

Supplementary table 6: GRADE tables

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Is antenatal corticosteroid therapy effective and safe for reducing adverse maternal and child outcomes in pregestational and/or gestational diabetic women?

Setting: 3 studies: 2 in the USA, 1 in Israel

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with PGDM	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section												
2	observational studies	not serious	serious ^a	not serious	serious ^a	none	31/65 (47.7%)	58/150 (38.7%)	OR 1.75 (0.63 to 4.82)	138 more per 1,000 (from 102 fewer to 366 more)	⊕○○○ Very low	
Neonatal death within 48 hours of birth												
1	observational studies	not serious	not serious	not serious	serious ^a	none	6/536 (1.1%)	2/79 (2.5%)	OR 0.44 (0.09 to 2.20)	14 fewer per 1,000 (from 23 fewer to 29 more)	⊕○○○ Very low	
Apgar score <seven at 5 minutes												
1	observational studies	not serious	not serious	not serious	serious ^a	none	1/47 (2.1%)	21/114 (18.4%)	OR 0.79 (0.10 to 5.89)	33 fewer per 1,000 (from 162 fewer to 387 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate/severe RDS												
2	observational studies	not serious	serious ^a	not serious	serious ^a	none	179/583 (30.7%)	37/193 (19.2%)	OR 2.79 (0.85 to 9.08)	207 more per 1,000 (from 24 fewer to 491 more)	⊕○○○ Very low	
Neonatal hypoglycemia												
2	observational studies	not serious	not serious	not serious	serious ^a	none	14/65 (21.5%)	66/150 (44.0%)	OR 1.44 (0.70 to 2.97)	91 more per 1,000 (from 85 fewer to 260 more)	⊕○○○ Very low	
Admission to neonatal intensive care unit												
1	observational studies	not serious	not serious	not serious	serious ^a	strong association	19/47 (40.4%)	36/114 (31.6%)	OR 7.41 (5.04 to 10.89)	458 more per 1,000 (from 384 more to 518 more)	⊕⊕○○ Low	

CI: confidence interval; OR: odds ratio

Explanations

- Heterogeneity is high (I-square=>60%).
- Estimate based on wide confidence interval crossing the line of no effect.
- Estimate based on small sample size.

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Is antenatal corticosteroid therapy effective and safe for reducing adverse maternal and child outcomes in women undergoing elective cesarean birth in late preterm?

Setting: 2 studies: 1 in Israel, 1 in Spain

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with elective CS in the late preterm period	placebo	Relative (95% CI)	Absolute (95% CI)		
Hypertensive disorders												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	3/58 (5.2%)	15/107 (14.0%)	OR 0.33 (0.09 to 1.21)	89 fewer per 1,000 (from 126 fewer to 25 more)	⊕○○○ Very low	
Gestational diabetes mellitus												
1	observational studies	not serious	not serious	not serious	very serious ^{b,c}	strong association	3/30 (10.0%)	4/10 (40.0%)	OR 0.17 (0.03 to 0.95)	298 fewer per 1,000 (from 380 fewer to 12 fewer)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate/severe RDS												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	12/88 (13.6%)	11/117 (9.4%)	OR 0.80 (0.29 to 2.24)	17 fewer per 1,000 (from 65 fewer to 95 more)	⊕○○○ Very low	
Use of mechanical ventilation												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	12/88 (13.6%)	11/117 (9.4%)	OR 0.80 (0.30 to 2.12)	17 fewer per 1,000 (from 64 fewer to 86 more)	⊕○○○ Very low	
Admission to neonatal intensive care unit												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	10/88 (11.4%)	14/117 (12.0%)	OR 0.78 (0.23 to 2.72)	24 fewer per 1,000 (from 89 fewer to 150 more)	⊕○○○ Very low	
Neonatal hypoglycemia												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	30/88 (34.1%)	37/117 (31.6%)	OR 1.50 (0.81 to 2.78)	93 more per 1,000 (from 44 fewer to 246 more)	⊕○○○ Very low	
Interventricular haemorrhage												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	0/58 (0.0%)	1/107 (0.9%)	OR 0.61 (0.02 to 15.13)	4 fewer per 1,000 (from 9 fewer to 116 more)	⊕○○○ Very low	
Necrotizing enterocolitis												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	0/58 (0.0%)	1/107 (0.9%)	OR 0.61 (0.02 to 15.13)	4 fewer per 1,000 (from 9 fewer to 116 more)	⊕○○○ Very low	
Apgar score =\leq7 at 5minutes												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	2/58 (3.4%)	0/107 (0.0%)	OR 9.51 (0.45 to 201.57)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Mean duration of mechanical ventilation												

1	observational studies	not serious	not serious	not serious	serious ^{a,b}	none	30	10	-	MD 0.2 lower (1.35 lower to 0.95 higher)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	------------------------	------	----	----	---	---	------------------	--

Oxygen requirement for at least 4 hours

1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	13/58 (22.4%)	25/107 (23.4%)	OR 0.95 (0.44 to 2.03)	9 fewer per 1,000 (from 115 fewer to 149 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	-----------------------------	------	---------------	----------------	---------------------------	---	------------------	--

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Wide confidence interval crossing line of no effect; estimate based on small sample size.
 b. Estimate based on small sample size.
 c. The data were extracted from one study.

