*)	17* (0 to 46*)	100* (98 to 100*)	35.00* (14.75 to 83*)	0.00* (0.02 to 2.85*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
ively	(n=1)	risk women on index test, women aged 35 years or more, or other risk (1 choroid plexus cysts, 1 carrier of balanced translocation). Data regarding perinatal outcome ascertained from delivery room records or by phone enquiry if not delivered in study centre												positive screening test result, 10 because of advanced maternal age despite low-risk result, 3 parental anxiety and 2 other reasons Blinding of reference standard not reported No clinically important outcomes reported Source of funding not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Leung 2007[69] Aim of study: To evaluate the effectiveness of first trimester trisomy 21 screening using a combination of maternal age, nuchal translucency thickness and maternal serum free beta-hCG and PAPP-A levels in a predomin-antly Chinese population	Population: N= 57 twin pregnancies from total of 2990 in screening programme Chorionicity not reported Inclusion criteria: Women attending for first trimester combined screening programme FMF screening programme protocols adhered to including case selection, measurement of NT and	Index test: Ultrasound measurement of NT between 11^{+0} and 13^{+6} weeks' gestation, serum sample performed at the same time and measured immediately, risk of trisomy 21 calculated using the FMF algorithm and software. Risk for each fetus calculated on the individual NT and maternal serum biochemistry corrected for twin pregnancy. For monoamniotic	Combined NT + free beta-hCG + PAPP-A according to FMF Risk ≥ 1:300	1	6	0	107	100* (29 to 100)	95* (89 to 98)	14* (0 to 40*)	100* (97 to 100*)	13.2* (4.4 to 39.3)	0.27* (0.02 to 2.92)	TP case trisomy 21 As the chorionicity was not reported, it was not possible to analyse the data separately for monochorionic and dichorionic pregnancies In overall study population (2990 pregnancies) 18 lost to follow up, however not possible to tell from paper if any of these

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Setting: University hospital, Hong Kong Study design: Prospective cohort study	biochemical analysis Exclusion criteria: None specified	twin pairs, the highest calculated risk among the cotwins was used Risk of 1:300 or greater was regarded as screen positive test result and invasive test offered Reference test: Karyotype if invasive test offered, outcome ascertained in others but method not described												were from the twin group Blinding of reference standard not reported Source of funding not reported
First author, year:	Population: N= 448 twin	Index test: Nuchal	NT > 95th centile All twin fetuses,	10	43	1	842	91* (74 to	95* (94 to	19* (8 to	99.8* (99.6	18.71* (13.23	0.10* (0.01	TP= 7 fetuses with T21, 3

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Sebire 1996[65] Aim of study: To determine the prevalence of increased fetal nuchal translucency in twin pregnancies and evaluate screening for trisomy 21 by a combination of translucency thickness and maternal age Setting: Fetal medicine	pregnancies 95 monochorionic twin pregnancies (86 conceived spontane-ously) 353 dichorionic twin pregnancies (231 conceived spontane-ously) Inclusion criteria: Fetal crown-rump length 38-84 mm Exclusion criteria:	translucency > 95th centile (Pandya 1995) for crown-rump length alone or in combination with maternal age When combined with maternal age risk >1 in 300 defined as high risk Reference test: Karyotype in 64 cases, method or rate of ascertainment of outcome in other cases not reported	T21, T18 or T13					100*)	97*)	29*)	to 100*)	to 26.45*)	to 0.62*)	with other abnormalities FN= 1 fetus with T21, 1 with other abnormality Other abnormalities included 2 fetuses with T13 (1 concordant pregnancy), 1 T18, 1 unbalanced translocation. Of T21 pregnancies 2 concordant 4 discordant All chromosomal abnormalities occurred in dichorionic
			NT > 95th centile All twin fetuses, trisomy 21	7	58	1	830	88* (47-100)	94* (92-97)	11* (3 to 18*)	99.8* (99 to 100*)	13.4* (9.3-19.2)	0.13* (0.02-0.84)	
			NT > 95th centile Dichorionic twins, T21, T18 or T13	10	27	1	668	91* (74 to 100*)	96* (95 to 98*)	27* (13 to 41*)	99.8* (99 to 100*)	23.40* (15.46 to 35.41*)	0.09* (0.01 to 0.61*)	
			NT > 95th centile, Monochorionic twins, any chromosomal abnormality	0	16	0	190	NC*	92 (89 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			NT > 95th centile, Monochorionic twins, T21	0	16	0	190	NC*	92 (89 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			NT > 95th centile, Monochorionic twins, T18	0	16	0	190	NC*	92 (89 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			NT > 95th centile, Monochorionic twins, other chromosomal abnormality	0	16	0	190	NC*	92 (89 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
centre, London September 1992-August 1995 <u>Study design</u> Prospective screening study	Not reported		NT + Maternal age risk >1: 300 to detect T21	8	167	0	721	100 (63 to 100)	81 (79 to 84)	5 (1 to 8*)	100 (99 to 100*)	5.0* (4.1 to 6.2)	0.07* (0.01 to 1.01)	twin pregnancies NB: Same centre as Vandecruys 2005[64] and overlap in study dates therefore likely overlap in population. The Vandecruys study, however, only includes monochorionic pregnancies Unable to analyse T18 and T13 separately due to reporting in the paper

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
														Blinding of reference standard not reported Study funded by a grant from the Fetal Medicine Foundation
<u>First author, year:</u> Vandecruys 2005[64] <u>Aim of study:</u> To determine whether screening for trisomy 21 in monochor-ionic pregnancies using measure-	<u>Population:</u> N= 769 monochorionic twin pregnancies Median maternal age 33 (range 16-45 years) Median gestational age 12 weeks (range 11-13^{+6})	<u>Index test:</u> Nuchal translucency for each fetus (threshold > 95^{th} centile) Pregnancy risk using NT and maternal age using largest, smallest or an average of the NT measurements	NT ≥ 95^{th} centile to detect T21 and T18	12	160	2	1364	86* (67 to 100*)	90* (88 to 91*)	7* (3 to 11*)	99.8* (99 to 100*)	8.16* (6.30 to 10.58*)	0.16* (0.04 to 0.58*)	Any anomaly TP=10 T21, 2 T18. FN= 2 T21, 2 XXX NB: Same centre as Sebire 1996[65] and overlap in study dates therefore likely overlap in population. However, Sebire study also includes
			NT ≥ 95th centile to detect T21	10	162	2	1362	83 (52 to 98)	89 (88 to 91)	6 (2 to 9*)	99.8 (99 to 100*)	7.8* (5.9-10.5)	0.19* (0.05-0.66)	
			NT ≥ 95^{th} centile to detect T18	2	170	0	1366	100 (16 to 100)	89 (87 to 91)	1 (0 to 3*)	100 (99 to 100*)	7.5* (4.4 to 12.7)	0.19* (0.02 to 2.35)	
			NT ≥ 95^{th} centile to detect other chromosomal abnormalities	0	170	2	1366	0* (0 to 0*)	89* (87 to 91*)	0* (0 to 0*)	99.8 (99 to 100*)	0.00* (NC*)	1.12* (1.10 to 1.14*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
ment of NT is better using the higher, smaller or average NT Setting: Fetal medicine centre, London January 1993-May 2004 Study design: Retrospect-ive cohort study	Inclusion criteria: Both fetuses alive at 11 to 13^{+6} week scan and pregnancy outcome or karyotype known Exclusion criteria: Pregnancy outcome unknown	Reference test: Karyotype or pregnancy outcome known	NT and age risk ≥ 1/300 per pregnancy using fetus with highest NT, T21	6	148	0	613	100 (54-100)	81 (78-83)	4 (1 to 7*)	100 (99 to 100*)	4.8* (3.7-6.1)	0.09* (0.01-1.28)	dichorionic pregnancies It was not possible to calculate accuracy data for NT and age risk ≥1:300 per pregnancy for all anomalies, T18 or other anomalies Blinding of reference standard not reported Study funded by a grant from the Fetal Medicine Foundation
			NT and age risk ≥ 1/300 per pregnancy using fetus with smallest NT, T21	4	57	2	704	67* (22-96)	93* (90-94)	7* (0 to 13*)	99.7* (99 to 100*)	8.9* (4.8-16.5)	0.36* (0.12-1.12)	
			NT and age risk ≥ 1/300 per pregnancy using average of NT, T21	6	106	0	655	100* (54-100)	86* (83-89)	5* (1 to 10*)	100* (99 to 100*)	6.6* (5.1-8.7)	0.08* (0.01-1.20)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Gonce 2010[67] Aim of study: To evaluate the prevalence of and perinatal outcome associated with increased NT thickness in dichorionic and monochor-ionic twins with normal karyotype Setting: Fetal medicine department,	Population: N= 206 consecutive twin pregnancies seen for routine screening or referred due to an increased risk of chromosomal abnormalities Mean maternal age 33.4 years (range 27-39 years) and mean CRL 60 mm (range 45-84 years) 166 dichorionic 40 monochorionic	Index test: NT ultrasound performed by experienced sonographers certified by the Fetal Medicine Foundation (FMF), NT measurements according to FMF guidelines Reference test: Karyotype or clinical outcome	NT > 99th percentile in all fetuses to detect T21	1	11	1	399	50* (0 to 100*)	97* (96 to 99*)	8* (0 to 24*)	99.7* (99 to 100*)	18.64* (4.14 to 83.82*)	0.51* (0.13 to 2.05*)	TP= 1 T21, 1 X0. FN= 1 T21, 1 XXY NB Some overlap in study period with Gonce 2005 [63] Blinding of reference standard not reported Source of funding: 2 authors supported by hospital clinic research grants
			NT > 99th percentile dichorionic fetuses to detect any chromosome anomaly	2	5	2	323	50* (7 to 93)	99* (97 to 100)	29* (0 to 62*)	99* (99 to 100*)	32.8* (8.8 to 121.6)	0.51* (0.19 to 1.35)	
			NT > 99th percentile dichorionic fetuses to detect T21	1	6	1	324	50* (1 to 99)	98* (96 to 99)	14* (0 to 40*)	99.7* (99 to 100*)	27.5* (5.6 to 135.8)	0.51* (0.13 to 2.04)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Barcelona, Spain October 2002-September 2006 <u>Study design:</u> Prospective cohort study	<u>Inclusion criteria:</u> Both fetuses alive at the 11^{+0} to 13^{+6} week scan <u>Exclusion criteria:</u> Not reported		NT > 99th percentile dichorionic fetuses to detect other chromosomal anomalies	1	6	1	324	50* (1 to 99)	98* (96 to 99)	14* (0 to 40*)	99.7* (99 to 100*)	27.5* (5.6 to 135.8)	0.51* (0.13 to 2.04)	
			NT > 99th percentile to detect any chromosome anomaly monochorionic fetuses	0	5	0	75	NC*	97* (95 to 100*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			NT > 99th percentile monochorionic fetuses to detect T21	0	5	0	75	NC*	97* (95 to 100*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			NT > 99th percentile monochorionic fetuses to detect other chromosomal anomalies	0	5	0	75	NC*	97* (95 to 100*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
First author, year: Sepulveda 2009[66] Aim of study: To report experience with first-trimester screening for chromosom-al abnormal-ities in multiple pregnancy	Population: N= 206 twin pregnancies 8 triplet pregnancies 1 quadruplet pregnancy (excluded from guideline analysis) Of twins: 175 dichorionic, 31 monochorionic	Index test: Ultrasound Nuchal translucency measurement at 11-13+6 weeks' gestation, following FMF guidelines Reference test: Karyotype and review of maternal and	Nuchal translucency > 95th centile to detect T21 and T18	4	9	0	422	100* (40 to 100*)	98* (97 to 99*)	31* (6 to 56*)	100* (99 to 100*)	47.89* (25.09 to 91.41*)	0.00* (0.01 to 1.42)	TP= 3 T21, 1 T18, 1 45 X. FN= 1 45 X, 46 XX mosaic TP 45 X and FN 45 X, 46 XX mosaic co-twins monochorionic twin pregnancy 3 T21 and 1 T18 all dichorionic
			Nuchal translucency > 95th centile to detect T21 anomaly in all fetuses	3	11	0	422	100* (29-100)	98* (96-99)	21* (0 to 43*)	100* (100 to 100*)	33.0* (16.7-65.2)	0.13* (0.01-1.72)	
			Nuchal translucency > 95th centile to detect T18 anomaly in all fetuses	1	13	0	422	100* (3-100)	97* (95-98)	7* (0 to 21*)	100* (99 to 100*)	24.2* (9.3-63.1)	0.26* (0.02-2.85)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
using NT measure-ment and nasal bone assessment Setting: Fetal medicine centre, Chile Study design: Prospective cohort study	, including 1 monoamniotic Median maternal age 33 years (range 24 to 48 years) Median gestational age at time of scan 12^{+3} weeks, range 11–14 weeks Inclusion criteria: More than one viable fetus at time of scan and CRL 45-84 mm Exclusion criteria: Not reported	neonatal charts, telephone contact with patients delivered outside the study centre	Nuchal translucency > 95th centile to detect T21 and T18 in monochorionic twin fetuses	0	5	0	55	50* (13-99)	92* (82-97)	17* (0 to 46*)	98* (95 to 100*)	6.0* (1.2-30.3)	0.54* (0.14-2.19)	twin pregnancies with normal co-twin All triplet pregnancies normal NT Nasal bone reported but not possible to calculate combined accuracy with NT and nasal bone alone excluded from protocol Blinding of reference standard not reported Study funded by Sociedad Profesional de
			Nuchal translucency > 95th centile to detect T21 in monochorionic twin fetuses	0	6	0	56	NC*	90* (83 to 98*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			Nuchal translucency > 95th centile to detect T18 in monochorionic twin fetuses	0	6	0	56	NC*	90* (83 to 98*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			Nuchal translucency > 95th centile to detect any other chromosomal abnormalities in monochorionic twin fetuses	1	5	1	55	50* (0 to 100*)	92* (85 to 99*)	17* (0 to 46*)	98* (95 to 100*)	6.00* (1.19 to 30.33*)	0.55* (0.14 to 2.19*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Nuchal translucency > 95th centile to detect T21 and T18 in dichorionic twin fetuses	4	6	0	340	100* (40-100)	98* (96-99)	40* (10 to 70*)	100* (99 to 100*)	48.0* (21.3-108.6)	0.10* (0.01-1.41)	Medicina Fetal, FetalMEd Limitada, Chile
			Nuchal translucency > 95th centile to detect T21 in dichorionic twin fetuses	3	7	0	340	100* (99 to 100*)	98* (97 to 99*)	30* (2 to 58*)	100* (99 to 100*)	49.57* (23.81 to 103.20 *)	0.00 (0.0 to 1.7)*	
			Nuchal translucency > 95th centile to detect T18 in dichorionic twin fetuses	1	9	0	340	100* (3 to 100*)	97* (96 to 99*)	10* (0 to 29*)	100* (99 to 100*)	38.78* (20.35 to 73.90*)	0.00* (0.0 to 2.8*)	
			Nuchal translucency > 95th centile to detect any other chromosomal abnormalities in dichorionic twin fetuses	0	10	0	240	NC*	96* (94 to 98*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
First author, year: Maymon 2001[71] Aim of study: To report the results of a twin screening study for Down's syndrome using nuchal translucency and to compare screening results in twins from spontaneous and assisted conceptions Setting:	Population: N= 174 twin pregnancies, 348 fetuses (107 pregnancies from Israel, 67 pregnancies from the UK; 91 spontaneous pregnancies, 83 assisted conception pregnancies; 32 monochorionic, 142 dichorionic pregnancies) Inclusion criteria: Consecutive twin	Index test: Ultrasound – nuchal translucency thickness obtained in the sagittal section of the fetus (fetuses with NT ≥95 centiles of the normal range in singletons were considered screen positive) Reference test: Fetal karyotyping, (for the 16 screen positive fetuses and 80	Nuchal translucency > 95th centile to detect T21 and Turner syndrome in all pregnancies	5*	11*	0*	332*	100* (100 to 100*)	97* (95 to 99*)	31* (9 to 54*)	100* (100 to 100*)	31.18* (17.43 to 55.77*)	0.00* (NC)	TP= 2 Down's syndrome, 3 Turner syndrome Blinding of assessors was not reported Not all participants received the same reference test. The reference standard was not always described in enough detail to allow replication The data were not reported in a way that

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Two fetal medicine units (one in the UK and one in Israel) June 1998 – November 1999 <u>Study design:</u> Prospective diagnostic accuracy study	pregnancies referred to a twin clinic at each centre Only fetuses with a CRL of 38-84 mm were included <u>Exclusion criteria:</u> Data from twins after fetal reduction from higher-order multiple pregnancies were excluded Gestational age range: not reported (but CRL of 38-84 mm implies | fetuses with other indications for testing), midpregnancy detailed anomaly and fetal echocardio-graphy scans (for the 16 screen positive cases), pregnancy outcome and medical history from parents by telephone interview or from medical records (all fetuses)	Nuchal translucency > 95th centile to detect T21 in all pregnancies	3*	13*	0*	332 *	100* (100 to 100*)	96* (94 to 98*)	19* (0 to 38*)	100* (100 to 100*)	26.54* (15.57 to 45.23*)	0.00* (NC)	allowed the accuracy for monochorionic and dichorionic pregnancies to be calculated separately No clinical outcomes were reported in this study This study was conducted in Israel and the UK No sources of funding were reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	this is within the 10 to 13^{+6} week GA range) Maternal age: spontaneous group,mean 32 years; assisted group, mean 31 years (difference not statistically significant; no CI or p-value reported)		Nuchal translucency > 95^{th} centile to detect Turner syndrome in all pregnancies	2*	14*	0*	332 *	100* (100 to 100*)	96* (94 to 98*)	13* (0 to 29*)	100* (100 to 100*)	24.71* (14.79 to 41.29*)	0.00* (NC)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
First author, year: Monni 2000[68] Aim of study: To evaluate the prevalence of increased nuchal translucency in multiple pregnancies and its relation to fetal karyotype and pregnancy outcome Setting: Obstetrics and gynaecology	Population: N= 100 twin pregnancies (70 dichorionic, 30 monochor-ionic) and 9 triplet pregnancies (chorionicity not reported); 41 pregnancies from assisted reproduction (all 9 sets of triplets and 32 dichorionic twin pregnancies) Inclusion criteria: Multiple pregnancies	Index test: Ultrasound – nuchal translucency thickness (sagittal section of the fetus; NT ≥95th centile considered screen positive) Reference test: Karyotype analysis (n= 53 pregnancies; conducted if maternal age ≥35 years and either parent a carrier of chromosomal abnormalities or	Nuchal translucency > 95th centile to detect any chromosomal abnormality in all pregnancies	1*	17*	1*	208*	50* (19 to 100*)	93* (89 to 96*)	6* (0 to 16*)	99.5* (99 to 100*)	6.68* (1.55 to 28.73*)	0.54* (0.14 to 2.16*)	5 sets of quadruplets and 1 set of quintuplets were included in this study but have been excluded from the guideline analyses TP: 1= Trisomy 21 (dichorionic twin); FN: 1= 47, XXY (triplet) Blinding of assessors was not reported Not all participants received the same
			Nuchal translucency > 95th centile to detect T21 in all pregnancies	1*	18*	0*	208*	100* (3 to 100*)	93* (89 to 96*)	6* (0 to 16*)	100* (98 to 100*)	13.41* (8.49 to 21.19*)	0.00* (NC)	
			Nuchal translucency > 95th centile to detect 47, XXY in all pregnancies	0*	18*	1*	208*	0* (0 to 0*)	93* (89 to 96*)	0* (0 to 0*)	99.5* (99 to 100*)	0.00* (0.02 to 3.00)	1.08* (1.04 to 1.12*)	
			Nuchal translucency > 95th centile to detect T21 in dichorionic twins	1*	9*	0*	130*	100* (3 to 100*)	94* (89 to 98*)	10* (0 to 29*)	100* (97 to 100*)	15.44* (8.21 to 29.05*)	0.00* (0.0 to 2.96*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
department, Italy Study design: Retrospective diagnostic accuracy study	with nuchal translucency testing in the first trimester of pregnancy and available follow up data Exclusion criteria: Delivery date estimated after January 2000 (n= 23) Gestational age: median 11^{+4} weeks (range 10^{+3} to 13+6 weeks) Maternal age: median 33 years (range 20 to 33 years)	malformations visualised by ultrasound of positive results from biochemical tests for abnormalities). Unclear how the other pregnancies were assessed	Nuchal translucency > 95th centile to detect T21 in monochorionic twins	0	7	0	53	NC*	88* (90 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	reference test. The reference standard was not always described in enough detail to allow replication. It is unclear whether the reference standard would classify the target condition correctly No clinical outcomes were reported in this study This study was conducted in Italy
			Nuchal translucency > 95th centile to detect T21 in monochorionic twins	0	7	0	53	NC*	88* (90 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			Nuchal translucency > 95th centile to detect 47, XXY in monochorionic twins	0	7	0	53	NC*	88* (90 to 96*)	0* (0 to 0*)	100* (100 to 100*)	NC*	NC*	
			Nuchal translucency > 95th centile to detect any chromosomal abnormality in triplets	0	0	1	27	0* (0 to 0*)	100* (100 to 100*)	NC*	96* (90 to 100*)	NC*	1.00* (1.00 to 1.00*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Nuchal translucency > 95th centile to detect T21 in triplets	0	0	0	28	NC*	100* (100 to 100*)	NC*	100* (100 to 100*)	NC*	NC*	The study was supported by grants from the Assessorato Igiene e Sanita Regione Sardegna, Italy
			Nuchal translucency > 95th centile to detect 47, XXY in triplets	0	0	1	27	0* (0 to 0*)	100* (100 to 100*)	NC*	96* (90 to 100*)	NC*	1.00* (1.00 to 1.00*)	
First author, year: Spencer 2003[70] Aim of study: To assess the accuracy of screening for trisomy 21 using maternal serum biochemistry	Population: N= 199 twin pregnancies with complete data** Chorionicity not reported Inclusion criteria: Gestational age of 10^{+3} to 13^{+6} weeks (in	Index test: Composite – risk calculated from maternal age, nuchal translucency, maternal serum free beta-hCG and PAPP-A (if gestational age > 13^{+6} weeks or CRL > 84mm,	Down's syndrome risk per fetus ≥ 1: 300, according to maternal age, nuchal translucency, maternal serum free beta-hCG and PAPP-A (or alpha-fetoprotein) to detect trisomy 21 in all pregnancies	3	1	0	394	100* (29 to 100*)	99.8* (99 to 100*)	75* (33 to 100*)	100* (99 to 100*)	395.00* (55.78 to 2797.28*)	0.00* (0.01 to 1.68*)	**7 women with twin pregnancies at risk of abnormality (≥ 1:300) declined invasive testing and were lost to follow up. They have therefore have been excluded

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
and ultrasono-graphy Setting: District general hospital maternity unit in the UK June 1998 to September 2001 Study design: Retrospec-tive diagnostic accuracy study	first year of screening), or 11^{+0} to 13^{+6} weeks (in second and third years of screening) Exclusion criteria: Gestational age < 11 weeks or crown–rump length < 45 mm (< 38 mm in first year) Fetal death at presentation, those declining screening and those with CRL > 84mm) Gestational age: median 12 weeks 1	alpha-fetoprotein was measured instead of PAPP-A) Reference test: Chorionic villus sampling (n= 10 pregnancies) or amniocentesis at 14 weeks (n= 2 pregnancies)												from the guideline analyses The accuracy for monochorionic and dichorionic pregnancies could not be assessed separately as chorionicity was not reported TP: 3= Trisomy 21; FN: 1= Trisomy 21 Blinding of assessors was not reported Not all participants

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	day (range 10 weeks 4 days to 13 weeks 6 days) Maternal age: median 31.5 years (range 19.1 to 42.7 years)													received the same reference test No clinical outcomes were reported in this study This study was conducted in the UK The study was supported by grants from the Assessorato Igiene e Sanita Regione Sardegna, Italy

Screening for structural abnormalities

Review question

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

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
First author, year: Li 2007 [73] Aim of study To analyse the frequency of congenital heart diseases in twins and the sensitivity of fetal echocardio-gram (Yagel method) Setting: 2 Chinese hospitals	Population: 1103 pregnant women with twins (age 21-39 years). 127 high risk of CHD including family history (4), neonate with malformations (16), diabetes (4), elderly pregnant women (21), abnormal amniotic fluid (21), fetal growth restriction (19), teratogen exposure (23),	Index test: Fetal echocardio-gram at 20-37 weeks' gestation using GE VIVID7 ultrasound Doppler machine with 3.5 MHz or 5 MHz transducer and Acuson Sequoia 512 with 6C2 transducer and fetal echocardio-graphy program. Fetal heart scan performed in	Cardiac anomalies	**14**	0	2	1190	88* (62 to98)	100* (99.7 to100)	100* (77 to 100*)	99.8* (99.6 to 100)	2031.7* (126.3 to3269 2)	0.15* (0.05 to0.46)	It is unclear from the paper whether the echocardio-gram was used as a primary screening test or following referral from other centres, although the large number of women included implies that it is a screening population TP= 5 Tetralogy of Fallot, 1 transposition

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
Study design: Prospective cohort study	other malformations (5), arrhythmia (14) Inclusion criteria: Pregnant women with twins treated at one of 2 centres from 2003 to 2006. Chorionicity reported for fetuses diagnosed with malformations but not for others	supine position, 5 heart transverse sections scanned with method described by Yagel and colleagues Reference test: If TOP performed then fetal autopsy. For fetuses with normal heart and nonterminated cases close follow up until 1 year after												of great vessels, 1 AVSD, 1 VSD,2 double outlet right ventricle, 1 univentricular heart, 1 hypoplastic left heart syndrome, 2 mass (rhabdomyoma) FN= 2 VSD. TN= normal and 1 persistent open ductus arteriosus diagnosed postnatally
			Lethal anomalies	1	0	0	2203	100* (3 to 100)	100* (99.8 to 100)	100* (3 to 100*)	100* (99 to 100*)	3306.0* (184.7 to 59171.2)	0.25* (0.02 to 2.76)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
	<u>Exclusion criteria:</u> Conjoined twins	delivery, with neonatal heart examination performed to confirm the accuracy of antenatal diagnosis	Possible survival/ long-term morbidity	10	0	0	2194	100* (69 to 100)	100* (99.8 to 100)	100 (69 to 100)	100* (99 to 100)	4190.5* (261.4 to 67175.5)	0.05* (0.01 to 0.68)	Note: 2 cases of rhabdomyoma excluded from meta-analysis due to rarity Among cases diagnosed prenatally, 4 from high risk group and 8 from low risk group.

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
			Anomalies with short-term morbidity	1	0	2	2201	33* (1 to 91)	100* (99.8 to 100)	100* (3 to 100)	99.9* (99 to 100)	1651.5* (78.5 to 34754.0)	0.63* (0.29 to 1.34)	Unreported which group 1 of the false negative cases (VSD) or the PDA were in Blinding not reported <u>Funding:</u> Source of funding not reported
<u>First author, year:</u> Sperling 2007 [74] <u>Aim of study</u> To evaluate the outcome of screening for structural malforma-tions in twins and the	<u>Population:</u> Twin pregnancies diagnosed before 14+6 weeks' gestation 46% natural conception, 54% IVF/ICSI/ egg donation or IUI	<u>Index test:</u> Nuchal translucency scan if not exceeded 13+6 weeks (in 337 pregnancies), All cases ultrasound scan for anomaly at week 19 and	All anomalies All twins	7	0	18	965	28* (12 to 49)	100* (99.6 to 100)	100* (59 to 100)	98* (97 to 99)	557.3* (32.7 to 9501.6)	0.7* (0.56 to 0.91)	TP- diagnosed at 1st trimester scan: 1 anencephaly, 1 bilateral renal agenesis, 1 hypoplastic left heart syndrome. Diagnosed at 19 wk scan: 1 transposition

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
outcome of screening for FFTS in monochorionic twins Setting: 5 university fetal medicine centres (4 in Denmark and 1 Sweden) Study design: Prospective cohort study	411 dichorionic, 102 monochorionic twin pregnancies Inclusion criteria: Twin pregnancy diagnosed before 14+6 weeks' gestation, estimated from the crown-rump length or biparietal diameter of the larger twin Exclusion criteria: Maternal age < 18 years,	fetal echocardiography week 21 performed by specialists in fetal echocardiography Reference test: Information about fetal outcome from obstetric records and contacted by phone 8 months after the birth. If contact details unavailable, personal records checked for admittance to hospital and discharge summaries												of the great arteries, 2 hypoplastic left heart syndrome, 1 coarctation of the aorta Echocardiogram at 21 weeks confirmed the diagnoses in the anomaly scan but no additional malformations detected
			All anomalies Dichorionic twins	7	0	14	821	33* (15 to 57)	100* (99.6 to 100)	100* (59 to 100)	98.3* (97 to 99)	560.4* (33.0 to 9508.9)	0.66* (0.49 to 0.89)	
			All anomalies Monochorionic twins	0	0	4	144	NC	NC	NC	NC	NC	NC	FN- 1 cerebellar atrophia, 2 cleft lip/palate, 1 obstructive uropathy+ ASD+clubfoot, 1 single kidney, 1

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
	lack of fluency in Danish or Swedish	sought	Lethal anomalies All twins	5	0	0	985	100* (48 to100)	100* (99.6 to 100)	100* (48 to 100*)	100* (99 to 100*)	1807.7* (112.0 to 29184.3)	0.08* (0.01 to1.19)	AVSD,1 double outlet right ventricle, 2 coarctation of the aorta, 2 ASD, 4 VSD, 1 aortic stenosis, 1 collapse of lumbar spine, 2 talipes Of the overall anomalies 4 FN were in monochorionic twin pregnancies: 2 co-arctation of the aorta, 1 VSD, 1 talipes. No TP in monochorionic twins Detection rate for major cardiac
			Possible survival/ long term morbidity all twins	2	0	7	981	22* (3 to 60)	100* (99.6 to 100)	100*	99*	491.0* (25.1 to 9587.6)	0.75* (0.53 to 1.07)	
			Anomalies with short term morbidity all twins	0	0	12	978	NC	NC	NC	NC	NC	NC	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	abnormalities using NT cut off of ≥ 2.5mm 20% Blinding not reported <u>Funding:</u> Source of funding not reported
<u>First author, year:</u> Chang 2004 [72] <u>Aim of study:</u> To examine the effect on	<u>Population:</u> 1400 fetuses from twin pregnancies Chorionicity not reported <u>Inclusion criteria:</u>	<u>Index test:</u> Ultrasound scan Mean gestational age at diagnosis 21.3 weeks (range 16-35	Any major anomaly	25	0	7	1365	78* (60 to 91)	100* (99.7 to 100)	100* (86 to 100)	99* (99 to 100)	2111.1* (131.3 to 33943)	0.23* (0.13 to 0.43)	It is unclear whether the ultrasound performed in the study was a primary screening ultrasound or whether cases

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
outcome of twin pregnancy with one fetus affected by structural abnormality Setting: Department of obstetrics and gynaecology, Hospital, Taiwan Study design: Retrospec-tive cohort study	Twin pregnancies managed between May 1992 and July 2003 Exclusion criteria: Twin pregnancies where both twins had a major anomaly (n=3) and where delivery occurred before 24 weeks. NB : 3 fetuses reported from paper excluded from this analysis because anomaly reported was	weeks) Reference test: Postmortem examination or postnatal examination for all those with antenatally detected anomalies, unclear from paper if all those with normal ultrasound had the same reference standard	Lethal anomalies	3	0	0	1391	100* (29 to100)	100* (99.7 to 100)	100* (29 to 100*)	100* (99 to 100*)	2436.0* (148.7 to 39898)	0.13* (0.01 to 1.67)	were referred from other centres, which may explain the wide range of gestational ages at diagnosis. TP included: 1 tricuspid atresia, 6 hydrocephalus, 1 pulmonary stenosis, 1 pulmonary atresia, 1 coarctation of the aorta, 1 holoprosen-cephalus+ interruption of aorta, 4 gastroschisis, 1 gastroschisis + meningocele, 1
			Possible survival/long-term morbidity	16	0	1	1377	94* (71 to 99)	100* (99.7 to 100)	100* (79 to 100)	99.9* (99 to 100)	2526.3* (157.6 to 40511.3)	0.08* (0.02 to 0.39)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
	chromosomal (Trisomy 21, Trisomy 13, Turner syndrome)		Anomalies amenable to IU therapy	1	0	0	1393	100* (16 to 100)	100* (99.7 to 100)	100* (3 to 100)	100* (99 to 100)	2091.0* (116.9 to 37418.4)	0.25* (0.02 to 2.76)	omphalocele, 1 encephalocele, 1 TGA +single ventricle, 1 HLHS, 1 imperforate anus with bowel obstruction, 2 anencephalus, 1 meningocele, 1 hydrops fetalis The anomalies not detected antenatally (FN) were 3 pulmonary stenosis, 2 imperforate anus, 1 aortic stenosis, 1 oro-facial-digital syndrome.
			Anomalies with short-term morbidity	3	0	4	1387	43 (10 to 82)	100* (99.7 to 100)	100* (29 to 100)	99.7* (99 to 100)	1214.5* (68.1 to 21647.4)	0.56* (0.31 to 1.04)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
														Note that 3 cases of imperforate anus (1TP and 2FN) excluded from meta-analysis as rarely diagnosed by USS Blinding of assessors not reported <u>Funding:</u> Source of funding not reported

Monitoring for feto-fetal transfusion syndrome

Review question

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

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
First author, year: Sebire 2000[75] Aim of study: To explore a possible association between increased fetal nuchal translucency thickness (NT) and inter-twin membrane folding in the early prediction of severe feto-fetal transfusion syndrome	Population: Fetal nuchal translucency test N=287 monochorio-nionic and diamniotic twin pregnancies Intertwin membrane folding at 15-17 weeks. N=153 monochorio-nionic and diamniotic twin pregnancies Inclusion criteria: All monochorio-nionic and	Index test: Ultrasound - Fetal nuchal translucency test at 10-14 weeks -Intertwin membrane folding at 15-17 weeks Reference test: Ultrasound at 15-17 weeks and 20-24 weeks: Features of severe FFTS (anhydramnios and non-visible bladder in the donor fetus	NT > 95th centile for gestational age in at least one fetus (for pregnancies N=287)	12	25	25	225	32.4 (17.3 to 47.5)	90.0 (86.3 to 93.7)	32.4 (17.4 to 47.5)	90.0 (86.3 to 93.7)	3.2 (1.8 to 5.9)	0.8 (0.6 to 0.9)	Blinding of assessors was not reported Funding: Fetal Medicine Foundation
			NT thickness > 95th centile for gestational age (for fetuses N=574 fetuses)	15	32	25	502	37.5 (22.5 to 52.50)	94.0 (92.0 to 96.0)	31.9 (18.6 to 45.2)	95.3 (93.4 to 97.1)	6.3 (3.7 to 10.6)	0.7 (0..5 to 0.9)	Continuation of an earlier study (Sebire, 1997) Severe FFTS is the end point (before 24 weeks)
			Intertwin membrane folding	21	28	2	102	91.3 (73.2 to 97.6)	78.5 (71.4 to 85.5)	42.9 (29.0 to 56.7)	98.1 (93.3 to 99.5)	4.2 (3.0 to 6.0)	0.11 (0.01 to 0.49)	This study was conducted in the UK
			Clinical outcomes: Fetal loss: 40/287 (13.9%) Both fetuses:											

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
(FFTS) Setting: Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London Study design: Review of data collected prospectively for another study Quality: High	diamniotic twin pregnancies with two live fetuses at the 10-14 weeks' ultrasound for which birth outcomes were available (N=303) in the computer database Exclusion criteria: One or both fetuses was structurally or chromosom-ally abnormal, or in which, parents opted for termination of pregnancy for social reasons (N=16)	plus polyhydram-nios and distended bladder in the recipient fetus)	26/287 One fetus: 14/287 Total fetal loss rate: 66/574 (11.5%) Severe FFTS: 43/285 (15%) Fetal loss due to FFTS: Both fetuses: 19 One fetus: 10										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
First author, year: Matias 2010[78] Aim of study: To assess the association between antenatal ultrasound findings and the diagnosis of feto-fetal transfusion syndrome (FFTS) Setting: Department of Obstetrics and Gynaecology, University Hospital of S. Joao,	Population: N=99 consecutive monochorionic and diamniotic twin pregnancies assessed at 11-14 weeks' gestation at study centre during the study period (December 1997-October 2004) Inclusion criteria: Monchorionicity diagnosed at the first trimester scan by the absence of the lambda sign Exclusion criteria: Cases with	Index test: Ultrasound at 11-14 weeks to assess Nuchal translucency thickness (NT) Crown–rump length (CRL) Ductus venosus blood flow (DV) considered abnormal if the A wave was absent or reversed Reference test: Diagnosis of FFTS by subsequent fortnightly ultrasound and severe FFTS was defined by the presence	NT discrepancy (inter-twin difference of ≥ 0.6mm)	6	6	7	80	50.0 (21.7 to 78.3)	92.0 (86.2 to 97.7)	46.2 (19.1 to 73.3)	93.0 (87.6 to 98.4)	6.2 (2.5 to 15.4)	0.5 (0.3 to 1.0)	This study was conducted in Portugal Funding: not reported
			CRL difference ≥ 10 mm	1*	11*	NR	NR	8	NC	NC	NC	NC	NC	
			At least one of the fetuses presented an abnormal DV waveform (the A wave absent or reversed) ROC curve analyses: blood flow evaluation of DV (best predictor of FFTS) AUC=0.84, 95% CI 0.70 to 1.00 intertwin difference in NT:	9	3	7	80	56.3 (33.2 to 76.9)	96.4 (89.9 to 98.8)	75.0 (46.8 to 91.1)	92.0 (84.3 to 96.0)	15.6 (4.7 to 51.3)	0.5 (0.3 to 0.8)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Porto, Portugal Study design Prospective study Quality: High	malformation (n=2) and single fetal death before the development of FFTS (n=2)	of oligohydramnios and no visible bladder in the donor fetus combined with polyhydromnios and dilated bladder in the recipient, along with different stages of Doppler deterioration in both arterial and the venous compartments	AUC=0.76, 95% CI 0.60 to 0.91 intertwin ratio of NT: AUC=0.75, 95% CI 0.60 to 0.89 intertwin difference in CRL: AUC=0.57, 95%CI 0.40 to 0.75 intertwin ratio of CRL: AUC=0.58, 95%CI 0.42 to 0.75 Relative risks: Unadjusted RR (95% CI): difference in NT: 1.61 (1.19 to 2.08) difference in CRL: 1.24 (0.71 to 2.05) NT ratio: 1.58 (1.16 to 2.03) CRL ratio: 1.36										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			(0.81 to 2.15) At least one abnormal DV: 15.5 (4.64 to 70.14) Adjusted RR (95% CI): (adjusted for all variables except the one being examined) difference in NT: 1.20 (0.84 to 1.62) difference in CRL: 1.07 (0.65 to 1.67) NT ratio: 1.20 (0.82 to 1.63) CRL ratio: 1.07 (0.67 to 1.60) At least one abnormal DV: 11.86 (3.05 to 57.45)										
First author, year: Kagan, 2007[76]	Population: N= 512 monochorionic diamniotic twin	Investigation : NT and CRL discordance	NT discordance >20% (excluding the group with fetal death, N=52)*	33*	93*	25*	319 *	56.9 (44.2 to 69.6)*	77.4 (73.4 to 81.5)	26.2 (18.5 to 33.9)	92.7 (90.0 to 95.5)*	2.5 (1.9 to 3.4)*	0.6 (0.4 to 0.8)*	Early fetal death group (death <18 weeks'

