Appendix J GRADE findings

The GRADE findings (evidence profiles) are presented with the same table numbers as the abbreviated tables in the main text of the full guideline to assist cross-referencing.

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?

Table 4.1 GRADE findings for effectiveness of dating twin and triplet pregnancies using measurements and charts for singleton pregnancies

Quality assessment							Summary of findings					
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Twins or triplets		Singletons		Effect	Quality
							Number	Mean or mean difference ± SD	Number	Mean or mean difference ± SD	Mean difference (95% CI)	
Differences in size between twins or triplets and singletons												
Using crown–rump length measurement at 52 days of gestation												
1[31]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	11.48 mm ±0.22	20	11.74 mm ±0.27	NR; P =0.45	Very low
Using crown–rump length measurement at 59 days of gestation												

Quality assessment							Summary of findings					
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Twins or triplets		Singletons		Effect	Quality
							Number	Mean or mean difference ± SD	Number	Mean or mean difference ± SD	Mean difference (95% CI)	
1[31]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	19.36 mm ±0.31	20	19.26 mm ±0.43	NR; P =0.85	Very low
Using crown–rump length measurement at 66 days of gestation												
1[31]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	26.51 mm ±0.33	20	26.44 mm ±0.57	NR; P =0.91	Very low
Using crown–rump length measurement at 73 days of gestation												
1[31;32]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	35.87 mm ±0.54	20	36.19 mm ±0.90	NR; P =0.76	Very low
Using crown–rump length measurement at 80 days of gestation												
1[32]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	50.8 mm ±2.8	20	50.4 mm ±3.0	NR; P =0.62	Very low
Using crown–rump length measurement at 87 days of gestation												
1[32]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	63.4 mm ±2.3	20	64.4 mm ±2.3	NR; P =0.19	Very low
Using crown–rump length measurement at 94 days of gestation												
1[32]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	75.4 mm ±2.5	20	74.7 mm ±2.7	NR; P =0.41	Very low
Using crown–rump length measurement at 101 days of gestation												
1[32]	Prospective cohort	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	85.2 mm ±5.5	20	85.6 mm ±5.5	NR; P =0.83	Very low
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Robinson's chart at 11–14 weeks of gestation												

Quality assessment							Summary of findings					
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Twins or triplets		Singletons		Effect	Quality
							Number	Mean or mean difference ± SD	Number	Mean or mean difference ± SD	Mean difference (95% CI)	
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	4.7 mm (4.4 to 5.1)	266	2.72 mm (2.49 to 2.95)	1.98 mm	Very low
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Rossavik's chart at 11–14 weeks of gestation												
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	2.1 mm (1.8 to 2.5)	266	0.24 mm (0.01 to 0.46)	1.86 mm	Very low
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Von Kaisenberg's chart at 11–14 weeks of gestation												
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	−0.91 mm (−0.7 to −1.13)	266	0.98 mm (0.6 to 1.35	1.89 mm	Very low
Using biparietal diameter measurement at 111 and 173 days of gestation												
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	20 twins	−0.12 mm ± 2.07	39	0.14 mm ±2.21	0.26mm (−0.66 to 1.18)	Very low
Using head circumference measurement at 16–26 weeks of gestation												
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 larger twins	NR	269	NR	NR; P <0.05	Very low
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 smaller twins	NR	269	NR	NR; P <0.05	Very low
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 twin pairs (using average from each pair)	NR	269	NR	NR; P =1	Very low
Using femur length measurement at 16–26 weeks of gestation												
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 larger twins	NR	269	NR	NR; P =0.07	Very low

Quality assessment							Summary of findings					
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Twins or triplets		Singletons		Effect	Quality
							Number	Mean or mean difference ± SD	Number	Mean or mean difference ± SD	Mean difference (95% CI)	
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 smaller twins	NR	269	NR	NR; P <0.005	Very low
1[34]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	119 twin pairs (using average from each pair)	NR	269	NR	NR; P =1	Very low
Differences in dating between twins or triplets and singletons												
Using formula based on mean head circumference , femur length and abdominal circumference measurements at 14–22 weeks of gestation												
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	134 twins	NR	152	NR	–0.3 days	Very low
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	67 triplets	NR	152	NR	–1.3 days	Very low
Using formula based on biparietal diameter measurement s in the second trimester												
1[36]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	168 twins	116.8 days ±6.1	253	118.9 days ±9.0	NS (p = NR)	Low
Using mean difference between true gestational age and estimated gestational age based on Robinson's crown–rump length formula at 11–14 weeks of gestation												
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	2.4 days (2.4 to 2.6)	266	1.41 days (1.15 to 1.68)	1.01 days	Very low
Using mean difference between true gestational age and estimated gestational age based on Rossavik's crown–rump length formula at 11–14 weeks of gestation												
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	1.27 days (1.05 to 1.5)	266	0.14 days (0.01 to 0.28)	1.13 days	Very low
Using mean difference between true gestational age and estimated gestational age based on Von Kaisenberg's crown–rump length formula at 11–14 weeks of gestation												

Quality assessment							Summary of findings					
Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Twins or triplets		Singletons		Effect	Quality
							Number	Mean or mean difference ± SD	Number	Mean or mean difference ± SD	Mean difference (95% CI)	
1[33]	Retrospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	110 larger twins	0.58 days (0.36 to 0.8)	266	–0.54 days (–0.41 to -0.67)	1.12 days	Very low
Using day of oocyte retrieval												
1[36]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	168 twins	120.9 days ±8.6	253	118.2 days ±5.3	NS (p = NR)	Low

CI confidence interval, NR not reported, NS not significant, SD standard deviation

[a] Twin measurements were combined and averaged

[b] Sample size < 400

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?

Table 4.2 GRADE findings for choosing which fetus to use to date twin and triplet pregnancies

Quality assessment							Summary of findings		
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twins or triplets**	**Mean difference ± SD or accuracy (RMSD)**	**Quality**
Prediction of growth discordance									
Between the larger and smaller twin based on crown–rump length measurement at 11–14 weeks of gestation									
1[37]	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	182 twins	3.4 days ±3.18	Very low
Accuracy of dating									
Among twins in pregnancies resulting from assisted reproduction and based on comparison of crown–rump length measurement and true gestational age at 11–14 weeks of gestation in the larger fetus									
1[37]	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	47 twins	1.45 days±2.17	Very low
Among twins in pregnancies resulting from assisted reproduction and based on comparison of crown–rump length measurement and true gestational age at 11–14 weeks of gestation in the smaller fetus									
1[37]	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	47 twins	–0.06 days ±2.21	Very low
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the larger fetus									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	67 twins	RMSD 4.17 days[b]	Very low
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the smaller fetus									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	67 twins	RMSD 4.11 days[b]	Very low

Quality assessment							Summary of findings		
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twins or triplets**	**Mean difference ± SD or accuracy (RMSD)**	**Quality**
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation averaged over both fetuses									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	67 twins	RMSD 3.91 days[b]	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the largest fetus									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	19 triplets	RMSD 4.07 days[b]	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the smallest fetus									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	19 triplets	RMSD 4.87 days[b]	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation averaged over all fetuses									
1[35]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	19 triplets	RMSD 3.73 days[b]	Very low

NR not reported, RMSD root mean square deviation, SD = standard deviation

[a] Sample size < 400

[b] Accuracy defined as RMSD between true and estimated gestational age (RMSD = $\sqrt{(\text{systematic error}^2 + \text{random error}^2)}$; systematic error defined as mean difference between true and estimated gestational ages; random error defined as residual SD (between true and estimated gestational ages)

Chorionicity

Review question

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

Table 4.3 GRADE findings for scans performed at 11–14 weeks of gestation

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Membrane thickness																
1[38]	Prospective study	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	105	95 (75 to 100)	96 (90 to 99)	88 (72 to 100)	99 (96 to 100)	27 (9 to 82)	86 (67 to 95)	0.1 (0.0 to 0.4)	1 (0 to 8)	Moderate
1[38]	Prospective study	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	105	100 (83 to 100)	92 (84 to 97)	74 (58 to 91)	100 (95 to 100)	12 (6 to 25)	74 (57 to 84)	0.0 (NC)	0 (0 to 9)	Moderate
1[39]	Prospective study	Serious[b]	No serious inconsistency	Serious[a]	No serious imprecision	None	140	100 (89 to 100)	94 (89 to 98)	82 (70 to 94)	100 (96 to 100)	15 (8 to 32)	82 (68 to 90)	0.0 (NC)	0 (0 to 7)	Low
Number of placental masses and Lambda or T-Sign																
3[38-40]	Retrospective and prospective studies	Serious[b]	Very serious[c]	Serious[a d]	Serious[e]	None	502	93 (87 to 97)	79 (75 to 83)	Range: 19 to 98	Range: 75 to 100	18 (0 to 1000)	NC	0.2 (0.0 to 1.7)	NC	Very low
Composite measures																
Membrane thickness and number of placental masses and Lambda or T-sign																
1[39]	Prospective study	Serious[b]	No serious inconsistency	Serious[a]	No serious imprecision	None	140	100 (89 to 100)	92 (85 to 96)	78 (65 to 91)	100 (96 to 100)	12 (6 to 22)	78 (65 to 86)	0.0 (NC)	0 (0 to 7)	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Lambda or T-sign and number of placental masses, and concordant/discordant fetal sex																
1[41]	Prospective study	Serious[f]	No serious inconsistency	Serious[a]	No serious imprecision	None	96	100 (84 to 100)	99 (96 to 100)	95 (87 to 100)	100 (95 to 100)	75 (11 to 526)	95 (74 to 99)	0.0 (NC)	0 (0 to 9)	Low

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value , NR not reported, NS not significant, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), SD standard deviation

[a] No clinical outcomes were reported

[b] The selection criteria were not described clearly. Not all of the participants received the same reference test

[c] Meta-analysis showed inconsistency in sensitivity data. Specificity and likelihood ratios showed serious inconsistency

[d] Clinical outcomes were only reported for some pregnancies

[e] Width of 95% CI ≥ 40 percentage points

[f] Not all of the participants received the same reference test

Table 4.4 GRADE findings for scans performed at more than 14 weeks of gestation

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Membrane thickness																
1[42]	Prospective study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	44 twin 0 triplet	76 (29 to 96)	86 (71 to 95)	50 (19 to 81)	94 (86 to 100)	5 (2 to 14)	50 (28 to 73)	0.3 (0.1 to 1.1)	6 (2 to 17)	Very low
Number of placental sites																
1[43]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	None	66 twin 0 triplet	100 (87 to 100)	33 (19 to 49)	49 (36 to 63)	100 (75 to 100)	1 (1 to 2)	49 (43 to 54)	0.0 (NC)	0 (0 to 37)	Moderate
Composite methods																
Number of placental masses and Lambda or T-sign and concordant or discordant fetal sex																
1[41]	Prospective study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	42 twin 0 triplet	77 (54 to 100)	90 (79 to 100)	77 (54 to 100)	90 (79 to 100)	7 (2 to 23)	77 (52 to 91)	0.9 (0.8 to 1.0)	10 (4 to 24)	Very low
1[40]	Retrospective study	No serious limitations	No serious inconsistency	Serious[d]	No serious imprecision	None	163 twin 0 triplet	88 (79 to 97)	95 (91 to 99)	88 (79 to 97)	95 (91 to 99)	17 (8 to 36)	88 (77 to 94)	0.1 (0.1 to 0.3)	5 (3 to 11)	Very low
Membrane thickness, number of placental masses and Lambda or T-sign, and concordant or discordant fetal sex																
1[44]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	None	0 twin 50 triplet	94 (73 to 100)	94 (79 to 99)	89 (76 to 100)	97 (91 to 100)	15 (4 to 58)	89 (69 to 97)	0.1 (0.0 to 0.2)	3 (1 to 18)	Moderate

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value , NR not reported, NS not significant, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), SD standard deviation

[a]The selection criteria were not described clearly

[b] No clinical outcomes were reported

[c] Width of 95% CI ≥ 40 percentage points

[d] Clinical outcomes were only reported for some pregnancies

Table 4.5 GRADE findings for scans performed before 11 weeks of gestation or over a wide range of gestational ages with no mean age reported

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Membrane thickness																
1[45]	Prospective study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	82	100 (59 to 100)	94 (86 to 98)	64 (35 to 92)	100 (94 to 100)	17 (7 to 45)	63 (37 to 78)	0.0 (NC)	0 (0 to 9)	Very low
1[46]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	54	25 (5 to 57)	90 (77 to 97)	43 (6 to 80)	81 (70 to 92)	3 (1 to 10)	43 (16 to 74)	0.8 (0.6 to 1.2)	19 (14 to 25)	Low
1[47]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	None	75	74 (55 to 88)	89 (75 to 96)	83 (68 to 96)	83 (72 to 94)	7 (3 to 15)	82 (66 to 91)	0.3 (0.2 to 0.5)	17 (10 to 27)	Moderate
Number of membrane layers																
1[48]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	None	69	100 (90 to 100)	98 (90 to 100)	94 (84 to 100)	100 (93 to 100)	52 (7 to 362)	94 (70 to 98)	0.0 (NC)	0 (0 to 13)	Moderate
Number of placental masses and Lambda or T-sign																
1[45]	Prospective study	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	82	100 (69 to 100)	44 (32 to 55)	20 (9 to 31)	100 (89 to 100)	2 (1 to 2)	20 (15 to 23)	0.0 (NC)	0 (0 to 18)	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[49]	Prospective study	No serious limitations	No serious inconsistency	Serious[a]	Serious[e]	None	45	89 (52 to 100)	94 (81 to 99)	80 (55 to 100)	97 (92 to 100)	16 (4 to 63)	80 (50 to 94)	0.1 (0.0 to 0.8)	3 (0 to 16)	Low
Composite measures																
Membrane thickness and number of placental masses																
1[50]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	No serious imprecision	None	33	100 (66 to 100)	100 (85 to 100)	100 (66 to 100)	100 (85 to 100)	500 (3 to 711)	100 (53 to 100)	0.0 (0 to 0.8)	0 (0 to 23)	Moderate
Membrane thickness, number of placental sites and Lambda or T-sign, number of gestational sacs and number of fetal poles																
1[51]	Prospective study	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	47	100 (29 to 100)	100 (92 to 100)	100 (29 to 100)	100 (92 to 100)	1000 (5 to 1271)	100 (25 to 100)	0.0 (0.0 to 1.7)	0 (0 to 10)	Low

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value , NR not reported, NS not significant, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), SD standard deviation

[a] The selection criteria were not described clearly

[b] No clinical outcomes were reported

[c] Width of 95% CI ≥ 40 percentage points

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?

Table 5.1 GRADE findings for effectiveness of giving women with twin pregnancies additional information and emotional support

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Maternal morbidity (including anxiety and depression)											
Anaemia (Hgb <10mg/dl)											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17/89 (19%)	11/51 (22%)	OR 0.85 (0.36 to 2.01)	25 fewer per 1000 (from 126 fewer to 140 more)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	5/30 (17%)	7/41 (17%)	OR 0.97 (0.27 to 3.4)	4 fewer per 1000 (from 118 fewer to 242 more)	Very low
Bleeding ≥ 20 weeks											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/89 (2%)	4/51 (8%)	OR 0.28 (0.05 to 1.47)	56 fewer per 1000 (from 74 fewer to 33 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	2/339 (1%)	OR 1.78 (0.25 to 12.5)	5 more per 1000 (from 4 fewer to 63 more)	Very low
Caesarean section											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	12/30 (40%)	19/41 (46%)	OR 0.77 (0.29 to 2.00)	63 fewer per 1000 (from 263 fewer to 170 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	29/89 (33%)	15/51 (29%)	OR 1.16 (0.54 to 2.45)	32 more per 1000 (from 110 fewer to 217 more)	Very low
Gestational diabetes											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	6/89 (7%)	1/51 (2%)	OR 3.61 (0.42 to 30.9)	47 more per 1000 (from 11 fewer to 337 more)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	8/190 (4%)	7/339 (2%)	OR 2.08 (0.74 to 5.8)	21 more per 1000 (from 5 fewer to 88 more)	Very low
Gestational hypertension											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
Pre-eclampsia											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	10/89 (11%)	4/51 (8%)	OR 1.16 (0.37 to 3.61)	34 more per 1000 (from 48 fewer to 157 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	15/190 (8%)	57/339 (17%)	OR 0.41 (0.23 to 0.75)	89 fewer per 1000 (from 37 fewer to 124 fewer)	Very low
Premature rupture of membranes											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	11/89 (12%)	13/51 (26%)	OR 0.40 (0.16 to 1.00)	131 fewer per 1000 (from 203 fewer to 1 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	19/190 (10%)	84/339 (25%)	OR 0.35 (0.2 to 0.6)	148 fewer per 1000 (from 83 fewer to 186 fewer)	Very low
Preterm labour											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	44/190 (23%)	142/339 (42%)	OR 0.42 (0.28 to 0.62)	186 fewer per 1000 (from 110 fewer to 251 fewer)	Very low
Urinary tract infection											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	4/89 (5%)	3/51 (6%)	OR 0.75 (0.16 to 3.50)	14 fewer per 1000 (from 49 fewer to 121 more)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/30 (7%)	4/41 (10%)	OR 0.66 (0.11 to 3.86)	31 fewer per 1000 (from 86 fewer to 197 more)	Very low
Perinatal and neonatal mortality											
Perinatal mortality											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/178 (1%)	8/102 (8%)	OR 0.06 (0.009 to 0.53)	72 fewer per 1000 (from 33 fewer to 78 fewer)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	2/41 (5%)	RR 0.68 (0.06 to 7.19)	16 fewer per 1000 (from 46 fewer to 236 more)	Very low
Perinatal and neonatal morbidity (including preterm birth)											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Anaemia											
1[54]	Prospective observational study	Serious [b]	No serious inconsistency	No serious indirectness	Serious[a]	None	8/190 (4%)	44/339 (13%)	OR 0.31 (0.17 to 0.56)	90 fewer per 1000 (from 53 fewer to 105 fewer)	Very low
Antibiotics											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	80/190 (42%)	203/339 (60%)	OR 0.50 (0.37 to 0.67)	180 fewer per 1000 (from 99 fewer to 243 fewer)	Very low
Apnea, bradycardia or cyanosis											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	13/190 (7%)	78/339 (23%)	OR 0.27 (0.17 to 0.44)	162 fewer per 1000 (from 114 fewer to 182 fewer)	Very low
Hyperbilirubinaemia											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	36/190 (19%)	98/339 (29%)	OR 0.56 (0.40 to 0.79)	100 fewer per 1000 (from 46 fewer to 149 fewer)	Very low
Intravenous fluids											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	72/190 (38%)	200/339 (59%)	OR 0.43 (0.32 to 0.57)	210 fewer per 1000 (from 139 fewer to 275 fewer)	Very low
Low birthweight											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	78/190 (41%)	217/339 (64%)	OR 0.39 (0.27 to 0.56)	231 fewer per 1000 (from 141 fewer	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
										to 316 fewer)	
Major neonatal morbidity (retinopathy of prematurity, necrotising enter-colitis, ventilator support, or intra-ventricular haemorrhage)											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	32/190 (17%)	108/339 (32%)	OR 0.44 (0.31 to 0.62)	151 fewer per 1000 (from 94 fewer to 192 fewer)	Very low
Mechanical ventilation											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	29/190 (15%)	102/339 (30%)	OR 0.41 (0.28 to 0.59)	150 fewer per 1000 (from 98 fewer to 193 fewer)	Very low
Necrotising enterocolitis											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	10/339 (3%)	OR 0.21 (0.05 to 0.95)	20 fewer per 1000 (from 1 fewer to 28 fewer)	Very low
NICU admission											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	24/178 (14%)	39/102 (38%)	OR 0.35 (0.22 to 0.55)	247 fewer per 1000 (from 128 fewer to 262 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	82/190 (43%)	214/339 (63%)	OR 0.48 (0.36 to 0.64)	199 fewer per 1000 (from 108 fewer to 250 fewer)	Very low
Parenteral nutrition											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	25/190 (13%)	105/339 (31%)	OR 0.32 (0.22 to 0.46)	180 fewer per 1000 (from 139 fewer to 220 fewer)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Phototherapy											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	30/190 (16%)	125/339 (37%)	OR 0.34 (0.24 to 0.49)	210 fewer per 1000 (from 146 fewer to 246 fewer)	Very low
Patent ductus arteriosus											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	4/190 (2%)	17/339 (5%)	OR 0.37 (0.15 to 0.88)	30 fewer per 1000 (from 6 fewer to 42 fewer)	Very low
Preterm birth <37 weeks											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	69/89 (78%)	37/51 (73%)	OR 1.30 (0.59 to 2.87)	23 more per 1000 (from 116 fewer to 158 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	44/190 (23%)	142/339 (42%)	OR 0.45 (0.3 to 0.68)	187 fewer per 1000 (from 90 fewer to 241 fewer)	Very low
Preterm birth <36 weeks											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	38/60 (63%)	68/82 (83%)	OR 0.36 (0.16 to 0.77)	193 fewer per 1000 (from 40 fewer to 392 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	77/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)	126 fewer per 1000 (from 29 fewer to 204 fewer)	Very low
Preterm birth <32 weeks											
1[54]	Prospective observational	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	14/190 (7%)	72/339 (21%)	OR 0.27 (0.15 to 0.51)	138 fewer per 1000	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
	study									(from 91 fewer to 174 fewer)	
Preterm birth <30 weeks											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/30 (0%)	12/41 (29%)	Not calculable	Not calculable	Very low
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/89 (2%)	9/51 (18%)	OR 0.29 (0.11 to 0.76)	154 fewer per 1000 (from 36 fewer to 153 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)	59 fewer per 1000 (from 20 fewer to 80 fewer)	Very low
Respiratory distress syndrome											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	34/190 (18%)	105/339 (31%)	OR 0.44 (0.31 to 0.62)	131 fewer per 1000 (from 92 fewer to 188 fewer)	Very low
Retinopathy of prematurity											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	24/339 (7%)	OR 0.19 (0.07 to 0.50)	60 fewer per 1000 (from 34 fewer to 65 fewer)	Very low
Supplemental oxygen											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	53/190 (28%)	153/339 (45%)	OR 0.49 (0.36 to 0.67)	170 fewer per 1000 (from 96 fewer to 223 fewer)	Very low
Very low birthweight (<1500g)											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	5/30 (17%)	16/41 (39%)	OR 0.42 (0.17 to 1.03)	223 fewer per 1000 (from 292 fewer to 7 more)	Very low
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	10/178 (6%)	27/102 (27%)	OR 0.21 (0.10 to 0.42)	209 fewer per 1000 (from 133 fewer to 230 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	9/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low

Hgb haemoglobin, OR odds ratio

[a] Total number of events < 300

[b] There were significantly fewer smokers in the additional information and support group than in the standard care group

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?