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
Country: UK Aim of study: To examine the value of intertwin discordance in nuchal translucency thickness (NT) in the prediction of early fetal death or severe FFTS Setting: Harris Birthright Research Centre for Fetal Medicine, King's College Hospital	pregnancies underwent ultrasound at 11 to 13^{+6} weeks' gestation during the study period (January 2001 to April 2006) at the study centre as a part of policy of screening for chromosomal abnormalities by a combination of maternal age and fetal NT thickness Inclusion criteria: Pregnancies diagnosed as being	Index test: Transabdom-inal ultrasound examination for measurement of the nuchal translucency (NT) thickness and crown–rump length (CRL) of each twin. at 11 to 13^{+6} weeks In each pregnancy the intertwin discordance in NT and CRL was calculated as the difference in each measurement between the two fetuses (NT1−NT2 and	CRL discordance >10% (excluding the group with fetal death, N=52)* * Discordance is defined as absolute difference in measurement between the two fetuses expressed as a percentage of larger measurement. Normal outcome (pregnancy resulted in two live births): 412/512 (80.5%) Median gestational age (weeks): 35 (range 26–40) Severe FFTS treated by	13*	35*	55*	377 *	19.1 (9.8 to 28.5)	* 91.5 (88.8 to 94.20	* 27.1 (14.5 to 39.7)	87.3 (84.1 to 90.4)	2.3 (1.3 to 4.0)	0.9 (0.8 to 1.0)	gestation) has been excluded from the diagnosis which could likely be the cases of FFTS. Cut-off point for CRL discordance was taken as 10% to work out diagnostic accuracy data This study was conducted in the UK Funding: Fetal Medicine Foundation

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
Medical School, London Study design: Prospective cohort study Quality: High	monochorionic because there was a single placental mass with no extension of placental tissue into the base of the intertwin membrane (lambda sign; n=560) Exclusion criteria: Chromosomal or structural defects (n = 28) Unavailability of data on pregnancy outcome (n = 20) Other details:	CRL1−CRL2, respectively) expressed as a percentage of the larger measurement Reference test: Diagnosis of FFTS on follow-up ultrasound scans 4 weekly (if there was evidence of FFTS then frequency was increased as necessary). Severe FFTS was diagnosed when there was polyhydromnios in one fetus along with anhydromnios	endoscopic laser surgery: 58/512 (11.3%) Early fetal death: pregnancies with fetal death of one or both fetuses at or before18 weeks (median 16 (range, 13–18) weeks): 19 Fetal death with the death of one fetus (n=13) or both fetuses (n=29): 42/512 (8.2%) Discordance in nuchal translucency (NT) thickness: Median NT discordance (%): Normal group: 11.1% Endoscopic laser										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	Follow-up policy of monochorionic twins included ultrasound examinations at 16–18 weeks and 4-weekly thereafter, unless there was evidence of FFTS, in which case the frequency of major examinations was increased as necessary In cases of severe FFTS endoscopic laser coagulation of the communica-ting placental	in the other and absent or reversed end-diastolic flow in either the umbilical artery or ductus venosus in one or both the fetuses Methods described adequately? Yes	treatment group: 22.2% Early fetal death group: 35.3% NT discordance 0-9% n (%): Normal group: 185 (44.9) Endoscopic laser treatment group: 15 (25.9), OR 0.47, 95% CI 0.27 to 0.82 Early fetal death group: 4 (21.1), OR 0.34, 95% CI 0.12 to 1.01 NT discordance 10-19% : Normal group: 134 (32.5) Endoscopic laser treatment group: 10 (17.2), OR 0.47, 95% CI 0.25 to 0.91										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	vessels was performed. The indications for such treatment were: ultrasound diagnosis of polyhydramnios in one twin and anhydramnios in the other; or absent or reversed end-diastolic flow in either the umbilical artery or ductus venosus in one or both fetuses		Early fetal death group: 3 (15.8), OR 0.40, 95% CI 0.12 to 1.36 NT discordance 20-29% : Normal group: 63 (15.3) Endoscopic laser treatment group: 13 (22.4), OR 1.50, 95% CI 0.85 to 2.64 Early fetal death group: 2 (10.5), OR 0.66, 95% CI 0.16 to 2.80 NT discordance 30-39% : Normal group: 17 (4.1) Endoscopic laser treatment group: 6 (10.3, OR 2.24, 95% CI 1.08 to 4.67										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Early fetal death group: 2 (10.5), OR 2.55, 95% CI 0.64 to 10.25 <u>NT discordance 40-49% :</u> Normal group: 9 (2.2) Endoscopic laser treatment group: 5 (8.6), OR 3.07, 95% CI 1.46 to 6.49 Early fetal death group: 3 (15.8), OR 6.55, 95% CI 2.20 to 19.50 <u>NT discordance >50% :</u> Normal group: 4 (1.0) Endoscopic laser treatment group: 9 (15.5), OR 6.46, 95% CI 4.12 to 10.11										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Early fetal death group: 5 (26.3), OR 16.75, 95% CI 7.69 to 36.49 <u>Discordance in crown–rump length:</u> <u>Median CRL discordance (%):</u> Normal group: 3.6% Endoscopic laser treatment group: 6.0% Early fetal death group: 5.9% <u>CRL discordance 0-4%</u> Normal group: 271 (65.8) Endoscopic laser treatment group: 24 (41.4), OR 0.42, 95% CI 0.26 to 0.88 Early fetal death										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			group: 8 (42.1), OR 0.40, 95% CI 0.16 to 0.96 <u>CRL discordance 5-9%</u> Normal group: 106 (25.7) Endoscopic laser treatment group: 21 (36.2), OR 1.53, 95% CI 0.93 to 2.52 Early fetal death group: 4 (21.1), OR 0.78, 95% CI 0.26 to 2.30 <u>CRL discordance 10-14%</u> Normal group: 29 (7.0) Endoscopic laser treatment group: 8 (13.8), OR 1.87, 95% CI 0.96 to 3.65 Early fetal death										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			group: 6 (31.6), OR 5.22, 95% CI 2.12 to 12.89 <u>CRL discordance 15-19%</u> Normal group: 5 (1.2) Endoscopic laser treatment group: 3 (5.2), OR 3.15, 95% CI 1.25 to 7.97 Early fetal death group: 0 (0), OR -, 95% CI - to - <u>CRL discordance >20%:</u> Normal group: 1 (0.2) Endoscopic laser treatment group: 2 (3.4), OR 5.56, 95% CI 2.41to 12.84 Early fetal death group: 1 (5.3), OR 11.92, 95% CI 2.77										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			to 51.20 <u>ROC curve analysis:</u> Regression analysis showed that significant prediction of early fetal death and severe FFTS requiring endoscopic laser treatment was provided by both the discordance in fetal NT and the discordance in CRL at 11 to 13^{+6} weeks The prediction provided by the discordance in NT, expressed as the area under the receiver–operating characteristic (ROC) curve (AUC) was not										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			significantly improved by including the discordance in CRL <u>Early fetal death:</u> AUC for NT discordance (95% CI): 0.727 (0.576 to 0.877) AUC for NT and CRL discordances (95% CI): 0.741(0.593 to 0.888) <u>Severe FFTS:</u> AUC for NT (95% CI) 0.691 (0.607 to 0.774) AUC for NT and CRL (95% CI): 0.716 (0.638 to 0.795) If the discordance in NT was 20% or more then the false										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			positive rate was 20%, the detection rate of early fetal death was 63%, and the detection rate of severe FFTS was 52%											
First author, year: Linsken 2009[77] Aim of study: To assess the value of discordance in fetal nuchal translucency thickness (NT) measure-ment in monochor-ionic diamniotic twins to	Population: N=55 women with monochorio-nionic and diamniotic twin pregnancies with live fetuses who were screened at the study centre during the study period (2004-2008) Inclusion criteria: All monochorio-	Index test: Ultrasound - Fetal nuchal translucency thickness in the first trimester Reference test: Detection of FFTS on follow-up ultrasounds. FFTS was classified according to Quintero stages	NT discordance ≥ 20% NT discordance defined as percentage of delta (absolute difference in NT between fetus1 and fetus 2) of the largest measurement Survival of both fetuses: 5/14 (36%) Survival of at least one fetus: 10/14 (71%)	9	5	9	32	64.3 (39.2 to 89.4)	78.0 (65.4 to 90.7)	50.0 (26.9 to 73.1)	86.5 (75.5 to 97.5)	2.9 (1.5 to 5.9)	0.5 (0.2 to 0.9)	Blinding of assessors was not reported Details of gestational age not reported; presumed 11-14 weeks as Fetal Medicine Foundation standards used Not true screening study as two groups compared

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
predict feto-fetal transfusion syndrome (FFTS) Setting: A tertiary fetal medicine referral centre at VU University Medical Centre, Amsterdam Study design: Retrospective cohort study (review of data collected for Down's Syndrome screening)	nionic and diamniotic twin pregnancies, data from whom data were available on first-trimester NT, serial follow-up ultrasono-graphy and fetal outcome (n=61) Exclusion criteria: Death of one or both fetuses (n=3) or prematurity unrelated to FFTS (n=3) Other details: Ethnicity: Caucasian : 52/55 Non-		An ROC curve was constructed to evaluate the best cut-off level for NT discordance. The area under the ROC curve was 0.71										This study was conducted in Holland Funding: not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	Caucasian 3/55													
First author, year: Maiz, 2009[79] Country: UK Aim of study: To determine whether abnormal ductos venosus flow at 11-13 weeks predicts adverse pregnancy outcome Setting: Not reported Authors based at a	Population: N= 695 twin pregnancies 516 dichorionic 179 monochorionic Chorionicity determined by lambda sign in ultrasound Inclusion criteria: Diamniotic twin pregnancies with two live fetuses at 11-13 weeks during the study period	Index test: Doppler studies measuring Reversed a-wave in the ductus venosus and nuchal translucency at 11-13 weeks' gestation. Monochorionic pregnancies underwent ultrasound scan again at 16-18 weeks and monthly after that Reference test: Severe FFTS identified by	Reversed a-wave in the ductus venosus observed in at least one fetus Reversed a-wave in at least one fetus: FFTS= 38.5% (95% CI 22.4 to 57.5%) Two healthy live births= 7.7% (95% CI 5.8 to 10.1%) P<0.001 In FFTS pregnancies (n= 26), reversed a-wave in: One fetus= 6 (32%) Both fetuses= 4 (15%)	10*	23*	16*	130*	38.5 (19.8 to 57.2)*	85.0 (79.3 to 90.6)*	30.3 (14.6 to 46.0)*	89.0 (84.0 to 94.1)*	2.6 (1.4 to 4.7)*	0.7 (0.5 to 1.0)*	No limitations It is unclear where this study was conducted. The authors are based in the UK Funding: Fetal Medicine Foundation

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
fetal medicine research centre in the UK Study design: Prospective cohort study	January 2006 to January 2008 Exclusion criteria: Cases with missing pregnancy outcomes. Results of dichorionic pregnancies have been excluded from further guideline analysis Other Details: Median maternal age: 33.3 years (IQR 29 to 36 years) Mean gestational	the ultrasonographic diagnosis of hydromnios in one twin and anhydromnios in the other and absent or reversed end diastolic flow in either the umbilical artery or ductus venosusin one or both fetuses FFTS treated by endoscopic laser coagulation of the communicating vessels	In monochorionic pregnancies, FFTS developed: Reversed a-wave in at least one fetus= 10/33 (30.3%) Normal a-wave in both fetuses= 16/146 (11%) P=0.01 Prevalence of reversed a-wave: FFTS pregnancies= 38.5% Normal pregnancies= 10.9% Difference reported to be statistically significant, but no p value or CI reported) Mean intertwin										

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	age: 89 days (IQR 86 to 92 years) Ethnicity: Monochorio-nic: White= 80% African= 11% Indian or Pakistani= 5% Chinese or Japanese= 2% Mixed= 2%		discordance in nuchal translucency: FFTS group= 19.6% Non FFTS group= 16.7% P= 0.78 Multiple logistic regression analysis for severe FFTS: Contribution of reversed a-wave in at least one fetus: OR 5.09, 95% CI 1.94 to 13.37, p=0.001 Contribution of intertwin discordance in nuchal translucency: p= 0.16										
First author, year: van	Population: N= 52 twin pregnancies	Index test: Intertwin amniotic	Intertwin amniotic discordance of 3.1cm for FFTS	9*	23*	2*	18*	81.8 (59 to 100*)	43.9 (29 to 59*)	28.1 (13 to 44*)	90.0 (77 to 100*)	1.46* (0.99 to	0.41* (0.11 to	The study was in two parts. The first part

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Miegham, 2010[80] Country: Spain Aim of study: To develop a method of predicting FFTS and to test this method Setting: Not reported One author based at a University in Barcelona Study design: Prospective diagnostic accuracy study	Chorionicity not reported Inclusion criteria: Consecutive women with moderately discordant amniotic fluid levels Exclusion criteria: Not reported Other Details: Gestational age at first presentation: FFTS group at final diagnosis: 18.4 weeks (range 15.3 to 23.4 weeks)	discordance of 3.1cm Reference test: Presence of oligo-uric oligohydramnios in the donor sac with a deepest vertical pocket (DVP) of 2cm combined with polyuric polyhdramnios in the recipient sac with a DVP of 8 cm prior to 20 weeks, and 10 cm after 20 weeks									2.15*)	1.52*)	looked at factors that may predict FFTS and retrospectively calculated their accuracy. A model was derived from this data for predicting FFTS prospectively in other women. The second part tested this model and provided diagnostic accuracy statistics; the results of the second part are presented here. Women were placed into

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	No FFTS at final diagnosis: 20.2 weeks (15.1 to 29.0 weeks) Ethnicity not reported													groups depending on final diagnosis: Group I= FFTS (n=11, 21%) Group II= sIUGR (n=27, 52%) Group III= neither FFTS nor sIUGR (n= 14, 27%). The results of the sIUGR group are not reported here as they are not relevant for this review question

Monitoring for intrauterine growth restriction

Review question

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

a) Studies using symphysio-fundal height measurement as index test

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Egan 1994[83] Country: USA Study design: Prospective cross-sectional study Study dates: April 1987 – November 1991 Aim of study: To establish a	Population: 160 women with twin pregnancies Using a cut-off of 20% difference for BWD, 143 of these were deemed normal and 17 discordant Inclusion criteria: Women with confirmed twin pregnancies, referred by physicians from the Division of Maternal-Fetal Medicine	Screening test: Symphysio-fundal height (SFH) measurement Reference test: Intertwin birthweight discordancy ≥20% Method: SFH and USS measurements (BPD, HC, AC, FL and amniotic fluid volume - single vertical pocket) were obtained in all women, at three different locations	Diagnostic accuracy of symphysio-fundal height (SFH) measurement in detecting intertwin weight discordance ≥20% * Calculations carried out by the NCC-WCH technical team	4	25	13	118	23.5* (3.4 to 43.7)	82.5* (76.3 to 88.7)	13.8* (1.2 to 26.3)	90.1* (85.0 to 95.2)	1.3* (0.5 to 3.4)	0.93* (0.70 to 1.22)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
normogram for symphysio-fundal height (SFH) measure-ment in normal twin pregnancies and to determine whether twins with growth discordancy, as defined by ultrasound (US), can be detected by the normogram	(MFM) at the University of Connecticut Health Center, Farmington, USA, for further ultrasound evaluation, during April 1987 to November 1991 Exclusion criteria: Pregnancies with fetal anomalies or known medical or obstetrical complications Other details: Women were 16 to36 weeks pregnant at referral and had reliable menstrual dates that were	EFW was derived using Hadlock formulae (BPD/AC and/or FL/AC) Using regression analysis, a normogram for SFH of the 143 normal twin pregnancies was obtained which was then used to determine the diagnostic accuracy of SFH measurement Discordancy was confirmed at birth in all cases Details of techniques and equipment reported											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	confirmed by USS before the 20th week of pregnancy 128 women (80%) were white; 20 (12.5%) Hispanic, 11 (7%) black, and 1 (0.5%) Other Details of chorionicity not reported													

Review question

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

b) Studies using ultrasound scan measurement of fetal biometry only as index test

Study details	Participants	Diagnostic tools	Outcome measures and results											Study details
			Outcome measures and results	True positive	False posit ive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Neilson 1981[88] Country: UK Study design: Retrospec-tive study Study dates: 1975 to 1979 Aim of study: To demonstrate the relative effectiveness of two USS indices (BPD and	Population: 66 twin pregnancies (132 fetuses) Inclusion Criteria: For BPD: twin pregnancies in which serial BPD measurements had been carried out during the previous 5 years; confirmed menstrual data or early ultrasound assessment of gestational age; at least	Screening test: BPD measurement Reference test: SGA - babies with birthweight <5th centile Method: All ultrasound examinations were carried out by medically qualified people. BPD values were plotted on the chart of Campbell and Newman (1971) derived	Prediction of SGA using BPD measurements * Calculations carried out by the NCC-WCH technical team For the guideline review CRL and TA were not tests of interest so data were extracted only for BPD	24	23	12	61	66.7* (51.3 to 36.8)	72.6* (63.1 to 82.2)	51.1* (36.8 to 65.4)	83.6* (75.1 to 92.1)	2.4* (1.6 to 3.7)	0.46* (0.28 to 0.74)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Study details
			Outcome measures and results	True positive	False posit ive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
CRL×TA) in detecting SGA twin fetuses	two ultrasound examinations after the 28th week, the last within 3 weeks of delivery Exclusion criteria: None reported Other details: No details of chorionicity or ethnicity were reported	from measurement of singleton fetuses. Late-flattening and low growth profile BPD patterns (Campbell 1974) were classified as abnormal In all cases both fetuses were measured Details of techniques and equipment used were reported												

Review question

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

c) Studies using estimated fetal weight based on formulae only as index test

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Jensen 1995[89] Country: Norway Study design: Retrospective cohort study Study dates: January 1990 to March 1993 Aim of study: To determine the relative accuracy of ultrasound	Population: 73 twin pregnancies with last USS performed within 7 days of birth Inclusion criteria: All consecutive twin pregnancies delivered at Aker University Hospital between 1 January 1990 and 31 March 1993; EDD established by USS at 18 weeks of pregnancy; last	Screening tests: 1) EFW of an individual fetus ≤10th percentile 2)Intertwin EFW difference ≥20% EFW was calculated using Hadlock's formula (1984) based on BPD and AC Reference tests: 1) IUGR at birth (weight <10th percentile) 2)Intertwin birthweight discordance ≥20% Method: BPD and AC measurements were carried out	Prediction of IUGR (fetal weight ≤10th centile) using EFW ≤10th centile Prediction of intertwin birthweight discordance ≥20% using EFW difference ≥20% Weight percentiles were calculated from a table for singletons adjusted for gestational	NR 9	NR 5	NR 5	NR 49	85 64.3* (39.2 to 89.4)	87 90.7* (83.0 to 98.5)	80 64.3* (39.2 to 89.4)	NR 90.7* (83.0 to 98.5)	6.5* 6.9* (2.8 to 17.5)	0.17* 0.39* (0.19 to 0.80)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
estimated fetal weight (EFW) in twin pregnancies and to assess the accuracy of identifying discordant twins	USS performed within 7 days of birth Exclusion criteria: None reported Other details: Details of ethnicity and chorionicity not reported	in all women and EFW calculated from Hadlock's formula Details of equipment/method reported	age and sex, according to Bjerkedal et al. (1980) * Calculations carried out by the NCC-WCH technical team											
First author, year: Storlazzi 1987[95] Country: USA Study design: Retrospective review of hospital records Study dates:	Population: 43 consecutive twin pregnancies with last USS within 2 weeks of birth Inclusion criteria: Consecutive twin pregnancies delivered at the Connecticut Health Centre,	Screening tests: Intertwin EFW difference ≥20% EFW calculation was based on BPD and AC, using the formula of Shepard et al. (1982) or on AC and FL using the formula of Hadlock (1984), when BPD was unobtainable Reference test: Intertwin BWD	Prediction of BWD ≥20% by EFWD ≥20% As absolute differences (and not percentage differences or centiles) were reported for BPD, AC and FL only data for EFW difference was extracted (as	8	2	2	26	80.0* (55.2 to 100)	92.9* (83.3 to 100)	80.0 (55.2 to 100)	92.9 (83.3 to 100)	11.2* (2.8 to 44.1)	0.22* (0.06 to 0.75)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Not reported Aim of study: To investigate the value of intrapair difference in BPD, AC, FL and EFW in predicting discordant fetal growth	USA Exclusion criteria: Congenital anomalies Other details: An attempt was made to measure BPD, AC and FL in both fetuses Babies were weighed within 24 hours of birth Details of chorionicity and ethnicity not reported	≥20% Method: Only the results of the last scan were considered for analysis Cut-offs used for discordancy were as follows: BPD (6mm), AC (20mm), FL (5mm) Details of methods and equipment reported	specified in the review protocol) * Calculations carried out by the NCC-WCH technical team											
First author, year: Hill 1994[97] Country: USA Study	Population: 49 twin pregnancies scanned within 21 days of birth Inclusion criteria:	Screening test: Intertwin EFW difference ≥20% EFW calculated from HC and AC according to Hadlock (1984) Reference test:	Prediction of fetal weight discordancy ≥20% using difference in EFW ≥20% Transverse	13	5	1	30	92.9* (79.4 to 100)	85.7* (74.1 to 97.3)	72.2* (51.5 to 92.9)	96.8* (90.6 to 100)	6.5* (2.9 to 14.8)	0.08* (0.01 to 0.55)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
design: Retrospective case review Study dates: Not reported Aim of study: To evaluate the effectiveness of fetal biometry - AC, FL and transverse cerebellar diameter (TCD) - for detecting twin growth discordancy	Ultrasound examination at or after 15 weeks of pregnancy; last examination within 3 weeks of birth Exclusion criteria: Late pregnancy test, first examination later than 10 weeks of gestation, use of oral contraceptives up to 3 months before conception; irregular menses Other details: Details of ethnicity or chorionicity not	Intertwin BWD ≥20% Method: All pregnancies underwent measurements of AC, FL, EFW, and TCD Efficacies of the difference in AC (cut-off 20mm), FL (cut-off 5mm), TCD (cut-off 4mm) and EFW (cut-off 20%) in predicting twin discordancy was calculated Details of equipment and method reported	cerebellar diameter was not a test of interest for the guideline and so these data were not extracted Absolute differences (and not percentage differences or centiles) were used for AC and FL and so only data for EFW difference ≥20% was extracted (in accordance with the review protocol) * Calculations carried out by the NCC-WCH											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	reported		technical team											
First author, year: Caravello 1997[101] Country: USA Study design: Retrospective review of hospital records Study dates: Not reported Aim of study: To determine the relative accuracy of intrapair differences in AC and EFW to identify twins with	Population: 242 women with twin pregnancies scanned within 3 weeks of birth Inclusion criteria: All live-born twin pairs at a tertiary centre during a 6-year period; gestational age more than 23 weeks; no anomalies; USS within 3 weeks of birth Exclusion criteria: None reported Other details: Details of	Screening tests: Intertwin EFW difference ≥25% EFW calculation was based on AC and FL according to Hadlock (1984) Reference test: Intertwin BWD ≥25% Method: USS performed by obstetric residents or sonographic technologists using the same equipment A difference of ≥20mm in AC was used for discordancy ROC curves were generated for differences in AC	Prediction of BWD ≥25% by EFWD ≥25% As absolute differences (and not percentage differences or centiles) were used for AC, only data for EFW difference was extracted (in accordance with the review protocol) * Calculations carried out by the NCC-WCH technical team	NR	NR	NR	NR	33	94	33	94	5.26	0.71*	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
birthweight discordancy of ≥25%	chorionicity and ethnicity not reported	and EFW Details of methods and equipment reported												
First author, year: Blickstein 1996[91] Country: Israel Study design: Retrospective review of hospital files Study dates: Not reported Aim of study: To compare the predictivity of discordance based on EFW and AC	Population: 90 women with twin pregnancies Inclusion criteria: Last 200 liveborn twin pairs born at Kaplan Hospital; complete sets of ultrasound measurements (AC, FL and EFW based on these parameters) performed within 2 weeks of birth Exclusion	Screening tests: Intertwin EFWD >15%, >20 and >25% EFW calculation was based Hadlock's formula using AC and FL Reference test: Intertwin BWD >15%, >20 and >25% Method: All measurements were performed by experienced sonographers using the same methods A difference of	Prediction of birth weight discordance >15% using EFWD >15% Prediction of birth weight discordance >20% using EFWD >20% Prediction of birth weight discordance >25% using EFWD >25% As absolute differences (and not percentage differences or centiles) were	17 10 3	18* 10* 10*	9* 5* 3*	46 65 74	65.4* (47.1 to 83.7) 66.7* (42.8 to 90.5) 50.0* (10.0 to 90.0)	71.9* (60.9 to 82.9) 86.7* (79.0 to 94.4) 88.1* (81.2 to 95.0)	48.6* (32.0 to 65.1) 50.0* (28.1 to 71.9) 23.1* (0.2 to 46.0)	83.6* (73.9 to 93.4) 92.9* (86.8 to 98.9) 96.1* (91.8 to 100)	2.3* (1.4 to 3.8) 5.0* (2.5 to 9.9) 4.2* (1.6 to 11.3)	0.48* (0.28 to 0.83) 0.38* (0.19 to 0.79) 0.57* (0.25 to 1.27)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
differences in a large sample of twins	criteria: Measurements performed more than 2 weeks before birth; incomplete measurements Other details: Details of chorionicity and ethnicity not reported	≥18mm in AC was used for discordancy Details of methods and equipment reported	used for AC, only data for EFW difference were extracted (in accordance with the review protocol) * Calculations carried out by the NCC-WCH technical team											
First author, year: Sayegh 1993[93] Country: USA Study design: Prospective cohort study Study dates:	Population: 78 women with twin pregnancies (including one with FFTS) Inclusion criteria: All consecutive twin pregnancies at Sentara Norfolk General	Screening tests: Intertwin EFW difference of ≥15%, ≥20% and ≥25% Calculation of EFW was based on BPD and AC, according to Shepard's formula (1982) Reference test: Intertwin birth weight	Prediction of BWD ≥25% using EFWD ≥25% using EFWD ≥20% using EFWD ≥15% * Calculations carried out by	10* NR NR	5 NR NR	3 NR NR	60* NR NR	76.9 (54.0 to 99.8) 74 71	92.3 (85.8 to 98.8) 90 88	66.7 (42.8 to 90.5) 70 77	95.2 (90.0 to 100) 91 85	10.0 (4.1 to 24.4) 7.4* 5.9*	0.25 (0.09 to 0.68) 0.33*	Funding: Not reported Limitations: The study included one twin pregnancy with feto-fetal transfusion syndrome

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
July 1984 to June 1987 Aim of study: To examine the ability of ultrasound to accurately predict discordant growth in twin pregnancies and to define the percent intertwin EFWD that best correlated with the previously established neonatal outcome	Hospital between 1 July 1984 and 20 June 1987 referred for targeted USS to the Division of Maternal-Fetal Medicine at Eastern Virginia Medical School Exclusion criteria: Accurate EFW not calculable (NC) Other details: When more than one scan was performed the most recent one prior to birth was used and this varied from 1 day to 6 weeks and no	discordance of ≥25% Method: Only data from scans performed at more than 23 weeks of pregnancy, when EFW could be calculated, were used in the analysis Scans were reviewed by the authors without knowledge of birthweight outcomes Details of equipment and methods reported	the NCC-WCH technical team											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	standard interval was required to be included in the study Details of chorionicity and ethnicity not reported													
First author, year: Van Mieghem 2009[100] Country: Belgium Study design: Prospective cohort study Study dates: January 2002 to January 2007	Population: 60 monochorionic diaminiotic (MCDA) twin pregnancies Inclusion criteria: All MCDA twin pregnancies recruited between 11 and 14 weeks of gestation for the EuroTwin2Twin project during January 2002 to January	Screening tests: Intertwin EFW difference of ≥25% EFW was calculated using Hadlock's formula (1985) based on HC, AC, BPD and FL Reference test: Intertwin birth weight discordance of ≥15%, ≥20% and ≥25% Method: EFW was calculated at each time point	Diagnostic accuracy of intertwin EFWD >25% at the last USS (≤ 2 weeks) before birth for the prediction of birthweight differences: >20% (n = 10) >25% (n = 8) >30% (n = 5) Detection of intertwin birthweight discordance ≥25% using	NR NR NR	NR NR NR	NR NR NR	NR NR NR	86.4 87.5 99.1	99.9 96.2 92.0	99.5 77.8 55.0	97.1 98.0 99.9	86.4* 23.0* 2.0*	0.14* 0.13* 0.01*	Funding: Supported by the European Commission

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Aim of study: To estimate the accuracy of ultrasound to predict birthweight and birthweight discordance in monochor-ionic diamniotic twin (MCDA) pregnancies	2007; entire 2-weekly USSs and birth of two live-born babies at ≥26 weeks in the University hospitals Leuven Exclusion criteria: Single or double intrauterine fetal death or twin-reversed arterial perfusion sequence (TRAPS) at the time of study entry; missing ultrasound parameters Other details: Details of ethnicity not	from 16 weeks onwards Diagnostic accuracy at various cut-offs were reported and ROC curves constructed to compare the accuracy of USS at 16, 20 and 26 weeks and the last scan (within 2 weeks) before birth to predict a BWD of ≥25% Details of methods reported	intertwin EFW difference of ≥25% at 16 weeks Area under ROC curve = 0.79 (0.57 to 1.02) at 20 weeks Area under ROC curve = 0.87 (0.69 to 1.05) at 26 weeks Area under ROC curve = 0.93 (0.85 to 1.00) at last scan before birth Area under ROC curve = 0.95 (0.94 to 1.01) * Calculations carried out by the NCC-WCH technical team											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	reported													
First author, year: Machado 2007[98] Country: Brazil Study design: Retrospec-tive review Study dates: December 1998 to December 2004 Aim of study: To evaluate the ability of USS carried out at different intervals	Population: 221 twin pregnancies Inclusion criteria: All women with twin pregnancies examined by ultrasound between December 1998 and December 2004, at the Obstetrics Department of Sao Paulo University Medical School; Brazil, gestational age from 26 to 39 completed weeks	Screening tests: EFW difference ≥20% EFW was calculated by Hadlock's formula (1985) based on HC, AC, BPD, FL Reference test: Intertwin birth weight discordance ≥20% Method: EFW was calculated using four parameters Prediction of intertwin discordance was examined at four different intervals before birth: 0-7	Prediction of intertwin birthweight discordance of ≥20% using EFW difference ≥20% performed at different intervals before birth 0 – 7 days 7 – 14 days 15 – 21 days 22 – 28 days * Calculations carried out by the NCC-WCH technical team	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	93.6 95.8 95.6 90.9	79.4 55.6 46.2 66.7	89.2 85.2 86.0 88.9	87.1 85.2 86.0 84.4	4.5* 2.2* 1.8* 2.7*	0.08* 0.08* 0.10* 0.14*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
before delivery, to estimate actual birthweight discordance in twin pairs	Exclusion criteria: Pregnancies with fetal malformations, FFTS, fetal death, or unknown outcome Other details: Details of ethnicity and chorionicity not reported	days, 8-14 days, 15-21 days, 22-28 days Details of equipment and methods reported												
First author, year: Gernt 2001[99] Country: USA Study design: Retrospec-tive database review	Population: 192 twin pregnancies with last USS performed within 16 days of birth Inclusion criteria: All women with twin pregnancy followed	Screening tests: Intertwin EFW difference ≥25% EFW was calculated using Hadlock's formula (1984) based on HC, AC, BPD and FL Reference test: Intertwin birth weight	Prediction of intertwin birthweight discordance ≥25% using EFW difference ≥25% Last USS to birth interval ≤16 days	18 NR NR	4 NR NR	15 NR NR	155 NR NR	54.6* (37.6 to 71.5) 54 56	97.5* (95.1 to 99.9) 97 97	81.8* (65.7 to 97.9) NR NR	91.2* (86.9 to 95.4) NR NR	21.7* (7.8 to 59.9) 18.0* 18.7*	0.47* (0.32 to 0.68) 0.47* 0.45*	Funding: Not reported Limitations: Main limitation is the retrospective nature of the study. Also, only 17% (33 twin pairs) had BWD of 25% or more, thus

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
Study dates: 1988 to1998 Aim of study: To assess the accuracy of ultrasound prediction of intertwin birthweight discordance and to determine whether this was affected by maternal and fetal variables	through delivery in a specialised antenatal twin clinic directed by the Maternal Fetal Medicine Division at the Medical University of South Carolina; live birth of both twins at or beyond 24 weeks; birthweight of ≥500g; ultrasound prediction of EFW and percent discordance performed within 16 days of birth Exclusion criteria: Lack of USS	discordance ≥25% Method: USS was performed by one of seven certified registered diagnostic sonographers and each scan was reviewed by a Maternal Fetal Medicine faculty member EFW was calculated by applying the Hadlock formula using composite fetal biometry Details of equipment and method reported	Last USS to birth interval ≤10 days Last USS to birth interval ≤7 days Prediction of intertwin birthweight discordance ≥20% using EFW difference ≥20% Last USS to birth interval ≤16 days Last USS to birth interval ≤10 days Last USS to birth interval ≤7 days * Calculations carried out by the NCC-WCH	NR NR NR	NR NR	NR NR	NR NR	57 58 62	90 90 89	NR NR NR	NR NR NR	5.7* 5.8* 5.6*	0.48* 0.47* 0.43*	making the positive likelihood ratio very high

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	within 16 days of birth Other details: Of the 33 discordant twin pregnancies, 50% were white and 50% black; of the 159 non-discordant twins, 39% were white, 59% black and 2% other. Details of chorionicity not reported		technical team											
First author, year: Chang 2006[90] Country: Taiwan Study design:	Population: 575 twin pregnancies with gestational age of 24 weeks at birth who had received USS within 28 days of birth	Screening tests: Intertwin EFW difference ≥20% EFW calculated using AC, HC, FL and BPD Reference test: Intertwin birthweight	Detection of intertwin birthweight discordance ≥15% using EFW difference ≥15% EFW difference	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	64 89 73 81	89 73 73 71	71 NR NR NR	86 NR NR NR	5.8* 3.3* 2.7* 2.8*	0.40* 0.15* 0.40* 0.41*	Funding: Not reported Limitations: Retrospective study

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Retrospectiv		discordancy	≥10%											
e case	Inclusion	≥15%, ≥20%,	USS ≤7 days											
review	criteria:	≥25% and ≥30%	USS ≤14 days	NR										
	All available		USS ≤28 days		NR	NR	NR	61	95	73	93	12.2*	0.41*	
Study dates:	perinatal	Method:	Detection of	NR										
January	records of live	EFW was	intertwin	NR	NR	NR	NR	88	84	NR	NR	5.5*	0.14*	
1991 to	twins born	calculated using	birthweight	NR	NR	NR	NR	85	86	NR	NR	6.1*	0.17*	
December	between	AC, FL, HC, BPD	discordance		NR	NR	NR	83	86	NR	NR	5.9*	1.21*	
2002	January 1991	and the	≥20% using											
	and December	discordance was	EFW											
Aim of study:	2002 at Chang	also calculated	difference											
To predict	Gung Memorial	ROC curve was	≥20%	NR										
the different	Hospital Linkou	applied to test the	EFW		NR	NR	NR	60	98	75	95	30.0*	0.41*	
levels of	Medical Centre	predictability of	difference	NR										
BWD and	at gestational	significantly	≥15%	NR	NR	NR	NR	85	89	NR	NR	7.7*	0.17*	
discuss a	age (GA) ≥24	discordant twin	USS ≤7 days	NR	NR	NR	NR	84	92	NR	NR	10.5*	0.17*	
practical	weeks following	growth	USS ≤14 days		NR	NR	NR	78	95	NR	NR	15.6*	0.23*	
strategy to	USS 28 days or	USS was	USS ≤28 days											
detect	less before	performed by one	Detection of											
significant	birth were	of five certified	intertwin	NR										
intertwin	reviewed	diagnostic	birthweight											
birthweight		sonographers	discordance	NR	NR	NR	NR	56	98	75	97	28.0*	0.45*	
discordance	Exclusion		≥25% using	NR										
with higher	criteria:		EFW	NR	NR	NR	NR	86	92	NR	NR	10.8*	0.15*	
sensitivity	Incomplete		difference		NR	NR	NR	85	96	NR	NR	21.3*	0.16*	
	maternal or		≥25%		NR	NR	NR	78	96	NR	NR	19.5*	0.23*	
	fetal data		EFW											
			difference											
	Other details:		≥20%											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR− (95% CI)**	
	Not reported		USS ≤7 days USS ≤14 days USS ≤28 days Detection of intertwin birthweight discordance ≥30% using EFW difference ≥30% EFW difference ≥25% USS ≤7 days USS ≤14 days USS ≤28 days * Calculations carried out by the NCC-WCH technical team											
First author, year: Rodis 1990[96] Country: USA	Population: 25 women with twin pregnancy that delivered within 7 days of the last USS	Screening tests: 1) EFW difference ≥20% using BPD and AC measurements 2) EFW	Efficacy of predicting BWD ≥20% by EFWD ≥20% when EFW calculated using BPD,	12	3	2	12	85.7* (67.4 to 100)	80.0* (59.8 to 100)	80.0* (59.8 to 100)	85.7* (67.4 to 100)	4.3* (1.5 to 12.1)	0.18* (0.05 to 0.66)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Study design: Prospective cohort study Study dates: 1985 to 1987 Aim of study: To assess longitudinal growth of twins who are ultimately discordant at birth and to see how they differ from the concordant group and to assess the accuracy of both Shepard's formula (using BPD and AC) and Hadlock's	Inclusion criteria: All women with twin pregnancies between 1985 and 1987 at the University of Connecticut Health Centre underwent serial USS if there was birthweight discordancy ≥20%; confirmed dating and absence of major congenital anomalies in one or both fetuses Exclusion criteria: None reported	difference ≥20% using FL and AC measurements EFW was calculated for each fetus using two formulae: one based on BPD and AC (Shepard's formula) and the other based on FL and AC (Hadlock's formula) Reference test: Intertwin birth weight discordance ≥20% Method: 156 ultrasound examinations were performed and the mean discordancy was 27%	AC (Shepard's formula) when EFW calculated using FL and AC (Hadlock's formula) * Calculations carried out by the NCC-WCH technical team	13	4	3	25	81.3* (62.1 to 100)	86.2* (73.7 to 98.8)	76.5* (56.3 to 96.6)	89.3* (77.8 to 100)	5.9* (2.3 to 17.1)	0.22* (0.08 to 0.61)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
formula (employing FL and AC)	Other details: Details of ethnicity or chorionicity not reported	Details of equipment and methods reported												
First author, year: Chamberlain 1991[94] Country: Ireland Study design: Retrospec-tive review Study dates: January 1985 to December 1988 Aim of study: To determine the accuracy of ultrasound determined	Population: 85 twin pregnancies with last USS performed within 7 days or within 14 days of birth Inclusion criteria: All twin pregnancies identified in the Fetal Assessment Unit, Department of Obstetrics and Gynaecology, Regional Hospital, Galway, Ireland, who underwent	Screening tests: EFWD ≥20% and ≥25% using 1) AC only 2) FL and AC EFW calculation using FL and AC was based on Hadlock (1984) Reference test: Intertwin birthweight discordance ≥20% and ≥25% Method: At each examination AC and, if possible, femur length were measured and recorded EFW for each	Accuracy of EFW difference ≥20% estimated by AC and FL to determine BWD ≥20% Last USS to birth interval ≤7 days Last USS to birth interval ≤14 days Accuracy of EFW difference ≥25% estimated by AC and FL to determine BWD ≥25%	6 6	3 5	5 7	39 56	54.6* (25.1 to 84.0) 46.2* (19.1 to 73.3)	92.9* (85.1 to 100) 91.8* (84.9 to 98.7)	66.7* (35.9 to 97.5) 54.6* (25.1 to 84.0)	88.6* (79.3 to 98.0) 88.9* (81.1 to 96.7)	7.6* (2.3 to 25.8) 5.6* (2.0 to 15.7)	0.49* (0.25 to 0.94) 0.59* (0.35 to 0.98)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
interpair EFW percentage using EFW equations not dependent on BPD measurements in the antenatal identification of discordant birthweight in twins	sequential USSs at 1-4 week intervals Exclusion criteria: Interval between the last USS and delivery of ≥ 14 days; intrauterine death in one fetus at referral or ≥ 14 days before delivery; major congenital anomaly; failure to record birthweight within 6 hours of delivery; AC and FL measurements too small for EFW determination Other details: All ultrasound	fetus was determined from either AC measurement alone or from both AC and FL measurements Details of equipment and method reported	Last USS to birth interval ≤7 days Last USS to birth interval ≤14 days * Calculations carried out by the NCC-WCH technical team Data relating to EFW based on AC alone were not extracted (in accordance with the review protocol)	3 3	1 1	3 5	46 65	50.0* (10.0 to 90.0) 37.5* (4.0 to 71.1)	97.9* (93.8 to 100) 98.5* (95.5 to 100)	75.0* (32.6 to 100) 75.0* (32.6 to 100)	93.9* (87.2 to 100) 92.9* (86.8 to 98.9)	23.5* (2.9 to 191.5) 24.8* (2.9 to 210.6)	0.51* (0.23 to 1.14) 0.63* (0.37 to 1.09)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	examinations were performed by one examiner Details of ethnicity and chorionicity not reported													
First author, year: Diaz-Garcia 2010[92] Country: France Study design: Retrospective database review Study dates: 2004 to 2007 Aim of study: To assess the accuracy of ultrasound	Population: 283 twin pregnancies with at least one USS within 15 days of birth Inclusion criteria: All twin pregnancies at a tertiary referral centre in France between 2004 and 2007 with birth of both twins ≥ 22 weeks and at least one USS within 15 days	Screening tests: Intertwin EFW difference of ≥15%, ≥20% and ≥25% EFW was calculated using five different formulae: Warsof (AC, FL, 1986); Shepard (AC, FL, 1982); Ong (AC, FL, 1999); Hadlock1 (BPD,AC, FL, 1985) and Hadlock2 (BPD, HC, AC, FL, 1985) Reference test:	Diagnostic accuracy of Warsof's formula Prediction of BWD ≥15% by EFWD ≥15% Prediction of BWD ≥20% by EFWD ≥15% Prediction of BWD ≥20% by EFWD ≥20% Prediction of BWD ≥25% by EFWD ≥15% Prediction of BWD ≥25%by EFWD ≥20%	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	66 72 60 77 70	76 72 86 69 84	65 52 65 40 54	74 86 84 92 91	2.75 2.57 4.29 2.48 4.38	0.45 0.39 0.47 0.33 0.36	Funding: Not reported Limitations: Retrospective study; ultrasound examinations performed by different sonographers may introduce systematic errors.

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
examination to evaluate EFW to predict birthweight and birthweight discordance using five different formulas in a large twin population	of birth Exclusion criteria: Pregnancies with no first trimester USS; chromosomal abnormalities or congenital malformations Other details: Gestational age was based on first trimester USS When several USS were done within 15 days of birth, only the closest to birth was used Chorionicity and birthweight confirmed at birth; 49.9% were monochorionic	Intertwin birth weight discordance of ≥15%, ≥20% and ≥25% Method: USS was performed by senior sonographers; all measurements were performed using the same probes and machines ROC curves were constructed for the prediction of birthweight discordance (BWD) based on estimated fetal weight percentage difference (EFWD) Details of equipment and	Prediction of BWD ≥25%by EFWD ≥25% Diagnostic accuracy of Ong's formula Prediction of BWD ≥15% by EFWD ≥15% Prediction of BWD ≥20% by EFWD ≥15% Prediction of BWD ≥20% by EFWD ≥20% Prediction of BWD ≥25% by EFWD ≥15% Prediction of BWD ≥25% by EFWD ≥20% Prediction of BWD ≥25% by EFWD ≥25% Diagnostic accuracy of Shepard's formula Prediction of	NR NR NR NR NR NR NR	NR NR NR NR NR NR NR	NR NR NR NR NR NR NR	NR NR NR NR NR NR NR	60 72 78 69 82 73 67	93 75 71 84 67 80 90	71 65 53 64 40 49 64	90 80 89 86 93 92 91	8.57 2.88 2.69 4.31 2.48 3.65 6.70	0.43 0.37 0.31 0.37 0.27 0.34 0.37	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	Details of ethnicity not reported	method reported	BWD ≥15% by EFWD ≥15%	NR	NR	NR	NR	73	71	63	79	2.52	0.38	
			Prediction of BWD ≥20% by EFWD ≥15%	NR	NR	NR	NR	83	69	53	91	2.68	0.25	
			Prediction of BWD ≥20% by EFWD ≥20%	NR	NR	NR	NR	70	80	59	86	3.50	0.38	
			Prediction of BWD ≥25% by EFWD ≥15%	NR	NR	NR	NR	85	64	40	94	2.36	0.23	
			Prediction of BWD ≥25% by EFWD ≥20%	NR	NR	NR	NR	73	76	45	91	3.04	0.36	
			Prediction of BWD ≥25% by EFWD ≥25%	NR	NR	NR	NR	63	86	56	90	4.50	0.43	
			Diagnostic accuracy of Hadlock1											
			Prediction of BWD ≥15% by EFWD ≥15%	NR	NR	NR	NR	74	76	68	81	3.08	0.34	
			Prediction of BWD ≥20% by EFWD ≥15%	NR	NR	NR	NR	85	73	57	92	3.15	0.21	
			Prediction of BWD ≥20% by EFWD ≥20%	NR	NR	NR	NR	72	85	67	88	4.80	0.33	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
			Prediction of BWD ≥25% by EFWD ≥15%	NR	NR	NR	NR	92	69	44	97	2.97	0.12	
			Prediction of BWD ≥25% by EFWD ≥20%	NR	NR	NR	NR	76	80	51	93	3.80	0.30	
			Prediction of BWD ≥25% by EFWD ≥25%	NR	NR	NR	NR	68	91	68	91	7.56	0.35	
			Diagnostic accuracy of Hadlock2											
			Prediction of BWD ≥15% by EFWD ≥15%	NR	NR	NR	NR	74	75	67	81	2.96	0.35	
			Prediction of BWD ≥20% by EFWD ≥15%	NR	NR	NR	NR	84	72	55	91	3.00	0.22	
			Prediction of BWD ≥20% by EFWD ≥20%	NR	NR	NR	NR	72	84	66	86	4.50	0.33	
			Prediction of BWD ≥25% by EFWD ≥15%	NR	NR	NR	NR	90	67	42	96	2.73	0.15	
			Prediction of BWD ≥25% by EFWD ≥20%	NR	NR	NR	NR	76	80	51	93	3.80	0.30	
			Prediction of BWD ≥25% by	NR	NR	NR	NR	68	92	72	92	8.50	0.35	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
			EFWD ≥25%											

Review question

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

d) Studies reporting ultrasound measurements of fetal biometry and estimated fetal weight as index tests

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Klam 2005[87] Country: Canada Study design: Prospective cohort study Study dates: April 1994 – January 2002 Aim of study: To assess the accuracy of the abdominal circumfer-ence (AC)	Population: N = 503 diamniotic twin pregnancies 378 dichorionic; 125 monochorionic Inclusion criteria: Consecutive diamniotic twin pregnancies followed through to birth, with both twins born alive at a tertiary care centre in Canada between 1 April 1994 and 1 January 2002. Exclusion	Screening tests: Intertwin AC ratio Reference test: Intertwin birth weight discordance ≥25% Method: Serial measurements of BPD, AC and FL were carried out about every 2-4 weeks (from 11 to 38 weeks). Discrepant AC measurements were expressed as	Prediction of birth weight discordance ≥25% using AC ratio < 0.93 Monochorionic (all) 16-23 weeks 24-29 weeks 30-36 weeks Dichorionic (all) 16-23 weeks 24-29 weeks 30-36 weeks All twins * Calculations carried out by the NCC-WCH	 NR NR NR NR NR NR NR NR NR	 NR NR NR NR NR NR NR NR NR	 NR NR NR NR NR NR NR NR NR	 NR NR NR NR NR NR NR NR NR	 80 78 81 87 48 40 51 54 61	 73 76 72 71 88 86 89 88 84	 45 46 49 40 35 28 40 39 40	 93 93 92 96 92 92 92 93 93	 3.0* 3.3* 2.9* 3.0* 4.0* 2.9* 4.6* 4.5* 3.8*	 0.27* 0.29* 0.26* 0.18* 0.59* 0.70* 0.55* 0.52* 0.46*	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
ratio for the sonographic prediction of twin birth weight discordance	criteria: Pregnancies with chromosomal and fetal anomalies, intrauterine death of one or both fetuses, pregnancies with twin transfusion syndrome, twin pregnancy transfer accrued after 21 weeks gestation Other cetails: Details of ethnicity not reported	AC ratios ROC curves were generated and a cut off of 0.93 was obtained. Details of techniques and equipment used were reported	technical team Intertwin EFW difference ≥ 25% alaso reported but the formula used to calculate EFW was not reported, and so these data were not extracted											
First author, year: Shah 1994[84] Country: USA	Population: 90 twin pregnancies Inclusion criteria:	Screening tests: Intrapair differences in 1) BPD 2) HC	Prediction of birthweight discordancy ≥20% using ultrasound measure-											Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
Study design: Retrospec-tive cohort study Study dates: January 1983 – May 1988 Aim of study: To examine the predictability of intrapair percentage differences of ultrasonic fetal biometric parameters in detecting twin discordancy	All women with twin pregnancies that underwent USS of both fetuses within 7 days of a live twin birth in the perinatal ultrasound unit, Strong Memorial Hospital, New York between 1 January 1983 and 31 May 1988, and in whom measurements of BPD, HC, AC, FL, and EFW were obtained Exclusion criteria: Maternal gestational or	3) AC 4) FL 5) HC:AC ratio 6) EFW ≥20% EFW was computed by the method of Warsof et al. (1977) using FL and AC Reference test: Intertwin birth weight discordance ≥20% Method: Intrapair difference of 5% and 10% for all biometric measurements (BPD, HC, AC, FL and HC:AC ratio) were considered to be critical	ments with intrapair difference >5% BPD HC AC FL HC:AC ratio Prediction of birthweight discordancy ≥20% using ultrasound measure-ments with intrapair difference >10% BPD HC AC FL HC:AC ratio Prediction of birthweight	8 7 16 8 8 5 2 11 3 2 10	19* 11* 27* 13* 23* 3* 3* 7* 4* 9* 5	6* 4* 2* 9* 3* 9* 9* 7* 14* 9* 4	31* 32* 40* 49* 19* 47* 40* 60* 58* 33* 43	57.1 63.6 88.9 47.1 72.2 35.7 18.2 61.1 17.7 18.2 71.4* (47.8	62.0 74.4 59.7 79.0 45.2 94.0 93.0 89.6 93.6 78.6 89.6* (80.9	29.6 38.9 37.2 38.1 25.8 62.5 40.0 61.1 42.9 18.2 66.7* (42.8	83.8 88.9 95.2 84.5 86.4 83.9 81.6 89.6 80.6 78.6 91.5* (83.5	1.5* 2.4* 2.2* 2.2* 1.3* 6.0* 2.6* 5.8* 2.7* 0.8* 6.8* (2.8	0.69* 0.48* 0.19* 0.67* 0.60* 0.68* 0.88* 0.43* 0.88* 1.04* 0.3* (0.1 to	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	type 1 diabetes; fetal anomalies and congenital toxoplasmosis, rubella, cytomegalo-virus, herpes complex (TORCH) infection. Other details: Details of ethnicity and chorionicity not reported	values for predicting discordancy and were compared with birthweight Details of techniques and equipment reported	discordance ≥20% using EFW difference ≥20% * Calculations carried out by the NCC-WCH technical team					to 95.1)	to 98.2)	to 90.5)	to 99.5)	to 16.8)	0.7)	
First author, year: Chitkara 1985[85] Country: USA Study design: Prospective	Population: 36 women with twin pregnancies with last scan at least 21 days before birth Inclusion criteria:	Screening tests: 1) BPD 2) HC 3) AC 4) FL 5) HC:AC ratio 6) EFW The calculation of EFW was based on BPD	Ability of ultrasound parameters to correctly detect IUGR in the smaller birthweight twin (using logistic regression) BPD	NR	NR	NR	NR	77.8	90.5	NC	NC	8.2*	0.25*	Funding: Not reported Limitations: A possible limitation is the use of a singleton chart as the reference standard for IUGR

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
cohort study Study dates: September 1981 – December 1983 Aim of study: To determine the diagnostic accuracy of antenatal ultrasound scan (USS) using multiple parameters in the prediction of IUGR and birthweight discordancy in twin pregnancies	Consecutive twin pregnancies evaluated at the Perinatal Ultrasound Unit of the Mount Sinai Medical Center, New York, USA, during a 28-month period, from September 1981 to December 1983; only observations taken at the last scan ≤ 21 days before delivery were included in the analysis Exclusion criteria: Congenital	and AC, according to Shephard et al. (1982) Reference tests: 1) IUGR at birth (<10th percentile of expected neonatal birthweight corresponding to gestational age using Lubcheno's data for singleton pregnancies) 2) Intertwin birthweight discordance ≥20% Method: Measurements applied in ultrasound evaluation of	HC AC EFW (i.e BPD + AC) FL HC:AC ratio EFW + FL (i.e BPD + AC + FL) Ability of ultrasound parameters to correctly classify discordant growth (using logistic regression) BPD difference (based on actual measurement) BPD difference (dichotomised <5mm and ≥5mm)	NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR	37.5 100. 0 90.0 85.7 75.0 85.7 28.6 57.1	100.0 84.6 92.3 85.0 90.0 100.0 94.1 88.2	NC NC NC NC NC NC NC NC	NC NC NC NC NC NC NC NC	∞* 64.9* 11.7* 5.2* 7.5* ∞* 4.8* 4.8*	0.63* 0.00* 0.11* 0.17* 0.28* 0.14* 0.76* 0.49*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	malformations; intrauterine death of a twin; if women were undelivered at the end of study period Other details: Following the diagnosis of a twin pregnancy, women were followed-up with serial USS, performed by a single investigator at intervals of 4-6 weeks at <26 weeks' gestation and every 2-4 weeks thereafter until delivery	growth and IUGR were BPD, HC, FL, HC:AC ratio, EFW A model was fitted to the data by stepwise logistic regression and diagnostic accuracy was calculated from the fitted models Details of techniques and equipment reported	HC difference AC difference EFW difference FL difference * Calculations carried out by the NCC-WCH technical team	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	16.7 66.6 33.3 28.6	100.0 92.3 100.0 100.0	NC NC NC NC	NC NC NC NC	∞* 8.6* ∞* ∞*	0.83* 0.36* 0.67* 0.71*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	Details of ethnicity and chorionicity not reported													
First author, year: Deter 1992[86] Country: USA Study design: Prospective cohort study Study dates: Not reported Aim of study: To examine the effectiveness methods for predicting IUGR at birth, including	Population: 17 pairs of twins (34 twin fetuses) Inclusion criteria: Not clearly reported Exclusion criteria: None reported Other details: Twins were evaluated with USS at 2-3 week intervals from about 15 to 36 weeks. Measurements of head circumference	Screening tests: 1) HC 2) AC 3) FL 4) EFW EFW was obtained by using the measurement of head cube (A) and abdominal cube (B) Reference test: IUGR at birth Method: Rossavik growth models derived from second-trimester	Prediction of IUGR from third-trimester growth patterns of fetuses based on ≥1abnormal negative deviations EFW HC AC FL Prediction of IUGR from third-trimester growth patterns based on ≥3 parameters with abnormal negative	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	71.4 57.1 100.0 57.1 85.7	91.7 95.8 66.7 75.0 95.8	NC NC NC NC NC	NC NC NC NC NC	8.6* 13.6* 3.0* 2.3* 20.4*	0.31* 0.45* 0.00* 0.57* 0.15*	Funding: Not reported Limitations: Main limitation is a small sample size and that only sensitivity and specificity were reported; there are no raw data reported in the paper to enable calculation of other diagnostic accuracy measures

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
individualised growth assessment in the detection of IUGR twins during the third trimester	(HC), abdominal circumference (AC), thigh circumference (ThC - not relevant to the guideline review), femur length (FL), head cube (A) and abdominal cube (B) were obtained at each ultrasound examination if possible No details of ethnicity or chorionicity reported	biometries were used to determine expected growth curves in the third trimester. Differences between observed and predicted measurements were compared and expressed as percentage deviations classified as normal, abnormal positive, or abnormal negative deviations Four different predictor variables for IUGR were evaluated with	deviations in each fetus Prediction of IUGR from third-trimester growth patterns based on >10% abnormal negative deviations for 5 parameters (i.e. including ThC – not reported separately for the guideline review) Prediction of IUGR from third-trimester growth patterns based on anteatal	NR	NR	NR	NR	85.7	100.0	NC	NC	∞*	0.14*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR− (95% CI)**	
		details of techniques and methods reported Sensitivity and specificity were calculated for each predictor variable	growth assessment score EFW HC AC FL Antenatal assessment score calculated after last scan * Calculations carried out by the NCC-WCH technical team	 NR NR NR NR	 NR NR NR NR	 NR NR NR NR	 NR NR NR NR	 71.4 57.1 85.7 57.1	 100.0 95.8 87.5 83.3	 NC NC NC NC	 NC NC NC NC	 ∞* 13.6* 6.9* 3.4*	 0.29* 0.45* 0.16* 0.52*	
First author, year: Grobman 1999[106] Country: USA Study design: Retrospectiv	Population: 44 women with twin pregnancies Inclusion criteria: All twin pregnancies monitored by ultrasound	Screening tests: 1) Abdominal circumference (AC) <5th percentile or 2) Estimated fetal weight (EFW) <10th percentile or 3) EFW	Diagnostic accuracy of AC (<5th percentile) or EFW (<10th percentile) or EFW difference (≥20%) for detection of IUGR											Funding: Not reported Limitations: Main limitation is the retrospective design of the study and also details of chorionicity are not provided

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
e database review Study dates: January 1992 – March 1998 Aim of study: To assess the PPV of serial ultrasound measure-ments for growth abnormali-ties in twin pregnancies as a function of gestational age Growth abnormality was defined as AC <5th percentile,	scan (USS) at Northwestern Memorial Hospital, Chicago, between 1 January 1992 and 1 March 1998, were identified by a database search and only women whose fetuses were anatomically normal; who had undergone a baseline scan between 20 and 24 weeks; and who had at least one USS with a finding of a possible growth abnormality were included	difference ≥20% EFW was derived according to the parameters by Sabbagha et al. (1989) Reference test: 1) IUGR at birth (weight <10th percentile) 2) Intertwin birthweight discordance ≥20% Method: Findings of each USS were extracted from medical records and reviewed specifically for gestational age	at 20-24 weeks	10	3*	7*	24*	58.8* (35.4 to 82.2)	88.9* (77.0 to 100)	76.9* (54.0 to 99.8)	77.4* (62.7 to 92.1)	5.3* (1.7 to 16.5)	0.46* (0.26 to 0.83)	
			at 25-28 weeks	0	6*	17*	21*	0* (0 to 20*)	77.8* (62.1 to 93.5)	0* (0 to 46*)	55.3* (39.5 to 71.1)	0* (NC)	1.29* (1.05 to 1.57)	
			at 29-32 weeks	6	9*	11*	18*	35.3* (12.6 to 58.0)	66.7* (48.9 to 84.4)	40.0* (15.2 to 64.8)	62.1* (44.4 to 79.7)	1.0* (0.5 to 2.4)	0.97* (0.62 to 1.51)	
			at 33-39 weeks Diagnostic accuracy of AC (<5th percentile) or EFW (<10th percentile or EFWD ≥20%) for detection of intertwin	1	9*	16*	18*	5.9* (0 to 17.1)	66.7* (48.9 to 84.4)	10.0* (0 to 28.6)	52.9* (36.2 to 69.7)	0.2* (0.0 to 1.3)	1.41* (1.05 to 1.89)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
EFW<10th percentile or EFW difference ≥20%	Exclusion criteria: None reported Other details: Details of chorionicity and ethnicity not reported	at each scan, together with AC and EFW Gestational age at birth and birthweights were identified using a computer database and confirmed by a search of the labour and delivery records	discordance ≥20%											
			at 20-24 weeks	9	4*	9*	22*	50.0* (26.9 to 73.1)	84.6* (70.8 to 98.5)	69.2* (44.4 to 94.3)	71.0* (55.0 to 87.0)	3.3* (1.2 to 8.9)	0.59* (0.36 to 0.96)	
			at 25-28 weeks	0	6*	18*	20*	0* (0 to 19*)	76.9* (60.7 to 93.1)	0* (0 to 46*)	52.6* (36.8 to 68.5)	0* (NC)	1.30* (1.05 to 1.60)	
			at 29-32 weeks	6	9*	12*	17*	33.3* (11.6 to 55.1)	65.4* (47.1 to 83.7)	40.0* (15.2 to 64.8)	58.6* (40.7 to 76.6)	1.0* (0.4 to 2.2)	1.02* (0.66 to 1.57)	
			at 33-39 weeks	3	7*	15*	19*	16.7* (0.0 to 33.9)	73.1* (56.0 to 90.1)	30.0* (1.6 to 58.4)	55.9* (39.2 to 72.6)	0.6* (0.2 to 2.1)	1.14* (0.84 to 1.56)	

Review question

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

e) Studies using Doppler velocimetry as index test

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
First author, year: Hastie 1989[102] Country: UK Study design: Prospective cohort study Study dates: Not reported Aim of study: To determine the predictive	Population: 89 twin pregnancies (178 babies) Inclusion criteria: Consecutive unselected twin pregnancies Exclusion criteria: Not reported Other details: No details of ethnicity or chorionicity reported	Screening test: Umbilical artery Doppler S:D ratio >90th percentile Reference test: SGA at birth – defined as birth weight ≤5th centile for gestational age using Scottish birthweight data Method: Doppler recordings of each twin fetus were obtained at approximately monthly	Prediction of SGA fetuses using umbilical artery S:D ratio >90th percentile measured at 20-23 weeks 24-27 weeks 28-31 weeks 32-35 weeks	4 1 2 11	5* 6* 12* 17*	7* 18* 10* 17*	59 88 78 64	36.4* (7.9 to 64.8) 5.3* (0 to 15.3) 16.7* (0 to 37.8) 39.3* (21.2	92.2* (85.6 to 98.8) 93.6* (88.7 to 98.6) 86.7* (79.6 to 93.7) 79.0* (70.1	44.4* (12.0 to 76.9) 14.3* (0 to 40.2) 14.3* (0 to 32.6) 39.3* (21.2	89.4* (82.0 to 96.8) 83.0* (75.9 to 90.2) 88.6* (82.0 to 95.3) 79.0* (70.1	4.7* (1.5 to 14.7) 0.8* (0.1 to 6.5) 1.3* (0.3 to 4.9) 1.9* (1.0 to	0.69* (0.44 to 1.09) 1.01* (0.90 to 1.14) 0.96* (0.74 to 1.25) 0.77* (0.56	Funding: Not reported Limitations: S:D ratio was considered abnormal when >90th percentile for gestational age using the normal range previously determined from 58 normal singleton pregnancies

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
value of Doppler studies in identifying twin fetuses destined to be SGA at birth		intervals from 22 weeks Systolic:diasto-lic (S:D) ratio was determined for each fetus Details of techniques and equipment were reported	36-39 weeks * Calculations carried out by the NCC-WCH technical team	6	6	6*	36	to 57.4) 50.0* (21.7 to 78.3)	to 87.9) 85.7* (75.1 to 96.3)	to 57.4) 50.0* (21.7 to 78.3)	to 87.9) 85.7* (75.1 to 96.3)	3.5) 3.5* (1.4 to 8.9)	to 1.06) 0.58* (0.33 to 1.04)	
First author, year: Chittacha-roen 1999[103] Country: Thailand Study design: Prospective cohort study Study dates: May 1994 to April 1996	Population: 40 twin pregnancies (80 twin babies) Inclusion criteria: All twin pregnancies in the third trimester evaluated at the Maternal-Fetal Medicine Unit at Ramathibodi Hospital, Mahidol University, Thailand, during May 1994 to April 1996, with both	Screening test: Difference in umbilical artery Doppler S:D ratio >0.4 Reference test: Birthweight discordance >25% Method: Umbilical artery velocimetry waveforms were analysed with pulsed duplex Doppler	Prediction of intertwin BWD >25% using a difference in S:D ratio >0.4 * Calculations carried out by the NCC-WCH technical team	6	10	2	22	75.0* (45.0 to 100)	68.8* (52.7 to 84.8)	37.5* (13.8 to 61.2)	91.7* (80.6 to 100)	2.4* (1.3 to 4.6)	0.36* (0.11 to 1.24)	Funding: Not reported Limitations: The study included one case of FFTS which could not be excluded

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
Aim of study: To examine the diagnostic value of umbilical artery Doppler velocimetry as a test for detection of twin discordancy	fetuses alive at the time of examination; well documented dates (by reliable menstrual history in agreement with USS at 18-20 weeks); intact membranes and mother not in labour; birth within two weeks of USS-Doppler evaluation; signed consent form. Exclusion criteria: Not reported Other details: 15 of the placentas were monochorionic diamniotic, 27 were dichorionic diamniotic, and 3 were monochorionic monoamniotic Details of ethnicity	ultrasound and three separate ratios of peak S:D frequencies per fetus were obtained. The differences between S:D ratios for each twin were calculated and averaged Based on previously published reports, difference in S:D ratio >0.4 was chosen as the cut-off for abnormal test All evaluations were performed by two people Details of techniques and equipment reported											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
	not reported													
First author, year: Kurmanavcius 1992[104] Country: Switzerland Study design: Prospective cohort study Study dates: Not reported Aim of study: To evaluate umbilical artery Doppler ultrasound velocimetry in twin pregnancy	Population: 31 twin pregnancies (62 babies) The study included 32 women but one case of FFTS was excluded from guideline analysis in accordance with the review protocol Inclusion criteria: Consecutive unselected twin pregnancies Exclusion criteria: Not reported Other details: Birthweight discordancy was present in nine twin pairs, three of which (including one case of FFTS) were	Screening test: Umbilical artery Doppler RI difference ≥0.1 Reference test: Intertwin birthweight discordance >25% Method: Umbilical artery blood flow velocity waveforms were recorded on 125 occasions among the 32 women, with the last recording within 14 days of delivery Each fetus was examined separately and	Prediction of BWD >25% using umbilical artery RI difference ≥0.1 at the last examination (14 days before birth) * Calculations carried out by the NCC-WCH technical team	6*	1	2	22	75.0* (45.0 to 100)	95.7* (87.3 to 100)	85.7* (59.8 to 100)	91.7* (80.6 to 100)	17.3* (2.4 to 122.2)	0.3* (0.1 to 0.9)	Funding: Not reported.

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
with discordant fetal growth	monochorionic Details of ethnicity and further details of chorionicity not reported	the resistance index (RI) calculated. RI difference of 0.1 was used as a cut-off for discordancy Details of technique and equipment reported												
First author, year: Gerson 1987 [105] Country: USA Study design: Prospective cohort study Study dates: Start date July 1984 End date	Population: 55 pregnancies 51 twin, 4 triplet pregnancies The study included 52 women with twin pregnancies but 1 with FFTS was excluded from guideline analysis in accordance with the review protocol Inclusion criteria: All consecutive unselected women with suspected multiple pregnancies seen	Screening test: 1) Umbilical venous flow <10th percentile 2) abnormal umbilical artery Doppler S:D ratio Reference test: Intertwin BWD >25% Method: BPD, FL, HC, AC, umbilical venous blood flow and S:D ratio were measured (by	Prediction of BWD >25% by Doppler measurements of umbilical venous blood flow <10th percentile and/or abnormal S:D ratio among women with twin or triplet pregnancies The four sets of triplets included in this study did	8*	1	2	44	80.0* (55.2 to 100)	97.8* (93.5 to 100)	88.9* (68.4 to 100)	95.7* (89.8 to 100)	36.0* (5.1 to 256.3)	0.2* (0.1 to 0.7)	Funding: Not reported. Limitation: Physicians providing care were not blinded to the results of the Doppler ultrasound examinations Normal values of umbilical venous blood flow volume and S:D ratio

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR– (95% CI)	
not reported Aim of study: To determine the value of duplex Doppler ultrasound in identifying discordant fetal growth	routinely in the Antenatal Testing Unit, Pennsylvania Hospital and then evaluated monthly for fetal growth following confirmation of multiple pregnancy during the study period Exclusion criteria: Not reported Other details: Details of chorionicity and ethnicity not reported	Doppler) in each pregnancy Results of the first ultrasound examination in each twin pregnancy (rather than the last one before birth) were compared with pregnancy outcomes Details of equipment and method reported	not show any discordance by traditional or Doppler scan and were concordant at birth Among nine twin pregnancies characterised as abnormal by Doppler measurements, three had evidence of discordancy at initial scan based on EFW. The other six (67%) had normal EFW at initial scan (mean gestational age=26.1 weeks) and discordancy became										were based on the criteria for singleton pregnancy .

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			apparent only at later scans (mean=4.8 weeks) * Calculations carried out by the NCC-WCH technical team											

Review question

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

f) Studies using Doppler velocimetry and estimated fetal weight as a combined index test

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
First author, year: Divon 1989[108] Country: USA Study design: Retrospec-tive review of records Study dates: Not reported Aim of study: To examine the diagnostic value of ultrasono-graphic	Population: 58 consecutive twin pregnancies with birth within 2 weeks of scan Inclusion criteria: Third trimester twin pregnancies evaluated at the Maternal-Fetal Assessment Centre, Albert Einstein College of Medicine, New York, USA; both fetuses alive at time of	Screening tests: 1) EFWD >15% 2) Difference in S:D ratio >15% 3) either 1 or 2 EFW was calculated based on AC and FL, according to Russell (1985) Reference test: Intertwin BWD >15% Method: All women underwent measurements of BPD, AC, FL, EFW and	Prediction of BWD ≥15% using a difference in S:D ratio of >15% Prediction of BWD ≥15% using a difference in EFW of >15% Prediction of BWD ≥15% using either a difference in S:D ratio of >15% or difference in EFW of >15% Absolute differences (and not percentage differences or centiles) were reported for BPD,	NR NR 14	NR NR 5	NR NR 4	NR NR 35	66 47 77.8* (59 to 97)	64 81 87.5* (77.3 to 97.8)	55 56 73.7* (53.9 to 93.5)	75 74 89.7* (80.2 to 99.3)	1.8* 1.6* 6.2* (2.6 to 14.6)	0.53* 0.65* 0.25* (0.11 to 0.61)	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
indices combined with Doppler assessment of umbilical artery velocity waveforms as a test for detection of twin discordancy	examination; well-documented dates; intact membranes and mother not in labour; delivery within 2 weeks of Doppler-USS Exclusion criteria: None reported Other details: Details of chorionicity and ethnicity not reported	umbilical artery velocity waveforms The following cut-offs were used for discordancy: BPD difference >6mm, AC difference >20mm, FL difference >5mm, difference in S:D ratio >15%, EFWD >15% Details of equipment and method reported	AC and FL, and so only data for S:D ratio and EFW difference were extracted in accordance with the review protocol											
First author, year: Chittacha-roen 2000[107] Country: Thailand	Population: 40 twin pregnancies with birth within 2 weeks of scan Inclusion	Screening tests: 1) EFWD >15% 2) Difference in S:D ratio >15% 3) either 1 or 2 EFW was	Prediction of BWD ≥15% using a difference in S:D ratio of >15% Prediction of BWD ≥15% using a difference in	NR NR	NR NR	NR NR	NR NR	69 62	70 81	53 62	83 81	2.3* 3.3*	0.44* 0.47*	Funding: Not reported

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
Study design: Retrospective review of records Study dates: Not reported Aim of study: To examine the diagnostic value of sonographic biometry combined with Doppler velocimetry of the umbilical arteries as a predictive test for detection of twin discordancy	criteria: Third trimester twin pregnancies evaluated at the Maternal Fetal Medicine Unit, Ramathibodi Hospital, Mahidol University, Thailand; both fetuses alive at time of examination; well-documented dates; intact membranes and mother not in labour; delivery within 2 weeks of scan; signed consent form Exclusion criteria:	calculated based on AC and FL, according to Hadlock (1984) Reference test: Intertwin BWD >15% Method: All women underwent measurements of BPD, AC, FL, EFW and umbilical artery velocity waveforms The following cut-offs were used for discordancy: BPD difference >6mm, AC difference >20mm, FL difference >5mm,	EFW of >15% Prediction of BWD ≥15% using either a difference in S:D ratio of >15% or difference in EFW of >15% Absolute differences (and not percentage differences or centiles) were reported for BPD, AC and FL, and so only data for S:D ratio and EFW difference were extracted in accordance with the revew protocol	12	NR	NR	NR	92	70	60	95	3.1*	0.11*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)	
	None reported Other details: 15 pregnancies were monochorionic diamniotic, 22 were dichorionic diamniotic and three were monochorionic monoamniotic Details of ethnicity not reported	difference in S:D ratio >15%, EFWD >15% Details of equipment and method reported												

Chapter 7 Maternal complications

Hypertension

Review question

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

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	-LR (95% CI)	
First author, year: Geipel, 2002[115] Aim of study: To compare nomograms of uterine circulation for singleton and twin pregnancies for use in twin pregnancies Setting: Antenatal medicine department	Population: N= 256 twin pregnancies All dichorionic (chorionicity determined by ultrasound in early pregnancy) Inclusion criteria: Pregnancies with second-trimester Doppler studies of uterine arteries	Index test: Resistance index (RI), or unilateral or bilateral notching (method of scanning not reported) Reference test: Records in perinatal database, birth protocols, and telephone interview with	RI > 95th centile according to singleton nonogram for predicting pre-eclampsia	4*	5*	18*	229*	18 (2 to 34*)	98 (96 to 100*)	50 (12 to 77*)	92 (89 to 96*)	10.6 (2.9 to 39.6)	0.84* (0.69 to 1.02*)	Prevalence of pre-eclampsia= 22/256 (9%) Pre-eclampsia defined as repeated blood pressure of ≥ 140/90 mmHg with proteinuria ≥ 300 mg/day No clinical outcomes were reported This study was conducted in Germany Funding:
			RI > 95th centile according to twin nonogram for predicting pre-eclampsia	8*	28*	14*	206*	36 (16 to 56*)	88 (84 to 92*)	22 (9 to 36*)	94 (90 to 97*)	3.0 (1.6 to 5.8)	0.72* (0.52 to 0.99*)	
			RI > 95th centile according to twin nonogram	7*	16*	15*	218*	32 (12 to 51*)	93 (90 to 96*)	29 (11 to 49*)	94 (90 to 97*)	4.4 (2.0 to 9.4)	0.94* (0.90 to 0.97*)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity% (95% CI)**	**Specificity% (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
of a hospital in Germany Study design: Retrospec-tive cohort study Quality: No limitations	between 18^{+0} and 24^{+0} weeks Exclusion criteria: Fetal malforma-tions, premature rupture of membranes, unclear chorionicity and pregnancies with an unknown outcome Median gestational age at Doppler: 21.1±2.3 weeks 125 women were	obstetrician	and notching for predicting pre-eclampsia											Not reported
			Unilateral/bilateral notching for predicting pre-eclampsia	9*	33*	13*	201*	41 (20 to 61*)	86 (81 to 90*)	21 (9 to 34*)	94 (91 to 97*)	2.9 (1.6 to 5.3)	0.69* (0.48 to 0.98*)	
			Bilateral notching for predicting pre-eclampsia	4*	9*	18*	225*	18 (2 to 34*)	96 (94 to 99*)	29 (6 to 56*)	93 (89 to 96*)	4.3 (1.5 to 12.5)	0.93* (0.89 to 0.96*)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity% (95% CI)**	**Specificity% (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
	nulliparous													
<u>First author, year:</u> Yu, 2002[116] <u>Aim of study:</u> To determine the accuracy of Doppler at 23 weeks for predicting adverse outcomes in twins <u>Setting:</u> Seven hospitals in the UK <u>Study design:</u> Prospective screening study <u>Quality:</u> No limitations	<u>Population:</u> N= 351 twin pregnancies 316 dichorionic and 35 monochor-ionic (results could not be distinguished by chorionicity) <u>Inclusion criteria:</u> Pregnancies with two live fetuses between January 2000 and April 2002 <u>Exclusion criteria:</u> Major fetal	<u>Index test:</u> Pulsatility index (PI) or bilateral notches (transvaginal scanning) <u>Reference test:</u> Examination of individual women's notes and labour ward records	Pulsatility index > 95th centile for predicting pre-eclampsia	7*	11*	14*	319*	33 (13 to 54*)	97 (95 to 99*)	39 (16 to 61*)	96 (94 to 98*)	10.00 (4.24 to 21.88)	0.69* (0.51 to 0.93*)	Prevalence of pre-eclampsia= 21/351 (6%) Pre-eclampsia – two recordings of diastolic blood pressure of ≥ 90 mmHg at least 4 hours apart in previously normotensive women, and proteinuria of 300mg or more in 24 hours, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24 hour collection was available No clinical outcomes were
			Bilateral notches for predicting pre-eclampsia	4*	8*	17*	322*	19 (2 to 36*)	98 (96 to 99*)	33 (7 to 60*)	95 (93 to 97*)	7.86 (2.61 to 21.86)	0.83* (0.67 to 1.02*)	
			PI > 95th centile and bilateral notching for predicting pre-eclampsia	4	3	17	327	19* (2 to 36*)	99* (98 to 100*)	57* (20 to 94*)	95* (93 to 97*)	20.95* (5.01 to 87.60*)	0.82* (0.66 to 1.01*)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity% (95% CI)**	**Specificity% (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**+LR (95% CI)**	**-LR (95% CI)**	
	abnormalities or evidence of feto-fetal transfusion syndrome, incomplete data Gestational age range at time of scan: 22-24 weeks													reported This study was conducted in the UK <u>Funding:</u> Not reported

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?

a) Evidence tables for studies that reported diagnostic accuracy measures

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Gibson 2004[125] Country: UK Study design: Prospective observational study Study dates: 1991-2001 Aim of study: To evaluate cervical length measurement and fetal fibronectin	Population: N = 91 women with twin pregnancies 22 pregnancies were monochorionic Inclusion criteria: Women with twin pregnancies following completion of routine 18-week anomaly scan; informed consent obtained	Screening test: 1) Cervical length measurements 2) Fetal fibronectin test Reference test: Spontaneous preterm birth (<35 weeks' gestation) Method: Transvaginal ultrasound measurement of cervical length at 18, 24, 28 and 32 weeks' gestation	1) Prediction of spontaneous preterm birth (before 35 weeks' gestation) using cervical length: Results included in systematic review (see below)[119] 2) Prediction of spontaneous preterm birth (before 35 weeks'											Funding: Not reported Limitations: Women and their care providers were blinded to all study results Cut-offs derived from ROC curve No definition reported for suspected feto-fetal transfusion syndrome Data for both tests in combination not reported

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
detection as predictors of spontaneous preterm delivery in twin pregnancies	Exclusion criteria: Pregnancies complicated by fetal anomaly or suspected feto-fetal transfusion; elective delivery Other details: All pregnancies dated using last menstrual period (LMP) unless > 7 days' difference between LMP and expected date of delivery (EDD) based on first-trimester scan 15 women delivered spontaneously at <35 weeks; 76 women delivered at ≥35	The presence of fetal fibronectin (positive test if >50ng/ml) in maternal vaginal secretions was tested for before cervical length measurement in all but the first assessment, using a commercially available bedside assay Fibronectin test not carried out if there was a history of recent (<24 hours) bleeding or sexual intercourse Equipment/testing details reported	gestation) using fetal fibronectin testing Positive fibronectin test at 24 weeks (n =73)	8*	29*	8*	28*	50* (26 to 75*)	49* (36 to 62*)	22* (8 to 35*)	78* (64 to 91*)	0.98* (0.57 to 1.71*)	1.02* (0.58 to 1.78*)	95% CIs for fetal fibronectin not calculable (NC) from data reported in the article Main bias will arise from operator, equipment and a small sample size Not possible to analyse diagnostic accuracy separately for different chorionicities
			Positive fibronectin test at 28 weeks (n =74)	NC	NC	NC	NC	NC	NC	NC	NC	1.6	0.9	
			Positive fibronectin test at 32 weeks (n =65) † Cut-off derived from ROC curve	NC	NC	NC	NC	NC	NC	NC	NC	2.4	0.5	
			Prediction of spontaneous preterm birth (before 32 weeks' gestation)	12*	2*	4*	18*	75 (54 to 96*)	90 (77 to 100 *)	85* (67 to 100*)	81* (66 to 98*)	7.50 (1.95 to 28.78)*	0.28 (0.12 to 0.66)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	weeks Maternal ethnicity not reported		among women with triplet pregnancies and cervical length <25mm measured between 14 and 20 weeks' gestation											
First author, Year: Maslovitz 2004[124] Country: Israel Study design: Retrospective cohort study Study dates: January 2001 –December 2003	Population: N=36 women with triplet pregnancies All trichorionic 14 women had a short cervix (cervical length <25mm) Inclusion criteria: Trichorionic triplet pregnancies conceived	Screening test: Short cervix (cervical length <25mm) Reference test: Spontaneous preterm birth (<32 weeks) Method: Data for first-trimester sonography were obtained from medical files of women	Prediction of spontaneous preterm birth: For birth at <28 weeks using cervical length of ≤2.5 cm† at 15-20 weeks (16%, n=8/50) using cervical length of ≤2.5 cm† at 21-24 weeks (14%, n=7/50) using cervical length of ≤2.0	4 6 4	0* 9* 18*	4* 1* 0*	42 34 24	50 (15 to 85*) 86 (60 to 100*) 100 (100	100 (92 to 100*) 79 (67 to 91*) 57 (42	100 (40 to 100*) 40 (15 to 65*) 18 (2 to	91 (83 to 99*) 97 (92 to 100*) 100 (100	NC* 4.10 (2.13 to 7.88)* 2.33 (1.65 to	0.50 (0.25 to 0.99)* 0.18 (0.03 to 1.12)* 0* (NC*)	Funding: Not reported Limitations: Retrospective study Main bias will arise from operator, equipment and a small sample size Not possible to analyse diagnostic accuracy separately for