Table 5.2 GRADE findings for effectiveness of daily intake of additional calories and protein in women with twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Additional nutrition group**	**Normal antenatal care group**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Pre-eclampsia											
1[55]	Observational study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	21/177 (12%)	52/343 (15%)	OR 0.75 (0.44 to 1.30)	38 fewer per 1000 (from 85 fewer to 45 more)	Very low
Maternal weight gain (measured in kg; better indicated by higher values)											
1[55]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	mean 18 (SD 7) N=177	mean 16 (SD 6) N=343	-	MD 2.00 higher (0.79 higher to 3.21 higher)	Low
Preterm birth											
Preterm birth <37 weeks											
1[55]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	142/354 (40%)	322/686 (47%)	OR 0.68 (0.51 to 0.92)[c]	94 fewer per 1000 (from 21 fewer to 158 fewer)	Low
Preterm birth <34 weeks											

1[55]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	64/354 (18%)	110/686 (16%)	OR 0.96 (0.64 to 1.44) [c]	5 fewer per 1000 (from 51 fewer to 55 more)	Very low
Birthweight (measured in g; better indicated by higher values)											
1[55]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	mean 2468 (SD 559) N=354	mean 2378 (SD 620) N=686	-	MD 80.00 higher [c] (P <0.06)	Low

CI confidence interval, MD mean difference, N sample size, OR odds ratio, SD standard deviation

[a] Serious indirectness because study reported pregnancy-induced hypertension, not pre-eclampsia

[b] Total number of events < 300

[c] OR or MD adjusted for confounders; adjusted OR/MD obtained using logistic/linear regression analysis

Table 5.3 GRADE findings for effectiveness of daily supplementation with vitamins C and E in women with twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Daily vitamins**	**Placebo**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Pre-eclampsia											
1[56]	Randomised controlled trial	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	23/81 (28.4%)	23/100 (23.0%)	1.2 (0.7 to 2.0)	46 more per 1000 (from 69 fewer to 230 more)	Low

CI confidence interval, MD mean difference, OR odds ratio

[a] Serious indirectness because the populations in the countries in which the study was carried out (India, Peru, South Africa and Vietnam) are likely to be different from the UK population

[b] Total number of events < 300

Table 5.4 GRADE findings for effectiveness of daily supplementation with fish oil in women with twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fish oil group**	**Placebo group**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Pre-eclampsia											
1[57]	Randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	14/246 (5.7%)	6/251 (2.4%)	OR 2.46 (0.93 to 6.52)	33 more per 1000 (from 2 fewer to 114 more)	Moderate
Preterm birth											
Preterm birth <37 weeks											
1[57]	Randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	129/286 (45.1%)	127/283 (47%)	OR 1.01 (0.73 to 1.40)	2 more per 1000 (from 76 fewer to 84 more)	Moderate
Preterm birth <34 weeks											
1[57]	Randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	37/286 (12.9%)	44/283 (15.5%)	OR 0.81 (0.50 to 1.29)	26 fewer per 1000 (from 71 fewer to 36 more)	Moderate
Birthweight (measured in g; better indicated by higher values)											
1[57]	Randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	mean 2512 (SD 627) N=556	mean 2498 (SD 599) N=556	-	MD 8.20 higher[b] (52.8 lower to 36.4 higher)	High

CI confidence interval, MD mean difference, N sample size, OR odds ratio, SD standard deviation

[a] Total number of events < 300

[b] Adjusted MD (adjusted by including gestational age at delivery as explanatory variable in a multiple linear regression)

Diet and lifestyle advice

Review question

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

Table 5.5 GRADE findings for effectiveness of nutritional advice specific to twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nutritional advice group**	**Normal antenatal care group**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Birthweight											
Birthweight (measured in g; better indicated by higher values)											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Modelling unsatisfactory[a]	190	339	-	MD 220 higher (P <0.0001)	Very low
Low birthweight											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	78/190 (41%)	217/339 (64%)	OR 0.42 (0.29 to 0.61)[c]	213 fewer per 1000 (from 120 fewer to 300 fewer)	Very low
Very low birthweight											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	10/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)[c]	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low
Pre-eclampsia											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	15/190 (8%)	58/339 (17%)	OR 0.41 (0.23 to 0.75)	93 fewer per 1000 (from 37 fewer to 126 fewer)	Very low
Preterm birth											
Preterm birth <36 weeks											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	78/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)[c]	119 fewer per 1000 (from 29 fewer to 204 fewer)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nutritional advice group**	**Normal antenatal care group**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Preterm birth <32 weeks											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	13/190 (7%)	71/339 (21%)	OR 0.27 (0.15 to 0.51)[c]	143 fewer per 1000 (from 90 fewer to 171 fewer)	Very low
Preterm birth <30 weeks											
1[54]	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	Modelling unsatisfactory[a]	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)[c]	63 fewer per 1000 (from 20 fewer to 80 fewer)	Very low

CI confidence interval, MD mean difference, OR odds ratio

[a] The study used a logistic regression model in a way that the GDG judged to be unsatisfactory because the effect of nutritional advice could not be separated from the effect of other advice and care that differed between the intervention and control groups

[b] Total number of events < 300

[c] OR adjusted for maternal age, insurance status and smoking in the multiple logistic regression models

Specialist care

Review question

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

Table 5.6 GRADE findings for comparisons based on case numbers in study and control groups

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Maternal morbidity (including anxiety and depression)											
Anaemia (Hgb <10mg/dl)											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17/89 (19%)	11/51 (22%)	OR 0.85 (0.36 to 2.01)	25 fewer per 1000 (from 126 fewer to 140 more)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	5/30 (17%)	7/41 (17%)	OR 0.97 (0.27 to 3.4)	4 fewer per 1000 (from 118 fewer to 242 more)	Very low
Bleeding ≥ 20 weeks											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/89 (2%)	4/51 (8%)	OR 0.28 (0.05 to 1.47)	56 fewer per 1000 (from 74 fewer to 33 more)	Very low
1[54]	Prospective observational study	Serious [b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	2/339 (1%)	OR 1.78 (0.25 to 12.5)	5 more per 1000 (from 4 fewer to 63 more)	Very low
Caesarean section											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	12/30 (40%)	19/41 (46%)	OR 0.77 (0.29 to 2.00)	63 fewer per 1000 (from 263 fewer to 170 more)	Very low
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	29/89 (33%)	15/51 (29%)	OR 1.16 (0.54 to 2.45)	32 more per 1000 (from 110 fewer to 217 more)	Very low
Gestational diabetes											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	6/89 (7%)	1/51 (2%)	OR 3.61 (0.42 to 30.9)	47 more per 1000 (from 11 fewer to 337 more)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	8/190 (4%)	7/339 (2%)	OR 2.08 (0.74 to 5.8)	21 more per 1000 (from 5 fewer to 88 more)	Very low
Gestational hypertension											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Pre-eclampsia											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	10/89 (11%)	4/51 (8%)	OR 1.16 (0.37 to 3.61)	34 more per 1000 (from 48 fewer to 157 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	15/190 (8%)	57/339 (17%)	OR 0.41 (0.23 to 0.75)	89 fewer per 1000 (from 37 fewer to 124 fewer)	Very low
Prelabour rupture of membranes											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	11/89 (12%)	13/51 (26%)	OR 0.40 (0.16 to 1.00)	131 fewer per 1000 (from 203 fewer to 1 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	19/190 (10%)	84/339 (25%)	OR 0.35 (0.2 to 0.6)	148 fewer per 1000 (from 83 fewer to 186 fewer)	Very low
Preterm labour											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	44/190 (23%)	142/339 (42%)	OR 0.42 (0.28 to 0.62)	186 fewer per 1000 (from 110 fewer to 251 fewer)	Very low
Urinary tract infection											
1[52]	Prospective observational	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	4/89 (5%)	3/51 (6%)	OR 0.75 (0.16 to	14 fewer per 1000	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
	study								3.50)	(from 49 fewer to 121 more)	
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/30 (7%)	4/41 (10%)	OR 0.66 (0.11 to 3.86)	31 fewer per 1000 (from 86 fewer to 197 more)	Very low
Perinatal and neonatal mortality											
Perinatal mortality											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/178 (1%)	8/102 (8%)	OR 0.06 (0.01 to 0.53)	72 fewer per 1000 (from 33 fewer to 78 fewer)	Very low
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/30 (3%)	2/41 (5%)	RR 0.68 (0.06 to 7.19)	16 fewer per 1000 (from 46 fewer to 236 more)	Very low
Neonatal morbidity											
Preterm birth <37 weeks											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	69/89 (78%)	37/51 (73%)	OR 1.30 (0.59 to 2.87)	23 more per 1000 (from 116 fewer to 158 more)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	44/190 (23%)	142/339 (42%)	OR 0.45 (0.3 to 0.68)	187 fewer per 1000 (from 90 fewer to 241	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
										fewer)	
Preterm birth <36 weeks											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	38/60 (63%)	68/82 (83%)	OR 0.36 (0.16 to 0.77)	193 fewer per 1000 (from 40 fewer to 392 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	77/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)	126 fewer per 1000 (from 29 fewer to 204 fewer)	Very low
Preterm birth <32 weeks											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	14/190 (7%)	72/339 (21%)	OR 0.27 (0.15 to 0.51)	138 fewer per 1000 (from 91 fewer to 174 fewer)	Very low
Preterm birth <30 weeks											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/30 (0%)	12/41 (29.3%)	NC	293 fewer per 1000	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)	59 fewer per 1000 (from 20 fewer to 80 fewer)	Very low
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/89 (2%)	9/51 (18%)	OR 0.29 (0.11 to 0.76)	154 fewer per 1000 (from 36 fewer to 153	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
										fewer)	
Anaemia											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	8/190 (4%)	44/339 (13%)	OR 0.31 (0.17 to 0.56)	90 fewer per 1000 (from 53 fewer to 105 fewer)	Very low
Antibiotics											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	80/190 (42%)	203/339 (60%)	OR 0.50 (0.37 to 0.67)	180 fewer per 1000 (from 99 fewer to 243 fewer)	Very low
Apnea, bradycardia or cyanosis											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	13/190 (7%)	78/339 (23%)	OR 0.27 (0.17 to 0.44)	162 fewer per 1000 (from 114 fewer to 182 fewer)	Very low
Hyperbilirubinaemia											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	36/190 (19%)	98/339 (29%)	OR 0.56 (0.40 to 0.79)	100 fewer per 1000 (from 46 fewer to 149 fewer)	Very low
Intravenous fluids											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	72/190 (38%)	200/339 (59%)	OR 0.43 (0.32 to 0.57)	210 fewer per 1000 (from 139	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
										fewer to 275 fewer)	
Low birthweight											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	78/190 (41%)	217/339 (64%)	OR 0.39 (0.27 to 0.56)	231 fewer per 1000 (from 141 fewer to 316 fewer)	Very low
Major neonatal morbidity (retinopathy of prematurity, necrotising enterocolitis, ventilator support, or intraventricular haemorrhage)											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	32/190 (17%)	108/339 (32%)	OR 0.44 (0.31 to 0.62)	151 fewer per 1000 (from 94 fewer to 192 fewer)	Very low
Mechanical ventilation											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	29/190 (15%)	102/339 (30%)	OR 0.41 (0.28 to 0.59)	150 fewer per 1000 (from 98 fewer to 193 fewer)	Very low
Necrotising enterocolitis											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	10/339 (3%)	OR 0.21 (0.05 to 0.95)	20 fewer per 1000 (from 1 fewer to 28 fewer)	Very low
NICU admission											
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	24/178 (14%)	39/102 (38%)	OR 0.35 (0.22 to 0.55)	247 fewer per 1000 (from 128	Low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
										fewer to 262 fewer)	
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	82/190 (43%)	214/339 (63%)	OR 0.48 (0.36 to 0.64)	199 fewer per 1000 (from 108 fewer to 250 fewer)	Very low
Parenteral nutrition											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	25/190 (13%)	105/339 (31%)	OR 0.32 (0.22 to 0.46)	180 fewer per 1000 (from 139 fewer to 220 fewer)	Very low
Phototherapy											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	30/190 (16%)	125/339 (37%)	OR 0.34 (0.24 to 0.49)	210 fewer per 1000 (from 146 fewer to 246 fewer)	Very low
Patent ductus arteriosus											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	4/190 (2%)	17/339 (5%)	OR 0.37 (0.15 to 0.88)	30 fewer per 1000 (from 6 fewer to 42 fewer)	Very low
Respiratory distress syndrome											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	34/190 (18%)	105/339 (31%)	OR 0.44 (0.31 to 0.62)	131 fewer per 1000 (from 92 fewer to 188 fewer)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
Retinopathy of prematurity											
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	2/190 (1%)	24/339 (7%)	OR 0.19 (0.07 to 0.50)	60 fewer per 1000 (from 34 fewer to 65 fewer)	Very low
Small for gestational age (resulting in preterm birth)											
1[60]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	14,365/165,120 (9%)	57,067/425,876 (13%)	OR 0.62 (0.60 to 0.63)	46 fewer per 1000 (from 45 fewer to 49 fewer)	Low
1[60]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	23,117/165,120 (14%)	62,178/425,876 (15%)	OR 0.95 (0.94 to 0.97)	6 fewer per 1000 (from 4 fewer to 8 fewer)	Low
Small for gestational age (birth at term)											
1[60]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	47,720/165,120 (29%)	93,693/425,876 (22%)	OR 1.44 (1.42 to 1.46)	69 more per 1000 (from 66 more to 72 more)	Low
1[60]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	31,537/165,120 (19%)	72,399/425,876 (17%)	OR 5.08 (5.00 to 5.16)	340 more per 1000 (from 336 more to 344 more)	Low
Supplemental oxygen											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialist clinics**	**Normal clinics**	**Relative effect (95% CI)**	**Absolute effect**	**Quality**
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	53/190 (28%)	153/339 (45%)	OR 0.49 (0.36 to 0.67)	170 fewer per 1000 (from 96 fewer to 223 fewer)	Very low
Very low birthweight (<1500g)											
1[53]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	5/30 (17%)	16/41 (39%)	OR 0.42 (0.17 to 1.03)	223 fewer per 1000 (from 292 fewer to 7 more)	Very low
1[52]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	10/178 (6%)	27/102 (27%)	OR 0.21 (0.10 to 0.42)	209 fewer per 1000 (from 133 fewer to 230 fewer)	Very low
1[54]	Prospective observational study	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	9/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low

CI confidence interval, Hgb haemoglobin, NICU neonatal intensive care unit, NC not calculable, OR odds ratio, RR relative risk

[a] Total number of events < 300

[b] 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

Table 5.7 GRADE findings for comparison of case rates per 1000 live births

Quality assessment							Summary of findings					
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Women with twin and/or triplet pregnancies**		**Rate per 1000 Live Births**			**Quality**
							Study sub group	**Study population**	**Rate in study sub group**	**Overall rate in study population**	**Z score**	
Perinatal and neonatal mortality												
1[60] (data for 1983 to 1984)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	165,120 intensive care	811,505 all care	27.6 (24.6 to 30.5)	50.0 (48.7 to 51.3)	Significant (p value not reported)	Low
1[60] (data for 1989 to 1990)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	165,120 intensive care	811,505 all care	22.1 (20.5 to 23.7)	41.1 (40.1 to 42.1)	Significant (p value not reported)	Low
1[60] (data for 1995 to 1996)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	165,120 intensive care	811,505 all care	17.8 (16.5 to 19.1)	29.2 (28.4 to 30.0)	Significant (p value not reported)	Low
1[60] (data for 1983 to 1984)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	425,876 adequate care	811,505 all care	53.8 (51.9 to 55.8)	50.0 (48.7 to 51.3)	Significant (p value not reported)	Low
1[60] (data for 1989 to 1990)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	425,876 adequate care	811,505 all care	43.4 (42.0 to 44.8)	41.1 (40.1 to 42.1)	Significant (p value not reported)	Low
1[60] (data for 1995 to 1996)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	425,876 adequate care	811,505 all care	33.0 (31.9 to 34.1)	29.2 (28.4 to 30.0)	Significant (p value not reported)	Low
Neonatal morbidity												

Quality assessment							Summary of findings					
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Women with twin and/or triplet pregnancies**		**Rate per 1000 Live Births**			**Quality**
							Study sub group	**Study population**	**Rate in study sub group**	**Overall rate in study population**	**Z score**	
Preterm birth												
1[60] (data for 1981)	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Figures derived from graph	165,120 intensive care	425,876 adequate care	350	510	Not reported	Very low
1[60] (data for 1997)	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Figures derived from graph	165,120 intensive care	425,876 adequate care	550	600	Not reported	Very low

Chapter 6 Fetal complications

Screening for chromosomal abnormalities

Review question

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

Table 6.1 GRADE summary of findings for studies evaluating screening tests for chromosomal abnormalities tests in monochorionic twins

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Combined tests																
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A - risk > 1:250 for trisomy 21																
1[63]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	24	100 (16 to 100)	91 (79 to 100)	50 (10 to 99)	100 (83 to 100)	11 (3 to 41)	50 (16 to 71)	0.0 (0.0 to 2.4)	0 (0 to 18)	Very low
Nuchal translucency with maternal age																
Risk > 1:250 per fetus for trisomy 21																
1[63]	Prospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	24	100 (16 to 100)	91 (79 to 100)	50 (10 to 99)	100 (83 to 100)	11 (3 to 41)	50 (16 to 71)	0.0 (0.0 to 2.4)	0 (0 to 18)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using fetus with highest nuchal translucency)																
1[64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Seriou [c]	None	1538	100 (54 to 100)	81 (78 to 83)	4 (1 to 7)	100 (99 to 100)	5 (4 to 6)	4 (3 to 5)	0.1 (0.0 to 1.3)	0 (0 to 1)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using fetus with smallest nuchal translucency)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	1538	67 (22 to 96)	93 (90 to 94)	7 (0 to 13)	99.7 (99 to 100)	9 (5 to 17)	7 (4 to 12)	0.4 (0.1 to 1.1)	0 (0 to 1)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using average of both fetuses' nuchal translucency)																
1[64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	1538	100 (54 to 100)	86 (83 to 89)	5 (1 to 10)	100 (99 to 100)	7 (5 to 9)	5 (4 to 7)	0.1 (0.0 to 1.2)	0 (0 to 1)	Very low
Nuchal translucency without maternal age																
>95th centile for trisomy 21 or trisomy 18																
1[64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	No serious imprecision	None	1538	86 (67 to 100)	90 (88 to 91)	7 (3 to 11)	99.8 (99 to 100)	8 (6 to 11)	7 (5 to 9)	0.2 (0.0 to 0.6)	0 (0 to 1)	Very low
>95th centile for trisomy 21																
1[64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	1538	83 (52 to 98)	89 (88 to 91)	6 (2 to 9)	99.8 (99 to 100)	8 (6 to 11)	6 (5 to 7)	0.2 (0.1 to 0.7)	0 (0 to 1)	Very low
>95th centile for trisomy 18																
1 [64]	Retrospective cohort study	Serious[d]	No serious inconsistency	Serious[b]	Serious[c]	None	1538	100 (16 to 100)	89 (87 to 91)	1 (0 to 3)	100 (99 to 100)	8 (4 to 13)	1 (0 to 1)	0.2 (0.0 to 2.4)	0 (0 to 0)	Very low