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Aim of study: To assess early second-trimester cervical length as a means of detecting triplet pregnancies at risk of preterm birth	spontaneously or resulting from *in vitro* fertilisation IVF) and referred to the ultrasound unit for consultation regarding multifetal reduction Exclusion criteria: Pregnancies that underwent fetal reductions; induction of preterm labour; loss to follow-up Other details: Gestational age calculated using crown-rump length measurement during the first 8 weeks of	with triplet pregnancies Transvaginal cervical length was measured between 14 and 20 weeks' gestation with a cut-off of 25 mm used for a short cervix Equipment and technique details were reported Number of sonographers not reported	cm† at 25-28 weeks (9%, n=4/46) For birth at <30 weeks using cervical length of ≤2.5 cm† at 15-20 weeks (22.5%, n=11/49) using cervical length of ≤2.5 cm† at 21-24 weeks (20%, n=10/49) using cervical length of ≤2.0 cm† at 25-28 weeks (15%, n=7/46) For birth at <32 weeks using cervical length of ≤2.5 cm† at 15-20 weeks (34%, n=16/47) using cervical	4 7 7 4 9	0* 7* 15* 0* 5*	7* 3* 0* 12* 6*	38 32 24 31 27	to 100*) 36 (8 to 65*) 70 (42 to 98*) 100 (59 to 100*) 25 (3 to 46*) 60	to 72*) 100 (91 to 100*) 82 (70 to 94*) 62 (46 to 77*) 100 (89 to 100*) 84	34*) 100 (40 to 100*) 50 (24 to 76*) 32 (12 to 51*) 100 (40 to 100*) 64	to 100*) 84 (74 to 95*) 91 (82 to 100*) 100 (86 to 100*) 72 (59 to 86*) 82	3.31)* NC* 3.9 (1.78 to 8.54)* 2.60 (1.75 to 3.87) * NC* 3.84	0.64 (0.41 to 0.99)* 0.37 (0.14 to 0.95)* 0* (NC*) 0.75 (0.57 to 0.99)* 0.47	different chorionicities

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	pregnancy (or by the date of embryo transfer for those who underwent IVF treatment) Details of ethnicity not reported		length of ≤2.5 cm† at 21-24 weeks (32%, n=15/47) using cervical length of ≤2.0 cm† at 25-28 weeks (27%, n=12/44) † Derived from ROC curve analysis	10	11*	2*	21	(35 to 85*) 83 (62 to 100*)	(72 to 97*) 66 (49 to 82*)	(39 to 89*) 48 (26 to 69*)	(69 to 95*) 91 (80 to 100*)	(1.55 to 9.49)* 2.42 (1.41 to 4.20)*	(0.25 to 0.90)* 0.25 (0.07 to 0.92)*	
First author, year: Guzman 2000[123] Country: USA Study design: Prospective cohort study Study dates: September 1993 - June	Population: N= 51 women with triplet pregnancies Inclusion criteria: Triplet pregnancies between September 1993 and June 1999 in the antenatal testing unit at	Screening test: Cervical length measurements Reference test: Spontaneous preterm birth Methods Transvaginal ultrasound and transfundal pressure were performed between 15 and	1) Prediction of spontaneous preterm birth in all twins using cervical length measured at 23 weeks' gestation: For birth at <28 weeks ≤20 mm†	3*	16*	6*	358*	33 (3 to 64*)	96* (94 to 98*)	16* (0 to 32*)	98* (97 to 99*)	7.79* (2.75 to 22.06*) 6.39*	0.70* (0.44 to 1.11*)	Funding: Not reported Limitations: Main bias will arise from operator, equipment and a small sample size Not possible to analyse diagnostic accuracy separately for different

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
1999 Aim of study: To assess the role of cervical ultrasongraphy in the prediction of spontaneous preterm birth in triplet pregnancies and to compare various ultrasonographic cervical parameters with respect to predictive ability	Saint Peter's University Hospital, New Brunswick, USA Exclusion criteria: Cervical cerclage; medically indicated births Other details: 76.5% of women (n= 39) were white, 9.8% (n=5) black, 5.9% (n=3) Hispanic and 7.9% (n=4) were of other ethnicity 80.4% (n=41) were nulliparous, 15.7% (n=8) primiparous and 3.9% (n=2)	28 weeks' gestation The shortest cervical length (and the greatest values of the other cervical parameters) were evaluated at 15-20, 21-24, and 25 -28 weeks Receiver operating characteristic (ROC) curve analysis was performed for cervical length measurements (and each ultrasonographic parameter) and the best cut-offs were determined Cut-off values	≤25 mm†	4*	26*	5*	348*	44 (12 to 77*)	93* (90 to 96*)	13* (1 to 26*)	99* (97 to 99.8*)	(2.82 to 14.50*)	0.60* (0.33 to 1.07*)	chorionicities
			≤30 mm†	4*	61*	5*	318*	44 (12 to 77*)	84* (80 to 88*)	6* (0 to 12*)	98* (97 to 99.8*)	2.7* (1.28 to 5.94*)	0.66* (0.37 to 1.19*)	
			≤35 mm† For birth at <32 weeks	6*	130*	3*	244*	67 (36 to 97*)	65* (60 to 70*)	4* (1 to 8*)	98* (97 to 100*)	1.92* (1.18 to 3.10*)	0.51* (0.20 to 1.29*)	
			≤20 mm†	6*	13*	17*	347*	26 (8 to 44*)	96* (94 to 98*)	32* (11 to 52*)	95* (93 to 98*)	7.22* (3.02 to 17.25*)	0.77* (0.60 to 0.98*)	
			≤25 mm†	7*	23*	16*	337*	30 (12 to 49*)	94* (91 to 96*)	23* (8 to 38*)	96* (93 to 98*)	4.76* (2.29 to 9.92*)	0.74* (0.57 to 0.98*)	
			≤30 mm†	8*	57*	15*	303*	35 (15 to 54*)	84* (80 to 88*)	12* (4 to 20*)	95* (93 to 98*)	2.19* (1.20 to 4.04*)	0.77* (0.57 to 1.05*)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	were multiparous Details of chorionicity and ethnicity not reported	were used to calculate sensitivity and specificity and positive and negative predictive values	≤35 mm†	14*	122*	9*	238*	61 (41 to 81*)	66* (61 to 71*)	10* (5 to 15*)	96* (94 to 99*)	1.80* (1.26 to 2.57*)	0.59* (0.35 to 0.99*)	
			For birth at <33 weeks											
			≤20 mm†	6*	13*	22*	342*	21 (6 to 37*)	96* (94 to 98*)	32* (11 to 52*)	94* (92 to 96*)	5.85* (2.40 to 14.21*)	0.82* (0.67 to 0.99*)	
			≤25 mm†	8*	22*	20*	333*	29 (12 to 45*)	94* (91 to 96*)	27* (11 to 42*)	94* (92 to 97*)	4.61* (2.26 to 9.40*)	0.76* (0.60 to 0.96*)	
			≤30 mm†	10*	55*	18*	300*	36 (18 to 53*)	85* (81 to 88*)	15* (7 to 24*)	94* (92 to 97*)	2.31* (1.33 to 4.01*)	0.76* (0.58 to 1.01*)	
			≤35 mm†	16*	120*	12*	235*	57 (39 to 75*)	66* (61 to 71*)	12* (6 to 17*)	95 (92 to 98*)	1.69* (1.19 to 2.40*)	0.65* (0.42 to 1.00*)	
			For birth at											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			<34 weeks											
			≤20 mm†	9*	10*	41*	323*	18 (7 to 29*)	97* (95 to 99*)	47* (25 to 70*)	89* (85 to 92*)	5.99* (2.56 to 14.03*)	0.84* (0.74 to 0.96*)	
			≤25 mm†	12*	18*	38*	315*	24 (12 to 36*)	95* (92 to 97*)	40* (22 to 58*)	89* (86 to 92*)	4.44* (2.28 to 8.65*)	0.80* (0.69 to 0.94*)	
			≤30 mm†	16*	49*	34*	284*	32 (19 to 45*)	85* (81 to 89*)	25* (12 to 35*)	89* (86 to 93*)	2.25 (1.35 to 3.51*)	0.80* (0.66 to 0.97*)	
			≤35 mm†	27*	109*	23*	224*	54 (40 to 68*)	67* (62 to 72*)	20* (13 to 27*)	91* (87 to 94*)	1.65* (1.22 to 2.22*)	0.68* (0.50 to 0.93*)	
			For birth at <35 weeks											
			≤20 mm†	10*	9*	61*	303*	14 (6 to 22*)	97* (95 to 99*)	53* (30 to 75*)	83* (79 to 87*)	4.88* (2.06 to 11.57*)	0.88* (0.80 to 0.97*)	
			≤25 mm†	14*	16*	57*	296*	20 (10 to 29*)	95* (92 to 98*)	47* (29 to 65*)	84* (80 to 88*)	3.85* (1.97 to 7.51*)	0.85* (0.75 to 0.95)	
			≤30 mm†	19*	46*	52*	266	27	85*	29*	84*	1.82*	0.86*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
							*	(16 to 37*)	(81 to 89*)	(18 to 40*)	(80 to 88*)	(1.14 to 2.90*)	(0.74 to 1.00)*	
			≤35 mm†	34*	102 *	37*	210 *	48 (36 to 60*)	67* (62 to 73*)	25* (18 to 32*)	85* (81 to 89*)	1.46* (1.10 to 1.96*)	0.77 (0.61 to 0.98*)	
			† Derived from ROC curve analysis											
First author, year: Sperling 2005[193] Country: Denmark and Sweden Study design: Prospective multicentre cohort study Study dates: November 1999 - May 2003	Population: N= 383 women with twin pregnancies 339 (89%) of pregnancies were dichorionic and 44 (11%) were monochorionic Inclusion criteria: Women with twin pregnancy <14+6 weeks, attending any of five university centres of fetal	Screening test: Transvaginal ultrasound measurement of cervical length in twins Reference test: Spontaneous preterm birth Methods: Results of transvaginal cervical scans performed at 23 weeks Clinicians were	Prediction of spontaneous preterm birth in asymptomatic twin pregnancies: Cervical length measurement at < 20 weeks (threshold 20mm) Spontaneous preterm birth < 34 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	59.89 (3.46 to 103.48)	0.71 (0.52 to 0.96)	Funding: Not reported Limitations: Main bias will arise from operator/equip-ment Not possible to analyse diagnostic accuracy separately for different chorionicities

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
Aim of study: To evaluate screening for spontaneous preterm delivery in women with twin pregnancy using transvaginal ultrasound assessment of cervical length at 23 weeks and to define a cut-off value for classifying twin pregnancies as being at low risk of spontaneous preterm birth	medicine (four in Denmark and one in Sweden) during November 1999 to May 2003; oral and written informed consent obtained Exclusion criteria: Induction of labour; history of conisation or cervical cerclage Other details: All pregnancies were dated according to the twin with greater biparietal diameter at the 18-week scan; last menstrual	blinded to the result if cervical length canal ≥ 15 mm Receiver-operating characteristic (ROC) curve analysis was used to differentiate cases with delivery before a certain number of weeks from those delivered after that time and at different cut-off levels for cervical length at 23 weeks' gestation Details of ultrasound technique reported	Cervical length measurement at 20-24 weeks (threshold 15 mm) Spontaneous preterm birth < 32 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	9.32 (2.76 to 31.49)	0.78 (0.60 to 1.02)	
			Spontaneous preterm birth < 34 weeks (1 study) Cervical length measurement at 20-24 weeks (threshold 20 mm) Spontaneous preterm birth < 32 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	7.60 (2.09 to 27.67)	0.89 (0.81 to 0.97)	
				NR	NR	NR	NR	NR	NR	NR	NR	2.75 (1.25 to 6.09)	0.69 (0.42 to 1.12)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	period or IVF dates were not used Details of ethnicity not reported		Spontaneous preterm birth < 34 weeks (2 studies) <u>Cervical length measurement at 20-24 weeks (threshold 25 mm)</u>	NR	NR	NR	NR	NR	NR	NR	NR	4.54 (1.46 to 14.14)	0.75 (0.64 to 0.90)	
			Spontaneous preterm birth < 32 weeks (2 studies)	NR	NR	NR	NR	NR	NR	NR	NR	5.04 (3.22 to 7.89)	0.56 (0.40 to 0.77)	
			Spontaneous preterm birth < 34 weeks (4 studies)	NR	NR	NR	NR	NR	NR	NR	NR	5.02 (3.31 to 7.61)	0.75 (0.54 to 1.06)[§]	
			Spontaneous preterm birth < 37 weeks (2 studies) <u>Cervical length</u>	NR	NR	NR	NR	NR	NR	NR	NR	2.71 (1.28 to 5.75)	0.87 (0.76 to 0.95)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			measurement at 20-24 weeks (threshold 30 mm)											
			Spontaneous preterm birth < 34 weeks (4 studies)	NR	NR	NR	NR	NR	NR	NR	NR	2.31 (1.08 to 4.93)[§]	0.69 (0.91 to 1.17)[§]	
			Cervical length measurement at 20-24 weeks (threshold 35 mm)											
			Spontaneous preterm birth < 32 weeks (2 studies)	NR	NR	NR	NR	NR	NR	NR	NR	1.55 (0.79 to 3.04)	0.72 (0.29 to 1.83)	
			Spontaneous preterm birth < 34 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	1.47 (1.09 to 1.97)	0.88 (0.69 to 1.12)	
			Spontaneous preterm birth	NR	NR	NR	NR	NR	NR	NR	NR	1.67 (0.49 to	1.17 (0.95	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			< 37 weeks (1 study)									5.71)	to 1.44)	
			<u>Cervical length measurement at 20-24 weeks (threshold 45 mm)</u>											
			Spontaneous preterm birth < 32 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	1.14 (0.99 to 1.30)	0.34 (0.05 to 0.81)	
			Spontaneous preterm birth < 34 weeks (2 studies)	NR	NR	NR	NR	NR	NR	NR	NR	1.12 (1.00 to1.26)	0.45 (0.15 to1.40)	
			<u>Cervical length measurement at >24 weeks (threshold 20 mm)</u>											
			Spontaneous preterm birth < 32 weeks (1 study)	NR	NR	NR	NR	NR	NR	NR	NR	2.31 (1.18 to 4.53)	0.59 (0.28 to 1.22)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Spontaneous preterm birth < 34 weeks (1 study) <u>Cervical length measurement at >24 weeks (threshold 25 mm)</u>	NR	NR	NR	NR	NR	NR	NR	NR	3.44 (2.05 to 5.78)	0.41 (0.21 to 0.80)	
			Spontaneous preterm birth < 34 weeks (3 studies)	NR	NR	NR	NR	NR	NR	NR	NR	1.82 (1.26 to 2.63)	0.83 (0.72 to 0.95)	
			Spontaneous preterm birth < 37 weeks (2 studies) <u>Cervical length measurement at >24 weeks (threshold 30 mm)</u>	NR	NR	NR	NR	NR	NR	NR	NR	1.89 (1.26 to 2.85)	0.73 (0.62 to 0.88)	
			Spontaneous preterm birth < 34 weeks	NR	NR	NR	NR	NR	NR	NR	NR	2.11 (1.43 to 3.12)	0.61 (0.42 to	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			(2 studies) Cervical length measurement at >24 weeks (threshold 35 mm) Spontaneous preterm birth < 34 weeks (2 studies) § Statistically significant heterogeneity (P < 0.05)	NR	NR	NR	NR	NR	NR	NR	NR	1.84 (1.48 to 2.29)	0.87) 0.29 (0.08 to 1.09)	
First author, year: Honest 2003[194] Country: Details not reported (but one study was conducted in the UK, one in the USA and one in Israel)	Population: N = 1436 asymptomatic women with twin pregnancy (11 trials) Inclusion criteria: Studies were selected if they contained the	Index test: Cervical length measurement Reference test: Spontaneous preterm birth Methods described adequately? Yes	Cervical length measurement at 22-24 weeks for detection of spontaneous preterm birth before 30 weeks: Cut-off of 15mm	16*	15*	22*	111 2*	42* (26 to	99* (98	52* (34 to	98* (97 to	32* (17 to	0.6* (0.4	Funding: Wellbeing of Women Limitations: Main limitation is unquantified heterogeneity in pooled likelihood ratios for women tested at 20-24 weeks' gestation

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	following information:	A prospective review protocol						58*)	to 99*)	69*)	99*)	59*)	to 0.8*)	using cervical thresholds of 25 mm and 30 mm with spontaneous preterm birth before 34 weeks' gestation as the reference standard
<u>Study design:</u> Systematic review <u>Study dates:</u> Studies published between 1966 and 2002 <u>Aim of study:</u> To obtain valid and reliable accuracy estimates of transvaginal cervical ultrasound in predicting spontaneous preterm birth	asymptomatic or symptomatic pregnant women; antenatal transvaginal sonographic cervical length measurement; known gestational age at spontaneous birth; cohort studies <u>Exclusion criteria:</u> Case-control studies <u>Other details:</u> Chorionicity and ethnicity not reported in the systematic review	was developed Studies were searched for in general databases (MEDLINE, EMBASE, PASCAL, BIOSIS) and specialist databases (Cochrane Library, MEDION, National Research Register, SCISEARCH) and conference papers published up to June 2002 References lists of articles were also checked and authors were contacted	Cut-off of 20mm	22*	46*	16*	1081*	58* (42 to 74*)	96* (95 to 97*)	32* (21 to 43*)	99* (98 to 99*)	14* (10 to 21*)	0.4* (0.3 to 0.6*)	
			Cut-off of 25mm	30*	130*	8*	997*	79* (66 to 92*)	88* (87 to 90*)	19* (13 to 25*)	99* (99 to 100*)	6.84* (5.44 to 8.62*)	0.24* (0.13 to 0.44*)	
			Cut-off of 30mm	34*	243*	4*	884*	89* (80 to 99*)	78* (76 to 81*)	12* (8 to 16*)	99.5* (99 to 100*)	4.15* (3.55 to 4.85*)	0.13* (0.05 to 0.34*)	
			Cut-off of 35mm <u>Cervical length measurement at 22-24 weeks for detection of spontaneous preterm birth before 32 weeks:</u>	36*	474*	2*	653*	95* (88 to 100*)	58* (55 to 61*)	7* (4 to 9*)	99.7* (99 to 100*)	2.25* (2.04 to 2.49*)	0.09* (0.02 to 0.35*)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
		if there was need for additional data No language restrictions were applied Details of search strategy and study selection reported	Cut-off of 15mm	25*	6*	47*	1107*	35* (24 to 46*)	99* (99 to 100*)	81* (67 to 95*)	96* (95 to 97*)	64.41* (27.30 to 151.99*)	0.66* (0.55 to 0.78*)	
			Cut-off of 20mm	35*	33*	37*	1080*	49* (37 to 60*)	97* (96 to 98*)	51* (40 to 63*)	97* (96 to 98*)	16.40* (10.86 to 24.74*)	0.53* (0.42 to 0.66*)	
			Cut-off of 25mm	48*	112*	24*	1001*	67* (56 to 78*)	90* (88 to 92*)	30* (23 to 37*)	98* (97 to 99*)	6.63* (5.21 to 8.42*)	0.37* (0.27 to 0.51*)	
			Cut-off of 30mm	57*	278*	15*	835*	79* (70 to 89*)	75* (72 to 78*)	17* (13 to 21*)	98* (97 to 99*)	3.17* (2.71 to 3.71*)	0.28* (0.18 to 0.44*)	
			Cut-off of 35mm	67*	500*	5*	613*	93* (87 to 99*)	55* (52 to 58*)	12* (9 to 14*)	99* (98 to 100*)	2.07* (1.89 to 2.27*)	0.13* (0.05 to 0.29*)	
			Cervical length measurement at 22-24 weeks for											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			detection of spontaneous preterm birth before 34 weeks:											
			Cut-off of 15mm	27*	4*	116*	1088*	19* (12 to 25*)	99.6* (99 to 100*)	87* (75 to 99*)	90* (89 to 92*)	51.55* (18.30 to 145.18*)	0.81* (0.75 to 0.88*)	
			Cut-off of 20mm	47*	20*	96*	1072*	33* (25 to 41*)	98* (97 to 99*)	70* (59 to 81*)	92* (90 to 93*)	18.21* (11.12 to 29.82*)	0.68* (0.61 to 0.77*)	
			Cut-off of 25mm	82*	27*	61*	1015*	57* (49 to 65*)	97* (96 to 98*)	75* (67 to 83*)	94* (93 to 96*)	22.13* (14.86 to 32.96*)	0.44* (0.36 to 0.53*)	
			Cut-off of 30mm	106*	221*	37*	871*	74* (67 to 81*)	80* (77 to 82*)	32* (27 to 37*)	96* (95 to 97*)	3.66* (3.14 to 4.27*)	0.32* (0.25 to 0.43*)	
			Cut-off of 35mm	126*	430*	17*	662*	88* (83 to 93*)	61* (58 to	23* (19 to 26*)	98* (96 to 99*)	2.24* (2.03 to 2.46*)	0.20* (0.13 to	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
									64*)				0.31*)	
			* Calculated by NCC-WCH technical team from data reported in the paper											
First author, year: To 2006[195] Country: UK Study design: Retrospective observational study Study dates: January 1998 and December 2004 Aim of study: To determine whether the risk of	Population: N= 1135 twin pregnancies Dichorionic= 844 (74%) Monochorionic= 291 (26%) Inclusion criteria: All women with twin pregnancies at 7 maternity hospitals in England who had a transvaginal ultrasonograph-ic measurement	Screening test: Cervical length (measurement, mm) Reference test: Preterm birth Methods described adequately? Yes	Fetal fibronectin positive at 24 weeks to predict birth before 35 weeks	7	12	6	63	36.8 (15 to 59*)	91.3 (85 to 98*)	53.8 (27 to 81*)	84 (76 to 92*)	4.24* (1.61 to 11.12*)	0.69* (0.49 to 0.98*)	Funding: Fetal Medicine Foundation Limitations: No subgroup analysis for monochorionic and dichorionic pregnancies Management of each pregnancy was influenced by the findings of the second-trimester ultrasound scan – women with cervical length of 20mm or more had normal
			Fetal fibronectin positive at 28 weeks to predict birth before 35 weeks	10	6	10	69	50 (28 to 72*)	92 (86 to 98*)	62.5 (39 to 86*)	87.3 (80 to 95*)	6.25* (2.58 to 15.13*)	0.54* (0.35 to 0.85*)	
			Fetal fibronectin positive at 24 and 28 weeks to predict	4	1	13	66	23.5 (3 to 44*)	98.5 (96 to 100*)	80 (45 to 100*)	83.5 (75 to 92*)	15.76* (1.88 to 132.09*)	0.78* (0.60 to 1.01*)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
spontaneous preterm birth can be predicted by combining maternal demographic and obstetric history data with cervical length measurement (at 22 to 24 weeks' gestation)	of cervical length at 22 to 24^{+6} weeks Exclusion criteria: Women with major fetal abnormalities, painful regular uterine contractions, or history of ruptured membranes or cervical cerclage in situ were excluded from screening The study authors excluded monochorionic pregnancies with severe feto-fetal transfusion syndrome		birth before 35 weeks Fetal fibronectin positive at 24, 26, 28, 30 or 32 weeks to predict birth before 37 weeks Fetal fibronectin positive at 24, 26, 28, 30 or 32 weeks to predict birth before 35 weeks Fetal fibronectin positive at 24, 26, 28, 30 and 32 weeks to predict birth before 37 weeks	19 13 5	17 23 1	17 9 31	48 56 64	52.8 (36 to 69*) 59.1 (39 to 80*) 13.9 (3 to 25*)	73.9 (63 to 85*) 70.9 (61 to 81*) 98.5 (95 to 100 *)	52.8 (36 to 69*) 36.1 (20 to 52*) 83.3 (54 to 100*)	73.9 (63 to 85*) 86.2 (78 to 95*) 67.4 (58 to 77*)	2.02* (1.21 to 3.37*) 2.03* (1.24 to 3.31*) 9.03* (1.10 to 74.32*)	0.64* (0.44 to 0.93*) 0.58* (0.34 to 3.31*) 0.87* (0.76 to 1.00*)	antenatal care and those with 19mm or less were managed expectantly or had cervical cerclage or administration of progesterone vaginal pessaries There were significantly more smokers in the group that delivered before 32 weeks, which may affect outcome data

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Fetal fibronectin positive at 24, 26, 28, 30 and 32 weeks to predict birth before 35 weeks	5	1	17	78	22.7 (5 to 40*)	98.7 (96 to 100 *)	83.3 (54 to 100*)	82.1 (74 to 90*)	17.95* (2.21 to 145.8*)	0.78* (0.62 to 0.98*)	
First author, year: Wennerholm, 1997[126] Country: Sweden Study design: Prospective cohort study Study dates: Women gave birth between January 1994 and June 1995 Aim of study: To compare	Population: N= 101 twin pregnancies 518 samples for fetal fibronectin (mean 5.1 per woman) Median age 32 years (range 19 to 49) Groups comparable for age, educational level, family income, race, infertility	Screening test: Fetal fibronectin Reference test: Birth before 35 or 37 weeks Methods Samples taken fortnightly between 24 and 34 weeks if no blood was visible and membrane rupture clinically excluded	Prediction of spontaneous preterm birth in asymptomatic women with twin pregnancies: Cervical length measurement at 20-24 weeks Spontaneous preterm birth <28 weeks ≤20mm (3 studies, n=591)	NR	NR	NR	NR	35 (14 to 62)	93 (91 to 95)	NR	NR	5.2 (2.6 to 10.6)	0.69 (0.49 to 1.01)	Funding Swedish Medical Research Council, Swedish Society for Medical Research, Goteborg Medical Society, Swedish Society of Medicine, Sven Jerrinf Foundation, Ake Wiberg Foundation, Ahlen Foundation, Magnus Bergvall Foundation, Frimurare Barnhus Foundation,

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
the accuracy of fetal fibronectin, bacterial vaginosis, endotoxin, and cervical length in predicting preterm birth	treatment and smoking habits Inclusion criteria: Asymptomatic women with twin pregnancies before 20 weeks' gestation Exclusion criteria: Iatrogenic preterm birth Other details: Chorionicity not reported		≤25mm (3 studies, n=637) ≤35mm (3 studies, n=637) Spontaneous preterm birth <32 weeks ≤20mm (5 studies, n= 1955) ≤25mm (6 studies, n= 2036) ≤30mm (4 studies, n= 1812) ≤35mm (5 studies, n= 1889) Spontaneous preterm birth	NR NR NR NR NR NR	NR NR NR NR NR NR	NR NR NR NR NR NR	NR NR NR NR NR NR	64 (41 to 83) 82 (60 to 95) 39 (31 to 48) 4 (45 to 62) 65 (56 to 74) 81 (73 to 87)	93 (91 to 95) 66 (62 to 69) 96 (95 to 97) 91 (90 to 92) 78 (76 to 80) 58 (56 to 61)	NR NR NR NR NR NR	NR NR NR NR NR NR	9.6 (5.8 to 14.8) 2.4 (1.9 to 3.0) 10.1 (7.4 to 13.9) 6.0 (4.8 to 7.4) 3.0 (2.5 to 3.5) 1.9 (1.7 to 2.2)	0.40 (0.23 to 0.68) 0.28 (0.11 to 0.67) 0.64 (0.55 to 0.73) 0.51 (0.43 to 0.61) 0.45 (0.35 to 0.57) 0.33 (0.23 to 0.48)	Medical Faculty of Goteborg, and 1:a Maj-blomman Limitations: Not enough data reported in the paper to assess diagnostic accuracy of cervical length by visual assessment in predicting preterm birth Preterm defined as <37 weeks Neonatal morbidity defined as intraventricular haemorrhage, sepsis, suspected sepsis and idiopathic respiratory distress syndrome

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			<u>≤34 weeks</u> ≤20mm (5 studies, n= 1760)	NR	NR	NR	NR	29 (23 to 35)	97 (96 to 98)	NR	NR	9.0 (6.1 to 12.7)	0.74 (0.68 to 0.80)	
			≤25mm (6 studies, n= 1987)	NR	NR	NR	NR	40 (38 to 46)	93 (92 to 94)	NR	NR	5.8 (4.5 to 7.2)	0.64 (0.58 to 0.71)	
			≤30mm (5 studies, n= 2014)	NR	NR	NR	NR	56 (50 to 62)	81 (79 to 83)	NR	NR	3.0 (2.6 to 3.4)	0.55 (0.48 to 0.63)	
			≤35mm (6 studies, n= 1884)	NR	NR	NR	NR	79 (74 to 84)	60 (57 to 62)	NR	NR	2.0 (1.8 to 2.2)	0.35 (0.27 to 0.44)	
			<u>Spontaneous preterm birth</u> <u><37 weeks</u> ≤20mm (4 studies, n= 434)	NR	NR	NR	NR	21 (15 to 27)	95 (92 to 98)	NR	NR	4.4 (2.4 to 8.2)	0.83 (0.75 to 0.92)	
			≤25mm (2 studies, n= 218)	NR	NR	NR	NR	29 (18 to 43)	91 (86 to 95)	NR	NR	3.4 (1.6 to 6.7)	0.78 (0.65 to 0.92)	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			≤35mm (2 studies, n= 134) <u>Cervical length measurement at >24 weeks: Spontaneous preterm birth <32 weeks</u>	NR	NR	NR	NR	56 (43 to 68)	78 (50 to 74)	NR	NR	1.5 (1.0 to 2.2)	0.71 (0.51 to 0.98)	
			≤25mm (3 studies, n= 511) <u>Spontaneous preterm birth <34 weeks</u>	NR	NR	NR	NR	65 (45 to 81)	76 (72 to 79)	NR	NR	2.7 (2.0 to 3.6)	0.47 (0.29 to 0.76)	
			≤25mm (4 studies, n= 594) <u>Spontaneous preterm birth <37 weeks</u>	NR	NR	NR	NR	44 (34 to 53)	81 (78 to 85)	NR	NR	2.3 (1.8 to 3.1)	0.70 (0.59 to 0.83)	
			≤25mm (2 studies, n= 276)	NR	NR	NR	NR	43 (35 to 51)	77 (68 to 84)	NR	NR	1.1 (1.3 to 2.6)	0.75 (0.63 to 0.89	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
First author, year: Conde-Agudelo 2010[119] Country: Details not reported Study design: Systematic review and meta-analysis Study dates: Not reported Aim of study: To assess the value of transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in women with	Population: N = 3523 women (21 studies) with twin pregnancies Only data for asymptomatic women (3213 women; 16 studies) were extracted for the guideline review Inclusion criteria: Studies were selected if they met the following criteria: a cohort or cross-sectional study that evaluated the accuracy of transvaginal sonographic cervical length	Index test: Transvaginal cervical length measurement Reference test: Spontaneous preterm birth Methods described adequately? Yes Studies were searched for in five major databases (databases not reported), proceedings of international meetings on preterm birth and twin or multiple pregnancy, reference lists of identified studies,	Cervical length ≤25mm measured at 16-24 weeks for the prediction of spontaneous preterm birth: at ≤28 weeks at ≤30 weeks at ≤32 weeks * Calculated by NCC-WCH technical team from data reported in the paper	2 3 3	11* 10* 10*	0 2 4	84* 82* 80*	100 (100 to 100)* 60 (17 to 100)* 43 (6 to 80)*	88 (82 to 95)* 89 (83 to 95)* 89 (82 to 95)*	15 (0 to 35)* 23 (0 to 46)* 23 (0 to 46)*	100 (100 to 100)* 98 (94 to 100)* 95 (91 to 100)*	8.6 (5.0 to 15.1)* 5.5 (2.2 to 13.9)* 3.9 (1.4 to 10.9)*	0* 0.5 (0.2 to 1.3)* 0.6 (0.3 to 1.2)*	Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda and Detroit, USA, Department of Obstetrics and Gynecology and the Center for Molecular Medicine and Genetics, Wayne State University, Detroit, USA Limitations: Study did not report on tests for heterogeneity

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
twin pregnancies	measurement to predict spontaneous preterm birth in asymptomatic or symptomatic pregnant women with twin pregnancies; outcome measure included any category of spontaneous preterm birth <37 weeks of pregnancy; the studies provided the necessary information to generate 2×2 tables; and the women had no therapeutic intervention resulting from the test result	textbooks, and previously published systematic reviews Data were extracted from studies meeting inclusion criteria Details of quality assessment, data extraction and synthesis reported												

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	Exclusion criteria: Not reported Other details: Chorionicity and ethnicity not reported in the systematic review													
First author, year: Schwartz 2010[118] Country: USA Study design: Retrospective chart review Study dates: 2006-2008 Aim of study: To examine the validity of	Population: N = 183 women with twin pregnancies 123 had documented cervical length measurements Only 97 met all inclusion criteria 22 monochorionic pregnancies (6 with a short cervix) 70 dichorionic pregnancies (7 had a short	Screening test: Cervical length measurement Reference test: Spontaneous preterm birth Method: A chart review was carried out to identify women who had cervical measurements during the second trimester	Prediction of spontaneous preterm birth before 28 weeks' gestation among women with short cervical length measured at 18-21 weeks (subgroup 1)	3*	11*	6*	221*	33.3 (2.5 to 64.1)*	95.2 (92.5 to 98.0)*	21.4 (0 to 42.9)*	97.3 (95.3 to 99.4)*	7.0 (2.4 to 20.0)*	0.7 (0.4 to 1.1)*	Funding: Not reported Limitations: Retrospective study; not clear if authors excluded women in labour; small sample size Operator bias may have resulted from the fact that measurements of cervical lengths were carried out by different people

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR− (95% CI)	
cervical length measurement as a screening method for spontaneous preterm birth in twin pregnancies	cervix) Inclusion criteria: All women with twin pregnancies who gave birth at Bayfront Medical Center, Saint Petersburg, Florida, between 1 January 2006 and 1 April 2008 and who had documented cervical length measurements between 16 and 24 weeks Exclusion criteria: Preterm birth due to a maternal or	Cervical length measurements were carried out by multiple certified ultrasonographers Sensitivities, specificities, positive predictive values and negative predictive values were calculated for cervical length ≤25mm and delivery ≤28, ≤30 and ≤32 weeks												

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	fetal indication, fetal congenital anomalies, women with cerclage and higher-order pregnancies <u>Other details:</u> Shortened cervical length defined as ≤25mm If more than one cervical length measurement was obtained between 16 and 24 weeks, the earliest measurement was used 64 women were white (11 had a short cervix), 20 were black (1 had a short cervix) and 3													

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	were Asian (all of whom had a normal cervix)													
First author, year: Hofmeister, 2010[117] Country: Brazil Study design: Retrospective cohort study Study dates: January 1998	Population: N=383 women with twin pregnancies and divided into two subgroups Subgroup 1: women examined at 18-21 weeks (N=241) Subgroup 2:	Screening test: Short cervix cervical length < 5th percentile for corresponding gestational age (based on published data on reference ranges for cervical length in normal twin pregnancies in the study	Prediction of spontaneous preterm birth before 28 weeks' gestation among women with short cervical length measured at 22-25 weeks (subgroup 2)	5*	17*	2*	242*	71.4 (38.0 to 100)*	93.4 (90.4 to 96.5)*	22.7 (5.2 to 40.2)*	99.1 (98.1 to 100)*	10.9 (5.6 to 21.0)*	0.3 (0.1 to 1.0)*	Funding Not reported Limitations: Retrospective study Women and caregivers were not blinded to cervical length measurement and bed rest at home was advised to

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
–June 2007 Setting: Department of Obstetrics, São Paulo University Medical School, São Paulo Aim of study: To evaluate the predictive accuracy of cervical length measurement and shortening rate between 18 and 25 weeks' gestation in the prediction of spontaneous preterm birth in twin pregnancies	women examined at 22-25 weeks (N=266) N=124 women were included in both subgroups (examined in both periods) Monochorionic pregnancies: Subgroup 1: 19.3% Subgroup 2: 14.6% Subgroup 3: 26.1% Inclusion criteria: All twin pregnancies with cervical length measured	population) Reference test: Spontaneous preterm birth before 34 weeks Method: All women underwent second trimester ultrasound examination which included assessment of fetal growth, a detailed anomaly scan and cervical length measurement Ultrasound of the cervix was performed with women in the lithotomy	Prediction of spontaneous preterm birth before 30 weeks' gestation among women with short cervical length measured at 18-21 weeks (subgroup 1)	5*	9*	10*	217 *	33.3 (9.5 to 57.2)*	96 (93.5 to 98.6)*	35.7 (10.6 to 60.8)*	95.6 (92.9 to 98.2)*	8.4 (3.2 to 21.9)*	0.7 (0.5 to 1.0)*	women with short cervix Adequate sample size was determined before the study Not possible to analyse diagnostic accuracy separately for different chorionicities
			Prediction of spontaneous preterm birth before 30 weeks' gestation among women with short cervical length measured at 22-25 weeks (subgroup 2)	8*	14*	6*	238 *	57.1 (32.1 to 83.1)*	94.4 (91.6 to 97.3)*	36.3 (16.3 to 56.5)*	97.5 (95.6 to 99.5)*	10.3 (5.2 to 20.3)*	0.4 (0.2 to 0.8)*	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	between 18 and 25 weeks' gestation All women with twin pregnancies were identified by searching the hospital database Perinatal outcome information was retrieved from the database for women who gave birth at the institution and by telephone contact who gave birth outside <u>Exclusion criteria:</u> Women who	position with an empty bladder with a 4-8 MHz transvaginal probe The probe was placed in the anterior fornix of the vagina avoiding undue pressure on the cervix The whole length of sonolucent endocervical mucosa was identified on a sagittal view of the cervix Cervical length was measured from the triangular area of echodensity	Prediction of spontaneous preterm birth before 32 weeks' gestation among women with short cervical length measured at 18-21 weeks (subgroup 1)	6*	8*	14*	213*	30 (9.9 to 50.1)*	96.4 (93.9 to 98.8)*	42.8 (16.9 to 68.8)*	93.8 (90.7 to 97.0)*	8.3 (3.2 to 21.5)*	0.7 (0.5 to 0.9)*	
			Prediction of spontaneous preterm birth before 32 weeks' gestation among women with short cervical length measured at 22-25 weeks (subgroup 2)	10*	12*	9*	235*	52.6 (30.2 to 75.1)*	95.1 (92.5 to 97.8)*	45.4 (24.6 to 66.3)*	96.3 (94.0 to 98.7)	10.83 (5.39 to 21.76)	0.50 (0.31 to 0.80)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
	underwent invasive procedures or cervical cerclage, those with monoamniotic pregnancies, feto-fetal transfusion syndrome, polyhydram-nios, intrauterine devices, fetal malformation or iatrogenic preterm birth were excluded Other details: Ethnicity not reported	at the external os to the V-shaped notch at the internal os The smallest measurement of three measurements obtained during a period of at least 3 minutes was registered as cervical length Gestational age was calculated from LMP and confirmed by a dating scan; if there was discrepancy between the two measures then ultrasound dates were considered	Prediction of spontaneous preterm birth before 34 weeks' gestation among women with short cervical length measured at 18-21 weeks (subgroup 1)	9*	5*	30*	197*	23 (9.9 to 36.3)*	97.5 (95.4 to 99.7)*	64.3 (39.2 to 89.4)*	86.8 (82.4 to 91.2)*	9.3 (3.3 to 26.3)*	0.8 (0.7 to 0.9)*	
			Prediction of spontaneous preterm birth before 34 weeks' gestation among women with short cervical length measured at 22-25 weeks (subgroup 2)	13*	9*	21*	223*	38.2 (21.9 to 54.6)*	96.1 (93.6 to 98.6)	59.1 (38.5 to 79.6)*	91.4 (87.9 to 94.9)*	9.9 (4.6 to 21.3)*	0.6 (0.5 to 0.8)	