CI confidence interval, f-beta-hCG free beta human chorionic gonadotrophin, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PAPP-A pregnancy-associated plasma protein-A, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] Different reference tests were used depending on the index test result. It is unclear whether the reference standard results were interpreted without knowledge of the results of the index test

[b] No clinical outcomes were reported

[c] Width of 95% CI ≥ 40 percentage points

[d] Different reference standards were used depending on the index test results. It was unclear whether the index text or the reference test could be replicated. It was unclear whether the reference test results were interpreted without knowledge of the index test results

Table 6.2 GRADE findings for studies evaluating screening tests for chromosomal abnormalities in dichorionic twins

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Combined tests																
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk 1:250 for trisomy 21																
1[63]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	176	100 (3 to 100)	97 (95 to 100)	17 (0 to 46)	100 (98 to 100)	35 (15 to 83)	17 (4 to 31)	0.0 (0.0 to 2.9)	0 (0 to 2)	Very low
Nuchal translucency with maternal age																
Risk > 1:250 per fetus for trisomy 21																
1[63]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	88	100 (3 to 100)	91 (87 to 96)	6 (0 to 18)	100 (98 to 100)	12 (3 to 22)	7 (2 to 12)	0.0 (0.0 to 3.0)	0 (0 to 2)	Very low
Nuchal translucency alone																
>95th centile for trisomy 21, trisomy 18 or trisomy 13																
1[65]	Prospective screening study	Serious[d]	No serious inconsistency	Serious[b]	No serious imprecision	None	706	91 (74 to 100)	96 (95 to 98)	27 (13 to 41)	99.8 (99 to 100)	23 (15 to 35)	27 (20 to 36)	0.1 (0.0 to 0.6)	0 (0 to 1)	Low
>95th centile for trisomy 21 or trisomy 18																
1[66]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[e]	Serious[c]	None	350	100 (40 to 100)	98 (96 to 99)	40 (10 to 70)	100 (99 to 100)	48 (21 to 109)	39 (19 to 55)	0.1 (0.0 to 1.4)	0 (0 to 2)	Very low
>99th centile for trisomy 21																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[67]	Prospective cohort study	Serious[f]	No serious inconsistency	Serious[b]	Serious[c]	None	332	50 (1 to 99)	98 (96 to 99)	14 (0 to 40)	99.7 (99 to 100)	28 (6 to 136)	14 (3 to 45)	0.5 (0.1 to 2.0)	0 (0 to 1)	Very low
>95th centile for trisomy 21																
1[68]	Retrospective cohort study	Serious[g]	No serious inconsistency	Serious[b]	Serious[c]	None	140	100 (3 to 100)	94 (89 to 98)	10 (0 to 29)	100 (97 to 100)	15 (8 to 29)	10 (3 to 17)	0.0 (0.0 to 3.0)	0 (0 to 2)	Very low
1[66]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Seriou [c]	None	350	100 (99 to 100)	98 (97 to 99)	30 (2 to 58)	100 (99 to 100)	50 (24 to 103)	31 (14 to 45)	0.0 (0.0 to 2.7)	0 (0 to 2)	Very low
>95th centile for trisomy 18																
1[66]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	350	100 (3 to 100)	97 (96 to 99)	10 (0 to 29)	100 (99 to 100)	39 (20 to 74)	11 (3 to 19)	0.0 (0.0 to 2.8)	0 (0 to 1)	Very low

CI confidence interval, f-beta-hCG free beta human chorionic gonadotrophin, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PAPP-A pregnancy-associated plasma protein-A, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] Different reference tests were used depending on the index test result. It is unclear whether the reference standard results were interpreted without knowledge of the results of the index test

[b] No clinical outcomes were reported

[c] Width of 95% CI ≥ 40 percentage points

[d] It was unclear whether the reference standard was likely to classify the target condition correctly. It was unclear whether the whole sample of a random selection of the sample received verification using the reference standard. It was unclear whether the reference standard results were interpreted without knowledge of the index test. Different reference tests were used depending on the index test results. The reference standard was not described in sufficient detail to permit its replication

[e] No clinical outcomes were reported. The study was conducted in Chile, which was judged to be somewhat indirect from a UK setting

[f] Different reference standards were used depending on the index test results. It was unclear whether the index test could be replicated. It was unclear whether the reference test results were interpreted without knowledge of the index test results

[g] It was unclear what the reference test was for the screen negative fetuses and whether it was likely to classify the target condition correctly. It was unclear whether the whole sample or a random selection of the sample was verified with the reference standard. It was unclear whether the results of the reference test were interpreted without knowledge of the results of the index test. The reference test used varied depending on the index test result

Table 6.3 GRADE findings for studies evaluating screening tests for chromosomal abnormalities in twin pregnancies with unreported or mixed chorionicity or in triplet pregnancies

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Combined tests																
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk >1:250 per fetus for trisomy 21																
1[63]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	200 twin 0 triplet	100 (29 to 100)	96 (93 to 99)	30 (2 to 58)	100 (98 to 100)	23 (10 to 51)	30 (13 to 44)	0.1 (0.0 to 1.7)	0 (0 to 3)	Very low
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk >1:300 per fetus for trisomy 21																
1[69]	Prospective cohort study	Serious[d]	No serious inconsistency	Serious[e]	Serious[c]	None	114 twin 0 triplet	100 (29 to 100)	95 (89 to 98)	14 (0 to 40)	100 (97 to 100)	13 (4 to 39)	15 (4 to 26)	0.3 (0.0 to 2.9)	0 (0 to 3)	Very low
1[70]	Retrospective screening study	Serious[f]	No serious inconsistency	Serious[b]	Serious[c]	None	398 twin 0 triplet	100 (29 to 100)	99.8 (99 to 100)	75 (33 to 100)	100 (99 to 100)	395 (56 to 2797)	76 (27 to 91)	0.0 (0.0 to 1.7)	0 (0 to 1)	Very low
Nuchal translucency with maternal age																
Risk > 1:250 per fetus for trisomy 21																
1[63]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Seriou[c]	None	200 twin 0 triplet	100 (29 to 100)	91 (87 to 95)	15 (0 to 31)	100 (29 to 100)	11 (7 to 17)	15 (8 to 21)	0.0 (0.0 to 0.9)	0 (0 to 3)	Very low
Risk > 1:300 per fetus for trisomy 21																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[65]	Prospective screening study	Serious[g]	No serious inconsistency	Serious[b]	No serious imprecision	None	896 twin 0 triplet	100 (63 to 100)	81 (79 to 84)	5 (1 to 8)	100 (99 to 100)	5 (4 to 6)	5 (4 to 5)	0.1 (0.0 to 1.0)	0 (0 to 1)	Low
Nuchal translucency alone																
>95th centile for trisomy 21, trisomy 18 or trisomy 13																
1[65]	Prospective screening study	Serious[g]	No serious inconsistency	Serious[b]	No serious imprecision	None	896 twin 0 triplet	91 (74 to 100)	95 (94 to 97)	19 (8 to 29)	99.8 (99 to 100)	19 (13 to 26)	19 (14 to 24)	0.1 (0.0 to 0.6)	0 (0 to 1)	Low
>95th centile for trisomy 21 or trisomy 18																
1[66]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	412 twin 24 triplet	100 (40 to 100)	98 (97 to 99)	31 (6 to 56)	100 (99 to 100)	48 (25 to 91)	30 (15 to 43)	0.0 (0.0 to 1.4)	0 (0 to 1)	Very low
>99th centile for trisomy 21																
1[67]	Prospective cohort study	Serious[h]	No serious inconsistency	Serious[b]	Serious[c]	None	412 twin 0 triplet	50 (1 to 99)	97 (95 to 99)	8 (0 to 24)	99.8 (99 to 100)	19 (4 to 84)	9 (2 to 30)	0.5 (0.1 to 2.1)	0 (0 to 1)	Very low
>95th centile for trisomy 21																
3[65;66;71]	Prospective cohort and screening studies	Serious[i]	Serious [j]	Serious[k]	No serious imprecision	None	828 twin 24 triplet	93 (66 to 100)	95 (94 to 96)	Range: 11 to 21	Range: 99.8 to 100	20 (12 to 35)	NC	0.1 (0.0 to 0.5)	NC	Very low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[68]	Retrospective cohort study	Serious[l]	No serious inconsistency	Serious[b]	Serious[c]	None	200 twin 0 triplet	100 (3 to 100)	93 (89 to 96)	6 (0 to 16)	100 (98 to 100)	13 (8 to 21)	5 (1 to 8)	0.0 (0.0 to 3.0)	0 (0 to 1)	Very low
>95th centile for trisomy 18																
1[66]	Prospective cohort study	Serious[a]	No serious inconsistency	Serious[e]	Serious[c]	None	412 twin 24 triplet	100 (3 to 100)	97 (95 to 98)	7 (0 to 21)	100 (99 to 100)	24 (9 to 63)	6 (2 to 11)	0.3 (0.0 to 2.9)	0 (0 to 1)	Very low

CI confidence interval, f-beta-hCG free beta human chorionic gonadotrophin, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PAPP-A pregnancy-associated plasma protein-A, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] Different reference tests were used depending on the index test result. It is unclear whether the reference standard results were interpreted without knowledge of the results of the index test

[b] No clinical outcomes were reported

[c] Width of 95% CI ≥ 40 percentage points

[d] It was unclear whether the reference standard was likely to classify the target condition correctly. It was unclear whether the whole sample or a random selection of the sample received verification using the reference standard. It was unclear whether the reference standard results were interpreted without knowledge of the index test. Different reference tests were used depending on the index test results. The reference standard was not described in sufficient detail to permit its replication. Withdrawals from the study were not explained

[e] No clinical outcomes were reported. The study was conducted in Chile, which was judged to be somewhat indirect from a UK setting

[f] Not all the participants in this study received the same reference standard. It is not clear whether the reference test results were interpreted without knowledge of the index test results

[g] It was unclear whether the reference standard was likely to classify the target condition correctly. It was unclear whether the whole sample of a random selection of the sample received verification using the reference standard. It was unclear whether the reference standard results were interpreted without knowledge of the index test. Different reference tests were used depending on the index test results. The reference standard was not described in sufficient detail to permit its replication

[h] Different reference standards were used depending on the index test results. It was unclear whether the index test could be replicated. It was unclear whether the reference test results were interpreted without knowledge of the index test results

[i] In the Maymon (2001) study different reference standards were used depending on the index test results. It was unclear whether the index test could be replicated. It was unclear whether the reference test results were interpreted without knowledge of the index test results. In the Sebire (1996) study it was unclear whether the reference standard was likely to classify the target condition correctly. It was unclear whether the whole sample or a random selection of the sample received verification using the reference standard. It was unclear whether the reference standard results were interpreted without knowledge of the index test. Different reference tests were used depending on the index test results. The reference standard was not described in sufficient detail to permit

its replication. In the Sepulveda (2009) study different reference tests were used depending on the index test result. It is unclear whether the reference standard results were interpreted without knowledge of the results of the index test

[j]The specificity data and positive likelihood ratio data showed serious inconsistency

[k] No clinical outcomes were reported. The Maymon (2001) study was conducted in Israel, which was judged to be somewhat indirect from a UK setting. The Sepulveda (2009) study was conducted in Chile, which was judged to be somewhat indirect from a UK setting

[l] It was unclear what the reference test was for the screen negative fetuses and whether it was likely to classify the target condition correctly. It was unclear whether the whole sample or a random selection of the sample was verified with the reference standard. It was unclear whether the results of the reference test were interpreted without knowledge of the results of the index test. The reference test used varied depending on the index test result

Screening for structural abnormalities

Review question

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

Table 6.4 GRADE findings for studies evaluating screening tests for structural abnormalities

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
All anomalies																
Ultrasound (second or third trimester anomaly scan)																
1[72]	Retrospective cohort study	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	1397 twin 0 triplet	78 (60 to 91)	100 (99 to 100)	100 (86 to 100)	99 (99 to 100)	2111 (131 to 33943)	100 (76 to 100)	0.2 (0.1 to 0.4)	1 (0 to 1)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan), and fetal echocardiography																
1[74]	Prospective cohort study	Very serious[c]	No serious inconsistency	Serious[d]	Serious[e]	Serious[f]	990 twin 0 triplet	28 (12 to 49)	100 (99 to 100)	100 (59 to 100)	98 (97 to 99)	557 (33 to 9502)	100 (46 to 100)	0.7 (0.6 to 0.9)	2 (1 to 2)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan), and fetal echocardiography in dichorionic twin pregnancies																
1[74]	Prospective cohort study	Very serious[c]	No serious inconsistency	Serious[d]	Serious[e]	Serious[f]	842 twin 0 triplet	33 (15 to 57)	100 (99 to 100)	100 (59 to 100)	98 (97 to 99)	560 (33 to 9509)	100 (46 to 100)	0.7 (0.5 to 0.9)	2 (1 to 2)	Very low
All cardiac anomalies																
Fetal echocardiography																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[73]	Prospective cohort study	Serious[g]	No serious inconsistency	Very serious[h]	No serious imprecision	None	1206 twin 0 triplet	88 (62 to 98)	100 (99 to 100)	100 (77 to 100)	99.8 (99 to 100)	2032 (126 to 32692)	100 (62 to 100)	0.2 (0.1 to 0.5)	0 (0 to 1)	Very low
Lethal anomalies																
Ultrasound (second or third trimester anomaly scan)																
1[72]	Retrospective cohort study	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1397 twin 0 triplet	100 (29 to 100)	100 (99 to 100)	100 (29 to 100)	100 (99 to 100)	2436 (149 to 39898)	100 (23 to 100)	0.1 (0.0 to 1.7)	0 (0 to 1)	Very low
Fetal echocardiography																
1[73]	Prospective cohort study	Serious[g]	No serious inconsistency	Very serious[h]	Serious[c]	None	2204 twin 0 triplet	100 (3 to 100)	100 (99 to 100)	100 (3 to 100)	100 (99 to 100)	3306 (185 to 59171)	100 (14 to 100)	0.3 (0.0 to 2.8)	0 (0 to 1)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan), and fetal echocardiography																
1[74]	Prospective cohort study	Very serious[d]	No serious inconsistency	Serious[e]	Serious[c]	Serious[f]	990 twin 0 triplet	100 (48 to 100)	100 (99 to 100)	100 (48 to 100)	100 (99 to 100)	1808 (112 to 29184)	100 (36 to 100)	0.1 (0.0 to 1.2)	0 (0 to 1)	Very low
Possible survival and long-term morbidity																
Ultrasound (second or third trimester anomaly scan)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[72]	Retrospective cohort study	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	1394 twin 0 triplet	94 (71 to 99)	100 (99 to 100)	100 (79 to 100)	99.9 (99 to 100)	2526 (158 to 40511)	100 (66 to 100)	0.1 (0.0 to 0.4)	0 (NC)	Very low
Fetal echocardiography																
1[73]	Prospective cohort study	Serious[g]	No serious inconsistency	Very serious[h]	No serious imprecision	None	2204 twin 0 triplet	100 (69 to 100)	100 (99 to 100)	100 (69 to 100)	100 (99 to 100)	4191 (261 to 67176)	100 (57 to 100)	0.1 (0.0 to 0.7)	0 (NC)	Very low
Anomalies amenable to intrauterine therapy																
Ultrasound (second or third trimester anomaly scan)																
1[72]	Retrospective cohort study	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1394 twin 0 triplet	100 (16 to 100)	100 (99 to 100)	100 (3 to 100)	100 (99 to 100)	2091 (117 to 37418)	100 (10 to 100)	0.3 (0.0 to 2.8)	0 (NC)	Very low
Anomalies associated with possible short-term/immediate morbidity																
Ultrasound (second or third trimester anomaly scan)																
1[72]	Retrospective cohort study	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1394 twin 0 triplet	43 (10 to 82)	100 (99 to 100)	100 (29 to 100)	99.7 (99 to 100)	1215 (68 to 21647)	100 (25 to 100)	0.6 (0.3 to 1.0)	0 (0 to 1)	Very low
Fetal echocardiography																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin and triplet pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[73]	Prospective cohort study	Serious[g]	No serious inconsistency	Very serious[h]	Serious[c]	None	2005 twin 0 triplet	33 (1 to 91)	100 (99 to 100)	100 (3 to 100)	99.9 (99 to 100)	1652 (79 to 34754)	100 (7 to 100)	0.6 (0.3 to 1.3)	0 (NC)	Very low

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] It was not clear whether the reference standard would classify the target condition or whether the reference standard results were interpreted without knowledge of the results of the index test. Neither the index test nor reference standard was described in enough detail to allow replication

[b] The study was conducted in Taiwan. It is not clear whether the person performing the tests was representative of clinicians who would be performing the tests in practice. Clinically important outcomes were not clearly reported

[c] It was not clear whether the reference standard results were interpreted without knowledge of the results of the index test. Neither the index test nor reference standard was described in enough detail to allow replication

[d] Clinically important outcomes were not reported clearly

[e] Width of 95% CI ≥ 40 percentage points

[f] Only anomaly rates for live births were reported

[g] It was not clear whether the reference standard results were interpreted without knowledge of the results of the index test. The reference standard was not described in enough detail to allow replication

[h] The study was conducted in China. It is not clear whether the person performing the tests was representative of clinicians who would be performing the tests in practice. Clinically important outcomes were not reported clearly

Monitoring forfeto-fetal transfusion syndrome

Review question

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

Table 6.5 GRADE findings for studies reporting diagnostic accuracy measures for screening tests for feto-fetal transfusion syndrome

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
First trimester methods																
Nuchal translucency – thickness >95th centile for gestational age at 10–14 weeks (for fetuses)																
1[75]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	574	38 (23 to 53)	94 (92 to 96)	32 (19 to 45)	95 (93 to 97)	6 (4 to 11)	32 (22 to 45)	0.7 (0.5 to 0.9)	5 (4 to 6)	Moderate
Nuchal translucency – thickness >95th centile for gestational age in at least 1 fetus at 10–14 weeks (for pregnancies)																
1[75]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	287	32 (17 to 48)	90 (86 to 94)	32 (17 to 48)	90 (86 to 94)	3 (2 to 6)	32 (21 to 47)	0.8 (0.6 to 0.9)	10 (8 to 12)	Moderate
Nuchal translucency – discordance ≥ 20% (as a percentage of larger measurement)																
2[76;77]	Meta-analysis of 1 prospective and 1 retrospective study	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	525	55 (43 to 67)	78 (74 to 82)	Range: 26 to 50	Range: 87 to 93	3 (1 to 3)	30 (25 to 36)	0.6 (0.4 to 0.7)	9 (7 to 11)	Low
Nuchal translucency – difference of ≥ 0.6mm at 11–14 weeks.																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[78]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	99	50 (22 to 78)	92 (86 to 98)	46 (19 to 73)	93 (88 to 98)	6 (3 to 15)	46 (26 to 67)	0.5 (0.3 to 1.0)	7 (4 to 12)	Moderate
Crown–rump length (CRL) - discordance > 10% at 11–14 weeks (as a percentage of larger measurement)																
1[76]	Prospective cohort study	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	480	19 (10 to 29)	92 (89 to 94)	27 (15 to 40)	87 (84 to 90)	2 (1 to 4)	27 (17 to 40)	0.9 (0.8 to 1.0)	13 (11 to 14)	Low
Ductus venosus blood flow – abnormal wave form in at least one fetus (at 11–14 weeks) (including absent, reversed or reversed a-wave)																
2[78;79]	Meta-analysis of prospective studies	No serious limitations	Very serious[c]	Serious[d]	No serious imprecision	None	278	45 (30 to 61)	89 (84 to 93)	Range: 30 to 75	Range: 89 to 92	6 (1 to 35)	42 (31 to 54)	0.6 (0.4 to 0.9)	10 (8 to 13)	Very low
Second trimester methods																
Intertwin membrane folding at 15–17 weeks																
1[75]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	153	91 (80 to 100)	79 (71 to 86)	43 (29 to 57)	98 (95 to 100)	4 (3 to 6)	43 (34 to 52)	0.1 (0.0 to 0.5)	2 (1 to 7)	Moderate
Intertwin amniotic discordance of 3.1cm at 18–21 weeks																
1[80]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	52	82 (59 to 100)	44 (29 to 59)	28 (13 to 44)	90 (77 to 100)	1 (1 to 2)	28 (21 to 37)	0.4 (0.1 to 1.5)	10 (3 to 29)	Moderate

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] Early fetal death group (death <18 weeks of gestation) has been excluded from the diagnosis which could have been due to feto-fetal transfusion (FFTS) in Kagan 2007[76]

[b] Width of 95% CI ≥ 40 percentage points

[c] When the results were meta-analysed, there was serious inconsistency (I^2= 86%)

[d] Absence or reversed a-wave in Matias 2010[78] and reversed a-wave only in Maiz 2009[79] were considered abnormal DV waveforms

Table 6.6 GRADE findings for studies that did not report diagnostic accuracy measures for screening tests for feto-fetal transfusion syndrome

Quality assessment							Summary of findings					
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**		**Effect**			**Quality**
							Number of twin pregnancies	**Non FFTS group**	**FFTS group**	**Odds Ratio**	**P value**	
Nuchal translucency												
Mean inter-twin discordance												
1[79]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	179	19.6%	16.7%	Not reported	Not significant (p= 0.78)	Very low
Mean inter-twin discordance - multiple logistical regression analysis (discordancy in nuchal translucency, discordancy in crown–rump length, maternal age, ethnicity, IVF and smoking)												
1[79]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	None	179	19.6%	16.7%	Not reported	Not significant (p= 0.16)	Very low

FFTS feto-fetal transfusion syndrome

[a] Sample size < 400

Monitoring forintrauterine growth restriction

Review question

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

Table 6.7 GRADE summary of findings of findings for symphysis-fundal height measurement

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
symphysis-fundal height measurement in detecting intertwin birthweight difference (BWD) ≥20%																
1[83]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	160	24 (3 to 44)	83 (76 to 89)	14 (1 to 26)	90 (85 to 95)	1 (1 to 3)	14 (6 to 29)	0.9 (0.7 to 1.2)	10 (8 to 13)	Moderate

BWD Birth weight discordance, CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points

Table 6.8 GRADE findings for ultrasound scan measurement of fetal biometry

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Abdominal circumference																
Intrapair difference in abdominal circumference >5% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	90	89 (74 to 100)	60 (48 to 72)	37 (23 to 52)	95 (89 to 100)	2 (2 to 3)	37 (30 to 45)	0.2 (0.1 to 0.7)	5 (1 to 16)	Moderate
Abdominal circumference to detect IUGR <10th percentile in the smaller weight twin (using logistic regression)																
1[85]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	36	100 (NR)	85 (NR)	NR	NR	6 (NR)	NC	0.0 (NR)	NC	Moderate
Abdominal circumference based on ≥1 abnormal negative deviation to predict intrauterine growth restriction (IUGR) in twins																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	100 (NR)	67 (NR)	NR	NR	3 (NR)	NC	0.0 (NR)	NC	Moderate
Abdominal circumference based on prenatal growth assessment score to predict IUGR in twins																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	86 (NR)	88 (NR)	NR	NR	7 (NR)	NC	0.2 (NR)	NC	Moderate
Intertwin abdominal circumference ratio <0.93 to predict BWD ≥25% between 11–38 weeks – all twins																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[87]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	503	61 (NR)	84 (NR)	40 (NR)	93 (NR)	4 (NR)	NC	0.5 (NR)	NC	Moderate
Intertwin abdominal circumference ratio <0.93 to predict BWD ≥25% between 11-38 weeks – monochorionic twins																
1[87]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	125	80 (NR)	73 (NR)	45 (NR)	93 (NR)	3 (NR)	NC	0.3 (NR)	NC	Moderate
Intertwin abdominal circumference ratio <0.93 to predict BWD ≥25% between 11–38 weeks – dichorionic twins																
1[87]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	378	48 (NR)	88 (NR)	35 (NR)	92 (NR)	4 (NR)	NC	0.6 (NR)	NC	Moderate
Head circumference																
Intrapair difference in head circumference >5% in the prediction of birthweight difference (BWD) ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	64 (35 to 92)	74 (61 to 88)	39 (16 to 61)	89 (79 to 99)	2 (1 to 5)	39 (24 to 56)	0.5 (0.2 to 1.1)	11 (5 to 22)	Low
Intrapair difference in head circumference >10% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	18 (0 to 41)	93 (85 to 100)	40 (0 to 83)	82 (71 to 93)	3 (1 to 14)	40 (11 to 78)	0.9 (0.7 to 1.2)	18 (14 to 23)	Low
Head circumference to detect IUGR<10th percentile in the smaller weight twin (using logistic regression)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[85]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	36	38 (NR)	100 (NR)	NR	NR	999 (NR)	NC	0.6 (NR)	NC	Moderate
Head circumference ≥1 abnormal negative deviation to predict IUGR in twins																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	57 (NR)	96 (NR)	NR	NR	14 (NR)	NC	0.5 (NR)	NC	Moderate
Head circumference based on prenatal growth assessment score to predict IUGR in twins																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	57 (NR)	96 (NR)	NR	NR	14 (NR)	NC	0.5 (NR)	NC	Moderate
Femur length																
Intrapair difference in femur length >5% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	47 (23 to 71)	79 (69 to 89)	38 (17 to 59)	85 (75 to 94)	2 (1 to 5)	38 (23 to 55)	0.7 (0.4 to 1.1)	16 (10 to 23)	Low
Intrapair difference in femur length >10% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	18 (0 to 36)	94 (87 to 99.7)	43 (6 to 80)	81 (71 to 90)	3 (1 to 11)	43 (16 to 75)	0.9 (0.7 to 1.1)	19 (16 to 23)	Low
Femur length to detect IUGR <10th percentile in the smaller weight twin (using logistic regression)																

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Numbers of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[85]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	36	88 (NR)	85 (NR)	NR	NR	5 (NR)	NC	0.2 (NR)	NC	Moderate
Femur length ≥1 abnormal negative deviation to predict IUGR																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	57 (NR)	75 (NR)	NR	NR	2 (NR)	NC	0.6 (NR)	NC	Moderate
Femur length based on prenatal growth assessment score to predict IUGR																
1[86]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17	57 (NR)	83 (NR)	NR	NR	3 (NR)	NC	0.5 (NR)	NC	Moderate
Biparietal diameter																
Intrapair difference in biparietal diameter >5% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	57 (31 to 83)	62 (49 to 76)	30 (12 to 49)	84 (72 to 96)	2 (1 to 3)	30 (19 to 43)	0.7 (0.4 to 1.3)	16 (9 to 27)	Low
Intrapair difference in biparietal diameter >10% in the prediction of BWD ≥20%																
1[84]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	90	36 (11 to 61)	94 (87 to 100)	63 (29 to 96)	84 (74 to 94)	6 (2 to 22)	63 (31 to 86)	0.7 (0.5 to 1.0)	16 (11 to 22)	Low
Biparietal diameter in the prediction of SGA twins																
1[88]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	132	67 (51 to 82)	73 (63 to 82)	51 (37 to 65)	84 (75 to 92)	2 (2 to 4)	51 (41 to 61)	0.5 (0.3 to 0.7)	16 (11 to 24)	Moderate

BWD Birth weight discordance, CI confidence interval, IUGR intrauterine growth restriction, LR^+ positive likelihood ratio, LR^- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points or 95% CI not reported

Table 6.9 GRADE findings for fetal weight or fetal weight difference estimation using formulae that incorporate two or more fetal biometric measurements

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
EFW ≤10th percentile for prediction of IUGR ≤10th percentile																
1[89]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	73	85 (NR)	87 (NR)	80 (NR)	NR	7 (NR)	NC	0.2 (NR)	NC	Low
EFWD ≥15% for prediction of intertwin BWD ≥15%																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	Method used to estimate fetal weight[b]	575	64 (NR)	89 (NR)	71 (NR)	86 (NR)	6 (NR)	NC	0.4 (NR)	NC	Low
1[91]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	90	65 (47 to 84)	72 (61 to 83)	49 (32 to 65)	84 (74 to 93)	2 (1 to 4)	49 (37 to 60)	0.5 (0.3 to 0.9)	16 (10 to 25)	Moderate
Using Warsof's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	66 (NR)	76 (NR)	65 (NR)	74 (NR)	3 (NR)	NC	0.5 (NR)	NC	Low
Using Ong's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	72 (NR)	75 (NR)	65 (NR)	80 (NR)	3 (NR)	NC	0.4 (NR)	NC	Low
Using Shepard's formula (abdominal circumference, femur length)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	73 (NR)	71 (NR)	63 (NR)	79 (NR)	3 (NR)	NC	0.4 (NR)	NC	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	74 (NR)	76 (NR)	68 (NR)	81 (NR)	3 (NR)	NC	0.3 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	74 (NR)	75 (NR)	67 (NR)	81 (NR)	3 (NR)	NC	0.4 (NR)	NC	Low
EFWD ≥15% for prediction of intertwin BWD ≥20%																
USS within 7 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	88 (NR)	84 (NR)	NR	NR	6 (NR)	NC	0.1 (NR)	NC	Low
USS within 14 days of birth																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	85 (NR)	86 (NR)	NR	NR	6 (NR)	NC	0.2 (NR)	NC	Low
USS within 28 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	83 (NR)	86 (NR)	NR	NR	6 (NR)	NC	1.2 (NR)	NC	Low
Using Warsof's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	72 (NR)	72 (NR)	52 (NR)	86 (NR)	3 (NR)	NC	0.4 (NR)	NC	Low
Using Ong's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	78 (NR)	71 (NR)	53 (NR)	89 (NR)	3 (NR)	NC	0.3 (NR)	NC	Low
Using Shepard's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	83 (NR)	69 (NR)	53 (NR)	91 (NR)	3 (NR)	NC	0.3 (NR)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	85 (NR)	73 (NR)	57 (NR)	92 (NR)	3 (NR)	NC	0.2 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	84 (NR)	72 (NR)	55 (NR)	91 (NR)	3 (NR)	NC	0.2 (NR)	NC	Low
EFWD ≥15% for prediction of intertwin BWD ≥25%																
1[93]	Prospective study	No serious limitations	No serious inconsistency	Serious[c]	Serious[a]	None	78	77 (54 to 99.8)	92 (86 to 99)	67 (43 to 91)	95 (90 to 100)	10 (4 to 24)	67 (45 to 83)	0.3 (0.1 to 0.7)	5 (2 to 12)	Low
Using Warsof's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	77 (NR)	69 (NR)	40 (NR)	92 (NR)	2 (NR)	NC	0.3 (NR)	NC	Low
Using Ong's formula (abdominal circumference, femur length)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	82 (NR)	67 (NR)	40 (NR)	93 (NR)	2 (NR)	NC	0.3 (NR)	NC	Low
Using Shepard's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	85 (NR)	64 (NR)	40 (NR)	94 (NR)	2 (NR)	NC	0.2 (NR)	NC	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	92 (NR)	69 (NR)	44 (NR)	97 (NR)	3 (NR)	NC	0.1 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	90 (NR)	67 (NR)	42 (NR)	96 (NR)	3 (NR)	NC	0.2 (NR)	NC	Low
EFWD ≥20% for prediction of intertwin BWD ≥20%																
6[89;91;94-97]	Retrospective studies	No serious limitations	Serious[d]	No serious indirectness	No serious imprecision	None	364 women	72 (61 to 81)	89 (85 to 92)	Range: 50 to 80	Range: 89 to 97	6 (4 to 9)	NC	0.4 (0.2 to 0.6)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
USS 0-7 days before birth																
1[98]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	221	94 (NR)	79 (NR)	89 (NR)	87 (NR)	5 (NR)	NC	0.1 (NR)	NC	Low
USS 7-14 days before birth																
1[98]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	221	96 (NR)	56 (NR)	85 (NR)	85 (NR)	2 (NR)	NC	0.1 (NR)	NC	Low
USS 15-21 days before birth																
1[98]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	221	96 (NR)	46 (NR)	86 (NR)	86 (NR)	2 (NR)	NC	0.1 (NR)	NC	Low
USS 21-28 days before birth																
1[98]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	221	91 (NR)	67 (NR)	89 (NR)	84 (NR)	3 (NR)	NC	0.1 (NR)	NC	Low
USS within 7 days before birth																
1[99]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	192	56 (NR)	97 (NR)	NR	NR	19 (NR)	NC	0.5 (NR)	NC	Low
USS within 10 days before birth																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[99]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	192	54 (NR)	97 (NR)	NR	NR	18 (NR)	NC	0.5 (NR)	NC	Low
USS within 16 days before birth																
1[99]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	192	55 (NR)	97 (NR)	NR	NR	22 (NR)	NC	0.5 (NR)	NC	Moderate
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	61 (NR)	95 (NR)	73 (NR)	93 (NR)	12 (NR)	NC	0.4 (NR)	NC	Low
Last USS within 14 days of birth																
1[94]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	85	46 (19 to 73)	92 (85 to 99)	55 (25 to 84)	89 (81 to 97)	6 (2 to 16)	55 (30 to 77)	0.6 (0.4 to 0.9)	11 (7 to 17)	Low
Using Warsof's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	60 (NR)	86 (NR)	65 (NR)	84 (NR)	4 (NR)	NC	0.5 (NR)	NC	Low
Using Ong's formula (*abdominal circumference, femur length)*																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	69 (NR)	84 (NR)	64 (NR)	86 (NR)	4 (NR)	NC	0.4 (NR)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Using Shepard's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	70 (NR)	80 (NR)	59 (NR)	86 (NR)	4 (NR)	NC	0.4 (NR)	NC	Low
Using Shepard's formula (based on biparietal diameter, abdominal circumference)																
1[96]	Retrospective study	Serious[c]	No serious inconsistency	No serious indirectness	Serious[a]	None	25	86 (67 to 100)	80 (60 to 100)	80 (60 to 100)	86 (67 to 100)	4 (2 to 12)	80 (59 to 92)	0.2 (0.1 to 0.7)	14 (4 to 38)	Very low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	72 (NR)	85 (NR)	67 (NR)	88 (NR)	5 (NR)	NC	0.3 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	72 (NR)	84 (NR)	66 (NR)	86 (NR)	5 (NR)	NC	0.3 (NR)	NC	Low
EFWD ≥20% for prediction of intertwin BWD ≥25%																
1[93]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	78	74 (NR)	90 (NR)	70 (NR)	90 (NR)	7 (NR)	NC	0.3 (NR)	NC	Moderate

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
USS within 7 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	85 (NR)	89 (NR)	NR	NR	8 (NR)	NC	0.2 (NR)	NC	Low
USS within 14 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	84 (NR)	92 (NR)	NR	NR	11 (NR)	NC	0.2 (NR)	NC	Low
USS within 28 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	78 (NR)	95 (NR)	NR	NR	16 (NR)	NC	0.2 (NR)	NC	Low
Using Warsof's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	70 (NR)	84 (NR)	54 (NR)	91 (NR)	4 (NR)	NC	0.4 (NR)	NC	Low
Using Ong's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	73 (NR)	80 (NR)	49 (NR)	92 (NR)	4 (NR)	NC	0.3 (NR)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Using Shepard's formula (abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	73 (NR)	76 (NR)	45 (NR)	91 (NR)	3 (NR)	NC	0.4 (NR)	NC	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length))																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	76 (NR)	80 (NR)	51 (NR)	93 (NR)	4 (NR)	NC	0.3 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	76 (NR)	80 (NR)	51 (NR)	93 (NR)	4 (NR)	NC	0.3 (NR)	NC	Low
EFWD ≥25% for prediction of intertwin BWD ≥20%																
1[100]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	60	86 (NR)	99.9 (NR)	99.5 (NR)	97 (NR)	86 (NR)	NC	0.1 (NR)	NC	Moderate
EFWD ≥25% for prediction of intertwin BWD ≥25%																
3[91;93;94]	Retrospective and prospective studies	No serious limitations	Serious[d]	No serious indirectness	No serious imprecision	None	242	59 (39 to 78)	93 (88 to 96)	Range: 23 to 75	Range: 93 to 96	8 (3 to 18)	NC	0.5 (0.3 to 0.9)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[101]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	242	33 (NR)	94 (NR)	33 (NR)	94 (NR)	5 (NR)	NC	0.7 (NR)	NC	Low
1[100]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	60	88 (NR)	96 (NR)	78 (NR)	98 (NR)	23 (NR)	NC	0.1 (NR)	NC	Moderate
Using Warsof's formula (AC, FL)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	60 (NR)	93 (NR)	71 (NR)	90 (NR)	9 (NR)	NC	0.4 (NR)	NC	Low
Using Ong's formula (AC, FL)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	6 (NR)	90 (NR)	64 (NR)	91 (NR)	7 (NR)	NC	0.4 (NR)	NC	Low
Using Shepard's formula (AC, FL)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	63 (NR)	86 (NR)	56 (NR)	90 (NR)	5 (NR)	NC	0.4 (NR)	NC	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	68 (NR)	91 (NR)	68 (NR)	91 (NR)	8 (NR)	NC	0.4 (NR)	NC	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)																
1[92]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	283	68 (NR)	92 (NR)	72 (NR)	92 (NR)	9 (NR)	NC	0.4 (NR)	NC	Low
EFWD ≥25% for prediction of intertwin BWD ≥30%																
1[100]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	60	99 (NR)	92 (NR)	55 (NR)	99.9 (NR)	2 (NR)	NC	0.0 (NR)	NC	Moderate
USS within 7 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	86 (NR)	92 (NR)	NR	NR	11 (NR)	NC	0.2 (NR)	NC	Low
USS within 14 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	85 (NR)	96 (NR)	NR	NR	21 (NR)	NC	0.2 (NR)	NC	Low

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
USS within 28 days of birth																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	78 (NR)	96 (NR)	NR	NR	20 (NR)	NC	0.2 (NR)	NC	Low
EFWD ≥30% for prediction of intertwin BWD ≥30%																
1[90]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	575	56 (NR)	98 (NR)	75 (NR)	97 (NR)	28 (NR)	NC	0.5 (NR)	NC	Low

BWD Birth weight discordance, CI confidence interval, EFW estimated fetal weight, EFWD estimated fetal weight discordance, IUGR intrauterine growth restriction, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity, USS ultrasound scan

[a] Width of 95% CI ≥ 40 percentage points or 95% CI not reported

[b] EFW calculated using four parameters

[c] Data included one pregnancy with feto-fetal transfusion syndrome (FFTS)

[d] Moderate to substantial heterogeneity (I-squared index = 35 to 71%)

Table 6.10 GRADE findings for Doppler ultrasound

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/twins**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Umbilical artery systolic:diastolic (S:D) ratio >90th percentile for the prediction of small-for-gestational age (SGA) twin																
Scan at 20–23 weeks																
1[102]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	178 twins	36 (8 to 65)	92 (86 to 99)	44 (12 to 77)	89 (82 to 97)	5 (2 to 15)	44 (20 to 72)	0.7 (0.4 to 1.1)	11 (7 to 16)	Moderate
Scan at 24–27 weeks																
1[102]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	178 twins	5 (0 to 15)	94 (89 to 99)	14 (0 to 40)	83 (76 to 90)	1 (0 to 7)	14 (2 to 57)	1.0 (0.9 to 1.0)	17 (15 to 19)	Moderate
Scan at 28–31 weeks																
1[102]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	178 twins	17 (0 to 38)	87 (80 to 94)	14 (0 to 33)	89 (82 to 95)	1 (0 to 5)	14 (4 to 40)	1.0 (0.7 to 1.3)	11 (9 to 14)	High
Scan at 32–35 weeks																
1[102]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	178 twins	39 (21 to 57)	79 (70 to 88)	39 (21 to 57)	79 (70 to 88)	2 (1 to 4)	39 (26 to 55)	0.8 (0.6 to 1.1)	21 (16 to 27)	High
Scan at 36–39 weeks																