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			Cervical length ≤15mm measured at 23 weeks for the prediction of spontaneous preterm birth:											
			at ≤28 weeks	4	5*	4*	202*	50 (15 to 85)*	98 (95 to 99)*	44 (12 to 77)*	98 (96 to 99)*	20.7 (6.8 to 62.8)*	0.51 (0.26 to 1.02)*	
			at ≤30 weeks	4	5*	6*	200*	40 (10 to 70)*	98 (95 to 99)*	44 (12 to 77)*	97 (95 to 99)*	16.4 (5.2 to 51.9)*	0.62 (0.37 to 1.02)*	
			at ≤32 weeks	4	5*	13*	193*	24 (3 to 44)*	97 (95 to 99)*	44 (12 to 77)*	94 (90 to 97)*	9.3 (2.8 to 31.5)*	0.78 (0.60 to 1.02)*	
			at ≤34 weeks	4	5*	33*	173	11 (1 to 21)*	97 (94 to 99)*	44 (12 to 77)*	84 (79 to 89)*	3.8 (1.1 to 13.6)*	0.92 (0.82 to 1.03)*	
			Cervical length ≤25mm											

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			measured at 23 weeks for the prediction of spontaneous preterm birth:											
			at ≤28 weeks	8	16*	0*	191*	100 (63 to 100)*	92 (87 to 96)*	33 (14 to 52)*	100 (98 to 100)*	12.9 (8.1 to 20.7)*	0 (0 to 0.9)*	
			at ≤30 weeks	8	16*	2*	189*	80 (55 to 100)*	92 (89 to 96)*	33 (14 to 52)*	99 (98 to 100)*	10.3 (5.8 to 18.0)*	0.22 (0.06 to 0.75)*	
			at ≤32 weeks	8	16*	9*	182*	47 (23 to 71)*	92 (88 to 96)*	33 (14 to 52)*	95 (92 to 98)*	5.8 (2.9 to 11.6)*	0.58 (0.37 to 0.90)*	
			at ≤34 weeks	13	11*	24*	167*	35 (20 to 51)*	94 (90 to 97)*	54 (34 to 74)*	87 (83 to 92)*	5.7 (2.8 to 11.7)*	0.69 (0.54 to 0.87)*	
			Cervical length ≤35mm measured at 23 weeks for the prediction of											

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			<u>spontaneous preterm birth:</u> at ≤28 weeks	8	78*	0*	129*	100* (63 to 100)	62 (56 to 69)*	9 (3 to 15)*	100* (97 to 100)	2.7 (2.2 to 3.2)*	0*	
			at ≤30 weeks	9	77*	1*	128*	90 (71 to 100)*	62 (56 to 69)*	10 (4 to 17)*	99 (98 to 100)*	2.4 (1.8 to 3.1)*	0.62 (0.56 to 0.69)*	
			at ≤32 weeks	12	74*	5*	124*	71 (49 to 92)*	63 (56 to 69)*	14 (7 to 21)*	96 (93 to 99)*	1.9 (1.3 to 2.7)*	0.47 (0.22 to 0.99)*	
			at ≤34 weeks	21	65*	16*	113*	57 (41 to 73)*	63 (56 to 71)*	24 (15 to 34)*	88 (82 to 93)*	1.6 (1.1 to 2.2)*	0.68 (0.56 to 0.71)*	
			<u>Cervical length ≤45mm measured at 23 weeks for</u>											

Study details	Participants	Diagnostic tools	Outcome measures and results										Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
			the prediction of spontaneous preterm birth:											
			at ≤28 weeks	8	172 *	0*	35*	100* (63 to 100)	17 (12 to 22)*	4 (1 to 7)*	100* (90 to 100)	1.2 (1.1 to 1.3)*	0.0 (0.0 to 4.9)*	
			at ≤30 weeks	10	170 *	0*	35*	100* (69 to 100)	17 (12 to 71)*	6 (2 to 9)*	100* (90 to 100)	1.2 (1.1 to 1.3)*	0* (0.0 to 4.0)	
			at ≤32 weeks	16	164 *	1*	34*	94 (83 to 100)*	17 (12 to 22)*	9 (5 to 13)*	97 (92 to 100)*	1.1 (0.99 to 1.3)*	0.34 (0.05 to 2.35)*	
			at ≤34 weeks	34	146 *	3*	32*	92 (83 to 100)*	18 (12 to 24)*	19 (13 to 25)*	91 (82 to 100)*	1.1 (1.00 to 1.3)*	0.45 (0.15 to 1.40)*	
			* Calculated by NCC-WCH technical team from data reported in the paper											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	**True positive**	**False positive**	**False negative**	**True negative**	**Sensitivity % (95% CI)**	**Specificity % (95%)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**LR+ (95% CI)**	**LR– (95% CI)**	
First author, year: Souka 1999[120] Country: UK Study design: Prospective cohort Study dates: Not reported Aim of study: To examine the possible value of cervical assessment at 23 weeks in predicting risk of spontaneous preterm delivery in women with twin pregnancies	Population: N = 215 women with twin pregnancies who gave birth to live babies and had cervical assessment at 23 weeks' gestation 133 (61.9%) pregnancies were dichorionic and 82 (38.1%) were monochorionic Inclusion criteria: All women with twin pregnancies who gave birth to live babies and who had cervical assessment at	Screening test: Cervical length measurement at 23 weeks' gestation Reference test: Spontaneous preterm birth Method: Subject characteristics, including demographic data and obstetric and medical histories, were obtained from the women at their first visit to the hospital and were entered into a computer database Women were asked to empty their bladders	Cervical length ≤15mm measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks	6	5	28	395	18 (5 to 31)*	99 (98 to 99)*	55 (25 to 84)*	93 (91 to 96)*	14.1 (4.5 to 43.9)*	0.83 (0.71 to 0.97)*	Funding: Fetal Medicine Foundation, London, UK. Limitations: Possibility of inter-operator bias as several people were involved in the ultrasound examination of cervical length
			Cervical length ≤20mm measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks	9	13	25	387	26 (12 to 41)*	97 (95 to 98)*	41 (20 to 61)*	94 (92 to 96)*	8.1 (3.8 to 17.7)*	0.76 (0.62 to 0.93)*	
			Cervical length ≤25mm	12	33	22	367	35 (19 to 51)*	92 (89 to	27 (14 to 40)*	94 (92 to 97)*	4.3 (2.4 to 7.5)*	0.71 (0.55 to	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	22-24 weeks' gestation (median 23 weeks), identified from a database of all women with twin pregnancies presenting to the authors' unit at 10-14 weeks' gestation for assessment of risk of chromosomal abnormalities Exclusion criteria: Monochorionic pregnancies in which severe feto-fetal transfusion syndrome developed (anhydramnios with anuria in	and were placed in the dorsal lithotomy position Transvaginal sonography was performed by one of four trained sonographers and findings were recorded in the database at the time of the scans Gestational age was determined from menstrual history and confirmed by measurement of fetal crown-rump length of the longer twin at first-trimester scan Data on pregnancy outcomes were	measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks * Calculated by NCC-WCH technical team from data reported in the paper						94)*				0.91)*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	the presumed donor and polyhydramnios with polyuria in the presumed recipient) requiring antenatal intervention; pregnancies that had elective cervical cerclage before the 23-week scan because of history suggestive of cervical incompetence Other details: None of the fetuses had any major abnormalities 173 (80.5%) women were white, 34 (15.8%) black	obtained from a computerised system in the delivery ward, or for those who delivered at home or in other hospitals from the women themselves or their primary care physicians Details of equipment reported												

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	and eight (3.7%) were of other ethnicity													
First author, year: Skentou 1999[121] Country: UK Study design: Prospective cohort Study dates: Not reported Aim of study: To examine the possible value of cervical assessment at 23 weeks in predicting risk of spontaneous preterm delivery in	Population: N = 464 women with twin pregnancies who gave birth to live babies and had cervical assessment at 23 weeks' gestation 30 of the women (17 in which the birth was iatrogenic, and 13 with cervical length <20mm who had a cervical suture placed) were excluded from the final analysis 313 pregnancies (67.5%) were	Screening test: Cervical length measurement at 23 weeks' gestation Reference test: Spontaneous preterm birth Method: Subject characteristics, including demographic data and previous obstetric and medical history, were obtained from the women at their first visit to the hospital and were entered into a computer	Cervical length ≤15mm measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks	6	5	28	395	18 (5 to 31)*	99 (98 to 99)*	55 (25 to 84)*	93 (91 to 96)*	14.1 (4.5 to 43.9)*	0.83 (0.71 to 0.97)*	Funding: Fetal Medicine Foundation, London, UK Limitations: Possibility of inter-operator bias as several sonographers were involved in the assessment of cervical length
			Cervical length ≤20mm measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks	9	13	25	387	26 (12 to 41)*	97 (95 to 98)*	41 (20 to 61)*	94 (92 to 96)*	8.1 (3.8 to 17.7)*	0.76 (0.62 to 0.93)*	
				12	33	22	367	35 (19 to 51)*	92 (89 to 94)*	27 (14 to 40)*	94 (92 to 97)*	4.3 (2.4 to 7.5)*	0.71 (0.55 to 0.91)*	

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
women with twin pregnancies	dichorionic and 151 (32.5%) were monochorionic Inclusion criteria: All women with twin pregnancies who gave birth to live babies and had cervical assessment at 22-24 weeks' gestation (median 23 weeks) identified from the database of all women with twin pregnancies presenting to the authors' unit for the 23-week fetal anomaly and growth	database Transvaginal sonography was carried out by trained sonographers and findings were recorded in a database at the time of the scans Gestational age was determined from menstrual history and confirmed by first-trimester ultrasound scan Data on pregnancy outcomes were obtained from a computerised system in the delivery ward, or for those who delivered at home or in other hospitals from	Cervical length ≤25mm measured at 22-24 weeks' gestation for the prediction of spontaneous preterm birth before 33 weeks * Calculated by NCC-WCH technical team from data reported in the paper											

Study details	Participants	Diagnostic tools	Outcome measures and results											Comments
			Outcome measures and results	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Specificity % (95%)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	
	scan Exclusion criteria: None reported Other details: All women included in the analysis were managed expectantly without bed rest, prophylactic antibiotics or tocolytics 378 women (81.5%) were Caucasians, 71 (15.3%) Afro-Caribbean and 15 (3.2%) were of other ethnicity	the women themselves or their primary care physicians Details of ultrasound technique and equipment reported												

Review question

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

b) Evidence tables for studies that reported clinical outcomes

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year Ong 2000[122] Country: UK Setting: Aberdeen maternity hospital Study design: Prospective diagnostic accuracy study Aim of study: To examine changes in cervical length in twin pregnancies using transvaginal and to evaluate its role in predicting preterm labour	Population: N= 46 women with twin pregnancy Chorionicity not reported Inclusion criteria: Non-consecutive twin pregnancies Exclusion criteria: Not reported Other details: Gestational age was calculated by the last menstrual period unless there was a greater than 10-day difference between menstrual data and ultrasound data in the first trimester Cervical length measurement from 24-34 weeks at minimum of 2-week intervals	Investigation : Measurement of cervical length and investigating preterm delivery within 1 week of measurement Methods described adequately? Yes - the study was conducted in a maternity hospital; transvaginal measurements of cervical length were performed from 24-34 weeks' gestation (minimum every 2 weeks); measurement was repeated three times and an average was calculated; the mean number of scans for each participant was 3 (range 0 to 3); results of cervical length measurement were not revealed to the clinician; the women and their providers were blinded to all study results Details of equipment and testing reported Operator number/experience: All scans were performed by the same sonographer	Prediction of spontaneous preterm delivery based on cervical length thresholds (mm): Delivery < 35 weeks : RR (95 % CI) Threshold of ≤20 : 2.12 (0.95 to 4.72) Threshold of ≤25 : 1.69 (0.78 to 3.67) Threshold of ≤30 : 0.91 (0.41 to 1.99) Threshold of ≤33 : 1.21(0.49 to 2.56) Delivery < 37 weeks : RR (95 % CI) Threshold of ≤20 : 1.71 (0.99 to 2.97) Threshold of ≤25 : 1.55 (0.91 to 2.61) Threshold of ≤30 : 1.21 (0.70 to 2.08) Threshold of ≤33 : 1.61 (0.65 to 2.05) Delivery within 1 week: Threshold of ≤20 : RR= 11.67 (95% CI 4.23 to 32.17) Sensitivity= 65% (95% CI not reported) Specificity= 79% (95% CI not reported) PPV= 52% (95% CI not reported) NPV= 87% (95% CI not reported) LR= 3.06 (95% CI not reported) Threshold of ≤25 : RR= 4.12 (95% CI 1.10 to 15.47) Sensitivity= 77% (95% CI not reported) Specificity= 59% (95% CI not reported) PPV= 39% (95% CI not reported) NPV= 88% (95% CI not reported) LR= 1.86 (95% CI not reported)	Funding: Not reported Limitations: The number of women who actually gave birth prematurely was not reported and so it was not possible to calculate 2x2 tables or CIs from the reported sensitivity, specificity, PPV and NPV statistics Participants were not scanned at the same intervals

Study details	Participants	Investigation	Outcome measures and results	Comments
			Threshold of ≤30 : RR= 7.25 (95% CI 0.94 to 55.85) Sensitivity= 88% (95% CI not reported) Specificity= 41% (95% CI not reported) PPV= 34% (95% CI not reported) NPV= 91% (95% CI not reported) LR= 1.51 (95% CI not reported) Threshold of ≤33 : RR= NC Sensitivity= 92% (95% CI not reported) Specificity= 37% (95% CI not reported) PPV= 34% (95% CI not reported) NPV= 93% (95% CI not reported) LR= 1.47 (95% CI not reported)	
First author, year: Goldenberg 2000[128] Country: USA Study design: Prospective observational study Study dates: 1992-1994 Aim of study: To investigate a sequence of positive test results and the influence of other risk factors (multiple	Population: N=2929 singleton pregnancies N=147 twin pregnancies Chorionicity of twin pregnancies not reported Inclusion criteria: Pregnant women at risk of preterm delivery (multiple pregnancy, previous preterm delivery, black race, body mass index, presence of bacterial vaginosis) Exclusion criteria: Cervical cerclage, placenta praevia, fetal anomaly	Investigation : Fibronectin test Cervical length measurement Demographic and medical history Methods described adequately? Yes - the study was a secondary analysis of a large prospective observational study (preterm prediction study); it was carried out in 10 centres and women were selected to reflect the population with respect to race and parity; participants were recruited before 24 weeks' gestation; an initial study visit occurred at	Risk of spontaneous preterm birth before 30 weeks based on results of fibronectin testing and cervical length measurements at 24-28 weeks in women with twin pregnancies No positive test result 6.4% One positive test result 15.6% Two positive test results 50.0% No P-values or CIs for differences between groups reported	Funding: National Institute of Child Health and Human Development, USA Limitations: Bias will arise from operator and equipment

Study details	Participants	Investigation	Outcome measures and results	Comments
pregnancy, previous preterm birth, black race, vaginosis, maternal body mass index (BMI)) on positive fibronectin test, short cervix and preterm delivery	Other details: Gestational age was based on last menstrual period if this was within 10 days of the estimate from the earliest ultrasonographically measured biparietal diameter; otherwise the estimate based on biparietal diameter was used	24± 1 weeks' gestation then every 2 weeks at approximately 26, 28 and 30 weeks' gestation Fibronectin test performed at each visit Cervical length measured at 24- and 28-week visits Operator number/experience: Nurses and sonographers; no further details reported		
First author, year: Fox 2009[127] Country: USA Study design: Retrospective cohort study Study dates: 2005 to 2008 Aim of study: To evaluate combined fetal fibronectin (fFN) test results and cervical length as predictors of preterm birth in asymptomatic twin pregnancies	Population: N= 155 twin pregnancies All dichorionic (monoamniotic twin pregnancies excluded) Inclusion criteria: Asymptomatic women with twin pregnancies with cervical length measurement and fibronectin testing at 22-32 weeks' gestation Exclusion criteria: Monoamniotic twins, pregnancies with aneuploidy, major fetal anomalies, women with medically indicated preterm birth Other details: Gestational age was confirmed by first-trimester	Investigation : Fetal fibronectin test Cervical length measurement Methods described adequately? No – methods not reported clearly; combined fibronectin test and cervical length measurement was performed between 22 and 32 weeks' gestation. Fetal fibronectin test was performed without use of speculum. Cervical length < 20 mm at any time from 22 to 32 weeks was considered to represent a short cervix Operator number/experience: Not reported	Both test results negative: n=120 One test result positive: n=24 Both test results positive: n=11 Women with a positive fetal fibronectin result at any time between 22 and 32 weeks' gestation (n= 20) were significantly more likely to deliver spontaneously at <28, <30, <32, <34, <35 or <37 weeks' gestation Women with a cervical length <20mm at any time between 22 and 32 weeks' gestation (n= 26) were significantly more likely to deliver spontaneously at <28, <30, <32, <34 or <37 weeks' gestation Risk of spontaneous preterm birth in twin pregnancies based on combined fibronectin and cervical length measurement at 22 to 32 weeks (n=155): Risk of spontaneous preterm birth <28 weeks: Both test results negative =1.6%	Funding: Not reported Limitations: No clear description of data collection method, operators or equipment Wide range of gestational ages at which testing was conducted (22 to 32 weeks) Retrospective study

Study details	Participants	Investigation	Outcome measures and results	Comments
	ultrasound in all women		One test result positive =13.3% Both test results positive = 50% P< 0.001 <u>Risk of spontaneous preterm birth < 30 weeks:</u> Both test results negative = 2.4% One test result positive = 9.5% Both test results positive = 33.3% P< 0.001 <u>Risk of spontaneous preterm birth < 32 weeks:</u> Both test results negative = 4.2% One test result positive = 8.3% Both test results positive = 54.5% P< 0.001 <u>Risk of spontaneous preterm birth < 34 weeks:</u> Both test results negative = 10.3% One test result positive = 26.1% Both test results positive = 54.5% P< 0.001 <u>Risk of spontaneous preterm birth < 35 weeks:</u> Both test results negative = 18.3% One test result positive = 39.1% Both test results positive = 54.5% P= 0.005 <u>Risk of spontaneous preterm birth < 37 weeks:</u> Both test results negative = 43.0% One test result positive = 77.3% Both test results positive = 100% P< 0.001 No CIs reported	

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Dyson 1998[130] Country: USA Study design: Randomised controlled trial (three arms) Study dates: July 1992- August 1996 Aim of study: To determine whether adding home monitoring of uterine activity to daily contact with a nurse improved clinical outcomes and whether daily contact (with or without the use of home monitoring) was more effective than weekly contact for pregnant women at increased risk of preterm labour	Population: Singleton and twin pregnancies: total n=2422; twins n=844 Chorionicity not reported 2480 women enrolled in the study; 58 women gave birth or withdrew consent before randomisation Inclusion criteria: Asymptomatic pregnant women with: at least one risk factor for preterm delivery (e.g. twin pregnancy); access to telephone; willing to comply with study protocol Exclusion criteria: Women in preterm labour or premature rupture of membranes Other details: Gestational age was confirmed from ultrasonography before 24 weeks' gestation	Investigation : Effect of frequent contact of nurse with pregnant women or home monitoring of uterine activity on the rate of preterm birth (< 35 weeks) Comparison: Three treatment groups: • weekly contact (with nurse • daily contact (with nurse) • home monitoring (daily contact with nurse and home monitoring of uterine activity) Methods described adequately? Yes - all women in 30 clinics in Northern California who were eligible for inclusion in the study were assigned to one of three groups using a computer-generated randomisation sequence Randomisation was stratified according to twin or singleton pregnancy and treatment centre All women received education on symptoms and signs of preterm labour (six or more contractions in 1 hour was	▪ Incidence of preterm birth in women with twin pregnancies Weekly contact (n=280) Preterm birth < 37 weeks = 49% < 35 weeks = 22% < 32 weeks = 7% Daily contact (n=277) Preterm birth < 37 weeks = 54% < 35 weeks = 24% < 32 weeks = 9% Home monitoring (n=287) Preterm birth < 37 weeks = 51% < 35 weeks = 24% < 32 weeks = 6% No significant difference (p-value not reported) among the three groups for birth at <37, <35 or <32 weeks' gestation ▪ Incidence of preterm labour < 35 weeks in women with twin pregnancies Weekly contact = 35% Daily contact = 34% Home monitoring = 40% P = 0.06 for the difference in preterm labour between the weekly contact and home monitoring groups	Funding: Sidney Garfield Memorial Fund Limitations: Women received education about the symptoms and signs of preterm labour but there was no assessment of their knowledge regarding these Reporting bias could have occurred due to self-reporting of contractions

Study details	Participants	Investigation	Outcome measures and results	Comments
		considered to be an excessive number of contractions in twin pregnancy) Women in the weekly contact group were told to assess themselves for symptoms and signs of preterm labour as follows: twice-daily self-palpation for uterine contractions for 1 hour; a nurse centre called women weekly to review their daily logs Women in the daily contact group were told to assess themselves for symptoms and signs of preterm labour as follows: twice-daily self-palpation for uterine contractions; a nurse called the women each day to review their symptoms Women in home monitoring group were each given a device that monitored uterine activity, stored the monitored information, and transmitted it to a central receiver through telephone lines; women were asked to use the device for 1 hour each morning and evening and to transmit the information after each session; the women had a daily call from a nurse The obstetrician and practitioner were not aware of		

Study details	Participants	Investigation	Outcome measures and results	Comments
		the treatment groups to which women were assigned There were no statistically significant differences in age, gravidity, parity, race, educational level, marital status, or cocaine use between the three groups		
First author, year: Colton 1995[129] Country: USA Study design: Meta-analysis of randomised controlled trials Aim of study: To assess the evidence from randomised controlled trials regarding home monitoring of uterine activity	Population: N= 1270 pregnancies N= 311 twin pregnancies Six RCTs were included Chorionicity not reported for twin pregnancies Inclusion criteria: Published RCTs reporting on home uterine activity monitoring plus unpublished data obtained by communication with the principal investigators for the trials Other details: The six included trials had already been reviewed by the United States Preventive Service Task Force on home uterine activity monitoring. This study supplemented the Task Force report, using a	Investigation : Home uterine activity monitoring Comparison: Not reported clearly Methods described adequately? Yes - random effects meta-analysis was used for pooling data from individual trials In four trials women who had home uterine activity monitoring received more intensive nursing contact than women in control group. The effect of nursing contact was controlled in two trials with nursing contact applied equally between the two treatment groups. The design and implementation of these two trials was stronger than for the other four trials, therefore	Incidence of spontaneous preterm birth in twin pregnancy 6 studies Number of women with preterm birth in the home uterine activity monitoring group = 72 Total number of women in home uterine activity monitoring group =165 Number of women with preterm birth in the control group (no monitoring) = 60 Total number of women in control group n=146 RR (random effects model) 1.01 (95% CI 0.79 to 1.30) Incidence of preterm labour in women with cervical dilatation > 2 cm in twin pregnancy 5 studies Number of women with preterm labour and cervical dilatation >2cm in the home uterine activity monitoring group = 15 Total number of women in home uterine activity monitoring group n=140 Number of women with preterm labour and cervical dilatation >2cm in the control (no monitoring) group = 29 Total number of women in the control group	Funding: Not reported Limitations: Main limitation is that the authors did not attempt to search for new studies/trials published since the first review was carried out Data were pooled using a conservative approach (random effects model), without first checking for heterogeneity

Study details	Participants	Investigation	Outcome measures and results	Comments
	meta-analysis of the same quantitative evidence but with a statistical method that was more appropriate in terms of approaches for pooling results of different studies. Stratified meta-analyses were conducted for singleton and twin pregnancies	separate meta-analyses were conducted to pool results of these higher-quality trials and the four other (lower-quality) trials	n=120 RR (random effects model) 0.44 (95% CI 0.25to 0.78)	
First author, year: Facco 2008[131] Country: USA Study design: Retrospective cohort study Study dates: June 1995 to May 2005 Aim of study: To determine whether preterm birth in singleton pregnancies is associated with an increased risk of preterm birth in the woman's next (twin) pregnancy	Population: 293 women who delivered a singleton previously and whose next pregnancy was a twin pregnancy Chorionicity not reported Inclusion criteria: Women who delivered a singleton followed a twin pregnancy >20 weeks Exclusion criteria: Cervical cerclage in either pregnancy, fetal anomaly, intrauterine death, iatrogenic preterm delivery, other premature delivery before study period Other details: Not reported	Investigation : Reviewing medical records in women with a history of preterm singleton birth followed by a twin pregnancy Comparison: Comparison made between data from women with a history of preterm singleton birth followed by a twin pregnancy (n= 23) and women with a history of term singleton birth followed by a twin pregnancy (n=270) Methods described adequately? Yes - medical and delivery records of all women who delivered between June 1995 and May 2005 and who met the inclusion criteria were reviewed The women were divided into	Outcome: Preterm twin delivery in women with history of preterm singleton birth Out of 23 women with premature singleton birth, 17 (73%) had a preterm twin delivery in the next (twin) pregnancy 120 (44%) of the 270 women who had delivered a term singleton had a preterm birth twin in the next (twin) pregnancy The association between preterm birth of a singleton and preterm birth of twins in the next pregnancy was statistically significant (OR 3.5, 95% CI 1.4 to 9.3) Mean gestational age of subsequent twin delivery 34 ± 3.7 weeks in the preterm singleton group versus 36.6 ± 2.4 weeks in the term singleton group (p< 0.01) After adjusting for maternal ethnicity, a preterm singleton delivery was statistically significantly associated with preterm delivery	Funding: Not reported Limitations: Main limitation is that this was a retrospective, non-randomised study and dependent on the prevalence of women with a history of a preterm delivery Data about parity and the number of previous term versus preterm deliveries not reported

Study details	Participants	Investigation	Outcome measures and results	Comments
		two groups: those who had a preterm singleton delivery and those who had a term singleton delivery in their previous pregnancy There were no statistically significant differences between the two groups in terms of medical history, caesarean section, or maternal age There was a statistically significant difference between the two groups in gestational age at delivery of the singleton and race ($p< 0.01$ and $p=0.02$, respectively)	in the next (twin) pregnancy (adjusted OR 3.3, CI 1.3 to 8.7)	

Preventing preterm birth

Review question

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

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Crowther 2010[132] Country: Four trials were conducted in Zimbabwe, two in Australia and one in Denmark Study design: Cochrane review Aim of study: To assess the effectiveness of hospital bed rest for prevention of preterm birth and other fetal, neonatal and maternal outcomes in women with multiple pregnancy	Population: N = 713 women with twin or triplet pregnancies, resulting in 1452 babies 7 trials were included, 5 involved twin pregnancies (687 women and 1374 babies) and 2 involved triplet pregnancies (26 women and 78 babies) Inclusion criteria: All published, unpublished and ongoing randomised trials that compared hospitalisation for bed rest with no routine hospitalisation, among women with a multiple pregnancy Exclusion criteria: None specified Other details: Details of chorionicity and ethnicity not reported	Investigation: Hospitalisation for bed rest Comparison: Selective admission (i.e. no routine hospitalisation) Methods described adequately? Yes Relevant trials were identified in the Cochrane Specialised Register of Controlled Trials, using appropriate search terms Identified trials were evaluated for inclusion and methodological quality Quality scores were assigned for: concealment of allocation; blinding of outcome assessment; and completeness of follow-up Details of quality scores reported Randomisation in the individual studies was reported – one used a central telephone agency, five trials used consecutively numbered sealed envelopes, and one study used quasi randomisation using odd	Preterm delivery (<37 weeks' gestation) Twin and triplet pregnancies 7 studies, 713 women Treatment group: 179/347 Control group: 176/366 RR 0.99 (95% CI 0.86 to 1.13) Uncomplicated twin pregnancies 4 studies, 548 women Treatment group: 117/264 Control group: 108/284 RR 1.12 (95% CI 0.89 to 1.42) Triplet pregnancies 2 studies, 26 women Treatment group: 11/13 Control group: 13/13 RR 0.88 (95% CI 0.66 to 1.16) Very preterm delivery (<34 weeks' gestation) Twin and triplet pregnancies 5 studies, 424 women Treatment group: 50/210 Control group: 39/214 RR 1.31 (95% CI 0.91 to 1.89) Uncomplicated twin pregnancies 2 studies, 259 women Treatment group: 33/127 Control group: 21/132 RR 1.57 (95% CI 0.72 to 3.43)	Funding: Not reported Limitations: The main limitation was that allocation concealment was not met in one of the trials included in the review. The same trial was only quasi-randomised No blinding to the intervention in any trial. Three trials blinded outcome assessment, the other trials did not report blinding Data were reported for preterm delivery but not for spontaneous preterm delivery. Preterm delivery may have included medically indicated births (e.g. births due to pre-eclampsia)

Study details	Participants	Investigation	Outcome measures and results	Comments
		or even year of birth	Triplet pregnancies 2 studies, 26 women Treatment group: 6/13 Control group: 6/13 RR 1.17 (95% CI 0.46 to 2.94) <u>Gestational age at delivery</u> Twin and triplet pregnancies 7 studies, 713 babies Treatment group: 347 women Control group: 366 women Mean difference -0.25 (95% CI -0.58 to 0.08) Uncomplicated twin pregnancies 4 studies, 548 babies Treatment group: 264 women Control group: 284 women Mean difference -0.39 (95% CI -0.78 to 0.01) Triplet pregnancies 2 studies, 26 babies Treatment group: 13 women Control group: 13 women Mean difference 0.58 (95% CI -1.35 to 2.51) <u>Perinatal death</u> Twin and triplet pregnancies 7 studies, 1448 babies Treatment group: 26/703 Control group: 26/745 RR 1.06 (95% CI 0.42 to 2.64)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Uncomplicated twin pregnancies 4 studies, 1092 babies Treatment group: 23/524 Control group: 19/568 RR 1.64 (95% CI 0.45 to 6.08) Triplet pregnancies 2 studies, 78 babies Treatment group: 1/39 Control group: 5/39 RR 0.28 (95% CI 0.05 to 1.65) <u>Caesarean delivery</u> Twin and triplet pregnancies 5 studies, 424 babies Treatment group: 56/210 Control group: 63/214 RR 0.96 (95% CI 0.74 to 1.25) Uncomplicated twin pregnancies 2 studies, 259 babies Treatment group: 47/127 Control group: 49/132 RR 1.04 (95% CI 0.78 to 1.38) Triplet pregnancies 2 studies, 40 babies Treatment group: 4/19 Control group: 4/21 RR 0.98 (95% CI 0.27 to 3.62) <u>Low birthweight (<2500g)</u> Twin and triplet pregnancies 7 trials, 1452 babies	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Treatment group: 359/707 Control group: 401/745 RR 0.92 (95% CI 0.85 to 1.00) Uncomplicated twin pregnancies 4 studies, 1096 babies Treatment group: 240/528 Control group: 280/568 RR 0.91 (95% CI 0.81 to 1.03) Triplet pregnancies 2 studies, 78 babies Treatment group: 35/39 Control group: 35/39 RR 1.08 (95% CI 0.66 to 1.78) <u>Very low birthweight (<1500g)</u> Twin and triplet pregnancies 7 studies, 1452 babies Treatment group: 38/707 Control group: 32/745 RR 1.22 (95% CI 0.77 to 1.95) Uncomplicated twin pregnancies 4 studies, 1096 babies Treatment group: 29/528 Control group: 17/568 RR 1.82 (95% CI 1.02 to 3.27) Triplet pregnancies 2 studies, 78 babies Treatment group: 5/39 Control group: 9/39 RR 0.56 (95% CI 0.20 to 1.54)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Admission to neonatal care unit Twin and triplet pregnancies 4 studies, 853 babies Treatment group: 148/424 Control group: 159/429 RR 0.91 (95% CI 0.79 to 1.04) Uncomplicated twin pregnancies 2 studies, 518 babies Treatment group: 72/254 Control group: 69/264 RR 1.08 (95% CI 0.82 to 1.42) Triplet pregnancies 1 study, 57 babies Treatment group: 25/30 Control group: 25/27 RR 0.90 (95% CI 0.74 to 1.09) Neonatal stay in hospital (≥7 days) Twin and triplet pregnancies 3 studies, 571 babies Treatment group: 56/286 Control group: 62/285 RR 0.93 (95% CI 0.62 to 1.39) Uncomplicated twin pregnancies 1 study, 236 babies Treatment group: 14/116 Control group: 21/120 RR 0.69 (95% CI 0.37 to 1.29) Triplet pregnancies 1 study, 57 babies Treatment group: 17/30	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Control group: 11/27 RR 1.39 (95% CI 0.80 to 2.42)	
First author, year: Kappel 1985[133] Country: Denmark Study design: Retrospective observational cohort study Study dates: July 1997 - October 1980 Aim of study: To investigate the effectiveness of bed rest at home (as an alternative to hospitalisation) in reducing the frequency of preterm birth	Population: N = 146 twin pregnancies 37 women hospital bed rest, 31 bed rest at home and 34 women no bed rest were included Inclusion criteria: Consecutive twin pregnancies, delivered at the Department of Gynaecology and Obstetrics, Aarhus Kommunehospital in the period from 1 January 1977 to 1 October 1980 Exclusion criteria: Women hospitalised other reasons than bed rest, women who could not be included in either of the three groups Other details: Details of ethnicity and chorionicity not reported	Investigation: Bed rest in hospital Comparisons: Bed rest at home No bed rest Methods described adequately? Yes – method reported clearly Women with twin pregnancy were divided into three treatment groups Group 1: Bed rest in hospital; bed rest in hospital for at least 2 weeks from 29-36 weeks inclusive (n=37) Group2: Bed rest at home; women who refused hospitalisation were advised to take bed rest at home from 29-36 weeks (n=31) Group3: No bed rest; women who rested for less than 2 weeks from 29-36 weeks or did not rest at all (n=34)	1) Hospital bed rest versus home bed rest Birth before the end of 33 weeks (%) Hopsital bed rest = 0/37 (0%) Home bed rest = 4/31 (12.9%) Relative risk = 0.09 (0.01 to 1.67)* Perinatal mortality Hopsital bed rest = 0/37 (0%) Home bed rest = 1/31 (3.2%) Relative risk = 0.28 (0.01 to 6.66)* 2) Hospital bed rest versus no bed rest Birth before the end of 33 weeks (%) Hopsital bed rest = 0/37 (0%) Home bed rest = 14/34 (41.2%) Relative risk = 0.03 (0.00 to 0.51)* Perinatal mortality Hospital bed rest = 0/37 (0%) Home bed rest = 4/34 (11.8%) Relative risk = 0.10 (0.01 to 1.83)*	* Calculated by NCC-WCH technical team from data reported in the article Funding: Not reported Limitations: Retrospective observational study Likelihood of bias on allocation of women to the groups
First author, year: Adams 1998[134] Country: USA Study design:	Population: N = 66 women with triplet pregnancies 32 women who were prescribed outpatient bed rest were compared with a	Investigation: Outpatient third trimester bed rest (at home) Comparison: Inpatient third trimester bed rest (routine hospitalisation)	Gestational age at delivery in weeks (SD): Inpatient bed rest group: 33.5(2.8) Outpatient bed rest group: 32.5 (2.8) p=0.16 Mean difference = 1.00 (0.22 to 1.78)* Perinatal mortality:	* Calculated by NCC-WCH technical team from data reported in the article Funding: Not reported

Study details	Participants	Investigation	Outcome measures and results	Comments
Retrospective observational study with historical comparison group Study dates: Study group: April 1993 to April 1996 Comparison group: January 1985 to March 1993 Aim of study: To compare duration of hospitalisation and birth outcomes in women with triplet pregnancies who were advised third trimester bed rest at home with corresponding data in historical records for women admitted to hospital for bed rest	historical cohort of 34 women in whom routine hospitalisation was undertaken Inclusion criteria: All triplet pregnancies cared for at the Division of Maternal-Fetal Medicine at Evanston Hospital during the study period Exclusion criteria: Birth before 24 weeks' gestation; women with cervical incompetence (n=3); triplet pregnancies that resulted from multifetal reduction from a higher-order pregnancy Other details: Details of chorionicity and ethnicity not reported	Methods described adequately? Yes Clinical outcome data were abstracted from maternity records and computerised labour room database	Inpatient bed rest group: 1/102 (1%) Outpatient bed rest group: 1/96 (1%) p=1.0 Odds ratio = 0.94 (0.06 to 5.25)* Maternal hospital days (SD): Inpatient bed rest group: 47.9 (22.6) Outpatient bed rest group: 21.2 (14.5) $p=10^{-7}$ Mean difference = 26.7 (17.59 – 35.81)* Caesarean section: Inpatient bed rest group: 31/34 (91%) Outpatient bed rest group: 26/32 (81%) Odds ratio = 2.38 (0.54 to 10.48)* Intraventricular haemorrhage (grades 1 to 4): Inpatient bed rest group: 1/102 (0.9%) Outpatient bed rest group: 10/96 (10.4%) p=0.004 Odds ratio = 0.09 (0.01 to 0.68)* Intraventricular haemorrhage (grades 3 and 4): Inpatient bed rest group: 0/102 (0%) Outpatient bed rest group: 1/96 (1%) p=0.48 Odds ratio = 0.31 (0.01 to 7.72)* Necrotising enterocloitis: Inpatient bed rest group: 0/102 (0%) Outpatient bed rest group: 0/96 (0%) p=1.0 Odds ratio = Not estimable*	Limitations: Retrospective observational study Low quality evidence

Study details	Participants	Investigation	Outcome measures and results	Comments
			Bronchopulmonary dysplasia: Inpatient bed rest group: 0/102 (0%) Outpatient bed rest group: 1/96 (1%) p=0.48 Odds ratio = 0.31 (0.01 to 7.72)* Infant special care unit days (SD): Inpatient bed rest group: 26.0 (21.2) Outpatient bed rest group: 26.1 (18.3) p=0.84 Mean difference = -0.10 (-9.64 to 9.44)* Newborn nursery days (SD): Inpatient bed rest group: 6.3 (1.8) Outpatient bed rest group: 6.0 (1.7) p=0.49 Mean difference = 0.30 (-0.54 to 1.14)*	
First author, year: Hartikainen-Sorri 1980[136] Country: Finland Study design: Placebo-controlled double-blind trial Study dates: Not reported Aim of study: To assess the effectiveness of 17 alpha-	Population: N = 77 twin pregnancies 39 women received weekly injections of intramuscular progesterone while 38 women received a placebo Inclusion criteria: All consecutive twin pregnancies entering the authors' outpatient clinic Exclusion criteria: Gestational age >33 weeks; signs of premature labour Other details: All pregnancies were at 28 –	Investigation: Weekly intramuscular injections of 17 alpha-hydroxyprogesterone caproate Comparison: Weekly intramuscular injections of a placebo Methods described adequately? Yes, apart from a lack of information about whether randomisation was undertaken Gestational age was calculated from the first day of the last menstruation and was	Spontaneous preterm delivery (<37 weeks' gestation) Progesterone group: 12/39 (30.8%) Placebo group: 9/38 (23.7%) No statistically significant difference between the two groups (P-value not reported) Gestational age at delivery (mean ± SD) Progesterone group: 36.9 (±2.6) weeks Placebo group: 37.3(±2.4) weeks Difference between the two groups not statistically significant (P-value not reported) Perinatal mortality: Progesterone group: 4/78 babies (5.2%) Placebo group: 2/76 babies (2.6%) Difference between the two groups not statistically significant (P-value not	Funding: Not reported 17 alpha-hydroxyprogesterone caproate was supplied by Schering AG Limitations: Main limitations were lack of clarity about whether randomisation was carried out and a small sample size Details of blinding were also not reported Randomisation at relatively advanced stage of pregnancy The use of bed rest and