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/twins**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[102]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	178 twins	50 (22 to 78)	86 (75 to 96)	50 (22 to 78)	86 (75 to 96)	4 (1 to 9)	50 (28 to 72)	0.6 (0.3 to 1.0)	14 (9 to 23)	Moderate
Intertwin umbilical artery S:D ratio difference >0.4 for the prediction of intertwin BWD >25%																
1[103]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	40 women	75 (45 to 100)	69 (53 to 85)	38 (14 to 61)	92 (81 to 100)	2 (1 to 5)	37 (24 to 53)	0.4 (0.1 to 1.2)	8 (3 to 24)	Moderate
Intertwin umbilical artery RI >0.1 measured 2 weeks before birth for the prediction of intertwin BWD >25%																
1[104]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	31 women	75 (45 to 100)	96 (87 to 100)	86 (60 to 100)	92 (81 to 100)	17 (2 to 122)	86 (46 to 98)	0.3 (0.1 to 0.9)	8 (3 to 23)	Moderate
Combination of umbilical venous blood flow <10th percentile and abnormal S:D ratio for the prediction of intertwin BWD >25% among twins and triplets																
1[105]	Prospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	31 women	80 (55 to 100)	98 (94 to 100)	89 (68 to 100)	96 (90 to 100)	36 (5 to 256)	89 (53 to 98)	0.2 (0.1 to 0.7)	4 (1 to 14)	Moderate

BWD Birth weight discordance, CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), RI resistance index, S: D Systolic/Diastolic ratio, Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points

Table 6.11 GRADE findings for composite screening strategies

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/twins**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
AC <5th percentile or EFW <10th percentile or EFWD >20% for detection of IUGR <10th percentile weight in twin pregnancies																
At 20–24 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	59 (35 to 82)	89 (77 to 100)	77 (54 to 100)	77 (63 to 92)	5 (2 to 17)	77 (52 to 91)	0.5 (0.3 to 0.8)	22 (14 to 34)	Low
At 25–28 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	0 (0 to 20)	78 (62 to 94)	0 (0 to 46)	55 (40 to 71)	0 (NC)	0 (0 to 56)	1.3 (1.1 to 1.6)	45 (39 to 50)	Low
At 29–32 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	35 (13 to 58)	67 (49 to 85)	40 (15 to 65)	62 (44 to 80)	1 (1 to 2)	40 (22 to 61)	0.97 (0.6 to 1.5)	38 (28 to 49)	Low
At 33–39 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	44	6 (0 to 17)	67 (49 to 85)	10 (0 to 29)	53 (36 to 70)	0 (0 to 1)	10 (1 to 44)	1.4 (1.1 to 1.9)	47 (40 to 54)	Moderate

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/twins**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
AC <5th percentile or EFW <10th percentile or EFWD >20% for detection of intertwin discordance ≥ 20%																
At 20–24 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	50 (27 to 73)	85 (71 to 99)	69 (44 to 94)	71 (55 to 87)	3 (1 to 9)	69 (45 to 86)	0.6 (0.4 to 1.0)	29 (20 to 40)	Low
At 25–28 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	0 (0 to 19)	77 (61 to 93)	0 (0 to 46)	53 (37 to 69)	0 (NC)	0 (0 to 56)	1.3 (1.1 to 1.6)	47 (41 to 53)	Low
At 29–32 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	33 (12 to 55)	65 (47 to 84)	40 (15 to 65)	59 (41 to 77)	1 (0 to 2)	40 (23 to 61)	1.0 (0.7 to 1.6)	41 (31 to 52)	Low
At 33–39 weeks																
1[106]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	44	17 (0 to 34)	73 (56 to 90)	30 (2 to 58)	56 (39 to 73)	1 (0 to 2)	30 (11 to 59)	1.1 (0.8 to 1.6)	44 (37 to 52)	Low
S:D ratio >15% combined with EFWD >15% for the prediction intertwin BWD >15%																
1[107;108]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	40	92 (NR)	70 (NR)	60 (NR)	95 (NR)	3 (NR)	NC	0.1 (NR)	NC	Low

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women/twins**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[108]	Retrospective study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	58	78 (59 to 97)	88 (77 to 98)	74 (54 to 94)	90 (80 to 99)	6 (3 to 15)	75 (56 to 88)	0.3 (0.1 to 0.6)	10 (5 to 22)	Low

AC abdominal circumference, BWD Birth weight discordance, CI confidence interval, EFW estimated fetal weight, EFWD estimated fetal weight discordance, IUGR intrauterine growth restriction, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), S: D Systolic/Diastolic ratio, Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points or 95% CI not reported

Chapter 7 Maternal complications

Hypertension

Review question

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

Table 7.1 GRADE findings for screening tests to detect hypertension in twin pregnancies

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Ultrasound																
Resistance index > 95th centile (according to singleton nonogram) for predicting pre-eclampsia																
1[115]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	256	18 (2 to 34)	98 (96 to 100)	50 (12 to 77)	92 (89 to 96)	11 (3 to 40)	44 (19 to 73)	0.8 (0.7 to 1.0)	7 (6 to 9)	Very low
Resistance index > 95th centile (according to twin nonogram) for predicting pre-eclampsia																
1[115]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	256	36 (16 to 56)	88 (84 to 92)	22 (9 to 36)	94 (90 to 97)	3 (2 to 6)	22 (13 to 35)	0.7 (0.5 to 0.9)	6 (5 to 9)	Very low
Resistance index > 95th centile (according to twin nonogram) for predicting pre-eclampsia																
1[115]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	256	41 (20 to 61)	86 (81 to 90)	21 (9 to 34)	94 (91 to 97)	3 (2 to 5)	21 (13 to 33)	0.7 (0.5 to 0.9)	6 (4 to 8)	Very low
Bilateral notching for predicting pre-eclampsia																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[115]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	256	18 (2 to 34)	96 (94 to 99)	29 (6 to 56)	93 (89 to 96)	4 (2 to 13)	31 (13 to 57)	0.9 (0.9 to 0.9)	7 (6 to 9)	Very low
1[116]	Prospective screening study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	351	19 (2 to 36)	98 (96 to 99)	33 (7 to 60)	95 (93 to 97)	8 (3 to 22)	33 (14 to 61)	0.8 (0.7 to 1.0)	5 (4 to 6)	Low
Pulsatility index > 95th centile for predicting pre-eclampsia																
1[116]	Prospective screening study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	351	33 (13 to 54)	97 (95 to 99)	39 (16 to 61)	96 (94 to 98)	10 (4 to 22)	39 (22 to 59)	0.7 (0.5 to 0.9)	4 (3 to 6)	Low
Resistance index > 95th centile (according to twin nonogram) with unilateral or bilateral notching for predicting pre-eclampsia																
1[115]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	256	32 (12 to 51)	93 (90 to 96)	29 (11 to 49)	94 (90 to 97)	4 (2 to 9)	30 (17 to 48)	0.9 (0.9 to 1.0)	6 (5 to 8)	Low
Pulsatility index > 95th centile with bilateral notching for predicting pre-eclampsia																
1[116]	Prospective screening study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	351	19 (2 to 36)	99 (98 to 100)	57 (20 to 94)	95 (93 to 97)	21 (5 to 88)	57 (24 to 85)	0.8 (0.7 to 1.0)	5 (4 to 6)	Low

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NPV negative predictive value, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] No clinical outcomes reported

[b] Width of 95% CI ≥ 40 percentage points

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?

Table 8.1 GRADE findings for cervical length measurement in twin pregnancies (diagnostic accuracy studies reporting diagnostic accuracy measurements only)

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Prediction of spontaneous birth before 28 weeks																
Measurement at 18 – 21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	241	33 (3 to 64)	95 (93 to 98)	21 (0 to 43)	97 (95 to 99)	7 (2 to 20)	21 (8 to 45)	0.7 (0.4 to 1.1)	3 (2 to 4)	Low
Measurement at 16 – 24 weeks; cut-off of 25mm																
1[118]	Retrospective chart review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	97	100 (16 to 100)	88 (82 to 95)	15 (0 to 35)	100 (96 to 100)	9 (5 to 15)	16 (7 to 24)	0 (0 to 0.8)	0 (0 to 5)	Low
Measurement at 20 – 24 weeks; cut-off of 20mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	591 (3 studies)	35 (14 to 62)	93 (91 to 95)	NR	NR	5 (3 to 11)	NC	0.7 (0.5 to 1.0)	NC	Moderate
Measurement at 20 – 24 weeks; cut-off of 25mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	637 (3 studies)	64 (41 to 83)	93 (91 to 95)	NR	NR	10 (6 to 15)	NC	0.4 (0.2 to 0.7)	NC	Moderate

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Measurement at 20 –24 weeks; cut-off of 35mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	637 (3 studies)	82 (60 to 95)	66 (62 to 69)	NR	NR	2 (2 to 3)	NC	0.3 (0.1 to 0.7)	NC	High
Measurement at 22 – 24 weeks; cut-off of 15mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	50 (15 to 85)	98 (95 to 99)	44 (12 to 77)	98 (96 to 99)	21 (7 to 63)	45 (21 to 71)	0.5 (0.3 to 1.0)	2 (1 to 4)	Moderate
Measurement at 22 – 24 weeks; cut-off of 25mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	100 (63 to 100)	92 (87 to 96)	33 (14 to 52)	100 (98 to 100)	13 (8 to 21)	33 (22 to 42)	0.0 (0.0 to 0.9)	0 (0 to 3)	High
Measurement at 22 – 24 weeks; cut-off of 35mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	100 (63 to 100)	62 (56 to 69)	9 (3 to 15)	100 (97 to 100)	3 (2 to 3)	9 (7 to 11)	0.0 (0.0 to 1.3)	0 (0 to 5)	High
Measurement at 22 – 24 weeks; cut-off of 45mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	100 (63 to 100)	17 (12 to 22)	4 (1 to 7)	100 (90 to 100)	1 (1 to 1)	4 (4 to 5)	0.0 (0.0 to 4.9)	0 (0 to 16)	High
Measurement at 22 to 25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	266	71 (38 to 100)	93 (90 to 97)	23 (5 to 40)	99 (98 to 100)	11 (6 to 21)	23 (13 to 36)	0.3 (0.1 to 1.0)	1 (0 to 3)	Low
Prediction of spontaneous birth before 30 weeks																
Measurement at 16 –24 weeks; cut-off of 25mm																
1[118]	Retrospective chart review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	97	60 (17 to 100)	89 (83 to 95)	23 (0 to 46)	98 (94 to 100)	6 (2 to 14)	23 (11 to 43)	0.5 (0.2 to 1.3)	2 (1 to 7)	Low
Measurement at 18 – 21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	241	33 (10 to 57)	96 (94 to 99)	36 (11 to 61)	96 (93 to 98)	8 (3 to 22)	36 (17 to 59)	0.7 (0.5 to 1.0)	4 (3 to 6)	Low
Measurement at 22 – 24 weeks; cut-off of 15mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	40 (10 to 70)	98 (95 to 99)	44 (12 to 77)	97 (95 to 99)	16 (5 to 52)	44 (20 to 72)	0.6 (0.4 to 1.0)	3 (2 to 5)	Moderate
Measurement at 22 – 24 weeks; cut-off of 25mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	80 (55 to 100)	92 (89 to 96)	33 (14 to 52)	99 (98 to 100)	10 (6 to 18)	33 (22 to 47)	0.2 (0.1 to 0.8)	1 (0 to 4)	Moderate
Measurement at 22 – 24 weeks; cut-off of 35mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	90 (71 to 100)	62 (56 to 69)	10 (4 to 17)	99 (98 to 100)	2 (2 to 3)	11 (8 to 13)	0.6 (0.6 to 0.7)	1 (0 to 5)	High
Measurement at 22 – 24 weeks; cut-off of 45mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	100 (69 to 100)	17 (12 to 71)	6 (2 to 9)	100 (90 to 100)	1 (1 to 1)	6 (5 to 6)	0 (0 to 4)	0 (0 to 17)	Moderate
Measurement at 22 – 25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	266	57 (32 to 83)	94 (92 to 97)	36 (16 to 57)	98 (96 to 100)	10 (5 to 20)	36 (23 to 53)	0.4 (0.2 to 0.8)	2 (1 to 4)	Low
Prediction of spontaneous birth before 32 weeks																
Measurement at 16 – 24 weeks; cut-off of 25mm																
1[118]	Retrospective chart review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	97	43 (6 to 80)	89 (82 to 95)	23 (0 to 46)	95 (91 to 100)	4 (1 to 11)	23 (10 to 46)	0.6 (0.3 to 1.2)	5 (3 to 9)	Low
Measurement at 18 – 21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	241	30 (10 to 50)	96 (94 to 99)	43 (17 to 69)	94 (91 to 97)	8 (3 to 22)	43 (22 to 67)	0.7 (0.5 to 0.9)	6 (5 to 8)	Low
Measurement at 20–24 weeks; cut-off of 20mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1955 (5 studies)	39 (31 to 48)	96 (95 to 97)	NR	NR	10 (7 to 14)	NC	0.6 (0.6 to 0.7)	NC	High
Measurement at 20–24 weeks; cut-off of 25mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	2036 (6 studies)	54 (45 to 62)	91 (90 to 92)	NR	NR	6 (5 to 7)	NC	0.5 (0.4 to 0.6)	NC	High
Measurement at 20–24 weeks; cut-off of 30mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1812 (4 studies)	65 (56 to 74)	78 (76 to 80)	NR	NR	3 (3 to 4)	NC	0.5 (0.4 to 0.6)	NC	High
Measurement at 20–24 weeks; cut-off of 35mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1889 (5 studies)	81 (73 to 87)	58 (56 to 61)	NR	NR	2 (2 to 2)	NC	0.3 (0.2 to 0.5)	NC	High
Measurement at 22 –24 weeks; cut-off of 15mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	24 (3 to 44)	97 (95 to 99)	44 (12 to 77)	94 (90 to 97)	9 (3 to 32)	44 (19 to 73)	0.8 (0.6 to 1.0)	6 (5 to 8)	Moderate
Measurement at 22 –24 weeks; cut-off of 25mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	47 (23 to 71)	92 (88 to 96)	33 (14 to 52)	95 (92 to 98)	6 (3 to 12)	33 (20 to 51)	0.6 (0.4 to 0.9)	5 (3 to 7)	Moderate
Measurement at 22 – 24 weeks; cut-off of 35mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	71 (49 to 92)	63 (56 to 69)	14 (7 to 21)	96 (93 to 99)	2 (1 to 3)	14 (10 to 19)	0.5 (0.2 to 1.0)	4 (2 to 8)	Moderate
Measurement at 22 – 24 weeks; cut-off of 45mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	94 (83 to 100)	17 (12 to 22)	9 (5 to 13)	97 (92 to 100)	1 (1 to 1)	9 (8 to 10)	0.3 (0.1 to 2.4)	3 (0 to 17)	High
Measurement at 22 – 25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	266	53 (30 to 75)	95 (93 to 98)	45 (25 to 66)	96 (94 to 99)	11 (5 to 22)	46 (29 to 63)	0.5 (0.3 to 0.8)	4 (2 to 6)	Low
Measurement at >24 weeks; cut-off of 25mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	511 (3 studies)	65 (45 to 81)	76 (72 to 79)	NR	NR	3 (2 to 4)	NC	0.5 (0.3 to 0.8)	NC	High
Prediction of spontaneous birth before 33 weeks																
Measurement at 22 to 24 weeks; cut off of 15mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[121]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	464	18 (5 to 31)	99 (98 to 99)	55 (25 to 84)	93 (91 to 96)	14 (5 to 44)	54 (28 to 79)	0.8 (0.7 to 1.0)	7 (6 to 8)	Moderate
Measurement at 22 to 24 weeks; cut off of 20 mm																
1[121]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	464	26 (12 to 41)	97 (95 to 98)	41 (20 to 61)	94 (92 to 96)	8 (4 to 18)	41 (24 to 60)	0.8 (0.6 to 0.9)	6 (5 to 7)	Moderate
Measurement at 22 to 24 weeks; cut off of 25 mm																
1[121]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	464	35 (19 to 51)	92 (89 to 94)	27 (14 to 40)	94 (92 to 97)	4 (2 to 8)	27 (17 to 39)	0.7 (0.6 to 0.9)	6 (4 to 7)	High
Prediction of spontaneous birth before 34 weeks																
Measurement at 18 –21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	241	23 (10 to 36)	98 (95 to 100)	64 (39 to 89)	87 (82 to 91)	9 (3 to 26)	64 (39 to 83)	0.8 (0.7 to 0.9)	13 (11 to 15)	Low
Measurement at 20–24 weeks; cut-off of 20mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1760 (5 studies)	29 (23 to 35)	97 (96 to 98)	NR	NR	9 (6 to 13)	NC	0.7 (0.7 to 0.8)	NC	High
Measurement at 20–24 weeks; cut-off of 25mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1987 (6 studies)	40 (38 to 46)	93 (92 to 94)	NR	NR	6 (5 to 7)	NC	0.6 (0.6 to 0.7)	NC	High
Measurement at 20–24 weeks; cut-off of 30mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	2014 (5 studies)	56 (50 to 62)	81 (79 to 83)	NR	NR	3 (3 to 3)	NC	0.6 (0.5 to 0.6)	NC	High
Measurement at 20–24 weeks; cut-off of 35mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	1884 (6 studies)	79 (74 to 84)	60 (57 to 62)	NR	NR	2 (2 to 2)	NC	0.4 (0.3 to 0.4)	NC	High
Measurement at 22–24 weeks; cut-off of 15mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	11 (1 to 21)	97 (94 to 99)	44 (12 to 77)	84 (79 to 89)	4 (1 to 14)	44 (18 to 74)	0.9 (0.8 to 1.0)	16 (15 to 18)	Moderate
Measurement at 22 – 24 weeks; cut-off of 25mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	215	35 (20 to 51)	94 (90 to 97)	54 (34 to 74)	87 (83 to 92)	6 (3 to 12)	54 (37 to 71)	0.7 (0.5 to 0.9)	13 (10 to 15)	Moderate
Measurement at 22 – 24 weeks; cut-off of 35mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	57 (41 to 73)	63 (56 to 71)	24 (15 to 34)	88 (82 to 93)	2 (1 to 2)	24 (19 to 31)	0.7 (0.6 to 0.7)	12 (9 to 17)	High
Measurement at 22 –24 weeks; cut-off of 45mm																
1[120]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	215	92 (83 to 100)	18 (12 to 24)	19 (13 to 25)	91 (82 to 100)	1 (1 to 1)	19 (17 to 21)	0.5 (0.2 to 1.4)	9 (3 to 23)	High
Measurement at 22 – 25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age																
1[117]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	266	38 (22 to 55)	96 (94 to 99)	59 (39 to 80)	91 (39 to 80)	10 (5 to 21)	59 (40 to 76)	0.6 (0.5 to 0.8)	9 (7 to 11)	Low
Measurement at >24 weeks; cut-off of 25mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	594 (4 studies)	44 (34 to 53)	81 (78 to 85)	NR	NR	2 (2 to 3)	NC	0.7 (0.6 to 0.8)	NC	High
Prediction of spontaneous birth before 37 weeks																
Measurement at 20–24 weeks; cut-off of 20mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	434 (4 studies)	21 (15 to 27)	95 (92 to 98)	NR	NR	4 (2 to 8)	NC	0.8 (0.8 to 0.9)	NC	High
Measurement at 20–24 weeks; cut-off of 30mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	218 (2 studies)	29 (18 to 43)	91 (86 to 95)	NR	NR	3 (2 to 7)	NC	0.8 (0.7 to 0.9)	NC	High
Measurement at 20–24 weeks; cut-off of 35mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	134 (2 studies)	56 (43 to 68)	78 (50 to 74)	NR	NR	2 (1 to 2)	NC	0.7 (0.5 to 1.0)	NC	High
Measurement at >24 weeks; cut-off of 25mm																
1[119]	Systematic review	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	276 (2 studies)	43 (35 to 51)	77 (68 to 84)	NR	NR	1 (1 to 3)	NC	0.8 (0.6 to 0.9)	NC	High

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points

Table 8.2 GRADE findings for cervical length measurement in twin pregnancies (diagnostic accuracy studies reporting relative risks and diagnostic accuracy measurements)

Quality assessment							Summary of findings							
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Relative risk**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**LR$^-$**	**Quality**
Prediction of spontaneous birth before 35 weeks															
Measurement at 24–34 weeks; cut-off of 20mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	2.12 (0.95 to 4.72)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 25mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	1.69 (0.78 to 3.67)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 30mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	0.91 (0.41 to 1.99)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 33mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	1.12 (0.49 to 2.56)	NR	NR	NR	NR	NR	NR	Very low
Prediction of spontaneous birth before 37 weeks															
Measurement at 24–34 weeks; cut-off of 20mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	1.71 (0.99 to 2.97)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 25mm															

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Relative risk**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**LR$^-$**	**Quality**
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	1.55 (0.91 to 2.61)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 30mm															
1[122]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	1.21 (0.70 to 2.08)	NR	NR	NR	NR	NR	NR	Very low
Measurement at 24–34 weeks; cut-off of 33mm															
1[122]	Prospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious [b]	None	46	1.16 (0.65 to 2.05)	NR	NR	NR	NR	NR	NR	Very low
Prediction of spontaneous birth within one week of measurement of cervical length															
Measurement at 24–34 weeks; cut-off of 20mm															
1[122]	Prospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious [b]	None	46	11.16 (4.23 to 32.17)	65 (NC)	79 (NC)	52 (NC)	87 (NC)	3.06 (NC)	NR	Low
Measurement at 24–34 weeks; cut-off of 25mm															
1[122]	Prospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious [b]	None	46	4.12 (1.10 to 15.47)	77 (NC)	59 (NC)	39 (NC)	88 (NC)	1.86 (NC)	NR	Low
Measurement at 24–34 weeks; cut-off of 30mm															
1[122]	Prospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious [b]	None	46	7.25 (0.94 to 55.85)	88 (NC)	41 (NC)	34 (NC)	91 (NC)	1.51 (NC)	NR	Low
Measurement at 24-34 weeks; cut-off of 33mm															

Quality assessment							Summary of findings								
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**	**Relative risk**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**LR−**	**Quality**
1[122]	Prospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious [b]	None	46	NC	92 (NC)	37 (NC)	34 (NC)	93 (NC)	1.47 (NC)	NR	Low

LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Unexplained withdrawals

[b] Total number of events < 300 for relative risk calculations and/or 95% CI not reported for diagnostic statistics

Table 8.3 GRADE findings for cervical length measurement in triplet pregnancies

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
Prediction of spontaneous birth before 28 weeks																
Measurement at 15-20 weeks; cut-off of 25mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	50	50 (15 to 85)	100 (92 to 100)	100 (40 to 100)	91 (83 to 99)	NC	NC	0.5 (0.3 to 0.9)	9 (5 to 16)	Low
Measurement at 21-24 weeks; cut-off of 25mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious	None	50	86 (60 to 100)	79 (67 to 91)	40 (15 to 65)	97 (92 to 100)	4 (2 to 8)	40 (26 to 56)	0.2 (0.0 to 1.1)	3 (0 to 15)	Low
Measurement at 25-28 weeks; cut-off of 20mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	100 (40 to 100)	57 (42 to 72)	18 (2 to 34)	100 (86 to 100)	2 (2 to 3)	18 (11 to 24)	0.0 (NC)	0 (0 to 19)	Low
Prediction of spontaneous birth before 30 weeks																
Measurement at 15-20 weeks; cut-off of 25mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49	36 (8 to 65)	100 (91 to 100)	100 (40 to 100)	84 (74 to 95)	NC	NC	0.6 (0.4 to 0.9)	16 (11 to 22)	Low
Measurement at 21-24 weeks; cut-off of 25mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49	70 (42 to 98)	82 (70 to 94)	50 (24 to 76)	91 (82 to 100)	4 (2 to 9)	50 (31 to 69)	0.4 (0.1 to 0.9)	9 (3 to 20)	Low
Measurement at 25-28 weeks; cut-off of 20mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46	100 (59 to 100)	62 (46 to 77)	32 (12 to 51)	100 (86 to 100)	3 (2 to 4)	32 (22 to 40)	0 (NC)	0 (0 to 21)	Low
Prediction of spontaneous birth before 32 weeks																
Measurement at 14-20 weeks; cut-off of 25mm																
1[124]	Retrospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	36	75 (54 to 96)	90 (77 to 100)	85 (67 to 100)	81 (66 to 98)	8 (2 to 29)	86 (61 to 96)	0.3 (0.1 to 0.7)	18 (9 to 35)	Low
Measurement at 15-20 weeks; cut-off of 25mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	47	25 (3 to 46)	100 (89 to 100)	100 (40 to 100)	72 (59 to 86)	NC	NC	0.8 (0.6 to 0.9)	28 (22 to 34)	Low
Measurement at 21-24 weeks; cut-off of 25mm																
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	47	60 (35 to 85)	84 (72 to 97)	64 (39 to 89)	82 (69 to 95)	4 (2 to 9)	64 (42 to 82)	0.5 (0.3 to 0.9)	18 (10 to 30)	Low
Measurement at 25-28 weeks; cut-off of 20mm																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR^{+}**	**PTP^{+}**	**LR^{-}**	**PTP^{-}**	**Quality**
1[123]	Prospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	83 (62 to 100)	66 (49 to 82)	48 (26 to 69)	91 (80 to 100)	2 (1 to 4)	48 (35 to 61)	0.3 (0.1 to 0.9)	9 (3 to 26)	Low

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Selection criteria not clearly described; withdrawals not explained

[b] Width of 95% CI ≥ 40 percentage points

Table 8.4 GRADE findings for fetal fibronectin test in twin pregnancies

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR$^+$**	**PTP$^+$**	**LR$^-$**	**PTP$^-$**	**Quality**
Prediction of spontaneous preterm birth before 35 weeks																
Positive test at 24 weeks																
1[125]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	73	50 (26 to 75)	49 (36 to 62)	22 (8 to 35)	78 (64 to 91)	1 (1 to 2)	22 (14 to 32)	1.0 (0.6 to 1.8)	22 (14 to 33)	Moderate
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	37 (15 to 59)	91 (85 to 98)	54 (27 to 81)	84 (76 to 92)	4 (2 to 11)	37 (22 to 55)	0.7 (0.5 to 0.9)	9 (5 to 15)	Moderate
Positive test at 28 weeks																
1[125]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	74	NR	NR	NR	NR	2 (NR)	20 (NR)	0.9 (NR)	12 (NR)	High
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	50 (28 to 71)	92 (86 to	63 (39 to 86)	87 (80 to 95)	6 (3 to 15)	63 (41 to 80)	0.5 (0.4 to 0.9)	13 (9 to 19)	Moderate
Positive test at 24 and 28 weeks																
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	24 (3 to 44)	99 (96 to	80 (45 to 100)	84 (75 to 92)	16 (2 to 132)	80 (32 to 97)	0.8 (0.6 to 1.0)	16 (13 to 20)	Moderate
Positive test at 32 weeks																

Quality assessment							Summary of findings									
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of twin pregnancies**	**Sens %**	**Spec %**	**PPV %**	**NPV %**	**LR+**	**PTP+**	**LR−**	**PTP−**	**Quality**
1[125]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	65	NR	NR	NR	NR	2 (NR)	17 (NR)	0.5 (NR)	4 (NR)	High
Positive test at 24, 26, 28, 30 or 32 weeks																
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	59 (39 to 80)	71 (61 to 81)	36 (20 to 52)	86 (78 to 95)	2 (1 to 3)	36 (26 to 48)	0.6 (0.3 to 3.3)	14 (9 to 21)	Moderate
Positive test at 24, 26, 28, 30 and 32 weeks																
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	23 (5 to 40)	99 (96 to 100)	83 (54 to 100)	82 (74 to 90)	18 (2 to 146)	83 (38 to 98)	0.8 (0.6 to 0.9)	18 (15 to 21)	Moderate
Prediction of spontaneous preterm birth before 37 weeks																
Positive test at 24, 26, 28, 30 or 32 weeks																
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	101	53 (36 to 69)	74 (63 to 85)	53 (36 to 69)	74 (63 to 85)	2 (1 to 3)	35 (21 to 51)	0.6 (0.4 to 0.9)	26 (21 to 33)	High
Positive test at 24, 26, 28, 30 and 32 weeks																
1[126]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	101	14 (3 to 25)	99 (95 to 100)	83 (54 to 100)	67 (58 to 77)	9 (1 to 74)	83 (38 to 98)	0.9 (0.8 to 1.0)	32 (30 to 36)	Moderate

CI confidence interval, LR+ positive likelihood ratio, LR- negative likelihood ratio, NC not calculable, NPV negative predictive value, NR not reported, PPV positive predictive value, PTP+ post-test probability (of a positive test), PTP- post-test probability (of a negative test), Sens sensitivity, SGA small for gestational age, Spec specificity

[a] Width of 95% CI ≥ 40 percentage points

Table 8.5 GRADE findings for combined cervical length measurement and fetal fibronectin test in twin pregnancies

Quality assessment							Summary of findings					
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**					**Quality**
							Number	**Risk for spontaneous preterm birth (%)**			**P-value of difference between risks**	
								Both tests positive	**One test**	**Tests negative**		
Prediction of spontaneous birth before 28 weeks												
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious [a]	No serious inconsistency	No serious indirectness	Serious[b]	None	155	50	13.3	1.6	<0.001	Very low
Prediction of spontaneous birth before 28 to 30 weeks												
Tests done at 24-26 weeks; cervical length threshold of 25mm												
1[128]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	149	50.0	15.6	6.4	Significance not reported	Very low
Prediction of spontaneous birth before 30 weeks												
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	155	33.3	9.5	2.4	< 0.001	Very low
Prediction of spontaneous birth before 32 weeks												
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	155	54.5	8.3	4.2	< 0.001	Very low
Prediction of spontaneous birth before 34 weeks												

Quality assessment							Summary of findings					
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**					**Quality**
							Number	**Risk for spontaneous preterm birth (%)**			**P-value of difference between risks**	
								Both tests positive	**One test**	**Tests negative**		
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	155	54.5	26.1	10.3	< 0.001	Very low
Prediction of spontaneous birth before 35 weeks												
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	155	54.5	39.1	18.3	< 0.001	Very low
Prediction of spontaneous birth before 37 weeks												
Tests done at 22-32 weeks; cervical length threshold of 20mm												
1[127]	Retrospective cohort study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	120/155	100	77.3	43.0	< 0.001	Very low

[a] It is not clear whether the index test results were interpreted without knowledge of the reference standard results. It is not clear if the reference standard results were interpreted without knowledge of the results of the index test. It is not clear whether uninterpretable, indeterminable or intermediate test results were reported

[b] Total number of events < 300

Table 8.6 GRADE findings for home uterine activity monitoring (with or without nursing contact) versus no monitoring in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of Preterm Births**		**Effect**		**Quality**
							Home monitoring	**No monitoring**	**Relative risk (95% CI)**	**P-value**	
Prediction of spontaneous preterm birth											
1[129]	Meta-analysis of 6 RCTs	No serious limitations	Serious[a]	Serious[b]	Serious[c]	None	72/165 (44%)	60/146 (41%)	1.01 (0.79 to 1.30)	0.95	Very Low

CI confidence interval

[a] Four of the six studies did not control for nursing contact that accompanied home uterine activity monitoring (the study authors used a random effects model for their meta-analysis)

[b] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[c] Total number of events < 300

Table 8.7 GRADE findings for home uterine activity monitoring and daily contact with a nurse versus daily contact alone versus weekly contact in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of Preterm Births**			**Effect**	**Quality**
							Home monitoring	**Daily contact only**	**Weekly contact only**	**Relative risk/ P-value**	
Prediction of spontaneous preterm birth <32 weeks (monitoring and contact started at 24 week)											
1[130]	Randomised controlled trial	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	17/287 (6%)	25/277 (9%)	20/280 (7%)	No significant difference (p-value not reported)	Low
Prediction of spontaneous preterm birth <35 weeks (monitoring and contact started at 24 week)											
1[130]	Randomised controlled trial	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	69/287 (24%)	62/277 (24%)	62/280 (22%)	No significant difference (p-value not reported)	Low
Prediction of spontaneous preterm birth <37 weeks (monitoring and contact started at 24 week)											
1[130]	Randomised controlled trial	No serious limitations	No serious inconsistency	Serious[a]	No serious imprecision	None	146/287 (51%)	150/277 (54%)	137/280 (49%)	No significant difference (p-value not reported)	Moderate

[a] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[b] Total number of events < 300

Table 8.8 GRADE findings for obstetric history (preterm singleton birth in the previous pregnancy) in twin pregnancies

Quality assessment							Summary of findings			
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number**		**Effect**	**Quality**
							Number of preterm births to women with a previous preterm singleton birth	**Number of preterm births to women with a previous term singleton birth**	**Odds Ratio (95% CI)**	
Prediction of spontaneous preterm birth										
1[131]	Retrospective cohort study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	17/23 (74%)	120/270 (44%)	3.5 (1.4 to 9.3)	Very low

CI confidence interval

[a] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[b] Total number of events < 300

Preventing preterm birth

Review question

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

Table 8.9 GRADE findings for routine hospitalisation for bed rest versus no bed rest for the prevention of spontaneous preterm birth in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine hospitalisation	**No bed rest**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<37 weeks											
1[132]	Cochrane review	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	117/264 (44%)	108/284 (38%)	RR 1.12 (0.89 to 1.42)	46 more per 1000 (from 42 fewer to 160 more)	Very low
34 weeks											
1[132]	Cochrane review	No serious limitations	Serious[d]	Serious[b]	Serious[c]	None	33/127 (26%)	21/132 (16%)	RR 1.57 (0.72 to 3.43)	91 more per 1000 (from 45 fewer to 387 more)	Very low
1[133]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	0/37 (0%)	14/34 (41%)	RR 0.03 (0 to 0.51)	399 fewer per 1000 (from 202 fewer to 412 fewer)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine hospitalisation	**No bed rest**	**Relative (95% CI)**	**Absolute**	
1[132]	Cochrane review	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	264 women in group	284 women in group	-	MD 0.39 lower (0.78 lower to 0.01 higher)	Moderate
Perinatal mortality											
1[132]	Cochrane review	Serious[a]	Serious[d]	No serious indirectness	Serious[c]	None	23/524 (4%)	19/568 (3%)	RR 1.64 (0.45 to 6.08) d	21 more per 1000 (from 18 fewer to 170 more)	Very low
1[133]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	0/37 (0%)	4/34 (12%)	RR 0.10 (0.01 to 1.83)	106 fewer per 1000 (from 116 fewer to 98 more)	Very low
Caesarean section											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	47/127 (37%)	49/132 (37%)	RR 1.04 (0.78 to 1.38)	15 more per 1000 (from 82 fewer to 141 more)	Moderate
Admission to neonatal care unit											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	72/254 (28%)	69/264 (26%)	RR 1.08 (0.82 to 1.42)	21 more per 1000 (from 47 fewer to 110 more)	Moderate
Low birthweight											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine hospitalisation	**No bed rest**	**Relative (95% CI)**	**Absolute**	
1[132]	Cochrane review	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	240/528 (46%)	280/568 (49%)	RR 0.91 (0.81 to 1.03)[e]	44 fewer per 1000 (from 94 fewer to 15 more)	Moderate
Very low birthweight											
1[132]	Cochrane review	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	29/528 (6%)	17/568 (3%)	RR 1.82 (1.02 to 3.27)[f]	25 more per 1000 (from 1 more to 68 more)	Low
Neonatal stay ≥ 7 days											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Seriou [c]	None	14/116 (12%)	21/120 (18%)	RR 0.69 (0.37 to 1.29)	54 fewer per 1000 (from 110 fewer to 51more)	Moderate

CI confidence interval, MD means difference, RR relative risk

[a] Lack of allocation concealment in one study (Hartikainen 1980)

[b] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[c] Total number of events < 300

[d] Substantial heterogeneity (I^2 value > 66%)

[e] Result remained insignificant when a sensitivity analysis to evaluate the effect of trial quality was carried out (i.e. by excluding the trial with no allocation concealment)

[f] Result became insignificant and imprecise when a sensitivity analysis to evaluate the effect of trial quality was carried out (i.e. by excluding the trial with no allocation concealment) [OR = 1.81 (0.94 to 3.46)]

Table 8.10 GRADE findings for routine hospitalisation for bed rest versus no bed rest for the prevention of spontaneous preterm birth in triplet pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine hospitalisation	**No bed rest**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<37 weeks											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	11/13 (85%)	13/13 (100%)	RR 0.88 (0.66 to 1.16)	120 fewer per 1000 (from 340 fewer to 160 more)	Low
34 weeks											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	6/13 (46%)	6/13 (46%)	RR 1.17 (0.46 to 2.94)	78 more per 1000 (from 249 fewer to 895 more)	Low
Gestational age at birth (measured in weeks; better indicated by higher values)											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	13 babies in group	13 babies in group	-	Mean difference 0.58 (-1.35 to 2.51)	Moderate
Perinatal mortality											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	1/39 (3%)	5/39 (13%)	RR 0.28 (0.05 to 1.65)	92 fewer per 1000 (from 122 fewer to 83 more)	Moderate
Caesarean section											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine hospitalisation	**No bed rest**	**Relative (95% CI)**	**Absolute**	
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	4/19 (21%)	4/21 (19%)	RR 0.98 (0.27 to 3.62)	4 fewer per 1000 (from 139 fewer to 499 more)	Moderate
Admission to neonatal care unit											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Seriou[b]	None	25/30 (83%)	25/27 (93%)	RR 0.90 (0.74 to 1.09)	93 fewer per 1000 (from 241 fewer to 83 more)	Moderate
Low birthweight											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	35/39 (90%)	35/39 (90%)	RR 1.08 (0.66 to 1.78)	72 more per 1000 (from 305 fewer to 700 more)	Moderate
Very low birthweight											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	5/39 (13%)	9/39 (23%)	RR 0.56 (0.20 to 1.54)	102 fewer per 1000 (from 185 fewer to 125 more)	Moderate
Neonatal stay ≥ 7 days											
1[132]	Cochrane review	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	17/30 (57%)	11/27 (41%)	RR 1.39 (0.80 to 2.42)	159 more per 1000 (from 81 fewer to 579 more)	Moderate

CI confidence interval, RR relative risk

[a] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[b] Total number of events < 300

[c] Sample size < 400

Table 8.11 GRADE findings for hospital bed rest versus home bed rest for the prevention of spontaneous preterm birth in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest	**Home bed rest**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth <34 weeks											
1[133]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	0/37 (0%)	4/31 (13%)	RR 0.09 (0.01 to 1.67)	117 fewer per 1000 (from 128 fewer to 86 more)	Very low
Perinatal mortality											
1[133]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	0/37 (0%)	1/31 (3%)	RR 0.28 (0.01 to 6.66)	23 fewer per 1000 (from 32 fewer to 183 more)	Very low

CI confidence interval, RR relative risk

[a] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[b] Total number of events < 300

Table 8.12 GRADE findings for hospital bed rest versus home bed rest (with advice for women in both groups to discontinue vaginal intercourse at 20 weeks of gestation) for the prevention of spontaneous preterm birth in triplet pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest	**Home bed rest**	**Relative (95% CI)**	**Absolute**	
Gestational age at birth (measured in weeks; better indicated by higher values)											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	102 women in group	96 women in group	-	MD 1.00 higher (0.22 to 1.78 higher)[b]	Very low
Perinatal mortality											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[c]	Serious[d]	None	1/102 (1%)	1/96 (1%)	OR 0.94 (0.06 to 15.25)	1 fewer per 1000 (from 10 fewer to 128 more)	Very low
Caesarean section											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	31/34 (91%)	26/32 (81%)	OR 2.38 (0.54 to 10.48)	99 more per 1000 (from 112 fewer to 166 more)	Very low
Respiratory distress syndrome											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[e]	Serious[d]	None	0/102 (0%)	1/96 (1%)	OR 0.31 (0.01 to 7.72)	7 fewer per 1000 (from 10 fewer to 65 more)	Very low
Intraventricular haemorrhage											
Grades 1 to 4											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest	**Home bed rest**	**Relative (95% CI)**	**Absolute**	
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	1/102 (1%)	10/96 (10%)	OR 0.09 (0.01 to 0.68)	94 fewer per 1000 (from 31 fewer to 103 fewer)	Very low
Grades 3 to 4											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	0/102 (0%)	1/96 (1%)	OR 0.31 (0.01 to 7.72)	7 fewer per 1000 (from 10 fewer to 65 more)	Very low
Necrotising enterocolitis											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	0/102 (0%)	0/96 (0%)	Not calculable	Not calculable	Very low
Neonatal length of stay											
Measured in days of stay in neonatal special care unit (better indicated by lower values)											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	102 women in group	96 women in group	-	MD 0.10 lower (9.64 lower to 9.44 higher)[f]	Very low
Measured in days of stay in nursery (better indicated by lower values)											
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	102 women in group	96 women in group	-	MD 0.30 higher (0.54 lower to 1.14 higher)[g]	Very low
Maternal length of stay (measured in days of hospital stay; better indicated by lower values)											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest	**Home bed rest**	**Relative (95% CI)**	**Absolute**	
1[134]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	102 women in group	96 women in group	-	MD 26.7 higher (17.59 to 35.81 higher)[h]	Very low