Study details	Participants	Investigation	Outcome measures and results	Comments
hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy	33 weeks' gestation at entry to the trial Bed rest was prescribed for 71 of the 77 women; use of betamimetics was allowed when required No details of ethnicity or chorionicity reported	confirmed by ultrasound, along with the diagnosis of twin pregnancy Women received equivalent volumes of weekly intramuscular injections of 250 mg of 17 alpha-hydroxyprogesterone caproate or placebo until 37 weeks (or birth if this occurred earlier)	reported) Neonatal respiratory problems: Progesterone group: 7 babies Placebo group: 3 babies No statistically significant difference between the two groups (P-value not reported)	betamimetics may have confounded the results for the effects of 17 alpha-hydroxyprogesterone caproate
First author, year: Rouse 2007[137] Country: USA Study design: Multi-centre, double blinded, placebo-controlled RCT Study dates: April 2004 to February 2006 Aim of study: To evaluate the effectiveness of 17 alpha-hydroxyprogesterone caproate in reduction of preterm birth in twin pregnancies	Population: 661 women were recruited at 14 centres and randomly assigned to the treatment (n=327) or control group (n=334) Inclusion criteria: Women with twin pregnancies at a gestational age of at least 16 weeks and no more than 20 weeks and 3 days Exclusion criteria: Serious fetal anomalies, spontaneous death of a fetus after 12 weeks, presumed monoamnionic placenta, suspected feto-fetal transfusion syndrome, marked ultrasonographic growth discordance (a difference of at least 3 weeks	Investigation : Weekly intramuscular injections of 250 mg 17 alpha-hydroxyprogesterone caproate were given until 34 weeks' gestation or until delivery, whichever occurred first Comparison: Control group was given a placebo (identical-appearing castor oil injections) Methods described adequately? Yes – randomisation using 'simple urn method' with stratification according to clinical centre. The participating women, their caregivers and the research personnel were unaware of the women's treatment group assignment	Spontaneous preterm birth (before 35 weeks): Intervention group: 101/324 (31.2%) Control group: 86/330 (26.1%) Relative Risk (95% CI): 1.2 (0.9 to 1.5) Mean gestational age at birth (+SD): Intervention group: 34.6 (±3.9) weeks Placebo group: 34.9 (±3.6) weeks No statistically significant difference Maternal side effects Intervention group: 211/320 (65.9%) Control group: 210/326 (64.4%) Relative Risk (95% CI): 1.0 (0.9 to 1.1) Caesarean delivery: Intervention group: 200/324 (61.7%) Control group: 204/328 (62.2%) Relative Risk (95% CI): 1.0 (0.9 to 1.1) Low birthweight (< 2500 g): Intervention group: 377/628 (60.0%) Control group: 415/648 (64%) Relative Risk (95% CI): 0.9 (0.8 to 1.0) Very low birthweight (<1500 g): Intervention group: 81/628 (12.9%) Control group: 64/648 (9.9%) Relative Risk (95% CI): 2.0 (1.0 to 3.9)	Funding: Supported by grants from the National Institute of Child Health and Human Development Limitations: None identified

Study details	Participants	Investigation	Outcome measures and results	Comments
	in estimated gestational age between fetuses), planned non-study progesterone treatment after 16 weeks, present or planned cerclage, major uterine anomaly (e.g., bicornuate uterus), treatment with 10,000 or more units/day of unfractioned heparin, treatment with low molecular weight heparin (any dosage), and major chronic medical disease (e.g., type 1 diabetes or pharmacologically treated hypertension) Twin pregnancies that resulted from intentional fetal reduction were also excluded <u>Other details:</u> Ethnicity: Intervention group: Black: 75/327 (22.9%) White: 218/327 (66.7%) Asian: 8/327 (2.4%) Other: 26/327 (8.0%) Hispanic/Latino: 51/327 (15.6%) Control group: Black: 80/334 (24.0%) White: 218/334 (65.3%) Asian: 5/334 (1.5%) Other: 31/334 (9.3%)		<u>Respiratory distress syndrome:</u> Intervention group: 96/632 (15.2%) Control group: 87/648 (13.4%) Relative Risk (95% CI): 1.2 (0.8 to 1.6) <u>Necrotising enterocolitis (stage 2or 3):</u> Intervention group: 3/632 (0.5%) Control group: 4/648 (0.6%) Relative Risk (95% CI): 1.2 (0.8 to 1.6) <u>Intraventricular haemorrhage (grade 3 or 4)</u>: Intervention group: 7/632 (1.1%) Control group: 6/648 (0.9%) Relative Risk (95% CI): 0.9 (0.3 to 2.8)	

Study details	Participants	Investigation	Outcome measures and results	Comments
	Hispanic/Latino: 54/334 (16.2%) 2 women in the intervention group and 4 in the control group were lost to follow-up, leaving 325 women (650 fetuses) in the intervention group and 330 women (660 fetuses) in the control group in the final analysis			
First author, year: Briery 2009[138] Country: USA Study design: RCT (double blinded, placebo controlled) Study dates: Not reported Aim of study: To investigate the effectiveness of 17 aplha-hydroxyprogesterone caproate (17α-OHP-C) in the prevention of prematurity associated with twin pregnancy	Population: N=30 women with twin pregnancy between 28 and 33 weeks' gestational age Inclusion criteria: Women with twin pregnancies who were cared for at the University of Mississippi Obstetric Clinics or Antenatal Diagnostic Units, at 20-30 weeks' gestation with intact membranes and able to give informed consent Exclusion criteria: Severe medical disorders (e.g. sickle cell disease, type 1 diabetes, chronic hypertension, cervical dilatation ≥1 cm, intrauterine growth restriction (<10th percentile), growth	Investigation : N=16 women were treated with weekly intramuscular injections of 250 mg of 17 alpha-hydroxy progesterone caproate until 34 weeks' gestation (or birth if this occurred earlier) Comparison: N=14 women were given placebo (castor oil) injections in a similar way as in the intervention group Methods described adequately? Yes - randomisation by selection of sequentially numbered, sealed, opaque envelopes generated and opened by a disinterested third party (pharmacy) to receive either weekly 17 alpha progesterone caproate or	Preterm birth rates (%)* a) <37 weeks Intervention group: 14/16 (88%) Placebo group: 13/14 (93%) P = 0.565 b) <35 weeks Intervention group: 7/16 (44%) Placebo group: 11/14 (79%) P = 0.117 Mean gestational age at birth (±SD): Intervention group: 33.9 (±4) weeks Placebo group: 33.1(±2.9) weeks P = 0.19 Perinatal Mortality: Intervention group: 2/32 (6%) Placebo group: 0/28 (0%) P = 0.36 NICU days: Intervention group: 18.4 (±65.8) days Placebo group: 17.3(±29.8) days P= 0.155	* The article does not report whether this includes only spontaneous preterm births Funding: Not reported 17 appha-hydroxyl progesterone caproate was donated by PharmAmerica Limitations: Small sample size

Study details	Participants	Investigation	Outcome measures and results	Comments
	discordance between twins (≥ 20%), cerclage, uterine abnormalities, or unwillingness to participate in the study protocol None of the twin pregnancies resulted from IVF and no women had undergone intentional fetal reduction or had spontaneous miscarriage Other details: Ethnicity: Intervention group: African American: 15/16 Caucasian: 1/16 Control group: African American: 13/14 Caucasian: 1/14 p=0.525	placebo injections. The placebo and the intervention drug were prepared by a commercial organisation and shipped to the pharmacy in opaque, number-coded syringes	Respiratory distress syndrome: Intervention group: 10/32 (31) Placebo group: 9/28 (32%) P= 0.838 Intraventricular haemorrhage: Intervention group: 3/32(9%) Placebo group: 4/28 (14%) P= 0.851 Necrotising enterocolitis: Intervention group: 1/32(3%) Placebo group: 0/28 (0%) P= 0.946	
First auuthor, year: Caritis 2009[142] Country: USA Study design: Multi-centre, double blinded, placebo-controlled RCT Study dates: April 2004 to	Population: 134 women were recruited at 14 centres and randomly assigned to the treatment (n=71) or control group (n=63) Inclusion criteria: Women with triplet pregnancies at a gestational age of at least 16 weeks and no more than 20^{+6} weeks	Investigation : Weekly intramuscular injections of 250 mg 17 alpha-hydroxyprogesterone caproate in 1 ml castor oil were given until 34 weeks' gestation or delivery, whichever occurred first Comparison: Control group was given placebo (identical-appearing 1 ml castor oil injections)	Spontaneous preterm birth (<35 weeks): Intervention group: 34/71 (48%) Control group: 27/63 (43%) Relative Risk (95% CI): 1.1 (0.8 to 1.6) Median gestational age at birth (interquartile range): Intervention group: 32.4 (30.0 to 34.4) weeks Placebo group: 33.0 (31.6 to 34.3) weeks P = 0.527 Neonatal death: Intervention group: 5/212 (2%)	Funding: Supported by grants from the National Institute of Child Health and Human Development Limitations: Unequal number of participants in intervention (71) and control (63) groups raises questions about randomisation or loss to follow-up

Study details	Participants	Investigation	Outcome measures and results	Comments
September 2006 Aim of study: To evaluate the effectiveness of 17 alpha-hydroxyprogesterone caproate in reduction of preterm birth in women with triplet pregnancies	Exclusion criteria: Serious fetal anomalies, two or more fetuses in one amniotic sac, suspected feto-fetal transfusion syndrome, marked ultrasonographic growth discordance (a difference of at least 3 weeks in estimated gestational age between any two fetuses), planned non-study progesterone therapy after 16 weeks, present or planned cerclage, major uterine anomaly (e.g., bicornuate uterus), treatment with 10,000 or more units of unfractioned heparin per day, treatment with low molecular weight heparin (any dosage), and major chronic medical disease (e.g., type 1 diabetes or pharmacologically treated hypertension), triplet pregnancies resulting from intentional fetal reduction from a quintuplet or higher-order pregnancy Other details: Ethnicity: Intervention group: African American: 6/71 (8%) Caucasian: 53/71 (75%)	Methods described adequately? Yes – randomisation using 'simple urn method' with stratification according to clinical centre. The participating women, their caregivers and the research personnel were unaware of the women's treatment group assignment	Control group: 2/183 (1%) Relative Risk (95% CI): 2.2 (0.4 to 12.4) Caesarean delivery: Intervention group: 71/71 (100%) Control group: 62/63 (98%) Relative Risk (95% CI): 1.0 (1.0 to 1.1) Low birthweight (<2500 g): Intervention group: 191/212 (91%) Control group: 175/183 (96%) Relative Risk (95% CI): 0.9 (0.9 to 1.0) Very low birthweight (<1500 g): Intervention group: 91/212 (43%) Control group: 46/183 (25%) Relative Risk (95% CI): 1.7 (1.1 to 2.7) Respiratory distress syndrome: Intervention group: 65/212 (31%) Control group: 50/183 (27%) Relative Risk (95% CI): 1.1 (0.7 to 1.8) Necrotising enterocolitis (stage 2 or 3): Intervention group: 2/212 (0.9%) Control group: 5/183 (3%) Relative Risk (95% CI): 0.3 (0.0 to 3.1) Intraventricular haemorrhage (grade 3 or 4): Intervention group: 2/212 (0.9%) Control group: 4/183 (2%) Relative Risk (95% CI): 0.4 (0.0 to 3.8)	High caesarean section rates in intervention and control groups

Study details	Participants	Investigation	Outcome measures and results	Comments
	Hispanic: 12/71 (17%) Control group: African American: 5/63 (8%) Caucasian: 56/63 (89%) Hispanic: 2/63 (3%) Chorionicity: Intervention group: Trichorionic: 49/71 (69%) Dichorionic: 13/71 (18%) Unknown: 9/71 (13%) Control group: Trichorionic: 42/63 (70%) Dichorionic: 14/63 (23%) Unknown: 4/63 (7%) Gestational age at randomisation in weeks (range): Intervention group: 19 (18 to 20) Control group: 19 (18 to 20)			

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Norman 2009[141] Country: UK Study design: Randomised controlled trial (multicentre, placebo-controlled double-blinded) Study dates: December 1, 2004 to April 30, 2008 Aim of study: To investigate whether delivery or intrauterine death before 34^{+0} weeks' gestation would be lower in women with twin pregnancy randomly assigned to vaginal progesterone gel or placebo	Population: N = 500 women with twin pregnancy were recruited from 9 NHS clinics specialising in the management of twin pregnancy and randomised into the intervention (n=250) and control groups (n=250); 3 women in each group were lost to follow-up and data for 347 women in each group were analysed Inclusion criteria: All women with twin pregnancy, with gestational age and chorionicity established by scan before 20 weeks' gestation, and attending the antenatal clinic during recruitment period Exclusion criteria: Women who had contraindications to progesterone, planned cervical suture, planned elective birth before 34 weeks' gestation or planned intervention for feto-fetal transfusion before 22 weeks' gestation. Women with higher-order multiple pregnancies were also	Investigation: Daily 1.125 g vaginal progesterone gel containing 8% progesterone Comparison: Daily placebo gel containing 8% of excipients (glycerine, light liquid paraffin, hydrogenated palm oil, glyceride, carbopol 974P, sorbic acid, polycarbophil, sodium hydroxide and purified water) Methods described adequately? Yes – block randomisation involving interactive voice-response software at the UK Clinical Research Network registered trials unit (University of Aberdeen) All study personnel and participants were blinded to treatment assignment for the duration of the study	Preterm birth* or intrauterine death before 34 weeks: Intervention group: 61/247 (24.7%) Control group: 48/247 (19.4%) Relative Risk (95% CI): 1.36 (0.89 to 2.09) Mean gestational age at birth (SD): Intervention group: 35.4 (3.5) weeks Placebo group: 35.7 (3) weeks P=0.527 Neonatal death: Intervention group: 8 Control group: 6 P =0.59 Intrauterine death: Intervention group: 6 Control group: 4 P=0.52 Involved or prolonged inpatient maternal hospital admission (number of events): Intervention group: 87 (103) Control group: 72 (87) P=0.16 Caesarean section: Intervention group: 148/250 (59.2%) Control group: 161/250 (64.4%) Odds ratio (95% CI): 0.53 (0.34 to 0.84) Admission to neonatal unit: Intervention group: 167/494 (33.8%) Control group: 158/494 (32.0%) Odds Ratio (95% CI): 1.08 (0.76 to 1.54) Duration of neonatal stay (only babies admitted to neonatal unit) in days (SD): Intervention group (n=167): 26.9 (33.5)	* Personal communication with the author: preterm birth covers spontaneous and iatrogenic deliveries **Neonatal death and intrauterine death combined by NCC-WCH technical team to provide perinatal mortality data Funding: Chief Scientist Office of the Scottish Government Health Directorate Active drug and placebo were manufactured and donated by Serono Limitations: Low rate of recruitment to the study; only 500/1249 (40%) of eligible women agreed to participate in the study The study was largely undertaken in tertiary referral centres which could affect external validity

Study details	Participants	Investigation	Outcome measures and results	Comments
	excluded. Women were not eligible if their pregnancy was complicated by a recognised structural or chromosomal fetal abnormality at the time of recruitment Other details: Chorionicity: Monochorionic pregnancies: Intervention group: 46 Control group:45 Dichorionic pregnancies: Intervention group:201 Control group:202		Control group (n=158): 23.6 (29.5) Mean difference (95% CI): 3.3 (-5.3 to 11.9) Involved persistent/significant maternal disability or incapacity: Intervention group: 1/247 Control group: 0/247 P=0.32 Overall maternal satisfaction with study treatment (1=very satisfied, 10 completely dissatisfied): Intervention group: 2.8 (2.1) Control group: 2.8 (1.9) P=0.89	
First author, year: Fonseca 2007[139] Country: USA Study design: Randomised controlled trial (placebo-controlled, double-blinded) Study dates: September 2003 - May 2006 Aim of study: To investigate the	Population: N =250 women with a short cervix (<15 mm) which included 226 with singleton and 24 with twin pregnancies. Of the women with twin pregnancies, 11 women were in the intervention group and 13 women were in the placebo group (This information was obtained from a meta-analysis in Norman et al. 2009) which has been included separately Inclusion criteria:	Investigation: Daily vaginal capsules containing 200 mg micronised progesterone Comparison: Identical capsules containing safflower oil Methods described adequately? Yes – randomisation using computer-generated random number lists All study personnel and participants were blinded to treatment assignment for the duration of the study	Spontaneous preterm birth before 34 weeks*: Intervention group: 4/11 (36.4%) Control group: 7/13 (53.8%) Odds ratio = 0.49, 95% CI 0.09 to 2.53	* Data for spontaneous preterm delivery not reported separately for twins and singletons in the main paper but was extracted from a meta-analysis Norman et al. 2009 that has been included separately Funding: Fetal Medicine Foundation Limitations: All participating women were advised to abstain from sex

Study details	Participants	Investigation	Outcome measures and results	Comments
effectiveness of progesterone in the reduction of spontaneous preterm birth in women with a short cervix (<15 mm) Data specific to twin pregnancies were not reported in this article but were available through another article[141] where the study authors had obtained the relevant data through personal communication with the authors of this study	Women identified as having a short cervix (<15 mm) on transvaginal ultrasongraphy at 20-25 weeks' gestation who agreed to participate in the study Exclusion criteria: Major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes and cervical cerclage Other details: Chorionicity: Monochorionic pregnancies: Intervention group: 3/11 Control group:4/13 Dichorionic pregnancies: Intervention group:8/11 Control group:9/11 Ethnicity for women with twin pregnancies not reported			
First author, year: Dor 1982[143] Country: Israel Study design: Randomised controlled trial	Population: N = 50 twin pregnancies 25 women underwent elective cervical suture and 25 did not receive a suture (5 women, 3 of whom received cerclage, had mid-trimester terminations and excluded from the final analysis)	Investigation: Cervical cerclage Comparison: No cervical cerclage Methods described adequately? Yes	Spontaneous preterm delivery (<37 weeks' gestation) Cerclage group: 10/22 women (45.4%) No cerclage group: 11/23 women (47.8%) Odds ratio = 0.83, 95% CI 0.25 to 2.72* Neonatal death (in the first week of life) Cerclage group: 8/44 babies (18.2%) No cerclage group: 7/46 babies (15.2%)	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Main limitations were that details of randomisation and

Study details	Participants	Investigation	Outcome measures and results	Comments
Study dates: 1975-1979 Aim of study: To assess the effectiveness of cervical cerclage in the prevention of premature labour in twin pregnancy	Inclusion criteria: Twin pregnancies resulting from ovulation induction at the authors' infertility clinic; diagnosis confirmed by ultrasound; informed consent Exclusion criteria: Triplet and quadruplet pregnancies Other details: All women underwent hysterography before sutures were placed at 13 weeks' gestation No woman had cervical incompetence, threatened miscarriage or fetuses with congenital anomalies, or was admitted to hospital routinely for bed rest during the study No details of ethnicity or chorionicity reported	Multiple pregnancies were diagnosed by ultrasound at 6-10 weeks' gestation and only twin pregnancies were included Cervical cerclage (McDonald's technique) was placed at 13 weeks' gestation and removed after 37 weeks or when miscarriage, premature contractions or premature rupture of membranes occurred Details of equipment and technique were reported	Odds ratio = 1.24, 95% CI 0.41 to 3.76* Caesarean section Cerclage group: 9/22 women (40.9%) No cerclage group: 7/23 women (30.4%) Odds ratio = 1.58, 95% CI 0.46 to 5.41*	blinding were not reported
First author, year: Bernasko 2006[147] Country: USA Study design: Retrospective observational study	Population: N = 95 women who had 13-week triplet pregnancies cared for at North Shore University Hospital at Manhasset 55 women were attended by non-full-time faculty members Maternal Fetal	Investigation: Prophylactic cervical cerclage Comparison: No prophylactic cerclage Methods described adequately? Yes Cervical cerclage (McDonald	Preterm birth <32 weeks: Prophylactic cerclage group: 11/55 (20%) No cerclage group: 9/40 (22.5%) Odds ratio = 0.86, 95% CI 0.32 to 2.33* Preterm birth <28 weeks: Prophylactic cerclage group: 1/55 (1.8%) No cerclage group: 0/40 (0%) Odds ratio = 2.23, 95% CI 0.09 to 56.15*	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Retrospective and observational study All pregnancies resulted from

Study details	Participants	Investigation	Outcome measures and results	Comments
Study dates: July 1999 - December 2003 Aim of study: To determine whether routine prophylactic cervical cerclage was associated with prolongation of pregnancy in women with triplet pregnancies	Medicine (MFM) and underwent prophylactic cerclage and 40 women were cared for by full-time faculty members who did not perform routine prophylactic cerclage Inclusion criteria: Medical records of all women with triplet pregnancies beyond 13 weeks during the study period were scrutinised and included Exclusion criteria: No details reported Other details: All except 2 women were Caucasian No details of chorionicity reported	type, under regional anaesthesia, using 5 mm Mersilene tape or suture) was placed between 11 and 14 weeks and removed after 37 weeks or when miscarriage, premature contractions or premature rupture of membranes occurred Details of equipment and technique were reported	Gestational age at delivery in weeks (SD): Prophylactic cerclage group: 33.6 (2.4) No cerclage group: 33.7 (2.3) p= 0.96 (Mann-Whitney test) Low birthweight (<1500g) of one or more neonates: Prophylactic cerclage group: 23/55 (41.8%) No cerclage group: 13/40 (32.5%) Odds ratio = 1.49, 95% CI 0.64 to 3.50* Low birthweight (<1000g) of one or more neonates: Prophylactic cerclage group: 5/55 (9.1%) No cerclage group: 1/40 (2.5%) Odds ratio = 3.9, 95% CI 0.44 to 34.76*	assisted reproduction 13/55 (32.5%) women in the comparison group (no prophylactic cerclage) underwent emergency cerclage in accordance with the hospital protocol (i.e. <24 weeks' gestation, dilation of the internal os, funnelling of fetal membrane into the cervical canal, >2 cm closed cervical length distal to the funnel and absence of uterine contraction)
First author, year: Elimian 1999[145] Country: USA Study design: Retrospective chart review Study dates: January 1988 - June	Population: N = 59 women who had given birth to triplets during the study period at Westchester Medical Centre and booked for antenatal care before 15 weeks' gestation 20 women underwent prophylactic cerclage and 39 women who were managed	Investigation: Prophylactic cervical cerclage Comparison: No prophylactic cerclage Methods described adequately? Yes Cervical cerclage (McDonald type) was placed between 13 and 15 weeks	Preterm birth <32 weeks: Prophylactic cerclage group: 4/20 (20%)* No cerclage group: 18/39 (46%) * Odds ratio =0.29, 95% CI 0.08 to 1.03* Preterm birth <31 weeks: Prophylactic cerclage group: 2/20 (10%) No cerclage group: 15/39 (38%) Odds ratio =0.18, 95% CI 0.04 to 0.89* Gestational age at delivery in weeks (SD): Prophylactic cerclage group: 32.8 (2.4)	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Retrospective study. No randomisation, risk of selection bias

Study details	Participants	Investigation	Outcome measures and results	Comments
1997 Aim of study: To compare perinatal outcome in triplet pregnancies with and without prophylactic cerclage	conservatively served as a comparison group Inclusion criteria: Outpatient, inpatient and discharge notes of all women who had given birth to triplets, and their babies, were reviewed Exclusion criteria: No explicit exclusion criteria reported Other details: Trichorionicity: Prophylactic cerclage group: 14/20 (70%) No cerclage group: 28/39 (72%) p= 0.89 No details of ethnicity reported	Details of equipment and technique were reported	No cerclage group: 31.5 (3.6) p= 0.66 Neonatal mortality: Prophylactic cerclage group: 0/60 (0%) No cerclage group: 5/117 (4%) p=0.16 Low birthweight (<1500g): Prophylactic cerclage group: 16/60 (27%) No cerclage group: 47/117 (40%) Odds ratio = 0.54, 95% CI 0.27 to 1.07* Low birthweight (<1000g): Prophylactic cerclage group: 1/60 (1.7%) No cerclage group: 18/117 (15.4%) Odds ratio = 0.09, 95% CI 0.01 to 0.72* Respiratory distress syndrome: Prophylactic cerclage group: 11/60 (18%) No cerclage group: 32/117 (27%) Odds ratio = 0.60, 95% CI 0.23 to 1.29* Intraventricular haemorrhage or periventricular leucomalacia: Prophylactic cerclage group: 6/35 (17%) No cerclage group: 19/57 (32%) Odds ratio = 0.44, 95% CI 0.15 to 1.23*	

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Mordel 1993[148] Country: Israel Study design: Retrospective chart review Study dates: January 1978 - December 1987 Aim of study: To evaluate the effectiveness of elective cervical suture in prolonging triplet pregnancies	Population: N = 35 women who received antenatal care and gave birth to triplets during the study period at the study hospital 12 women underwent prophylactic cerclage arbitrarily and 23 women who were managed conservatively served as a comparison group Inclusion criteria: All information retrieved retrospectively from clinical records Exclusion criteria: No explicit exclusion criteria reported Other details: No details of ethnicity and chorionicity were reported	Investigation: Prophylactic cervical cerclage Comparison: No prophylactic cerclage Methods described adequately? Yes - the decision whether or not to place cerclage was taken arbitrarily by attending physicians Details of equipment and technique were not reported	Gestational age at delivery in weeks (SD): Prophylactic cerclage group: 33.0 (5.1) No cerclage group: 34.7 (2.8) p= 0.2093* (Student's t-test) Perinatal mortality: Prophylactic cerclage group: 3/36 (8.3%) No cerclage group: 6/69 (8.7%) Odds ratio = 0.95, 95% CI 0.22 to 4.06*	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Retrospective study Low quality evidence
First author, year: Rebarber 2005[146] Country: USA Study design: Retrospective observational study	Population: N = 3278 women from throughout the USA who met the inclusion criteria were identified from a large database of Matria Healthcare (a private healthcare firm providing maternity services) and their medical records were	Investigation: Prophylactic cervical cerclage Comparison: No prophylactic cerclage Methods described adequately? Yes Prophylactic cerclage was	Preterm birth <32 weeks: Prophylactic cerclage group: 68/248 (27.4%) No cerclage group: 833/3030 (27.5%) Odds ratio =1.00, 95% CI 0.75 to 1.33* Preterm birth <28 weeks: Prophylactic cerclage group: 10/248 (4.0%) No cerclage group: 136/3030 (4.5%) Odds ratio =0.89, 95% CI 0.46 to 1.72*	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Low quality evidence Retrospective observational

Study details	Participants	Investigation	Outcome measures and results	Comments
Study dates: January 1990 - May 2004 Aim of study: To determine whether prophylactic cerclage is associated with improvement in birth outcome in women with triplet pregnancies	reviewed 248 women received prophylactic cerclage and the remaining 3030 women were managed conservatively Inclusion criteria: Women with triplet pregnancies who enrolled for preterm labour surveillance before 32 weeks' gestation for a minimum of 1 day Exclusion criteria: Unavailability of outcome data, history of cervical insufficiency in the index pregnancy or a previous pregnancy Other details: No details of chorionicity reported	defined as cerclage placement in women without history of cervical insufficiency or evidence of cervical change in the index pregnancy for the sole indication of triplet pregnancy	Gestational age at delivery in weeks (SD): Prophylactic cerclage group: 33.1 (2.6) No cerclage group: 33.0 (2.5) p= 0.63 (Student's t test) Very low birthweight: Prophylactic cerclage group: 186/744 (25.0%) No cerclage group: 2315/9090 (25.5%) Odds ratio = 0.96, 95% CI 0.82 to 1.16* Neonatal intensive care unit admission: Prophylactic cerclage group: 594/737 (81.1%) No cerclage group: 7376/9028 (79.8%) Odds ratio = 0.93, 95% CI 0.77 to 1.13* Neonatal length of stay in days (SD): Prophylactic cerclage group: 21.1(19.9) No cerclage group: 22.7 (20.6) p= 0.24 (Student's t-test)	study Possibility of selection bias The groups were statistically significantly different in terms of history of previous preterm birth (5.6% in cerclage group versus 3.1% in comparison group, p=0.04) and history of smoking (0.8% in cerclage group versus 2.6% in comparison group, p=0.008) Mean gestational age at entry was 23-24 weeks; women with earlier pregnancy loss were not included
First author, year: Newman 2002[144] Country: USA Study design: Prospective cohort study Study dates:	Population: N = 33 women with twin pregnancy with a short cervix (≤ 25 mm) and at least 18 weeks' gestation who were cared for at the study centre (a specialised multifetal pregnancy clinic) 21 women opted for cerclage and 12 women were	Investigation: Prophylactic cervical cerclage Comparison: No prophylactic cerclage Methods described adequately? Yes Transvaginal sonographic measurement of cervical length	Preterm birth <34 weeks: Prophylactic cerclage group: 9/21(42.9%) No cerclage group: 6/12 (50%) Odds ratio =0.75, 95% CI 0.18 to 3.12* Gestational age at delivery in weeks (SD): Prophylactic cerclage group: 33.5 (3.6) No cerclage group: 32.8 (3.9) p= 0.6057* (Student's t-test) Very low birthweight <1500 g:	* Calculated by NCC-WCH technical team using data reported in the article Funding: Not reported Limitations: Low quality evidence Prospective cohort study Possibility of selection bias

Study details	Participants	Investigation	Outcome measures and results	Comments
July 1994 - March 2001 Aim of study: To determine the impact of cerclage placement on obstetric and neonatal outcomes in women with twin pregnancies and a short cervix (≤ 25 mm)	managed without cerclage Inclusion criteria: Women with twin pregnancies who had a short cervix (≤ 25 mm) after 18 weeks' gestation Exclusion criteria: Women who had cerclage placement because of uterine anomaly, or as an attempt at delayed interval birth Women with preterm rupture of membrane before 18 weeks or indicated birth before 34 weeks because of maternal or fetal complications Other details: Ethnicity: 44% were Black Chorionicity: 82% were dichorionic	was conducted at 18-26 weeks. If cervical length was ≤ 25 mm women were offered transvaginal cerclage placement (McDonald type under regional anaesthesia)	Prophylactic cerclage group: 9/42 (21.4%) No cerclage group: 7/24 (29.2%) Odds ratio = 0.66, 95% CI 0.21 to 2.09*	
First author, year: Gummerus, 1987[135] Country: Finland Study design: Prospective interventional study	Population: N=200 women with twin and triplet pregnancies admitted to hospital for bed rest at an average of about 31 weeks' gestation Inclusion criteria: All women diagnosed as having multiple pregnancies	Investigation : N=101 women received 4 mg of salbutamol orally 5 times a day in addition to inpatient bed rest Medication was discontinued at 37 completed weeks' gestation Comparison:	Preterm birth (before 37 weeks): Intervention group: 37/101 (36.6%) Control group: group: 37/99 (37.4%) Relative Risk (95% CI): 0.98 (0.68 to 1.41) Preterm birth (before 33 weeks): Intervention group: 10/101 (9.9%) Control group: group: 9/99 (9.1%) Relative Risk (95% CI): 1.09 (0.46 to 2.57) Perinatal Mortality: Intervention group: 9/101	* Calculated by NCC-WCH technical team using data reported in the article Funding: Paulo Foundation Limitations: External validity of the study results may be compromised

Study details	Participants	Investigation	Outcome measures and results	Comments
Study dates: 15 September, 1978 to 15 September 1985 Aim of study: To assess the effectiveness of hospital-administered prophylactic long-term oral betamimetics in improving the prognosis of newborn babies and preventing maternal complication during multiple pregnancy	at the outpatient maternity clinic of State Maternity Hospital, Helsinki during the study period Exclusion criteria: No details reported Other details: No data on ethnicity and chorionicity were reported	N=99 women in control group were treated with inpatient bed rest only (no placebo was given) Methods described adequately? No - details of randomisation method were not reported in sufficient detail in that women were assigned randomly to treatment groups by the midwife on duty using a 'list of numbers'	Control group: 11/99 Relative Risk (95% CI): 0.8 (0.34 to 1.88)* Low birthweight (<2500g) Intervention group: 88/204 (43.1%) Control group: group: 84/199 (42.2%) Relative Risk (95% CI): 1.03 (0.82 to 1.29) Very low birthweight (<1500 g) Intervention group: 10/204 (4.9%) Control group: group: 14/199 (7.0%) Relative Risk (95% CI): 0.70 (0.32 to 1.53) Neonatal respiratory problems: Intervention group: 2 Control group: 4 Relative Risk (95% CI): 0.49 (0.09 to 2.56)	because all participating women were admitted to hospital for bed rest Some women in both treatment groups (15 in the intervention group and 8 in the control group) received salbutamol infusion for treatment of premature uterine contractions No blinding
First author, year: Yamasmit, 2009[149] Country: One trial in each of the following countries: UK, Ireland, Sweden, South Africa and Zimbabwe Study design: Systematic review and meta-analysis (Cochrane review) Aim of study: To assess the effectiveness of prophylactic oral	Population: 5 trials (N=344 women) were included Inclusion criteria: Randomised controlled trials which compared oral betamimetics (any dosage regimen, any agent) to placebo or any other intervention aimed at decreasing preterm labour and preterm birth. All study participants were women with twin pregnancies with no signs of preterm labour and a gestational age of 20- 37 weeks	Investigation : Oral betamimetic drugs: Salbutamol 4 mg four times a day Fenoterol 5 mg once a day Isoxurpine 30 mg four times a day Ritodrine 10 mg every 6 hours Terbutaline 5 mg three times a day Comparison: Placebo None of the included studies reported the composition of the placebo Methods described adequately?	Preterm birth (before 37 weeks): No. of studies: 4 No. of participants: 276 Treatment group: 57/140 (40.7%) Placebo group: 65/136 (47.8%) RR (95%CI): 0.85 (0.65 to 1.10) Salbutamol Treatment group: 37/74 (50%) Placebo group: 43/70 (61%) RR: 0.81, 95% CI 0.61 to 1.09 Fenoterol Treatment group: 6/20 (30%) Placebo group: 2/19 (10.5%) RR: 2.85, 95% CI 0.65 to 12.42 Ritodrine Treatment group: 7/21 (33.3%)	Funding: Not reported Limitations: All trials except one (Mathews, 1967) reported that women with medical or obstetric complications were excluded The authors of the review reported the methods of randomisation and allocation concealment to be unclear for two trials. The other three trials were reported to have allocation of concealment, but further details were not provided in the review

Study details	Participants	Investigation	Outcome measures and results	Comments
betamimetics administered to women with twin pregnancies	Exclusion criteria: Quasi-experimental studies; trials including triplet and higher-order pregnancies; trials that had not used allocation concealment, blinding of intervention or outcome assessment, or where more than 20% loss to follow up was reported Other details: Details of chorionicity and ethnicity were not reported in the Cochrane review	Yes Relevant trials were identified in the Cochrane Pregnancy and Childbirth Group Trials Register, MEDLINE and EMBASE and reference lists from reviewed articles were examined for additional studies Identified trials were evaluated for inclusion and methodological quality Quality scores were assigned for: concealment of allocation; blinding of outcome assessment; and completeness of follow-up Details of quality scores reported	Placebo group: 10/22 (45.5%) RR:0.73, 95% CI 0.34 to 1.57 Terbutaline Treatment group: 7/25 (28%) Placebo group: 10/25 (40%) RR:0.70, 95% CI 0.65 to 1.10 Preterm birth (before 34 weeks): No. of studies: 1 (Salbutamol) No. of participants: 144 Treatment group: 4/74 (5.4%) Placebo group: 8/70 (11.4%) RR (95%CI): 0.47 (0.15 to 1.50) Perinatal mortality (assuming independence between twins): No. of studies: 3 No. of participants: 452 Treatment group: 9/230 (3.9%) Placebo group: 11/220 (5%) RR (95%CI): 0.80 (0.35 to 1.82) Salbutamol Treatment group: 5/148 (3.4%) Placebo group: 10/140 (7.1%) RR: 0.47, 95% CI 0.17 to 1.35 Isuxorpine Treatment group: 4/40 (10%) Placebo group: 0/38 (0%) RR: 8.56, 95% CI 0.48 to 153.83 Ritodrine Treatment group: 0/42 (0%)	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Placebo group: 1/44 (2.3%) RR: 0.35, 95% CI 0.01 to 8.33 <u>Low birthweight (<2500g) [assuming independence between twins]</u> No. of studies: 2 No. of participants: 366 Treatment group: 99/188 (52.7%) Placebo group: 85/178 (47.8%) RR (95% CI): 1.19 (0.77 to 1.85) Salbutamol Treatment group: 80/148 (54%) Placebo group: 74/140 (52.9%) RR: 1.02, 95% CI: 0.82 to 1.27 Isoxurpine Treatment group: 19/40 (47.5%) Placebo group: 11/38 (28.9%) RR: 1.64, 95% CI: 0.90 to 2.98 <u>Respiratory distress syndrome (assuming independence between twins):</u> No. of studies: 2 No. of participants: 388 Treatment group: 5/198 (2.5%) Placebo group: 17/190 (8.9%) RR (95% CI): 0.30 (0.12 to 0.77) Salbutamol Treatment group: 5/148 (3.4%) Placebo group: 13/140 (9.3%) RR: 0.36, 95% CI 0.13 to 0.99 Isoxurpine	

Study details	Participants	Investigation	Outcome measures and results	Comments
			Treatment group: 0/50 (0%) Placebo group: 4/50 (8%) RR:0.11, 95% CI 0.01 to 2.01	
First author, year: Combs 2010[140] Country: USA Study design: Multicentre, double blind RCT Study dates: November 2004 to June 2008 Aim of study: To investigate whether 17 alpha-hydroxyprogesterone caproate (17P) reduces neonatal morbidity by increasing gestational age at birth in triplet pregnancies	Population: 81 women with trichorionic-triamniotic triplet pregnancies (243 babies), recruited at 18 centres in the US, and randomly assigned in a 2:1 ratio, to weekly injections of 17P (n=56 women, 168 babies) or placebo (n=25 women, 75 babies). Power calculation given for number of babies Inclusion criteria: Women with trichorionic-triamniotic triplet pregnancies; gestational age of 16-23 weeks; no major fetal anomalies Exclusion criteria: Women <18 years of age; allergy to 17P or its oil vehicle; progesterone-derivative medication after 15 weeks' gestation; cervical cerclage for treatment of cervical change in current pregnancy; symptomatic uterine contractions or rupture of membranes; contraindication to interventions intended to	Investigation : Weekly intramuscular injections of 250 mg 17 alpha-hydroxyprogesterone caproate (17P) in 1 ml castor oil given until 34 weeks' gestation or birth, whichever occurred first Comparison: Identical-appearing placebo injections (1 ml castor oil) given weekly from time of randomisation until 34 weeks' gestation or birth, whichever occurred first Methods described adequately? Women were screened for eligibility at 15-23 weeks' gestation after a detailed second-trimester ultrasound examination had been carried out showing trichorionic-triamniotic triplet pregnancy with normal fluid volume and no major fetal anomalies Following informed consent, each eligible woman was offered preliminary enrolment which involved a trial	Spontaneous preterm birth (<32 weeks): 17P group: 17/56 (30%) Placebo group: 7/25 (28%) RR (95% CI): 1.1 (0.5 to 2.3)* Gestational age at birth (mean ± SD): 17P group: 31.9 ± 4.1 weeks Placebo group: 31.8 ± 2.9 weeks P = 0.36 Perinatal death: 17P group: 19/168 (11%) Placebo group: 2/75 (3%) Odds Ratio (95% CI): 4.7 (1.0 to 22.0) Caesarean section: 17P group: 52/56 (93%) Placebo group: 25/25 (100%) P >0.99 Respiratory distress syndrome: 17P group: 44/155 (28%) Placebo group: 28/75 (37%) OR (95% CI): 0.68 (0.3 to 1.6) Necrotising enterocolitis (stage 2 or 3): 17P group: 8/154 (5%) Placebo group: 3/75 (4%) OR (95% CI): 01.4 (0.2 to 7.6) Intraventricular haemorrhage (grade 3 or 4):	Funding: Center for Research and Education, Pediatrix Medical Group, Sunrise, Florida, USA Limitations: High caesarean section rates in intervention and control groups Relatively small sample size in terms of number of women High proportion of pregnancies resulting from assisted reproduction techniques; typical IVF protocols included use of 17P or other progestins in the first trimester and use of these progestins in the placebo group may have had some beneficial effect that obscured any effects of the 17P that was given in the second and third trimesters in the investigation group

Study details	Participants	Investigation	Outcome measures and results	Comments
	prolong the pregnancy (including amnionitis, pre-eclampsia, severe growth delay, or imminent fetal death); pre-existing medical conditions that might be worsened by progesterone (including asthma requiring medication, impaired liver function, renal insufficiency, seizure disorders, ischaemic heart disease, active cholecystitis, or history of breast cancer, thromboembolism, or depression requiring hospitalisation); pre-existing medical conditions carrying a high risk of preterm delivery (including refractory hypertension, diabetes with retinopathy or nephropathy, active lupus) Other details: Women were drawn primarily from private practice settings; most pregnancies resulted from assisted reproduction techniques Ethnicity: 17P group: White: 39/56 (70%) Hispanic: 10/56 (18%) Asian/Pacific Islander: 5/56 (9%)	intramuscular injection (1 ml castor oil) with the woman asked to return for an enrolment-completion visit a week later Returning women were randomly assigned to receive either 17P or placebo, with the first dose of medication given at the same visit Randomisation, using a computer-generated scheme, was conducted at 16 weeks or later, but before 24 weeks The randomisation scheme required two women to be assigned to 17P for every one woman assigned to placebo, with stratification to ensure that each centre would have a similar ratio After delivery, maternal and newborn data were extracted from medical records and entered into a secure online database by study personnel who remained blinded to each subject's group assignment Intention-to-treat analysis was used	17P group: 4/150 (3%) Placebo group: 3/75 (4%) OR (95% CI): 0.7 (0.1 to 3.4) Neonatal total length of stay (mean ± SD): 17P group: 26.6 ± 26.4 days Placebo group: 37.6 ± 35.6 days P = 0.09 * *Calculated by NCC-WCH technical team using data reported in the article*	

Study details	Participants	Investigation	Outcome measures and results	Comments
	African American: 2/56 (4%) Placebo group: White: 17/25 (68%) Hispanic: 7/25 (28%) Asian/Pacific Islander: 0 African American: 1/25 (4%)			

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?