CI confidence interval, MD means difference, OR odds ratio, RR relative risk

[a]Sample size < 400

[b] Gestational age at delivery (weeks) reported in the paper (mean±SD) is: hospital bed rest (33.5±2.8), home bed rest (32.5±2.8); P = 0.16

[c] Only neonatal mortality reported

[d] Total number of events < 300

[e] Study reported data on bronchopulmonary dysplasia, not respiratory distress syndrome

[f] Neonatal length of stay in Infant Special Care Unit (days) reported in the paper (mean±SD) is: hospital bed rest (26.0±21.2), home bed rest (26.1±18.3); P = 0.84

[g] Neonatal length of stay in nursery (days) reported in the paper (mean±SD) is: hospital bed rest (6.3±1.8), home bed rest (6.0±1.7) ; P = 0.49

[h] Maternal length of stay in hospital (days) reported in the paper (mean±SD) is: hospital bed rest (47.9±22.6), home bed rest (21.2±14.5); P = 10-7

Table 8.13 GRADE findings for hospital bed rest and oral salbutamol versus hospital bed rest only for the prevention of spontaneous preterm birth in twin and triplet pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest and oral salbutamol	**Hospital bed rest only**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<37 weeks											
1[135]	RCT	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	37/101 (37%)	37/99 (37%)	RR 0.98 (0.68 to 1.41)	7 fewer per 1000 (from 120 fewer to 153 more)	Low
<33 weeks											
1[135]	RCT	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	10/101 (10%)	9/99 (9%)	RR 1.09 (0.46 to 2.57)	8 more per 1000 (from 49 fewer to 143 more)	Low
Perinatal mortality											
1[135]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	9/101 (9%)	11/99 (11%)	RR 0.80 (0.34 to 1.88)	22 fewer per 1000 (from 73 fewer to 98 more)	Moderate
Low birthweight											
1[135]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	88/204 (43%)	84/199 (42%)	RR 1.03 (0.82 to 1.29)	13 more per 1000 (from 76 fewer to 122 more)	Moderate
Very low birthweight											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Hospital bed rest and oral salbutamol	**Hospital bed rest only**	**Relative (95% CI)**	**Absolute**	
1[135]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	10/204 (5%)	14/199 (7%)	RR 0.70 (0.32 to 1.53)	21 fewer per 1000 (from 48 fewer to 37 more)	Moderate
Respiratory distress syndrome											
1[135]	RCT	No serious limitations	No serious inconsistency	Serious[c]	Serious[b]	None	2/204 (1%)	4/199 (2%)	RR 0.49 (0.09 to 2.56)	10 fewer per 1000 (from 18 fewer to 31 more)	Low

CI confidence interval, RR relative risk

[a] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[b] Total number of events < 300

[c] Serious indirectness because the study reported data for neonatal respiratory problems and not respiratory distress syndrome

Table 8.14 GRADE findings for intramuscular or vaginal progesterone versus placebo for the prevention of spontaneous preterm birth in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular or vaginal)	**Placebo**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<37 weeks - intramuscular progesterone											
2[136;138]	RCTs	Serious[a]	No serious inconsistency	Serious[b, c]	Serious[d]	None	19/55 (35%)	14/52 (27%)	OR 1.42 (0.62 to 3.27) [e]	74 more per 1000 (from 83 fewer to 277 more)	Very low
<35 weeks - intramuscular progesterone											
1[137]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	101/325 (31%)	86/330 (26%)	OR 1.28 (0.91 to 1.8)	50 more per 1000 (from 18 fewer to 128 more)	Moderate
<34 weeks - vaginal progesterone											
1[139]	RCT	No serious limitations	No serious inconsistency	Serious[f]	Serious[d]	Serious[g]	4/11 (36%)	7/13 (54%)	OR 0.49 (0.09 to 2.53)	175 fewer per 1000 (from 443 fewer to 208 more)	Very low
Spontaneous or iatrogenic preterm birth or intrauterine death < 34 weeks											
1[141]	RCT	No serious limitations	No serious inconsistency	Serious[f, h]	Serious[d]	Serious[i]	61/247 (25%)	48/247 (19%)	OR 1.36 (0.89 to 2.09)	53 more per 1000 (from 18 fewer to 141 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular or vaginal)	**Placebo**	**Relative (95% CI)**	**Absolute**	
Gestational age at birth (measured in weeks of gestation; better indicated by higher values)											
2[136;137]	RCTs	Serious[a, j]	No serious inconsistency	No serious indirectness	No serious imprecision	None	366 women in group	372 women in group	-	MD 0.32 lower (0.83 lower to 0.19 higher) [k]	Moderate
Perinatal mortality											
2[136;141]	RCTs	Serious[a]	No serious inconsistency	Serious[h]	Serious[d]	None	18/572 (3%)	12/570 (2%)	OR 1.51 (0.72 to 3.16) [e]	10 more per 1000 (from 6 fewer to 43 more)	Very low
Caesarean section											
2[137;141]	RCTs	No serious limitations	No serious inconsistency	Serious[h]	No serious imprecision	None	348/574 (61%)	365/578 (63%)	OR 0.90 (0.71 to 1.14)[l]	25 fewer per 1000 (from 83 fewer to 30 more)	Moderate
Maternal side effects (any of urticaria, nausea, injection site, fatigue, dizziness and headache)											
1[137]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	211/320 (66%)	210/326 (64%)	OR 1.0 (0.9 to 1.1)	0 fewer per 1000 (from 24 fewer to 22 more)	High
Admission to neonatal unit											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular or vaginal)	**Placebo**	**Relative (95% CI)**	**Absolute**	
1[141]	RCT	No serious limitations	No serious inconsistency	Serious[h]	Serious[d]	None	167/494 (34%)	158/494 (32%)	OR 1.08 (0.76 to 1.54)	17 more per 1000 (from 57 fewer to 100 more)	Low
Low birthweight (<2500 g)											
1[137]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	377/628 (60%)	415/648 (64%)	OR 0.9 (0.8 to 1.0)	25 fewer per 1000 (from 53 fewer to 1 more)	High
Very low birthweight (<1500 g)											
1[137]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[d]	None	81/628 (13%)	64/648 (10%)	OR 2.0 (1.0 to 3.39)	81 more per 1000 (from 1 more to 172 more)	Moderate
Respiratory distress syndrome											
2[137;138]	RCTs	No serious limitations	No serious inconsistency	Serious[h]	Serious[d]	None	106/664 (16%)	96/676 (14%)	OR 1.14 (0.84 to 1.54)	17 more per 1000 (from 20 fewer to 61 more)	Low
Intraventricular haemorrhage											
2[137;138]	RCTs	No serious limitations	No serious inconsistency	Serious[h]	Serious[d]	None	10/664 (2%)	10/674 (2%)	OR 0.97 (0.40 to 2.37)	1 fewer per 1000 (from 9 fewer to 20 more)	Low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular or vaginal)	**Placebo**	**Relative (95% CI)**	**Absolute**	
Necrotising enterocolitis											
2[137;138]	RCTs	No serious limitations	No serious inconsistency	Serious[h]	Serious[d]	None	4/664 (1%)	4/676 (1%)	OR 0.99 (0.26 to 3.70)	1 fewer per 1000 (from 4 fewer to 16 more)	Low
Neonatal length of stay in intensive care unit (measured in days; better indicated by lower values)											
1[138]	RCT	No serious limitations	No serious inconsistency	Serious[c]	Serious[m]	None	36 women in group	28 women in group	-	MD 1.10 higher (24.23 lower to 26.43 higher)[n]	Low
Maternal quality of life											
1[141]	RCT	No serious limitations	No serious inconsistency	Serious[o, h]	Serious[d]	None	1/247 (0.4%)	0/247 (0%)	OR 3.01 (0.12 to 74.30)	1 more per 1000 (from 1 fewer to 1 more)	Low
Maternal satisfaction (measured with Likert-type questionnaire; better indicated by lower values)											
1[141]	RCT	No serious limitations	No serious inconsistency	Serious[h]	No serious imprecision	None	250 women in group	250 women in group	-	MD 0.0 higher (0.5 lower to 0.4 higher)	Moderate

CI confidence interval, MD mean difference, OR odds ratio, RR relative risk

[a] Allocation concealment was unclear and the process of sequence generation was not stated in the study by Hartikainen-Sorri (1980). In addition, randomisation was done at a relatively late gestational age (28 weeks). Also, in the same study, there may be possible confounding effects of other interventions as betamimetics were used if required, and prophylactic bed rest in the hospital was prescribed for 71 of the 77 women from 32-36 week

[b] Study by Briery et al. (2009) reported data for preterm labour and not spontaneous preterm birth

[c] The data may have included iatrogenic preterm births as well as spontaneous preterm births

[d] Total number of events < 300

[e] Result remained insignificant when a sensitivity analysis to evaluate the effect of trial quality was carried out (i.e. by excluding the trial with no allocation concealment)

[f] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births
[g] Only women with a short cervix were included in this study
[h] The data included iatrogenic and spontaneous preterm births
[i] Results include spontaneous and iatrogenic preterm births
[j] independence between twins assumed in the calculation RR
[k] Result remained insignificant when a sensitivity analysis to evaluate the effect of trial quality or route of administration (intramuscular or vaginal) was carried out
[l] Result remained insignificant when a sensitivity analysis to evaluate the effect of route of administration (intramuscular or vaginal) was carried out
[m] Sample size < 400
[n] Neonatal length of stay in ICU (days) reported in the paper (mean±SD) is: progesterone group (18.4±65.8), placebo (17.3±29.8); P = 0.155
[o] Study reported data for 'involved persistent/significant maternal disability or incapacity'

Table 8.15 GRADE findings for intramuscular progesterone versus placebo for the prevention of spontaneous preterm birth in triplet pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular)	**Placebo**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<35 weeks											
1[142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	34/71 (48%)	27/63 (43%)	RR 1.1 (0.8 to 1.6)	43 more per 1000 (from 86 fewer to 257 more)	Low
< 32 weeks											
1[140]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[b]	None	17/56 (30%)	7/25 (28%)	RR 1.1 (0.5 to 2.3)	28 more per 1000 (from 140 fewer to 364 more)	Low
Gestational age at birth (measured in weeks; better indicated by higher values)											
1[142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	71 women in group	63 women in group	-	Median difference 0.6 (P = 0.527)[e]	Low
1[140]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	56 women in group	25 women in group	-	Median difference NR (P = 0.36)[f]	Low
Perinatal mortality											
1[142]	RCT	Serious[a]	No serious inconsistency	Serious[g]	Serious[b]	None	5/212 (2%)	2/183 (1%)	RR 2.2 (0.4 to 12.4)	13 more per 1000 (from 7 fewer to 125 more)	Very low
1[140]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[b]	None	19/168 (11%)	2/75 (3%)	OR 4.7 (1.0 to 22.0)	87 more per 1000 (from 1 fewer to 349 more)	Low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular)	**Placebo**	**Relative (95% CI)**	**Absolute**	
Caesarean section											
2[140;142]	RCT	Serious[a]	Serious[h]	No serious indirectness	Serious[b]	None	123/127 (97%)	87/88 (99%)	RR 0.99 (0.91 to 1.07)	10 fewer per 1000 (from 89 fewer to 69 more)	Very low
Low birthweight											
1[142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	191/212 (90%)	175/183 (96%)	RR 0.9 (0.9 to 1)[i]	96 fewer per 1000 (from 96 fewer to 1 more)	Moderate
Very low birthweight											
1[142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	91/212 (43%)	46/183 (25%)	RR 1.7 (1.1 to 2.7)[i]	176 more per 1000 (from 25 more to 427 more)	Low
Respiratory distress syndrome											
2[140;142]	RCT	Serious[a]	Serious[j]	No serious indirectness	Serious[b]	None	109/367 (30%)	78/258 (30%)	RR 0.94 (0.64 to 1.37)[i]	18 fewer per 1000 (from 73 fewer to 112 more)	Very low
Intraventricular haemorrhage (grades 3 and 4)											
2[140;142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	6/362 (2%)	7/258 (3%)	RR 0.54 (0.18 to 1.64)[i]	12 fewer per 1000 (from 22 fewer to 17 more)	Low
Necrotising enterocolitis (stage 2 and 3)											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Progesterone (intramuscular)	**Placebo**	**Relative (95% CI)**	**Absolute**	
1[140]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[b]	None	8/154 (5%)	3/75 (4%)	OR 1.4 (0.2 to 7.6)	15 more per 1000 (from 32 fewer to 201 more)	Low
Necrotising enterocolitis											
1[142]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	2/212 (1%)	5/183 (3%)	RR 0.3 (0 to 3.1)[i]	19 fewer per 1000 (from 27 fewer to 57 more)	Low
Neonatal length of stay (measured in days; better indicated by lower values)											
1[140]	RCT	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	168 babies in group	75 babies in group	-	MD 11.50 lower (from 24.49 lower to 2.51 higher)[k]	Low

CI confidence interval, RR relative risk

[a] Unequal numbers of women in the intervention group (71) and comparison (63) group, which raises questions about randomisation in one study[142]; high caesarean section rates in both studies[140;142] in intervention and control groups and a high proportion of pregnancies resulting from artificial reproduction techniques

[b] Total number of events < 300

[c] A high proportion of pregnancies resulted from artificial reproduction techniques

[d] Sample size < 400

[e] Gestational age (weeks) reported in the paper (median±interquartile range) is: progesterone (32.4±30.0,34.4), placebo (33.0±31.6,34.3) ; P = 0.527

[f] Gestational age (weeks) reported in the paper (mean±SD) is: progesterone (31.9±4.1), placebo (31.8±2.9); P = 0.36

[g] Neonatal mortality rather than perinatal mortality reported

[h] Substantial heterogeneity (I^2 = 64%)

[i] RR was based on worse-per-pregnancy outcome because of small sample (as reported in the paper)

[j] Moderate to substantial heterogeneity (I^2 = 58%)

[k] Total neonatal length of stay in hospital (days) reported in the paper (mean±SD) is: progesterone (26.6±26.4), placebo (37.6±35.6); P = 0.09

Table 8.16 GRADE findings for cervical cerclage versus no cerclage for the prevention of spontaneous preterm birth in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Cervical cerclage	**No cerclage**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
< 37 weeks											
1[143]	RCT	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	10/22 (46%)	11/23 (48%)	OR 0.83 (0.25 to 2.72)	46 fewer per 1000 (from 292 fewer to 235 more)	Very low
<34 weeks											
1[144]	Prospective observational study	No serious limitations	No serious inconsistency	Serious[b, d]	Serious[c]	Serious[e]	9/21 (43%)	6/12 (50%)	OR 0.75 (0.18 to 3.12)	71 fewer per 1000 (from 347 fewer to 257 more)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)											
1[144]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[f]	Serious[e]	33.5 weeks (SD 3.6)	32.8 weeks (SD 3.9)	-	MD 0.70 higher (0.99 lower to 3.39 higher)	Very low
Perinatal mortality											
1[143]	RCT	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	8/44 (18%)	7/46 (15%)	OR 1.24 (0.41 to 3.76)	30 more per 1000 (from 84 fewer to 251 more)	Very low
Caesarean section											
1[143]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	9/22 (41%)	7/23 (30%)	OR 1.58 (0.46 to 5.41)	104 more per 1000 (from 137 fewer to 399 more)	Low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Cervical cerclage	**No cerclage**	**Relative (95% CI)**	**Absolute**	
Very low birthweight (<1500 g)											
1[144]	Prospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	Serious[e]	9/42 (21%)	7/24 (29%)	OR 0.66 (0.21 to 2.09)	78 fewer per 1000 (from 212 fewer to 171 more)	Very low

CI confidence interval, MD means difference, OR odds ratio

[a] Details of randomisation and blinding not reported

[b] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[c] Total number of events < 300

[d] Only neonatal mortality reported

[e] Only women with a short cervix were included in this study

[f] Sample size < 400

Table 8.17 GRADE findings for cervical cerclage versus no cerclage for the prevention of spontaneous preterm birth in triplet pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Cervical cerclage	**No cerclage**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<32 weeks											
3[145-147]	Retrospective observational studies	No serious limitations	Serious[a]	Serious[b]	No serious imprecision	None	83/323 (26%)	860/3109 (28%)	OR 0.78 (0.44 to 1.42)	47 fewer per 1000 (from 133 fewer to 75 more)	Very low
<31 weeks											
1[145]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	2/20 (10%)	15/39 (39%)	OR 0.18 (0.04 to 0.89)	283 fewer per 1000 (from 27 fewer to 360 fewer)	Very low
<28 weeks											
2[146;147]	Retrospective observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	11/303 (4%)	136/3070 (4%)	OR 0.93 (0.49 to 1.76)	3 fewer per 1000 (from 22 fewer to 31 more)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)											
4[145-148]	Retrospective observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	320 women in group	3147 women in group	-	MD 0.11 higher (0.20 lower to 0.42 higher)	Low
Perinatal mortality											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Cervical cerclage	**No cerclage**	**Relative (95% CI)**	**Absolute**	
2[145;148]	Retrospective observational studies	No serious limitations	No serious inconsistency	Serious[d]	Serious[c]	None	3/96 (3%)	11/186 (6%)	OR 0.56 (0.16 to 1.94)	25 fewer per 1000 (from 49 fewer to 50 more)	Very low
Admission to neonatal intensive care unit											
1[146]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	594/737 (81%)	7376/9028 (82%)	OR 0.93 (0.77 to 1.13)	11 fewer per 1000 (from 42 fewer to 18 more)	Low
Very low birthweight (<1500 g)											
2[145;146]	Retrospective observational studies	No serious limitations	Serious[a]	No serious indirectness	No serious imprecision	None	202/804 (25%)	2362/9207 (26%)	OR 0.80 (0.46 to 1.38)	40 fewer per 1000 (from 120 fewer to 66 more)	Very low
Extremely low birthweight (<1000 g)											
1[145]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	1/60 (2%)	18/117 (15%)	OR 0.09 (0.01 to 0.72)	138 fewer per 1000 (from 38 fewer to 152 fewer)	Very low
Respiratory distress syndrome											
1[145]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	11/60 (18%)	32/117 (27%)	OR 0.60 (0.23 to 1.29)	89 fewer per 1000 (from 194 fewer to 53 more)	Very low
Intraventricular haemorrhage											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Cervical cerclage	**No cerclage**	**Relative (95% CI)**	**Absolute**	
1[145]	Retrospective observational study	No serious limitations	No serious inconsistency	Serious[e]	Serious[c]	None	6/35 (17%)	19/57 (33%)	OR 0.44 (0.15 to 01.23)	153 fewer per 1000 (from 264 fewer to 47 more)	Very low
Neonatal length of stay in the hospital (better indicated by lower values)											
1[146]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	248 women in group	3030 women in group	-	MD 1.6 lower[f]	Low

CI confidence interval, MD means difference, OR odds ratio

[a] Moderate to substantial heterogeneity (I-squared index > 33% but less than 66%)

[b] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[c] Total number of events < 300

[d] One study (Elimian 1999) reported neonatal mortality data only

[e] Study reported combined data for intraventricular haemorrhage and periventricular leucomalacia

[f] Neonatal length of stay in the hospital (days) reported in the paper (mean±SD) is: cerclage group (21.7±19.9), no cerclage group (22.7±20.6); P = 0.24

Table 8.18 GRADE findings for oral betamimetics versus placebo for the prevention of spontaneous preterm birth in twin pregnancies

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Oral betamimetics	**Placebo**	**Relative (95% CI)**	**Absolute**	
Spontaneous preterm birth											
<37 weeks											
1[149]	Cochrane review	Serious[a]	No serious inconsistency	Serious[b]	Serious[c]	None	57/140 (41%)	65/136 (48%)	RR 0.85 (0.65 to 1.10)	72 fewer per 1000 (from 167 fewer to 48 more)	Very low
<34 weeks											
1[149]	Cochrane review	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	4/74 (5%)	8/70 (11%)	RR 0.47 (0.15 to 1.50)	61 fewer per 1000 (from 97 fewer to 57 more)	Low
Perinatal mortality											
1[149]	Cochrane review	No serious limitations	Serious[d]	Serious[e]	Serious[c]	None	9/230 (4%)	11/220 (5%)	RR 0.80 (0.35 to 1.82)[f]	10 fewer per 1000 (from 33 fewer to 41 more)	Very low
Low birthweight (<2500 g)											
1[149]	Cochrane review	Serious[g]	No serious inconsistency	No serious indirectness	Serious[c]	None	99/188 (53%)	85/178 (48%)	RR 1.19 (0.77 to 1.85)[f]	91 more per 1000 (from 110 fewer to 406 more)	Low
Respiratory distress syndrome											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Oral betamimetics	**Placebo**	**Relative (95% CI)**	**Absolute**	
1[149]	Cochrane review	Serious[a, g]	No serious inconsistency	No serious indirectness	Serious[c]	None	5/198 (3%)	17/190 (9%)	RR 0.30 (0.12 to 0.77)[f]	63 fewer per 1000 (from 21 fewer to 79 fewer)	Low

CI confidence interval, RR relative risk

[a] Unclear allocation concealment in one study (Skjaerris 1982)

[b] Study reported preterm birth and not spontaneous preterm birth - preterm birth may have included iatrogenic causes of birth, e.g. medically indicated births

[c] Total number of events < 300

[d] Moderate to substantial heterogeneity (I-squared index > 33% but less than 66%)

[e] Only neonatal mortality reported

[f] Independence between twins assumed in the calculation of RR

[g] 10% loss to follow up rate in one study (Ashworth 1990) which occurred more frequently in the betamimetic group than in the placebo group

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?