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: Al-Yatama 2001[154] Country: Kuwait Study design: Prospective cohort Study dates: October 1, 1997 - March 30, 1999 Aim of study: To evaluate the effects of routine antenatal corticosteroid treatment in multiple pregnancy on the reduction in respiratory distress syndrome (RDS)	Population: N = 44 twin pregnancies 22 women received routine corticosteroids while the other 22 did not Chorionicity not reported Inclusion criteria: Women with twins, triplets and quadruplets* attending routine antenatal care during the study period at Maternity Hospital, Kuwait; informed consent obtained from the women Women who were admitted on an emergency basis with uterine contractions, ruptured membranes or vaginal bleeding at 24-34 weeks comprised a separate group (not relevant for this guideline) Exclusion criteria: Women on long term corticosteroid therapy Other details: Details of ethnicity and chorionicity not reported	Investigation: Dexamethasone treatment (12 mg every 12 hours for 24 hours) Route of administration not reported Comparison: Control (no dexamethasone) Methods described adequately? Yes Women were followed up in the authors' routine antenatal clinics (those admitted on an emergency basis were followed up on the ward). The intervention and control groups were followed up throughout pregnancy and delivery and their outcomes were documented immediately. Admission to a Special Care Baby Unit (SCBU) or Neonatal Intensive Care Unit (NICU) and duration of stay as well as perinatal mortality and incidence of neonatal	Incidence of RDS among twins of women who had routine antenatal corticosteroid treatment: ▪ Incidence of RDS Dexamethasone = 20/44 (45.5%) No dexamethasone = 30/44 (68.2%) P < 0.015 OR 0.39; 95% CI 0.16 to 0.93** ✓ Mild RDS Dexamethasone = 11/44 (25.0%) No dexamethasone = 12/44 (27.2%) P = not significant OR 0.89; 95% CI 0.34 to 2.30** ✓ Moderate or severe RDS Dexamethasone = 9/44 (20.5%) No dexamethasone = 18/44 (40.9%) P < 0.018 OR 0.37; 95% CI 0.14 to 0.96** Length of hospital stay among twins of women who had routine antenatal corticosteroid treatment: ▪ Median length of NICU stay (days) Dexamethasone = 3.5 No dexamethasone = 6.0 P = not significant Birthweight (g) in twins by gestational age: 24 to 27 weeks:	Funding: Kuwait Foundation for Advancement of Science Limitations: Main limitations are the non-randomised study design and a small sample size. In addition, no details of the control group other than that they did not receive dexamethasone were reported. RDS rates in treatment and control groups seem very high for 'routine' corticosteroid use, which may be due to a high preterm delivery rate (particularly as no data provided for gestations post 34 weeks) Gestational age at which dexamethasone treatment started was not reported but assumed to be before 24 weeks Birth weight differences

Study details	Participants	Investigation	Outcome measures and results	Comments
	Mean maternal age: 29 years in study group, 28 years in control group (difference not significant) Mean gestational age: 32.3 in study group, 31.9 in control group (difference not significant)	morbidity (RDS) were also documented	Dexamethasone= 725 ±35.36 No dexamethasone= 715±92 P= not significant 28 to 32 weeks: Dexamethasone= 1201 ±412 No dexamethasone= 1569 ±142 P <0.0001 33 to 34 weeks: Dexamethasone= 2054 ±517 No dexamethasone= 2043 ±367 P= not significant Birthweight (g) in triplets by gestational age: 24 to 27 weeks: Dexamethasone= 798 ±215 No dexamethasone= 878 ±26 P < 0.016 28 to 32 weeks: Dexamethasone= 1379 ±216 No dexamethasone= 1522 ±376 P < 0.031 33 to 34 weeks: Dexamethasone= 1696 ±515 No dexamethasone= 1469 ±271 P <0.011 ** Calculated by NCC technical team	may be due to steroid exposure Mild RDS defined as clinical signs of RDS, but not requiring ventilation Moderate RDS defined as clinical signs of RDS requiring ventilation and a single dose of surfactant Severe RDS defined as clinical signs of RDS requiring ventilation and two or more doses of surfactant *Study included triplet pregnancies but results for this group were not reported separately (results were reported for triplet and quadruplet pregnancies combined)

Study details	Participants	Investigation	Outcome measures and results	Comments
First author, year: D'Amore 2004[153] Country: UK Study design: Retrospective case note review Study dates: January 1 1986 – December 31, 1999 Aim of study: To review the outcome of triplet pregnancies and to determine the effect of different routine antenatal corticosteroid treatment regimens on fetal growth, survival, and neurodevelopmental outcome	Population: N = 173 live births (from 60 triplet pregnancies; selective fetal reduction in 3 pregnancies and 3 intrauterine deaths) Chorionicity not reported Inclusion criteria: Triplet pregnancies resulting in live births between January 1986 and December 1999 identified from the neonatal and obstetric database of The Rosie Maternity Hospital, Cambridge Exclusion criteria: Quadruplet and higher-order pregnancies and spontaneous fetal loss at less than 24 weeks' gestation Other details: Ethnicity was not considered in the study because it was not recorded systematically throughout the study. The study was carried out in East Anglia which has a predominantly Caucasian population Details of chorionicity not reported	Investigation: Complete course of corticosteroids (betamethasone or dexamethasone, n for each not reported) administered between 24 weeks and 32 weeks (or delivery if this occurred before 32 weeks) ▪ Single course (n= 15 babies) ▪ Multiple courses (n= 76 babies) Maximum number of doses = 8 Route of administration not reported Comparison: No corticosteroids or corticosteroids taken less than 24 hours before delivery (n= 82 babies) Methods described adequately? Yes Logistic regression was used to examine the effect of antenatal corticosteroids on survival (adjusting for gestational age at delivery, birthweight, use of surfactant	Survival [number of babies (%)]: No corticosteroids or corticosteroids taken less than 24 hours before delivery = 67/82 (81.7 %) Single course of corticosteroids = 15/15 (100%) Multiple courses of corticosteroids = 74/76 (97.4 %) The NCC technical team used survival data to calculate perinatal mortality, OR 0.10, 95% CI 0.02 to 0.45 for no corticosteroids versus single course; OR 0.12, 95% CI 0.03 to 0.55 for no corticosteroids versus multiple courses Logistic regression modelling resulted in gestational age as the only statistically significant predictor of survival (P-value not reported) Corticosteroid use, birth weight, administration of surfactant and time period of birth did not significantly affect survival (P > 0.14). A 1-week difference in gestational age at birth was associated with a two-fold better chance of survival (OR 2.2, 95% CI 1.5 to 3.2, P <0.0001) Comparing the corticosteroid group (single and multiple courses combined) with no corticosteroids or corticosteroids taken less than 24 hours before delivery (OR 3.4, 95% CI 0.8 to 14.2, P = 0.1) Comparing multiple courses of corticosteroids with no corticosteroids or corticosteroids taken less than 24 hours before delivery (OR 2.9, 95% CI 0.7 to 2.1, P = 0.15) Incidence of intraventricular haemorrhage [number of babies (%)]: Total = 11 babies No corticosteroids or corticosteroids taken less than 24 hours before delivery = 10/82 (12.2%) Single course of corticosteroids = 0/15 (0%)	Funding: No details reported Limitations: Main limitations are the non-randomised study design and a small sample size Definition of 'survival' not reported clearly Due to the retrospective design of the study, it is unclear whether the steroids were given routinely or were targeted. In addition to this, those that received full/multiple courses delivered later, which may explain the better outcomes

Study details	Participants	Investigation	Outcome measures and results	Comments
		and time period of birth (expressed as 5-year intervals)	Multiple courses of corticosteroids = 1/76 (1.3%) Incidence of adverse neurodevelopmental outcomes at age 1 year [number of babies (%)]: Total = 5 babies No corticosteroids or corticosteroids taken less than 24 hours before delivery = 4/82 (4.9%) Single course of corticosteroids = 0/15 (0%) Multiple courses of corticosteroids = 1/76 (1.3%)	
First author, year: Murphy 2002[156] Country: UK Study design: Retrospective cohort Study dates: January 1990 – January 1997 Aim of study: To compare the neonatal outcomes of two approaches to antenatal corticosteroid therapy for threatened preterm delivery in twins: a prophylactic approach in which corticosteroids were administered every 2 weeks from 24 to 32 weeks' gestation and a rescue approach in	Population: N = 1038 twin babies 136 babies were exposed to prophylactic therapy and 902 babies were treated expectantly with rescue therapy 10 twin pregnancies in the investigation group and 127 twin pregnancies in the comparison group were monochorionic Inclusion criteria: All twin pregnancies booked at St. Michael's Hospital, Bristol, and delivered at ≥ 24 weeks' gestation during the study period were identified from computerised records and included in the study Exclusion criteria: Unavailability of clinical notes Other details:	Investigation: Prophylactic corticosteroid treatment: 2 doses of dexamethasone within 24 hours every 2 weeks from 24 to 32 weeks or until delivery (whichever was sooner) Route of administration not reported Comparison: Rescue corticosteroid therapy: 2 doses of 12 mg of dexamethasone 12 hours apart when there was immediate risk of either preterm labour or elective preterm delivery Methods described adequately? Yes The clinical notes, computer records, and drug charts of both mothers and babies were examined independently with	Perinatal death: Prophylactic corticosteroid treatment: 2/136 (1.5%) Rescue corticosteroid therapy: 30/902(3.3%) Unadjusted OR 0.44, 95% CI 0.10 to 1.84 Adjusted OR 0.39, 95% CI 0.08 to 1.76 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 0.76, 95% CI 0.07 to 7.82 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Respiratory distress syndrome (RDS): Prophylactic corticosteroid treatment: 17/136 (13%) Rescue corticosteroid therapy: 96/902 (11%) Unadjusted OR 1.18, 95% CI 0.68 to 2.04 Adjusted OR 0.69, 95% CI 0.33 to 1.46 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 0.62, 95% CI 0.21 to 1.85 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) RDS in preterm babies: RDS <34 weeks: Prophylactic corticosteroid treatment: 16/32 (50%)	Funding: Not reported Limitations: Non-randomised study 86% in rescue therapy group did not receive any corticosteroid Women in prophylactic group were more likely to have assisted conception (66% compared to 9% in rescue group, RR 7.46, 95% CI 5.30 to 10.5, p<0.05) Women in rescue therapy group were more likely to be smokers, have monochorionic placentae, and undergo labour and vaginal birth Due to the retrospective design of the study, those that received full/multiple courses delivered later, which may explain the better

Study details	Participants	Investigation	Outcome measures and results	Comments
which corticosteroids were given to women at immediate risk of preterm birth	Details of ethnicity not reported 15% (10 sets of twins) in the prophylactic group and 28% (127 sets of twins) in the rescue therapy group were monochorionic	the researcher blind to corticosteroid exposure when neonatal data were being recorded. A detailed data set was completed by recording information on maternal demographics, pre-existing maternal disease, obstetric history, and antenatal, intrapartum, and neonatal complications. The use of corticosteroids was recorded in terms of number of doses administered, timing of administration, and indication. A course was considered optimal when > 24 hours had elapsed between administration of the first dose and delivery	Rescue corticosteroid therapy: 87/148 (59%) Unadjusted OR 0.70, 95% CI 0.33 to 1.50 Adjusted OR 0.62, 95% CI 0.27 to 1.42 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 0.68, 95% CI 0.21 to 2.21 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) <u>RDS <37 weeks:</u> Prophylactic corticosteroid treatment: 17/84 (20%) Rescue corticosteroid therapy: 95/374 (25%) Unadjusted OR 0.75, 95% CI 0.42 to 1.30 Adjusted OR 0.70, 95% CI 0.34 to 1.42 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 0.74, 95% CI 0.41 to 1.34 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) <u>Intraventricular haemorrhage:</u> Prophylactic corticosteroid treatment: 1/136 (0.7%) Rescue corticosteroid therapy: 7/902 (0.8%) Unadjusted OR 0.95, 95% CI 0.12 to 7.76 Adjusted OR 0.86, 95% CI 0.10 to 7.14 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 1.03, 95% CI 0.12 to 8.53 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) <u>Necrotising enterocolitis:</u> Prophylactic corticosteroid treatment: 2/136 (1.5%)	outcomes (for example, birthweight)

Study details	Participants	Investigation	Outcome measures and results	Comments
			Rescue corticosteroid therapy: 2/902 (0.2%) Unadjusted OR 6.71, 95% CI 0.94 to 48.1 Adjusted OR 13.44, 95% CI 0.26 to 143.8 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 8.61, 95% CI 1.14 to 64.92 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) <u>Admission to special care baby unit (SCBU):</u> Prophylactic corticosteroid treatment: 52/136 (38%) Rescue corticosteroid therapy: 249/902 (28%) Unadjusted OR 1.62, 95% CI 1.12 to 2.36 Adjusted OR 1.01, 95% CI 0.61 to 1.69 (adjusted for gestational age, birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) Adjusted OR 1.25, 95% CI 0.56 to 2.76 (adjusted for birthweight, sex, labour, vaginal delivery, infertility, smoker, chorionicity, and twin pairing) <u>Duration of SCBU admission:</u> Adjusted mean difference -1.5 days, 95% CI -5.3 to 2.4 (adjusted for gestational age, gender, parity, infertility, smoking, chorionicity and twin pairing using linear regression) <u>Birthweight:</u> Term babies (>37 weeks), adjusted mean difference -129 g, 95% CI -218 to -33, p=0.008 (adjusted for gestational age, gender, parity, infertility, smoking, chorionicity and twin pairing using linear regression) Preterm babies, adjusted mean difference -6.6 g, 95% CI -87 to 74, p=0.87 (adjusted for gestational age, gender, parity, infertility, smoking, chorionicity	

Study details	Participants	Investigation	Outcome measures and results	Comments
			and twin pairing using linear regression)	
First author, year: Murphy 2008[155] Country: International study involving 80 centres in 20 countries: Argentina, Bolivia, Brazil, Canada, Chile, China, Colombia, Denmark, Germany, Hungary, Israel, Jordan, Peru, Poland, Russia, Spain, Switzerland, Netherlands, United Kingdom and the USA Study design: Randomised controlled trial (multicentre, double-blind) Study dates: Aim of study: To find out whether multiple courses of antenatal corticosteroids would reduce neonatal mortality and morbidity without adversely affecting fetal growth	Population: N = 390 out of the 1858 pregnant women in this study were having twins (n=320) or triplets (n=70). The data reported separately for this subgroup are presented here Chorionicity not reported Inclusion criteria: Women at 25-32 weeks' gestation who had not delivered 14-21 days after an initial course of antenatal corticosteroids and continued to be at high risk of preterm birth were randomly assigned to the intervention group (N=198; 162 women with twins and 36 women with triplets) or a control (placebo) group (N=192; 158 women with twins and 34 women with triplets) Exclusion criteria: Women were not included in the study if they had contraindications to corticosteroids, needed chronic doses of these drugs, had evidence of chorioamnionitis, had a fetus with a lethal congenital	Investigation: Women in this group received 2 doses of 12 mg betamethasone (a combination of 6 mg betamethasone sodium phosphate and 6 mg betamethasone sodium acetate) intramuscularly 12 hours apart every 2 weeks until week 33 or delivery Comparison: Women in the comparison group received similarly appearing intramuscular injections containing a dilute concentration of aluminium monostearate (a pharmacologically inert substance working as placebo) Methods described adequately? Yes Randomisation was conducted using a 24-hour telephone service after eligibility and baseline information were recorded. A study number was assigned, corresponding to a box at the study centre	Composite primary outcome: (one or more of: neonatal mortality, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage grade 3 or 4, cystic periventricular leucomalacia, and necrotising enterocolitis) In multiple births: Antenatal corticosteroid group: 62/427 (15%) Placebo: 60/414 (15%) Calculated by NCC technical team: OR 1.00 (95% CI 0.68 to 1.47)	Funding: Canadian Institute of Health Research Limitations: Only the composite primary outcome was reported separately for multiple births There is a discrepancy in the reported numbers of participants with multiple pregnancies. In table 1 (page 2144) it is reported to be 390 (198 in intervention group and 192 in control group); later in the same table (page 2145) it is reported to be 370 (191 in intervention group and 179 in control group)

Study details	Participants	Investigation	Outcome measures and results	Comments
	abnormality, had an initial course of corticosteroids before 23 weeks' gestation, or previously participated in the same study (multiple courses of antenatal corticosteroids for preterm birth; MACS) Other details: Details of ethnicity and chorionicity not reported			

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

Review question

What are the clinical indications for referral to subspecialist services?

Study details	Participants	Intervention	Outcome measures and results	Comments
First author, year: Minakami, 1998[161] Country: Japan Study design: Retrospective observational study Study dates: January 1990 to December 2006 Settings: Jichi Medical School Hospital, a tertiary care hospital Aim of study: To determine whether neonatal outcomes of women who were referred to a tertiary care hospital are worse than those of women who receive care in the same hospital throughout pregnancy	Population: N= 269 women with twin pregnancies who gave birth at the study centre during study period 197/269 (73%) were dichorionic, 62/269 (23%) were monochorionic and chorionicity was unspecified in the rest 10/269 (4%) Inclusion criteria : All twins births > 24 weeks of gestation at Jichi Medical School Hospital during the study period Exclusion criteria: Not reported	Intervention: N=32 women referred to the tertiary care centre after 20 weeks' gestation (late referral group) 15/32 (47%) were dichorionic, 15/32 (47%) were monochorionic (all diamniotic) and 2/32 (6%) were with unspecified chorionicity Indications for referral: Premature labour: 21/32 Premature rupture of membranes: 4/32 Intertwin discordance of fetal weight: 3/32 Pre-eclampsia: 2/32 Other: 2/32 Mean gestational age at referral: 29.9 ± 3.7 weeks (range 21 to 38 weeks) Comparison: N=237 monitored at antenatal care clinic of the same hospital since <20 weeks' of gestation 182/237 (77%) were dichorionic, 47/237 (20%) were	Fetal/neonatal outcomes Birthweight in g (SD): Larger twins: Late referral group (n=64): 1778 (611) Comparison group (n=474): 2278 (443) p<0.001 Monochorionic twins: Late referral group (n=30): 1580 (570) Comparison group (n=94): 2158 (501) p value not reported p<0.05 monchorionic twins in late referral group versus dichorionic twins in comparison group Dichorionic twins: Late referral group (n=30): 1922 (598) Comparison group (n=364): 2302 (409) p value not reported Smaller twins: Late referral group (n=64): 1504 (628) Comparison group (n=474): 2003 (433) p<0.001 Monochorionic twins: Late referral group (n=30): 1304 (671) Comparison group (n=94): 1869 (495) p value not reported	Funding: Not reported Limitations: Only 3/32 women in late referral group had intertwin discordance and results of this subgroup were not reported separately There were no woman with other conditions specified in the review question (single fetal death, discordant anomaly and triplets) Comparison group was women already in tertiary care and this is not relevant when examining the effectiveness of referral

Study details	Participants	Intervention	Outcome measures and results	Comments
		monochorionic (all diamniotic) and 8/237 (3.4%) were with unspecified chorionicity Methods: Data were analysed using Student's t-test or the chi-square test with Yates' correction and Miettinen's method was used to to determine 95% CIs	p<0.05 monochorionic twins in late referral group versus dichorionic twin in comparison group Dichorionic twins: Late referral group (n=30): 1632 (530) Comparison group (n=364): 2030 (401) p value not reported Endotracheal intubation: Late referral group (n=64): 23 (36%) Comparison group (n=474): 50 (11%) p<0.001 Monochorionic twins: Late referral group (n=30): 15 (50%) Comparison group (n=94): 20 (21%) p value not reported p<0.01monochorionic twins in comparison group versus dichorionic twins in comparison group Dichorionic twins: Late referral group (n=30): 8 (27%) Comparison group (n=364): 30 (8.2%) p value not reported Infant mortality (before 1 year of age): Late referral group (n=64): 6 (9.4%) Comparison group (n=474): 11 (2.3%) p<0.01 Monochorionic twins: Late referral group (n=30): 5 (17%) Comparison group (n=94): 4 (4.3%)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			p value not reported Dichorionic twins: Late referral group (n=30): 1 (3.3%) Comparison group (n=364): 7 (1.9%) p value not reported Number of babies with disabilities* at 1 year of age: Late referral group (n=64): 10 (16%) Comparison group (n=474): 13 (2.7%) p<0.001 Monochorionic twins: Late referral group (n=30): 9 (30%) Comparison group (n=94): 7 (7.4%) p value not reported p<0.05 monochorionic twins in late referral group versus dichorionic twins p<0.01 monochorionic twins in comparison group versus dichorionic twins in the same group Dichorionic twins: Late referral group (n=30): 1 (3.3%) Comparison group (n=364): 6 (1.6%) p value not reported *Disability included cerebral palsy, epilepsy, deafness, blindness and mental retardation; diagnosis of mental retardation was based on K-shiki or Tanaka-Binet development tests	
First author, year: Papiernik, 2000[162]	Population: N=783 twin pregnancies (1566 babies)	Intervention: Referred group: N=54 women with twin	Fetal Deaths: Referred group: 13/108 (12%) Transferred group: 11/238 (5%)	Funding: Not reported

Study details	Participants	Intervention	Outcome measures and results	Comments
Country: France Study design: Retrospective observational study Study dates: 1 January 1993 to 31 December 1998 Settings: Port Royal Hospital Paris (a tertiary care hospital) Aim of study: To estimate the incidence of fetal death in twin pregnancies managed at a tertiary care hospital since the beginning of pregnancy and compare it to twin pregnancies referred to the hospital for complications	Inclusion criteria : All women with twin pregnancies who had given birth at the study centre during the study period Exclusion criteria: Not reported	pregnancy who were referred to the study centre for specific advice (mostly because of malformation, chromosomal abnormality or FFTS) and followed after that Transferred group: N=119 women who were transferred to the study centre from another institution where they had been admitted for a severe complication (most often because of early preterm labour or gestational hypertension) Comparison: Early-followed group: N=610 women who received antenatal care from early pregnancy (>20 weeks' gestation) at the outpatient clinic of the study centre	Early-followed group: 9/1220 (1%)	Comparison group was women already in tertiary care and this is not relevant when examining the effectiveness of referral No statistical analysis was reported

Chapter 10 Timing of birth

Review question

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

Study details	Participants	Intervention	Outcome measures and results	Comments
Gestational age profile in spontaneous labour and delivery in uncomplicated twin pregnancies				
First author, year: Roberts, 2002[163] Country: Australia Study design: Retrospective observational study (cross-sectional) Study dates: January 1,1990-December 31,1999 Setting: New South Wales Aim of study: To examine trends in gestational age at birth and mode of delivery	Population: All twin births in New South Wales (NSW) during the study period Inclusion criteria : All twin births > 20 weeks of gestation or > 400 g birthweight Exclusion criteria: Not reported Other details: No details on ethnicity or chorionicity reported	Study group: Data on gestational age at birth were presented for three groups: spontaneous labour; induction of labour; and caesarean section before labour Spontaneous labour data have been extracted for the guideline review Comparison group: Not applicable (NA) Methods: The data were obtained from computerised birth files of the NSW Midwives Data Collection	Spontaneous labour and birth (denominator is total number of spontaneous births in twin pregnancies in the relevant period) 1990-91 <32 weeks: 159/1123 (14.2%) 32-34 weeks: 170/1123 (15.1%) 35-36 weeks: 288/1123 (25.6%) ≥ 37 weeks: 506/1123 (45.1%) 1992-93 <32 weeks: 173/1218 (14.2%) 32-34 weeks: 190/1218 (15.6%) 35-36 weeks: 315/1218 (25.9%) ≥ 37 weeks: 540/1218 (44.3%) 1994-95 <32 weeks: 167/1226 (13.6%) 32-34 weeks: 198/1226 (16.2%) 35-36 weeks: 312/1226 (25.4%) ≥ 37 weeks: 549/1226 (44.8%) 1996-97 <32 weeks: 155/1143 (13.6%) 32-34 weeks: 225/1143 (19.7%) 35-36 weeks: 314/1143 (27.5%) ≥ 37 weeks: 449/1143 (39.3%)	Funding: Not reported

Study details	Participants	Intervention	Outcome measures and results	Comments
			1998-99 <32 weeks: 168/1220 (13.8%) 32-34 weeks: 241/1220 (19.8%) 35-36 weeks: 354/1220 (29.0%) ≥ 37 weeks: 457/1220 (37.5%) Total 1990-99: <32 weeks: 822/5930 (13.9%) 32-34 weeks: 1024/5930 (17.3%) 35-36 weeks: 1583/5930 (26.7%) ≥ 37 weeks: 2501/5930 (42.2%)	
Baby outcome by gestational age – 'multifetal' versus singletons (large studies)				
First author, year: Minakami, 1996[164] Country: Japan Study design: Retrospective observational study Study dates: 1989-1993 Setting: Whole country Aim of study: To identify the optimal timing of birth for multiple pregnancies	Population: All babies born at ≥ 26 weeks during the study period in Japan Inclusion criteria : As above Exclusion criteria: Unspecified gestational age at birth Other details: Ethnicity and chorionicity were not reported	Study group: Multifetal pregnancy group: N=88,936 babies Comparison group: Singleton pregnancy group: N=6,020,542 babies Methods: Data collected by the Japanese Ministry of Health and Welfare were examined Incidence of stillbirth and early neonatal birth were calculated for each gestational age Statistical analysis: Odds ratios were used to calculate the risk of perinatal death for babies of multifetal pregnancies compared with babies of singleton pregnancies	Fetal death rate per 1000 fetuses at risk: 26 weeks: Multifetal group: 166/421 (394 per 1000 live births)* Singleton group:1732/2335 (742 per 1000 live births)* 27 weeks: Multifetal group: 97/529 (183 per 1000 live births)* Singleton group:1564/2905 (538 per 1000 live births)* 28 weeks: Multifetal group: 115/679 (169 per 1000 live births)* Singleton group:1484/3654 (406 per 1000 live births)* 29 weeks: Multifetal group: 112/835 (134 per 1000 live births)*	Funding: Not reported The data did not include number of fetuses in multifetal pregnancies The authors estimated that 96% of babies born to multifetal pregnancy were from twin pregnancies Japan-wide data for 5 years but did not distinguish between complicated and uncomplicated twin pregnancies

Study details	Participants	Intervention	Outcome measures and results	Comments
			Singleton group:1331/4330 (307 per 1000 live births)* 30 weeks: Multifetal group: 111/1008 (110 per 1000 live births)* Singleton group:1446/5605 (258 per 1000 live births)* 31 weeks: Multifetal group: 122/1310 (93 per 1000 live births)* Singleton group:1334/6844 (196 per 1000 live births)* 32 weeks: Multifetal group: 120/1882 (64 per 1000 live births)* Singleton group:1313/9467 (139 per 1000 live births)* 33 weeks: Multifetal group: 126/2724 (46 per 1000 live births)* Singleton group:1374/13933 (99 per 1000 live births)* 34 weeks: Multifetal group: 120/41417 (29 per 1000 live births)* Singleton group:1431/23494 (61 per 1000 live births)* 35 weeks: Multifetal group: 159/6527 (24 per 1000 live	

Study details	Participants	Intervention	Outcome measures and results	Comments
			births)* Singleton group:1427/46658 (31 per 1000 live births)* <u>36 weeks:</u> Multifetal group: 182/12099 (15 per 1000 live births)* Singleton group:1580/119953 (31 per 1000 live births)* <u>37 weeks:</u> Multifetal group: 208/20272 (10 per 1000 live births)* Singleton group:1635/408726 (4 per 1000 live births)* <u>38 weeks:</u> Multifetal group: 150/17957 (8 per 1000 live births)* Singleton group:1670/1110685 (2 per 1000 live births)* <u>39 weeks:</u> Multifetal group: 105/10772 (10 per 1000 live births)* Singleton group:1709/1813951 (1 per 1000 live births)* <u>40 weeks:</u> Multifetal group: 65/4696 (14 per 1000 live births)* Singleton group:1612/1677499 (1 per 1000 live births)* <u>41 weeks:</u>	

Study details	Participants	Intervention	Outcome measures and results	Comments
			Multifetal group: 16/1002 (16 per 1000 live births)* Singleton group:775/648685 (1 per 1000 live births)* <u>>42 weeks:</u> Multifetal group: 3/109 (28 per 1000 live births)* Singleton group:285/96043 (3 per 1000 live births)* <u>Incidence of early neonatal death (<1 week of age):</u> <u>26 weeks:</u> Multifetal group: 97/421 (230 per 1000 live births)* Singleton group:348/2335 (149 per 1000 live births)* <u>27 weeks:</u> Multifetal group: 91/529 (172 per 1000 live births)* Singleton group:273/2905 (94 per 1000 live births)* <u>28 weeks:</u> Multifetal group: 73/679 (108 per 1000 live births)* Singleton group:253/3654 (58 per 1000 live births)* <u>29 weeks:</u> Multifetal group: 59/835 (71 per 1000 live births)*	

Study details	Participants	Intervention	Outcome measures and results	Comments
			Singleton group:251/4330 (58 per 1000 live births)* 30 weeks: Multifetal group: 44/1008 (44 per 1000 live births)* Singleton group:287/5605 (51 per 1000 live births)* 31 weeks: Multifetal group: 35/1310 (27 per 1000 live births)* Singleton group:299/6844 (44 per 1000 live births)* 32 weeks: Multifetal group: 33/1882 (18 per 1000 live births)* Singleton group:314/9467 (33 per 1000 live births)* 33 weeks: Multifetal group: 34/2724 (12 per 1000 live births)* Singleton group:356/13933 (26 per 1000 live births)* 34 weeks: Multifetal group: 31/41417 (8 per 1000 live births)* Singleton group:392/23494 (17 per 1000 live births)* 35 weeks: Multifetal group: 28/6527 (4 per 1000 live	

Study details	Participants	Intervention	Outcome measures and results	Comments
			births)* Singleton group:428/46658 (9 per 1000 live births)* <u>36 weeks:</u> Multifetal group: 41/12099 (3 per 1000 live births)* Singleton group: 589/119953 (5 per 1000 live births)* <u>37 weeks:</u> Multifetal group: 39/20272 (1.9 per 1000 live births)* Singleton group:718/408726 (1.8 per 1000 live births)* <u>38 weeks:</u> Multifetal group: 40/17957 (2.2 per 1000 live births)* Singleton group:922/1110685 (0.8 per 1000 live births)* <u>39 weeks:</u> Multifetal group: 28/10772 (3 per 1000 live births)* Singleton group:981/1813951 (0.5 per 1000 live births)* <u>40 weeks:</u> Multifetal group: 18/4696 (4 per 1000 live births)* Singleton group:1052/1677499 (0.6 per 1000 live births)* <u>41 weeks:</u>	

Study details	Participants	Intervention	Outcome measures and results	Comments
			Multifetal group: 6/1002 (6 per 1000 live births)* Singleton group:618/648685 (1 per 1000 live births)* >42 weeks: Multifetal group: 1/109 (9 per 1000 live births)* Singleton group:181/96043 (1.9 per 1000 live births)*	
First author, year: Sairam, 2002[165] Country: UK Study design: Retrospective observational study Study dates: 1989-1991 Setting: North-East Thames region of London Aim of study: To evaluate gestation-specific risk of fetal deaths in multiple pregnancies	Population: All women with multiple pregnancies who gave birth in one of 18 hospitals in North East Thames region of London from 1989 to 1991 Inclusion criteria : All records available via the Regional Interactive Child Health System Exclusion criteria: Records showing gestational age more than 45 weeks Other details: Ethnicity and chorionicity were not reported	Study group: Multiple pregnancy group: N=4154 available records of multiple pregnancies Comparison group: Singleton pregnancy group: Data on singleton pregnancies of same cohort published earlier Methods: Information on multiple births was obtained from a computerised database Records of fetal or neonatal death were linked to birth notification records in 96% of cases Statistical analysis: Risk of fetal death was calculated per 1000 fetuses at risk at the beginning of gestational age	Fetal death rate (per 1000 fetuses at risk at the beginning of gestational week): 28 weeks: 1/4070 (0.3 per 1000 fetuses at risk) 29 weeks: 0/4020 (0 per 1000 fetuses at risk) 30 weeks: 4/3974 (1.0 per 1000 fetuses at risk) 31 weeks: 10/3898 (2.6 per 1000 fetuses at risk) 32 weeks: 2/3793 (0.5 per 1000 fetuses at risk) 33 weeks: 1/3655 (0.3 per 1000 fetuses at risk) 34 weeks: 7/3493 (2.0 per 1000 fetuses at risk) 35 weeks: 6/3178 (1.9 per 1000 fetuses at risk) 36 weeks: 9/2847 (3.2 per 1000 fetuses at risk) 37 weeks: 9/2353 (3.8 per 11000 fetuses at risk) 38 weeks: 6/1527 (3.9 per 1000 fetuses at risk) 39+ weeks: 10/691 (14.5 per 1000 fetuses at	Funding: Supported by former North East Thames Regional health Authority, Review information Project Although available data included all multiple pregnancies, 99.8% of suchl pregnancies were twin pregnancies and so further analysis was performed assuming all multiple pregnancies were twin pregnancies

Study details	Participants	Intervention	Outcome measures and results	Comments
			risk)	
Neonatal morbidity in twins according to gestational age				
First author, year: Suzuki, 2010[172] Country: Japan Study design: Retrospective observational study Study dates: 2004-2008 Setting: Japanese Red Cross Katasushika Maternity Hospital Aim of study: To evaluate gestation-specific risk of neonatal morbidity in dichorionic twins versus singletons and define optimal timing of birth for dichorionic twins	Population: N=8269 dichorionic twins and singletons born at 34-40 weeks at the study centre during the study period Inclusion criteria : As above Exclusion criteria: Monochorionic twins Other details: Ethnicity was not reported	Study group: Dichorionic twins: N=578 dichorionic twins Comparison group: Singletons: N=7721 singletons Methods: Information was obtained from neonatal records	Neonatal morbidity (% of live born babies) according to gestational age: Transient tachypnoea of the newborn (TTN): 34 weeks; Dichorionic twins: 10/36 (28%) Singletons: 41/121 (34%) 35 weeks: Dichorionic twins: 9/64 (14%) Singletons: 35/120 (29%) 36 weeks: Dichorionic twins: 15/126 (12%) Singletons: 42/248 (17%) 37 weeks: Dichorionic twins: 11/210 (5.2%) Singletons: 59/893 (6.6%) 38 weeks: Dichorionic twins: 3/62 (4.8%) Singletons: 81/1696 (4.8%) 39 weeks: Dichorionic twins: 4/44 (9%) Singletons: 91 /2323 (3.9%) 40 weeks: Dichorionic twins: 0/6 (0%) Singletons: 67/2320 (2.9%)	Funding: Not reported Data on fetal death not extracted because of small sample size of the study and very low incidence (n=1) in dichorionic twins at 35 weeks

Study details	Participants	Intervention	Outcome measures and results	Comments
			Respiratory distress syndrome (RDS): 34 weeks; Dichorionic twins: 0/36 (0%) Singletons: 6/121 (5.0%) 35 weeks: Dichorionic twins: 1/64 (1.6%) Singletons: 3/120 (2.5%) 36 weeks: Dichorionic twins: 0 /126 (0%) Singletons: 2/248 (0.81%) 37 weeks: Dichorionic twins: 0/210 (0%) Singletons: 0/893 (0%) 38 weeks: Dichorionic twins: 3/62 (4.8%) Singletons: 0/1696 (0%) 39 weeks: Dichorionic twins: 4/44 (9.0%) Singletons: 0/2323 (0%) 40 weeks: Dichorionic twins: 0/6 (0%) Singletons: 0/2320 (0%) Intraventricular haemorrhage (IVH): 34 weeks; Dichorionic twins: 0/36 (0%)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			Singletons: 2/121 (1.7%) 35 weeks: Dichorionic twins: 0/64 (0%) Singletons: 0/120 (0%) 36 weeks: Dichorionic twins: 0 /126 (0%) Singletons: 0/248 (0%) 37 weeks: Dichorionic twins: 0/210 (0%) Singletons: 0/893 (0%) 38 weeks: Dichorionic twins: 0/62 (0%) Singletons: 0/1696 (0%) 39 weeks: Dichorionic twins: 0/44 (0%) Singletons: 0/2323 (0%) 40 weeks: Dichorionic twins: 0/6 (0%) Singletons: 0/2320 (0%)	
Baby outcome by gestational age – singletons versus twins versus triplets (large studies)				
First author, year: Alexander, 2005[159] Country: USA Study design: Population-based retrospective	Population: All live births and fetal deaths in the USA during the study period Inclusion criteria : Databases of US National Centre of Health Statistics, Linked Live Birth/Infant Death	Study group: Twin and triplet births in the USA during the study period Comparison group: Singleton births in the USA during the study period Methods:	Fetal Mortality Rate: < 28 weeks: Triplets: 107.5 per 1000 births Twins: 187.8 per 1000 births Singletons: 318.1 per 1000 births 28-32 weeks: Triplets: 11.9 per 1000 births	Funding: Not reported Number of fetal and neonatal deaths were not reported Fetal mortality rate is presented as rate per 1000 births and neonatal mortality rate is presented as rate per 1000 livebirths