Table 8.19 GRADE findings for routine single course of corticosteroids versus no routine corticosteroids

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**No corticosteroids**	**Relative (95% CI)**	**Absolute**	
Perinatal and neonatal mortality in twins											
1[153]	Retrospective case note review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	2/91 (2%)	15/82 (18%)	OR 0.10 (0.02 to 0.45)	161 fewer per 1000 (from 91 fewer to 178 fewer)	Very low
Respiratory distress syndrome											
All severities of respiratory distress syndrome in twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	20/44 (46%)	30/44 (68%)	OR 0.39 (0.16 to 0.93)	227 fewer per 1000 (from 16 fewer to 426 fewer)	Very low
Mild respiratory distress syndrome in twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	11/44 (25%)	12/44 (27%)	OR 0.89 (0.34 to 2.30)	22 fewer per 1000 (from 160 fewer to 190 more)	Very low
Moderate or severe respiratory distress syndrome in twins											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**No corticosteroids**	**Relative (95% CI)**	**Absolute**	
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	9/44 (21%)	18/44 (41%)	OR 0.37 (0.14 to 0.96)	205 fewer per 1000 (from 10 fewer to 321 fewer)	Very low
Neonatal length of stay											
In neonatal intensive care unit for twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	Median 3.5 days	Median 6 days	-	P-value reported as not significant	Very low
Birthweight by gestational age											
24 to 27 weeks in twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	725g ±35g	715g ±92g	-	P-value reported as not significant	Very low
24 to 27 weeks in triplets											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	798g ±215g	878g ±26g	-	P < 0.016	Very low
28 to 32 weeks in twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	1201g ±412g	1569g ±142g	-	P < 0.0001	Very low
28 to 32 weeks in triplets											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**No corticosteroids**	**Relative (95% CI)**	**Absolute**	
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	1379g ±216g	1522g ±376	-	P < 0.032	Very low
33 to 34 weeks in twins											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	2054g ±517g	2043g ±367g	-	P-value reported as not significant	Very low
33 to 34 weeks in triplets											
1[154]	Non-randomised controlled trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[c]	None	1696g ±515g	1469g ±271g	-	P <0.011	Very low

CI confidence interval, MD means difference, OR odds ratio

[a] Serious indirectness because study reported survival rather than mortality

[b] Total number of events < 300

[c] Sample size < 400

Table 8.20 GRADE findings for routine multiple courses of corticosteroids versus no routine corticosteroids

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**No corticosteroids**	**Relative (95% CI)**	**Absolute**	
Perinatal and neonatal mortality in triplets											
1[153]	Retrospective case note review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	2/76 (3%)	15/82 (18%)	OR 0.12 (0.03 to 0.55)	157 fewer per 1000 (from 73 fewer to 176 fewer)	Very low
Long-term neurodevelopmental outcomes											
At 1 year in triplets											
1[153]	Retrospective case note review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	1/76 (1%)	4/82 (5%)	OR 0.26 (0.03 to 2.38)	36 fewer per 1000 (from 47 fewer to 60 more)	Very low
Intraventricular haemorrhage in triplets											
1[153]	Retrospective case note review	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	1/76 (1%)	10/82 (12%)	OR 0.10 (0.01 to 0.77)	108 fewer per 1000 (from 25 fewer to 121 fewer)	Very low

CI confidence interval, OR odds ratio

[a] Serious indirectness because study reported survival rather than mortality

[b] Total number of events < 300

Table 8.21 GRADE findings for routine multiple courses of corticosteroids versus routine single course of corticosteroids

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**No corticosteroids**	**Relative (95% CI)**	**Absolute**	
Composite outcomes											
Composite of neonatal mortality and morbidity in twins											
1[155]	Randomised controlled trial	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	62/427 (15%)	60/414 (15%)	OR 1.00 (0.68 to 1.47)	0 fewer per 1000 (from 42 fewer to 55 more)	Low

CI confidence interval, OR odds ratio

[a] Serious indirectness because only composite outcome of neonatal mortality and morbidity was reported

[b] Total number of events < 300

Table 8.22 GRADE findings for routine multiple courses of corticosteroids versus targeted (rescue) corticosteroids

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**Rescue corticosteroids**	**Relative (95% CI)**	**Absolute**	
Perinatal and neonatal mortality in twins											
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/136 (2%)	30/902 (3%)	OR 0.43 (0.10 to 1.84)	19 fewer per 1000 (from 30 fewer to 26 more)	Very low
Respiratory distress syndrome in twins											
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	17/136 (13%)	96/902 (11%)	OR 1.20 (0.69 to 2.08)	19 more per 1000 (from 30 fewer to 92 more)	Very low
Intraventricular haemorrhage in twins											
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	1/136 (1%)	7/902 (1%)	OR 0.95 (0.12 to 7.76)	1 fewer per 1000 (from 7 fewer to 49 more)	Very low
Necrotising enterocolitis in twins											
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/136 (2%)	2/902 (0.2%)	OR 6.71 (0.94 to 48.1)	12 more per 1000 (from 1 fewer to 94 more)	Very low
Neonatal length of stay											
In special care baby unit for twins											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of women**		**Effect**		**Quality**
							Routine prophylactic corticosteroids	**Rescue corticosteroids**	**Relative (95% CI)**	**Absolute**	
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	Not reported	Not reported	-	Adjusted[b]MD -1.5 days (-5.3 days to +2.4 days)	Low
Birthweight in twins											
1[156]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	Not reported	Not reported	-	Adjusted[b]MD -129g (-218g to -33g)	Low

CI confidence interval, MD means difference, OR odds ratio

[a] Total number of events < 300

[b] Adjusted for gestational age, gender, parity, infertility, smoking, chorionicity and twin pairing using linear regression

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

Review question

What are the clinical indications for referral to subspecialist services?

Table 9.1 GRADE findings for indications for referral to subspecialist services (comparison of case numbers between study and control groups)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Referred for specialist care**	**Usual care**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Comparison of late referral to early followed up at tertiary care centre											
Fetal mortality rate											
1[162]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	13/108	9/1220	16.32 (7.14 to 37.30)	113 more per 1000 (from 45 more to 268 more)	Very low
Infant mortality (before 1 year of age)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	6/64	11/474	4.04 (1.55 to 10.55)[*]	71 more per 1000 (from 13 more to 222 more)	Very low
Infant mortality (before 1 year of age) – monochorionic											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	9/30	4/94	47.05 (2.34 to 21.26)[*]	1960 more per 1000 (from 57 more to 862 more)	Very low
Infant mortality (before 1 year of age) – dichorionic											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1/30	7/364	1.73 (0.22 to 13.63)[*]	14 more per 1000 (from 15	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Referred for specialist care**	**Usual care**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
										fewer to 243 more)	
Number of babies with disabilities at 1 year of age											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	10/64	13/474	5.70 (2.61 to 12.45)*	129 more per 1000 (from 44 more to 314 more)	Very low
Number of babies with disabilities at 1 year of age – monochorionic											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	9/30	7/94	4.03 (1.64 to 9.89)*	226 more per 1000 (from 48 more to 662 more)	Very low
Number of babies with disabilities at 1 year of age – dichorionic											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1/30	6/364	2.02 (0.25 to 16.25)*	17 more per 1000 (from 12 fewer to 251 more)	Very low

CI confidence interval

* Calculated by NCC technical team

[a] Unmatched comparison group

[b] Referred group not representative of population of interest

[c] Total number of events < 300

Table 9.2 GRADE findings for indications for referral for subspecialist advice (continuous outcome measures)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mean (SD)**		**Mean Difference**		**Quality**
							Referred for specialist care	**Usual care**	**Difference**	**P value**	
Comparison of late referral to early followed up at tertiary care centre											
Birthweight in grams – larger twins (all)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	1778 (611)	2278 (443)	-500	P <0.001	Very low
Birthweight in grams – larger twins (monochorionic)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1580(570)	2158(501)	-578	P <0.01[*]	Very low
Birthweight in grams – larger twins (dichorionic)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1922(598)	2302(409)	-380	P <0.01[*]	Very low
Birthweight in grams – smaller twins (all)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	1504(628)	2003(433)	-499	P <0.001	Very low
Birthweight in grams – smaller twins (monochorionic)											
1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1304(671)	1869(495)	-565	P <0.01[*]	Very low
Birthweight in grams – smaller twins (dichorionic)											

1[161]	Retrospective observational study	Serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	1632(530)	2030(401 -398)	P <0.01[*]	Very low

SD standard deviation

* Calculated by NCC technical team

[a] Unmatched comparison group

[b] Referred group not representative of population of interest

[c] Sample size < 400

Chapter 10 Timing of birth

Review question

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

Table 10.5 GRADE findings for the risk of fetal death by chorionicity at different gestational ages (studies reporting results for monochorionic and dichorionic twin pregnancies)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Monochorionic twins (fetal deaths/total number of fetuses)**	**Dichorionic twins (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Risk of fetal death at given gestational age											
At 26-27 weeks											
3[166-168]	Observational studies	No serious limitations	Serious[a]	Serious[b]	Serious[c]	None	4/847	3/3942	5.63 (0.61 to 52.14)*	4 more per 1000 (from 1 fewer to 39 more)	Very low
At 28-29 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	3/812	4/3840	4.53 (1.08 to 18.88)*	4 more per 1000 (from 1 more to 19 more)	Very low
At 30-31 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	4/768	7/3679	2.89 (0.89 to 9.39)*	4 more per 1000 (from 1 fewer to 16 more)	Very low
At 32-33 weeks											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Monochorionic twins (fetal deaths/total number of fetuses)**	**Dichorionic twins (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	3/618	2/3389	6.75 (1.27 to 35.79)*	2 more per 1000 (from 1 more to 21 more)	Very low
At 34-35 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	2/599	3/3077	3.36 (0.65 to 17.37)*	3 more per 1000 (from 1 fewer to 16 more)	Very low
At ≥ 36 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	5/283	3/2031	10.86 (2.82 to 41.89)*	15 more per 1000 (from 3 more to 60 more)	Very low

CI confidence interval

*Calculated by NCC technical team

[a] Moderate heterogeneity (I^2 = 47%)

[b] Study populations included complicated and uncomplicated twin pregnancies

[c] Total number of events < 300

Table 10.6 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for monochorionic twin pregnancies)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 36 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Risk of fetal death at given gestational age											
At 26-27 weeks											
6[166-171]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	10/2287	11/1098	0.49 (0.21 to 1.12)*	5 fewer per 1000 (from 8 fewer to 1 more)	Very low
At 28-29 weeks											
6[166-171]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	10/2233	11/1098	0.52 (0.22 to 1.22)*	5 fewer per 1000 (from 8 fewer to 2 more)	Very low
At 30-31 weeks											
6[166-171]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	6/2135	11/1098	0.30 (0.11 to 0.84)*	7 fewer per 1000 (from 8 fewer to 3 more	Very low
At 32-33 weeks											
6[166-171]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	10/1965	11/1098	0.54 (0.22 to 1.30)*	5 fewer per 1000 (from 2 fewer to 9 fewer)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 36 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
At 34-35 weeks											
6[166-171]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	13/1662	11/1098	0.84 (0.29 to 2.42)*	2 fewer per 1000 (from 7 fewer to 14 more)	Very low

CI confidence interval

*Calculated by NCC technical team

[a] Study populations included complicated and uncomplicated twin pregnancies

[b] Total number of events < 300

Table 10.7 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for dichorionic twin pregnancies)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 36 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Risk of fetal death at given gestational age											
At 26-27 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	3/3942	3/2031	0.20 (0.02 to 1.94)*	1 fewer per 1000 (from 1 fewer to 1 more)	Very low
At 28-29 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	4/3840	3/2031	0.77 (0.19 to 3.23)*	1 fewer per 1000 (from 1 fewer to 3 more)	Very low
At 30-31 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	7/3679	3/2031	1.00 (0.26 to 3.87)*	0 fewer per 1000 (from 1 fewer to 4 more)	Very low
At 32-33 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	3/3389	3/2031	0.47 (0.08 to 2.82)*	1 fewer per 1000 (from 1 fewer to 3 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 36 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
At 34-35 weeks											
3[166-168]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	5/2961	3/2031	0.82 (0.06 to 10.99)*	1 fewer per 1000 (from 1 fewer to 15 more)	Very low

CI confidence interval

*Calculated by NCC technical team

[a] Study populations included complicated and uncomplicated twin pregnancies

[b] Total number of events < 300

Table 10.8 Evidence profile for the risk of neonatal death at different gestational ages (studies reporting results for monochorionic twin pregnancies)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (neonatal deaths/total live births)**	**≥ 38 weeks (neonatal deaths/total live births)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Risk of neonatal death at given gestational age											
At 26-27 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	8/27	2/242	31.83 (6.91 to 146.66)*	255 more per 1000 (from 49 more to 1000 more)	Very low
At 28-29 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	7/44	2/242	18.22 (3.91 to 84.83)*	142 more per 1000 (from 24 more to 693 more)	Very low
At 30-31 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	4/75	2/242	5.38 (0.95 to 30.37)*	36 more per 1000 (from 1 fewer to 243 more)	Very low
At 32-33 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	1/112	2/242	1.31 (0.16 to 10.51)*	3 more per 1000 (from 7 fewer to 79 more)	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (neonatal deaths/total live births)**	**≥ 38 weeks (neonatal deaths/total live births)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
At 34-35 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	0/199	2/242	0.41 (0.04 to 3.95)*	5 fewer per 1000 (from 8 fewer to 24 more)	Very low
At 36-37 weeks											
2[166;170]	Observational studies	No serious limitations	No serious inconsistency	Serious[a]	Serious[b]	None	2/392	2/242	0.66 (0.10 to 4.47)*	3 fewer per 1000 (from 7 fewer to 29 more)	Very low

CI confidence interval

*Calculated by NCC technical team

[a] Study populations included complicated and uncomplicated twin pregnancies

[b] Total number of events < 300

Table 10.9 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for triplet pregnancies)

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 37 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Risk of fetal death at given gestational age											
At 33 weeks											
2[173;174]	Observational studies	No serious limitations	Serious[a]	Serious[b]	Serious[c]	None	24/111	6/18	0.18 (0.01 to 3.54)*	273 fewer per 1000 (from 330 fewer to 847 more) fewer)	Very low
At 34 weeks											
2[173;174]	Observational studies	No serious limitations	No serious inconsistency	Serious[b]	Serious[c]	None	6/78	6/18	0.14 (0.07 to 0.31)*	287fewer per 1000 (from 230 fewer to 310 fewer)	Very low
At 35 weeks											
2[173;174]	Observational studies	No serious limitations	Serious[d]	Serious[b]	Serious[c]	None	21/60	6/18	0.34 (0.04 to 3.32)*	220 fewer per 1000 (from 320 fewer to 773 more)	Very low
At 36 weeks											
2[173;174]	Observational studies	No serious limitations	Serious[e]	Serious[b]	Serious[c]	None	19/39	6/18	0.64 (0.12 to 3.44)*	120 fewer per 1000 (from 293 fewer to	Very low

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Given gestational age (fetal deaths/total number of fetuses)**	**≥ 37 weeks (fetal deaths/total number of fetuses)**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
										813 more)	

CI confidence interval

*Calculated by NCC technical team

[a] Substantial heterogeneity (I^2 = 76%)

[b] Study populations included complicated and uncomplicated twin pregnancies

[c] Total number of events < 300

[d] Substantial heterogeneity (I^2 = 63%)

[e] Substantial heterogeneity (I^2 = 62%)

Table 10.11 GRADE findings for comparison between elective birth and expectant management based on dichotomous outcome measures

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective birth**	**Expectant management**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Perinatal mortality											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/72	0/90	NC	NC	Very low
Birthweight <2500 gm											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	11/34	13/38	0.95 (0.49 to 1.82)*	17 fewer per 1000 (from 174 fewer to 281 more)	Moderate
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	23/72	54/90	0.53 (0.37 to 0.78)*	282 fewer per 1000 (from 132 fewer to 378 fewer)	Very low
Birthweight <2000 gm											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/34	2/38	NC	NC	Moderate

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective birth**	**Expectant management**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	3/72	6/90	0.63 (0.16 to 2.41)*	25 fewer per 1000 (from 56 fewer to 94 more)	Very low
Apgar score <7 at 1 min											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	9/72	12/90	0.94 (0.42 to 2.1)*	8 fewer per 1000 (from 77 fewer to 147 more)	Very low
Apgar score <7 at 5 min											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/72	3/90	NC	NC	Very low
Neonatal morbidity											
Admission to NICU – induction of labour at 36 weeks in twin pregnancies											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective birth**	**Expectant management**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	22/72	24/90	1.15 (0.70 to 1.87)*	40 more per 1000 (from 80 fewer to 232 more)	Very low
Admission to NICU – precise time of induction not reported (≥ 36 weeks)											
1[177]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	3/91	13/178	0.45 (0.13 to 1.54)*	8 fewer per 1000 (from 77 fewer to 147 more)	Very low
Immediate admission to NICU – induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	15/72	21/90	0.89 (0.50 to 1.60)*	26 fewer per 1000 (from 117 fewer to 140 more)	Very low
Delayed admission to NICU – induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	7/72	3/90	2.92 (0.79 to 10.88)*	43 more per 1000 (from 5 fewer to 220 more)	Very low
Neonatal sepsis – precise time of induction not reported (≥ 36 weeks)											
1[177]	Retrospective observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	3/91	9/178	0.65 (0.18 to 2.35)*	18 fewer per 1000 (from 41 fewer to 68 more)	Very low
Maternal outcomes											

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective birth**	**Expectant management**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
Caesarean section - induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	3/17	6/19	0.56 (0.16 to 1.90)	139 fewer per 1000 (from 265 fewer to 284 more)	Moderate
Caesarean section – induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	3/36	6/45	0.63 (0.17 to 2.33)	49 fewer per 1000 (from 111 fewer to 177 more)	Very low
Instrumental delivery – Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	19/36	21/45	1.13 (0.73 to 1.76)*	61 more per 1000 (from 126 fewer to 355 more)	Very low
Need for blood transfusion – Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	0/17	1/19	NC	NC	Moderate
Maternal Infection											
Need for blood transfusion – Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2/36	3/45	0.85 (0.15 to 4.83)*	10 fewer per 1000 (from 57 fewer to 255	Very low

Quality assessment							Summary of findings			
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Elective birth**	**Expectant management**	**Relative risk (95% CI)**	**Absolute risk reduction**	**Quality**
										more)	

CI confidence interval, NC not calculable, NS not significant

*Calculated by NCC technical team

[a] Total number of events < 300

Table 10.12 GRADE findings for comparison between elective birth and expectant management based on continuous outcome measures

Quality assessment							Summary of findings				
Number of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mean (SD)**		**Mean Difference**		**Quality**
							Referred for specialist care	**Usual care**	**Difference**	**P value**	
Birthweight in grams											
Induction of labour at 37 weeks in twin pregnancies											
1[175]	RCT	Serious[a]	No serious inconsistency	No serious indirectness	Serious[a]	None	2700 (330)	2672 (392)	28	Not significant	Moderate
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	2639 (352)	2463 (298)	176	P< 0.001	Very low
Duration of maternal hospital stay in days (SD)											
Induction of labour at 36 weeks in twin pregnancies											
1[176]	Prospective cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[a]	None	7.3 (2.0)	7.5 (2.3)	-0.2	Not significant	Very low

SD standard deviation

[a] Sample size < 400

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