Study details	Participants	Intervention	Outcome measures and results	Comments
observational study Study dates: 1995-1998 Setting: USA Aim of study: To describe perinatal mortality in US multiple births	Cohort Files, and Fetal Death files from the US Perinatal Mortality Data File and Matched Multiple Linked Files were analysed for relevant data Exclusion criteria: Not reported Other Details: Ethnicity and chorionicity not reported	Information was obtained from neonatal records	Twins: 25.0 per 1000 births Singletons: 62.3 per 1000 births 33-36 weeks: Triplets: 4.3 per 1000 births Twins: 5.6 per 1000 births Singletons: 10.6 per 1000 births 37-41 weeks: Triplets: 6.9 per 1000 births Twins: 2.8 per 1000 births Singletons: 1.4 per 1000 births ≥42 weeks: Triplets: Twins: 4.7 per 1000 births Singletons: 1.4 per 1000 births Neonatal Mortality rate: < 28 weeks: Triplets: 350.3 per 1000 live births Twins: 326.1 per 1000 live births Singletons: 254.0 per 1000 live births 28-32 weeks: Triplets: 13.4 per 1000 live births Twins: 26.5 per 1000 live births Singletons: 30.1 per 1000 live births 33-36 weeks: Triplets: 3.5 per 1000 live births Twins: 3.8 per 1000 live births Singletons: 5.0 per 1000 live births	

Study details	Participants	Intervention	Outcome measures and results	Comments
			37-41 weeks: Triplets: 2.1 per 1000 live births Twins: 1.9 per 1000 live births Singletons: 1.0 per 1000 live births ≥42 weeks: Triplets: 9.3 per 1000 live births Twins: 4.7 per 1000 live births Singletons: 1.4 per 1000 live births	
Baby outcome by gestational age – triplets (small studies)				
First Author, Year: Kaufman, 1998[174] Country: USA Study design: Hospital-based retrospective observational study Study dates: July 1992-December 1996 Setting: New England Medical Centre, Boston, Massachusetts Aim of study: To report neonatal outcomes of consecutive triplet pregnancies managed	Population: All women with triplet pregnancies who received antenatal care at the study centre throughout pregnancy or were transferred to the study centre during the antenatal period and gave birth there Inclusion criteria : Women with three live fetuses at more than 20 weeks' gestation Exclusion criteria: Termination of pregnancy or death of any fetus before 20 weeks' gestation and triplet pregnancies complicated by lethal congenital anomalies Other details: No details of chorionicity and ethnicity were reported	Study group: N=55 women with triplet pregnancies (165 triplets) Comparison group: All liveborn singleton and twin babies admitted at NICU after birth from 24-34 weeks' gestation during the study period, excluding babies with lethal congenital anomalies Methods: Triplet pregnancies were identified in a perinatal database of complicated pregnancies and an obstetric sonography database Antenatal, intrapartum and postnatal records, discharge summaries, ultrasound reports and neonatal records were reviewed for all included women and relevant information was extracted by	Neonatal outcomes according to gestational age at birth: Perinatal deaths: < 24 weeks: 12/12 (1000 per 1000 births) 24 weeks: 2/3 (667 per 1000 births) 25 weeks: 2/3 (667 per 1000 births) 26 weeks: 1/3 (333 per 1000 births) 27 weeks: 0/6 (0 per 1000 births) 28 weeks: 0/6 (0 per 1000 births) 29 weeks: 1/12 (83 per 1000 births) 30 weeks: 0/6 (0 per 1000 births) 31 weeks: 1/27 (37 per 1000 births) 32 weeks: 0/15 (0 per 1000 births) 33 weeks: 0/24 (0 per 1000 births) 34 weeks: 0/6 (0 per 1000 births) 35 weeks: 0/21 (0 per 1000 births) 36 weeks: 1/18 (55 per 1000 births) 37 weeks: 0/3 (0 per 1000 births) Neonatal deaths (calculated from reported data on neonatal survival): < 24 weeks: 0/0 (per 1000 live births) 24 weeks: 2/3 (667 per 1000 live births)	Funding: Not reported Maternal outcome not reported according to gestational age

Study details	Participants	Intervention	Outcome measures and results	Comments
at a single medical centre		two of the authors A similar protocol was followed for all triplet pregnancies at the study centre All triplet pregnancies were evaluated with serial ultrasound to detect growth discordance Antenatal corticosteroids were given only if there was a high risk of preterm birth Women who reached 37 weeks' gestation underwent elective caesarean section	25 weeks: 2/3 (667 per 1000 live births) 26 weeks: 0/2 (0 per 1000 live births) 27 weeks: 0/6 (0 per 1000 live births) 28 weeks: 0/6 (0 per 1000 live births) 29 weeks: 0/11 (0 per 1000 live births) 30 weeks: 0/11 (0 per 1000 live births) 31 weeks: 0/26 (0 per 1000 live births) 32 weeks: 0/15 (0 per 1000 live births) 33 weeks: 0/24 (0 per 1000 live births) 34 weeks: 0/6 (0 per 1000 live births) 35 weeks: 0/21 (0 per 1000 live births) 36 weeks: 0/17 (0 per 1000 live births) 37 weeks: 0/3 (0 per 1000 live births) <u>Fetal death rate per 1000 fetuses at risk (fetal deaths calculated by subtracting neonatal death from perinatal death):</u> < 24 weeks: 12/165 (72.7 per 1000 fetuses at risk) 24 weeks: 0/153 (0 per 1000 fetuses at risk) 25 weeks: 0/150 (0 per 1000 fetuses at risk) 26 weeks: 1/147 (6.8 per 1000 fetuses at risk) 27 weeks: 0/144 (0 per 1000 fetuses at risk) 28 weeks: 0/138 (0 per 1000 fetuses at risk) 29 weeks: 1/132 (7.5 per 1000 fetuses at risk) 30 weeks: 0/120 (0 per 1000 fetuses at risk) 31 weeks: 1/114 (8.8 per 1000 fetuses at risk) 32 weeks: 0/87 (0 per 1000 fetuses at risk) 33 weeks: 0/72 (0 per 1000 fetuses at risk) 34 weeks: 0/48 (0 per 1000 fetuses at risk) 35 weeks: 0/42 (0 per 1000 fetuses at risk) 36 weeks: 1/21 (47.1 per 1000 live births)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			37 weeks: 0/3 (0 per 1000 live births)	
First author, year: Daw, 1978[173] Country: UK Study design: Hospital-based retrospective observational study Study dates: 1958-1977 Setting: Not reported (author was based at North Manchester General Hospital, Crumpsall, Manchester) Aim of study: To analyse a series of 14 triplet pregnancies	Population: N=14 sets of triplets born between 1958 and 1977 Inclusion criteria : Not reported Exclusion criteria: Not reported Other details: No details of chorionicity and ethnicity were reported	Study group: N=14 set of triplets born between 1958 and 1977 Comparison group: No comparison group (birthweight compared with singleton birthweight percentile charts) Methods: Not reported	Fetal death rate per 1000 fetuses at risk: <32 weeks: 1/42 (23.8 per 1000 fetuses) 33 weeks: 0/39 (0 per 1000 fetuses) 34 weeks: 0/30 (0 per 1000 fetuses) 35 weeks: 0/18 (0 per 1000 fetuses) 36 weeks: 1/18 (55.6 per 1000 fetuses) 37 weeks: 2/25 (133.3 per 1000 fetuses) 38 weeks: 0/12 (0 per 1000 fetuses) 39 weeks: 1/6 (166.7 per 1000 fetuses)	Funding: Not reported Small sample size
Neonatal morbidity in triplets according to gestational age at birth				
First Author, Year: Devine, 2001[178] Country: USA Study design: Hospital-based retrospective	Population: All women with triplet pregnancies who received antenatal care at the study centre throughout pregnancy or who were transferred to the study centre during the antenatal period and gave birth there	Study group: N=100 women with triplet pregnancies (300 triplets) Comparison group: No comparison group Methods: All antenatal, intrapartum and	Neonatal complication according to gestational age at birth: Survival: 24 weeks: 1/3 (33%) 25 weeks: 3/6 (50%) 26 weeks: 5/5 (100%) 27 weeks: 6/6 (100%) 28 weeks: 11/11 (100%)	Funding: Not reported Maternal outcome not reported according to gestational age

Study details	Participants	Intervention	Outcome measures and results	Comments
observational study Study dates: January 1992-September 1999 Setting: New England Medical Centre, Boston, Massachusetts Aim of study: To report maternal and neonatal outcomes of 100 consecutive triplet pregnancies managed by one group of perinatologists and neonatologists at a single medical centre	Inclusion criteria : Women with three live fetuses at more than 20 weeks' gestation Exclusion criteria: Termination of pregnancy or death of any fetus before 20 weeks' gestation Other details: Mean maternal age: 33 (4.6) years No details of chorionicity or ethnicity reported	postnatal records, discharge summaries, ultrasound reports and neonatal records were reviewed for all included women Antenatal care was provided on an outpatient basis and hospital admission was reserved for clinical indications Prophylactic interventions, such as cervical cerclage, routine tocolytics, hospitalisation, or bed rest were not given routinely but offered only if there was a clinical indication Women who reached 37 weeks' gestation underwent elective caesarean section	29 weeks: 17/17 (100%) 30 weeks: 18/18 (100%) 31 weeks: 35/35 (100%) 32 weeks: 21/21 (100%) 33 weeks: 51/51 (100%) 34 weeks: 24/24 (100%) 35 weeks: 39/39 (100%) 36 weeks: 27/27 (100%) 36 weeks: 12/12 (100%) Respiratory distress syndrome (typical radiographic signs and requiring intubation and surfactant therapy): 24 weeks: 3/3 (100%) 25 weeks: 6/6 (100%) 26 weeks: 5/5 (100%) 27 weeks: 6/6 (100%) 28 weeks: 11/11 (100%) 29 weeks: 12/17 (71%) 30 weeks: 9/18 (50%) 31 weeks: 10/35 (29%) 32 weeks: 1/21 (5%) 33 weeks: 5/51 (10%) 34 weeks: 0/24 (0%) 35 weeks: 0/39 (0%) 36 weeks: 0/27 (0%) 36 weeks: 0/12 (0%) Chronic lung disease (oxygen therapy required past 36 weeks' corrected gestational age): 24 weeks: 3/3 (100%) 25 weeks: 6/6 (100%) 26 weeks: 3/5 (60%) 27 weeks: 0/6 (0%)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			28 weeks: 2/11 (20%) 29 weeks: 0/17 (0%) 30 weeks: 1/18 (6%) 31 weeks: 0/35 (0%) 32 weeks: 0/21 (0%) 33 weeks: 0/51 (0%) 34 weeks: 0/24 (0%) 35 weeks: 0/39 (0%) 36 weeks: 0/27 (0%) 36 weeks: 0/12 (0%) <u>Intra-ventricular haemorrhage (IVH) grade III-IV:</u> 24 weeks: 0/3 (0%) 25 weeks: 4/6 (67%) 26 weeks: 0/5 (0%) 27 weeks: 0/6 (0%) 28 weeks: 0/11 (0%) 29 weeks: 0/17 (0%) 30 weeks: 0/18 (0%) 31 weeks: 0/35 (0%) 32 weeks: 0/21 (0%) 33 weeks: 0/51 (0%) 34 weeks: 0/24 (0%) 35 weeks: 0/39 (0%) 36 weeks: 0/27 (0%) 36 weeks: 0/12 (0%) <u>Necrotizing enterocolitis:</u> 24 weeks: 0/3 (0%) 25 weeks: 1/6 (16%) 26 weeks: 2/5 (40%) 27 weeks: 0/6 (0%) 28 weeks: 1/11 (9%) 29 weeks: 0/17 (0%)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			30 weeks: 0/18 (0%) 31 weeks: 3/35 (9%) 32 weeks: 0/21 (0%) 33 weeks: 1/51 (2%) 34 weeks: 0/24 (0%) 35 weeks: 1/39 (3%) 36 weeks: 0/27 (0%) Proliferative retinopathy of prematurity: 24 weeks: 3/3 (100%) 25 weeks: 2/6 (33%) 26 weeks: 1/5 (20%) 27 weeks: 0/6 (0%) 28 weeks: 1/11 (0%) 29 weeks: 1/17 (6%) 30 weeks: 0/18 (0%) 31 weeks: 0/35 (0%) 32 weeks: 0/21 (0%) 33 weeks: 0/51 (0%) 34 weeks: 0/24 (0%) 35 weeks: 0/39 (0%) 36 weeks: 0/27 (0%)	
Gestational age outcome in twins by chorionicity				
First author, year: Hack, 2007[166] Country: The Netherlands Study design: Retrospective observational study Study dates:	Population: N=1407 women with twin pregnancies giving birth at the study centres during study period Inclusion criteria: N=1305 twin pregnancies (198 monochorionic and 1107 dichorionic twin pregnancies) without any of the following	Study group: N=1305 twin pregnancies (198 monochorionic and 1107 dichorionic) Comparison group: Monochrionic and dichorionic twin pregnancies were compared to each other Methods:	Fetal death rate per 1000 fetuses at risk according to gestational age (weeks +days): 20^{+0}-25^{+6} weeks: Monochorionic twins: 15/396 (37.9) Dichorionic twins: 20/2214 (9.0) 26^{+0}-27^{+6} weeks: Monochorionic twins: 3/377 (8.0) Dichorionic twins: 1/2122 (0.5)	Funding: Not reported In the second half of the study period elective birth at 37-38 weeks was applied to monochorionic twins (n=90) based on findings of an increased risk in continuing pregnancy after that

Study details	Participants	Intervention	Outcome measures and results	Comments
January 1995-December 2004 Settings: Two teaching hospitals: University Medical Centre, Utrecht and St Elisabeth Hospital, Tilburg Aim of study: To estimate the optimal timing of birth and compare perinatal outcomes between monochorionic and dichorionic twin pregnancies	exclusion criteria Exclusion criteria: Unknown chorionicity (n=50), monoamniocity (n=18), selective fetal reduction to singleton pregnancy (n=3), pregnancy loss at < 20 weeks' gestation (n=14), first-trimester termination for congenital anomalies or FFTS (n=2) and major lethal chromosomal and/or congenital malformations (n=15) Other Details: Monochorionic pregnancies: 198 Dichorionic pregnancies: 1107	The standard protocol of management of twin pregnancies was followed This included routine first-trimester ultrasound with determination of chorionicity, a detailed anomaly scan at 20 weeks' gestation for monochorionic twin pregnancies and fortnightly scans for growth, amniotic fluid and Doppler assessment thereafter Uncomplicated dichorionic pregnancies were managed expectantly while elective births were planned for uncomplicated monochorionic twin pregnancies at around 37-38 weeks' gestation	28^{+0}-29^{+6} weeks: Monochorionic twins: 3/354 (8.5) Dichorionic twins: 3/2060 (1.5) 30^{+0}-31^{+6} weeks: Monochorionic twins: 3/334 (9.0) Dichorionic twins: 4/1973 (2.0) 32^{+0}-33^{+6} weeks: Monochorionic twins: 2/293 (6.8) Dichorionic twins: 2/1813 (1.1) 34^{+0}-35^{+6} weeks: Monochorionic twins: 0/243 (0) Dichorionic twins: 1/1639 (0.6) 36^{+0}-37^{+6} weeks: Monochorionic twins: 3/185 (16.2) Dichorionic twins: 2/1285 (1.6) 38^{+0}-39^{+6} weeks: Monochorionic twins: 1/78 (12.8) Dichorionic twins: 0/688 (0) $>40^{+0}$ weeks Monochorionic twins: 0/7 (0) Dichorionic twins: 1/130 (7.7) Early neonatal mortality rate (death of neonate < 8days per 1000 live births): 20^{+0}-25^{+6} weeks: Monochorionic twins: 4/4 (1000) Dichorionic twins: 60/72 (833.3) 26^{+0}-27^{+6} weeks: Monochorionic twins: 5/20 (250)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			Dichorionic twins: 6/61 (98.4) 28^{+0}-29^{+6} weeks: Monochorionic twins: 3/17 (176.5) Dichorionic twins: 6/84 (71.4) 30^{+0}-31^{+6} weeks: Monochorionic twins: 3/38 (78.9) Dichorionic twins: 2/156 (12.8) 32^{+0}-33^{+6} weeks: Monochorionic twins: 0/48 (0) Dichorionic twins: 0/172 (0) 34^{+0}-35^{+6} weeks: Monochorionic twins: 0/58 (0) Dichorionic twins: 0/353 (0) 36^{+0}-37^{+6} weeks: Monochorionic twins: 0/104 (0) Dichorionic twins: 1/595 (1.7) 38^{+0}-39^{+6} weeks: Monochorionic twins: 0/70 (0) Dichorionic twins: 1/558 (1.8) $>40^{+0}$ weeks Monochorionic twins: 1/7 (142.9) Dichorionic twins: 0/129 (0)	
First Author, Year: Domingues, 2009[167] Country: Portugal	Population: Database (N=576) of women with complicated twin pregnancy who received care at the study centre during the study period	Study group: MCDA group: N=111 medical records of uncomplicated MCDA pregnancies were reviewed	Unexpected fetal deaths (rate per 1000 fetuses at risk) according to gestational age in weeks+days: 24+0 to 25+6: Monochorionic twins: 0/222 (0) Dichorionic twins: 3/580 (5.2)	Funding: Not reported The study authors reported that at autopsy some fetuses showed signs of (previously

Study details	Participants	Intervention	Outcome measures and results	Comments
Study design: Retrospective observational study Study dates: 1996-2007 Settings: Obstetrics Department, Coimbra University Hospitals, Coimbra (a tertiary care referral centre for fetal medicine) Aim of study: To estimate the optimal time of delivery and determine the prospective gestational-age-specific risk of unexpected death in uncomplicated monochorionic diamniotic (MCDA) twins in viable pregnancies (after 24 weeks' gestation)	Inclusion criteria: N=111 women with uncomplicated monochorionic diamniotic twin pregnancies who gave birth after 24 weeks' gestation Exclusion criteria: N=56 women with complicated monochorionic diamniotic pregnancies (e.g. feto-fetal transfusion syndrome, IUGR, discordant fetal growth, structural abnormality, monoamnionicity, twin reversed arterial perfusion, intrauterine death of one fetus before 24 weeks and higher-order multiple pregnancies Other details: Ethnicity not reported	Comparison group: N=290 uncomplicated dichorionic twin pregnancies out of 352 dichorionic pregnancies in the same period Methods: Antenatal surveillance included first-trimester ultrasound assessment and chorionicity determination, a detailed anomaly and fetal echocardiography scan at 21 weeks, followed by growth scans, amniotic fluid and Doppler evaluations every 2 weeks until 32 weeks and weekly thereafter. Prophylactic antenatal corticosteroids (2 intramuscular doses of 12 mg betamethasone, 24 hours apart) were administered if a preterm birth was anticipated. Induction was scheduled at 36-37 weeks if the pregnancy was otherwise uncomplicated Medical records of pregnancy, autopsy report of any unexpected intrauterine fetal death, gestational age and mode of delivery were reviewed	26+0 to 27+6: Monochorionic twins: 0/218 (0) Dichorionic twins: 2/572 (3.5) 28+0 to 29+6: Monochorionic twins: 0/212 (0) Dichorionic twins: 0/558 (0) 30+0 to 31+6: Monochorionic twins: 1/200 (0.5) Dichorionic twins: 2/524 (3.8) 32+0 to 33+6: Monochorionic twins: 1/158 (6.3) Dichorionic twins: 0/450 (0) 34+0 to 35+6: Monochorionic twins: 1/100 (10) Dichorionic twins: 2/334 (6.0)	undiagnosed) feto-fetal transfusion syndrome, which may have confounded the results

Study details	Participants	Intervention	Outcome measures and results	Comments
		Statistical analysis: Continuous data were analyzed with Student's t test and Mann-Whitney U test, where appropriate. Noncontinuous data were analysed using the 1-tailed Fisher's exact test		
First author, year: Lee, 2008[168] Country: USA Study design: Retrospective observational study Study dates: December 1, 2000 to May 11, 2007 Settings: Columbia University Medical Centre, Department of Obstetrics and Gynecology, Division of Maternal Fetal medicine (a tertiary care centre) Aim of study: To compare risk of fetal death between monochorionic-	Population: N=1024 twin pairs born at the study centres during study period Inclusion criteria: Twin pregnancies with two viable fetuses at 23^{+6} or 23^{+7} weeks'gestation and birth at 24 weeks or later Exclusion criteria: Monoamniotic twins (n=19), monochorionic diamniotic pairs in triplets or higher-order pregnancies (n=5), conjoined twins (n=0), twins reversed arterial perfusion sequence (n=0) Other details: All twins: Monochorionic pregnancies: 196 Dichorionic pregnancies: 804 Apparently normal twins subgroup:	Study group: N=741 'apparently normal' twin pregnancies (130 monochorionic and 641 dichorionic) Apparently normal twin pregnancies were defined as twin pregnancies excluding those with antenatal diagnosis of IUGR (n=103), significant twin discordance (n=120), major congenital anomaly (n=76), or FFTS (n=22) Comparison group: Monochrionic and dichorionic twin pregnancies were compared to each other Methods: All consecutive twin births were identified from a departmental perinatal database. Computerised and written medical records were reviewed and sonographic data were retrieved from	Fetal death rate per 1000 pregnancies at risk according to gestational age (weeks): 24-25 weeks: Monochorionic twins: 0/130 (0%) Dichorionic twins: 0/641 (0%) 26-27 weeks: Monochorionic twins: 1/126 (7.9%) Dichorionic twins: 0/624 (0%) 28-29 weeks: Monochorionic twins: 0/123 (0%) Dichorionic twins: 1/611 (1.6%) 30-31 weeks: Monochorionic twins: 0/117 (0%) Dichorionic twins: 1/591 (1.7%) 32-33 weeks: Monochorionic twins: 0/115 (0%) Dichorionic twins: 0/563 (0%) 34-35 weeks: Monochorionic twins: 1/99 (10.1%) Dichorionic twins: 2/494 (4.0%)	Funding: Not reported Data for the apparently normal group have been extracted here A stillbirth event was considered if one or both fetuses died *in utero*, and enumerated as a single event even if both fetuses died *in utero* together or one after the other

Study details	Participants	Intervention	Outcome measures and results	Comments
diamniotic and dichorionic-diamniotic twins	Monochorionic pregnancies: 130 Dichorionic pregnancies: 641	archives and examined Gestational age-specific risk of fetal death calculated and reported for fortnightly gestational age periods	36-37 weeks: Monochorionic twins: 1/49 (20.4%) Dichorionic twins: 0/373 (0%) ≥38 weeks: Monochorionic twins: 0/10 (0%) Dichorionic twins: 0/120 (0%)	
First Author, Year: Barigye, 2005[191] Country: UK Study design: Retrospective observational study Study dates: 6 October 1992-31 August 2004 Setting: Centre for Fetal Care, Queen Charlotte's and Chelsea Hospital (a tertiary referral centre for fetal medicine in London) Aim of study: To determine the prospective gestational age-specific risk of unexpected fetal death in uncomplicated	Population: N=408 monochorionic twin pregnancies that underwent fortnightly surveillance at the study centre during the study period Inclusion criteria: N=151 uncomplicated monochorionic twin pregnancies ≥ 24 weeks' gestation (after viability) for which all records were available Exclusion criteria: Complicated pregnancies, including FFTS (n=164), IUGR (n=62), structural abnormalities (n=27), monoamniotic pregnancies (n=21), high-order multiple pregnancies (n=14), twin with reversed arterial perfusion (n=9), conjoined twins (n=2), delivered < 24 weeks' gestation (n=4), referred back to local hospitals (n=20), birth records	Study group: N=151 uncomplicated monochorionic diamniotic twin pregnancies Comparison group: No comparison group Methods: Clinical details and ultrasound reports of monochorionic pregnancies were extracted from an electronic database (FileMaker Pro 5) and supplemented by examining clinical notes as required	Fetal death rate (per 1000 fetuses at risk): 24^{+0}–25^{+6} weeks: 0/302 (0) 26^{+0}–27^{+6} weeks: 0/302 (0) 28^{+0}–29^{+6} weeks: 2/300 (6.7) 30^{+0}–31^{+6} weeks: 0/292 (0) 32^{+0}–33^{+6} weeks: 2/278 (7.2) 34^{+0}–35^{+6} weeks: 5/240 (20.8) ≥36^{+0} weeks: 1/186 (5.4)	Funding: Funded by Richard and Jack Wiseman Trust and the Institute of Obstetrics and Gynaecology Trust

Study details	Participants	Intervention	Outcome measures and results	Comments
monochorionic diamniotic twins	unavailable (n=6) Other details: All were monochorionic, diamniotic pregnancies No details of ethnicity reported			
First Author, Year: Simoes, 2006[171] Country: Portugal Study design: Hospital-based prospective observational study Study dates: September 1994 to March 2005 Setting: Maternity Dr. Alfredo da Costa, Lisbon (a tertiary perinatal central Lisbon area and referral centre for southern Portugal Aim of study: To calculate the prospective risk of fetal death in monochorionic-diamniotic twins	Population: N=893 twin pregnancies cared for and delivered at the study centre during the study period Inclusion criteria: N=193 monochorionic-diamniotic twin pregnancies cared for and delivered at the study centre during the study period and born after 24 weeks' gestation Exclusion criteria: None Other details: All were monochorionic, diamniotic pregnancies No details of ethnicity reported Mean maternal age in years (SD): 28.2 (4.8) Nulliparous: 105/193 (54.4%) Spontaneous conception: 183/193 (94.8%) Feto-fetal transfusion syndrome pairs: 15/193 (7.8%) Birthweight discordance > 25%: 28/193 (14.5%)	Study group: N=193 monochorionic diamniotic twins born after 24 weeks' gestation Comparison group: None Methods: During the study period information about the pregnancy and birth were recorded prospectively on a preset form and subsequently entered in to a computerised database Monochorionicity was established by standard ultrasonographic criteria performed by level III ultrasonographers, confirmed by careful examination of the placenta after birth by experienced obstetricians and pathological examination Gestational age was determined from menstrual history and confirmed by first-	Fetal deaths (rate per 1000 fetuses at risk): 24–25 weeks: 2/386 (5.2) 26–27 weeks: 1/384 (2.6) 28–29 weeks: 0/379 (0) 30–31 weeks: 1/363 (2.8) 32–33 weeks: 0/332 (0) 34–35 weeks: 1/276 (3.6) 36–37 weeks: 0/171 (0) ≥38 weeks: 3/180 (16.2)	Funding: Not reported Pregnancies complicated by maternal and fetal factors were included in the analysis

Study details	Participants	Intervention	Outcome measures and results	Comments
	Major malformation: 16/381* (4.2%) * excluding stillbirths Vaginal births: 63/193 (32.6%) Elective caesarean section: 104/193 (53.9%) Emergency caesarean section: 26/193 (13.5%) <u>Gestational age at birth:</u> < 32 weeks: 18/193 (12.9%) 32-35 weeks: 89/193 (46.1%) ≥ 36 weeks: 86/193 (44.6%) <u>Maternal complications:</u> Premature contractions: 79/193 (40.9%) Hypertensive disorders; 37/193 (19.2%) Diabetes: 14/193 (7.3%) Preterm prelabour rupture of membranes: 13/193 (6.7%)	trimester ultrasound scans (and from the date of oocyte retrieval in the case of assisted reproduction) The surveillance protocol for monochorionic pregnancies included fortnightly assessments between 24 and 30 weeks and weekly assessments thereafter. Antenatal care included nonstress testing of both fetal hearts and biophysical profile of both twins. Longitudinal growth assessment was performed fortnightly After 30 weeks' gestation Doppler analyses were conducted for umbilical arteries and middle cerebral arteries Women with nonreassuring fetal findings or any maternal complications were evaluated daily to twice-weekly No elective preterm births were attempted. In cases of imminent preterm birth due to maternal or fetal complications, prophylactic antenatal corticosteroids were administered (2 intramuscular dose of 12 mg betamethasone, 24 hours apart)		

Study details	Participants	Intervention	Outcome measures and results	Comments
		In otherwise normal pregnancies elective birth was offered at 36-37 weeks' gestation		
First Author, Year: Tul, 2011[170] Country: Slovenia Study design: Population-based retrospective observational study Study dates: 1997-2007 Setting: Whole country Aim of study: To determine the prospective risk of fetal death in monochorionic-diamniotic twin pregnancies	Population: N=199,603 births occurred in the whole country during the study period Inclusion criteria: N=387 monochorionic-diamniotic twin pregnancies delivered at ≥ 24 weeks' gestation Exclusion criteria: None Other details: All were monochorionic, diamniotic pregnancies No details of ethnicity reported Mean maternal age in years (SD): 28.7 (4.8) Nulliparous: 215/387 (55.6%) Spontaneous conception: 306/387 (79.1%) Feto-fetal transfusion syndrome pairs: 27/387 (7.0%) Birthweight discordance > 25%: 37/387 (10.2 Vaginal births: 221/387 (57.1%) Gestational age at birth: < 32 weeks: 50/387 (12.9%) 32-35 weeks: 108/387 (27.9%) ≥ 36 weeks: 229/387 (59.2%)	Study group: N=387 monochorionic diamniotic twin pregnancies Comparison group: None Methods: The Slovenian National Perinatal Information System (NPIS) database was examined to identify all monochorionic twins born at ≥ 24 weeks' gestation during the study period (registration of all births >22 weeks' gestation or birthweight > 500 g is mandatory by law) Monochorionicity was diagnosed by standard ultrasonographic criteria and confirmed by placental examination at birth No specific protocol was followed for antenatal care of monochorionic pregnancies and decisions regarding the frequency of ultrasound surveillance and referral were at the discretion of the attending obstetrician	Fetal deaths (rate per 1000 fetuses at risk): 24–25 weeks: 7/774 (9.0) 26–27 weeks: 5/754 (6.6) 28–29 weeks: 5/742 (6.7) 30–31 weeks: 1/712 (1.4)* 32–33 weeks: 5/674 (7.4) 34–35 weeks: 5/605 (8.3) 36–37 weeks: 2/458 (4.4) ≥38 weeks: 3/180 (16.2) Neonatal deaths within 28 days of birth (mortality rate per 1000 live births): 24–25 weeks: 8/13 (615.4) 26–27 weeks: 2/7 (285.7) 28–29 weeks: 3/27 (111.1) 30–31 weeks: 1/37 (27.0) 32–33 weeks: 1/64 (15.6) 34–35 weeks: 0/141 (0)	Funding: Not reported Population-based study Pregnancies complicated by maternal and fetal factors were included in the analysis * There is an error in the reported fetal deaths for 30-31 weeks (Table 2, page 52 in the article). The number of fetal deaths is reported as 1 but involving two pregnancies. The guideline developers have assumed that there was one fetal death in one pregnancy (another possibility is that there were two fetal deaths in one pregnancy)

Study details	Participants	Intervention	Outcome measures and results	Comments
	Maternal complications: Premature contractions: 92/387 (23.8%) Hypertensive disorders; 32/387 (8.3%) Gestational diabetes: 221/387 (57.1%)	No elective preterm births were attempted in uncomplicated pregnancies (they continued until spontaneous birth)	36–37 weeks: 2/288 (6.9) ≥38 weeks: 1/165 (6.1)	
Effectiveness of elective delivery in uncomplicated twin pregnancies				
First author, year: Suzuki, 2000[175] Country: Japan Study design: Randomised controlled trial Study dates: 1994-1998 Setting: Nippon Medical School, Tokyo Aim of study: To compare induction of labour at 37 weeks to expectant management in multiple pregnancy	Population: N= 36 women with twin pregnancies who gave birth after 37 weeks' gestation at the study centre during the study period Inclusion criteria: Women having first twin in cephalic presentation Exclusion criteria: Women with previous caesarean section or with an estimated fetal weight <1500 g Other details: Induction group: Monochorionic diamniotic: 6/17 (35%) Dichorionic diamniotic: 11/17 (65%) Expectant management group: Monochorionic diamniotic: 8/19 (42%) Dichorionic diamniotic: 11/19	Intervention: Induction group: N=17 women underwent induction of labour at 37 weeks' gestation with 0.5 mg oral prostaglandin E_2 (PGE_2) given every 2-3 hours (maximum 1.5 mg/day) until the cycle of labour pains became <10 minutes If labour did not start within 24 hours, oral PGE_2 was repeated the next day up to a maximum of 7.5 mg/week, followed by artificial rupture of the membranes and oxytocin infusion as required Comparison: Expectant management group: N=19 women were evaluated daily with a non-stress test and twice weekly with an ultrasonic scan and cervical examination Methods Data were analysed using	Fetal/Neonatal Perinatal death: Induction group: 0/34 (0%) Expectant management group: 0/38 (0%) p=NS Birth weight in g (SD): First twin: Induction group:2771 (346) Expectant management group: 2690 (369) p=NS Second twin: Induction group:2629 (310) Expectant management group: 2654 (310) p=NS Average of first and second twins: Induction group:2700 (330) Expectant management group: 2672 (392) p=NS Birthweight <2500 g: Induction group: 11/34 (32%) Expectant management group: 13/38 (34%)	Funding: Not reported Limitations: Small sample size (underpowered trial) Allocation concealment was not reported Process of randomisation not described Data for monochorionic pregnancies not reported separately

Study details	Participants	Intervention	Outcome measures and results	Comments
	(58%)	Student's t-test, the chi-square test or Fisher's exact test	p=NS RR: 0.95 CI: 0.49 to 1.82* Birthweight <2000 g: Induction group: 0/34 (0%) Expectant management group: 2/38 (5.3%) p=NS Apgar scores: Apgar score <7 at 1 minute: Induction group: 0/34 (0%) Expectant management group: 0/38 (0%) Apgar score <7 at 5 minute: Induction group: 0/34 (0%) Expectant management group: 0/38 (0%) Maternal outcomes: Caesarean section rate: Induction group: 3/17 (32%) Expectant management group: 6/19 (32%) p=NS RR: 0.56, CI: 0.16 to 1.90 Need for blood transfusion: Induction group: 0/17 (0%) Expectant management group: 1/19 (5%) p=NS	
First author, year: Harle, 2002[176] Country: France	Population: N= 93 women with twin pregnancies who gave birth at 36-39 weeks' gestation at the study centre during the study period	Intervention: Labour induction group: N=36 women who underwent induction of labour at 36 weeks Bishop score was used to	Fetal/neonatal outcomes: Perinatal death: Induction group: 0/72 (0%) Expectant management group: 0/90 (0%) p=NS	Funding: Not reported Although the study was reported to be a case-control study the methodology

Study details	Participants	Intervention	Outcome measures and results	Comments
Study design: Prospective interventional study Study dates: January 1990 to December 1996 Settings: Department of Obstetrics and Gynaecology of Bordeaux University Hospital Aim of study: To compare perinatal and maternal outcomes of twin pregnancies managed by induction of labour with those managed expectantly after 36 weeks' gestation	Inclusion criteria : N=81 Women with uncomplicated twin pregnancies at 36 weeks' gestation Exclusion criteria: N=12 women with complications, including pre-eclampsia, diabetes, previous caesarean section, vaginal bleeding, non-vertex presentation of first twin, signs of fetal distress, or estimated fetal weight <1500 g Other details: Dichorionic diamniotic pregnancies: Induction group: 34/36 (94.4%) Expectant management group: 40/45 (88.9%) p=NS Nulliparous: Induction group: 34/36 (94.4%) Expectant management group: 40/45 (88.9%) p=NS	determine the method of induction: oxytocin infusion (n=18) was used if Bishop score was ≥ 5; vaginal PGE_2 was used if Bishop score was <5 (n=6); and intrauterine balloon catheter was used in the case of very unripe cervices (<3; n=12) Comparison: N=45, women who opted for expectant management Methods Statistical analysis: Qualitative variables of the study were compared by χ^2 test with Yates' continuity correction and Fisher's test. Students't-test was used to compare quantitative variables	Birthweight in g (SD): Induction group: 2639 (352) Expectant management group: 2463 (298) p<0.001 Birthweight <2500 g: Induction group: 23/72 (31.9%) Expectant management group: 54/90 (60%) p<0.001 RR: 0.53 CI: 0.37 to 0.78* Birthweight <2000 g: Induction group: 3/72 (4.1%) Expectant management group: 6/90 (6.6%) p=NS RR: 0.63 CI: 0.16 to 2.41* Apgar score <7 at 1 minute: Induction group: 9/72 (12.5%) Expectant management group: 12/90 (13.3%) p=NS RR: 0.94 CI: 0.42 to 2.1* Apgar score <7 at 5 minutes: Induction group: 0/72 (0%) Expectant management group: 3/90 (3.3%) p=NS Admission to NICU: Induction group: 22/72 (30.5%) Expectant management group: 24/90 (26.6%) p=NS	described suggests that it was a prospective interventional (cohort) study Data for monochorionic pregnancies not reported separately

Study details	Participants	Intervention	Outcome measures and results	Comments
			RR: 1.15 CI: 0.70 to 1.87* Immediate admission to NICU: Induction group: 15/72 (20.8%) Expectant management group: 21/90 (23.3%) p=NS RR: 0.89 CI: 0.50 to 1.60* Delayed admission to NICU: Induction group: 7/72 (9.7%) Expectant management group: 3/90 (3.3%) p=NS RR: 2.92 CI: 0.79 to 10.88* Maternal outcomes: Caesarean section rate: Induction group: 3/36 (8.3%) Expectant management group: 6/45 (13.3%) p=NS RR: 0.63, CI: 0.17 to 2.33* Non-spontaneous (instrumental) vaginal birth: Induction group: 19/36 (52.8%) Expectant management group: 21/45 (46.7%) p=NS RR: 1.13, CI: 0.73 to 1.76* Duration of maternal hospital stay in days (SD): Induction group: 7.3 (2.0) Expectant management group: 7.5 (2.3)	

Study details	Participants	Intervention	Outcome measures and results	Comments
			p=NS Maternal infection: Induction group: 2/36 (5.6%) Expectant management group: 3/45 (6.7%) p=NS RR: 0.85, CI: 0.15 to 4.83*	
First author, year: Udom-Rice,2000[177] Country: USA Study design: Retrospective observational (chart review) study Study dates: January 1, 1987 to December 31, 1993 Settings: New York Hospital Cornell Medical Centre Aim of study: To evaluate timing of birth with associated perinatal outcome in twin pregnancies of at least 36 completed weeks	Population: N=776 women with twin pregnancies who gave birth at the study centre during the study period Inclusion criteria: N=329 women who gave birth at ≥ 36 completed weeks, underwent serial antenatal ultrasound examinations, and whose perinatal medical records were available Exclusion criteria: Significant chronic maternal cardiac, renal or respiratory disease, feto-fetal transfusion syndrome, single fetus deatch at <36 weeks' gestation, regular substance misuse during pregnancy, and the presence of any major fetal congenital anomalies Other Details: No details of ethnicity or chorionicity were reported	Study group: Elective birth group: N=91 women with twin births which were not spontaneous or complicated with pre-eclampsia, oligohydramnios, IUGR or abruption Comparison group: Spontaneous birth group: N=178 women who had a spontaneous birth Methods Relevant information was collected from maternal and neonatal medical records Statistical analysis Categorical variables were assessed by chi-squared analysis or Fisher's exact test. Continuous variables were reported as mean + SD and were tested using Student's t-test or one-way analysis of variance with Tukey-Kramer multiple comparison tests	Neonatal outcomes: Admission to NICU: Elective birth group: 3/91 (3.3%) Spontaneous birth group: 13/178 (7.3%) RR (CI): 0.45 (0.13 to 1.54)* Neonatal sepsis: Elective birth group: 3/91 (3.3%) Spontaneous birth group: 9/178 (6.0%) RR (CI): 0.65 (0.18 to 2.35)* Comparison of early (36-37 weeks) versus late (38-39 weeks) for birth for truly elective delivery*: *Truly elective deliveries were defined as those that were not spontaneous or complicated with pre-eclampsia, oligohydramnios, IUGR or abruption NICU required: 36-37 weeks' gestation: 3/44 (6.8%) 38-39 weeks' gestation: 0/47 (0%) p=0.109 Respiratory distress syndrome: 36-37 weeks' gestation: 1/44 (2.3%)	Funding: Not reported No details reported on indications for induction, method of inductions, or mode of delivery Outcome data for elective delivery (indicated and non-indicated) reported together in the study but data for uncomplicated elective delivery have been extracted for the guideline

Study details	Participants	Intervention	Outcome measures and results	Comments
	No significant difference between the two groups in terms of previous history of preterm birth, use of cerclage and tocolytics, smoking or nulliparity	All tests were two-tailed	38-39 weeks' gestation: 0/47 (0%) p=0.484 <u>Sepsis:</u> 36-37 weeks' gestation: 3/44 (6.8%) 38-39 weeks' gestation: 0/47 (0%) p=0.109	

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