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Is antenatal corticosteroid therapy effective and safe for reducing adverse maternal and child outcomes in women with chorioamnionitis?

Setting: 8 studies (observational studies in the USA, the Netherlands, France, and Republic of Korea)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with chorioamnionitis	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	42/97 (43.3%)	2/12 (16.7%)	OR 3.82 (0.79 to 18.36)	266 more per 1,000 (from 30 fewer to 619 more)	⊕○○○ Very low	
Gestational diabetes mellitus (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	6/97 (6.2%)	2/12 (16.7%)	OR 0.33 (0.06 to 1.86)	105 fewer per 1,000 (from 155 fewer to 104 more)	⊕○○○ Very low	
Preeclampsia or eclampsia (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	5/97 (5.2%)	1/12 (8.3%)	OR 0.60 (0.06 to 5.59)	32 fewer per 1,000 (from 78 fewer to 254 more)	⊕○○○ Very low	
Neonatal death (HC)												
6	observational studies	not serious	not serious	not serious	not serious	none	63/677 (9.3%)	87/516 (16.9%)	OR 0.51 (0.31 to 0.85)	75 fewer per 1,000 (from 109 fewer to 22 fewer)	⊕⊕○○ Low	
Neonatal death (CC)												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b,d}	none	14/109 (12.8%)	14/81 (17.3%)	OR 0.71 (0.32 to 1.60)	44 fewer per 1,000 (from 110 fewer to 78 more)	⊕○○○ Very low	
Death before discharge home (CC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	7/45 (15.6%)	8/52 (15.4%)	OR 1.30 (0.13 to 13.44)	37 more per 1,000 (from 131 fewer to 556 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate/severe RDS (HC)												
6	observational studies	not serious	not serious	not serious	not serious	none	305/677 (45.1%)	289/516 (56.0%)	OR 0.59 (0.45 to 0.77)	131 fewer per 1,000 (from 196 fewer to 65 fewer)	⊕⊕○○ Low	
Respiratory distress syndrome (RDS) and moderate/severe RDS (CC)												
4	observational studies	not serious	not serious	not serious	serious ^a	none	99/209 (47.4%)	99/208 (47.6%)	OR 0.74 (0.48 to 1.12)	74 fewer per 1,000 (from 172 fewer to 28 more)	⊕○○○ Very low	
Surfactant use (HC)												
3	observational studies	not serious	serious ^a	not serious	serious ^a	none	176/355 (49.6%)	236/402 (58.7%)	OR 0.73 (0.32 to 1.65)	78 fewer per 1,000 (from 274 fewer to 114 more)	⊕○○○ Very low	

Severe interventricular haemorrhage (grade3-4) (HC)

4	observational studies	not serious	not serious	not serious	Serious ^{b,d}	strong association	25/414 (6.0%)	13/114 (11.4%)	OR 0.41 (0.19 to 0.87)	64 fewer per 1,000 (from 90 fewer to 13 fewer)	⊕○○○ Very low	
Severe interventricular haemorrhage (grade3-4) (CC)												
3	observational studies	not serious	not serious	not serious	serious ^a	none	5/163 (3.1%)	14/155 (9.0%)	OR 0.32 (0.03 to 3.19)	60 fewer per 1,000 (from 87 fewer to 150 more)	⊕○○○ Very low	
Intraventricular haemorrhage (HC)												
5	observational studies	not serious	not serious	not serious	serious ^{b,d}	strong association	42/502 (8.4%)	26/156 (16.7%)	OR 0.41 (0.23 to 0.72)	91 fewer per 1,000 (from 123 fewer to 41 fewer)	⊕⊕○○ Low	
Intraventricular haemorrhage (CC)												
3	observational studies	not serious	not serious	not serious	serious ^a	none	13/163 (8.0%)	20/155 (12.9%)	OR 0.43 (0.07 to 2.44)	69 fewer per 1,000 (from 119 fewer to 136 more)	⊕○○○ Very low	
Early-onset sepsis (HC)												
4	observational studies	not serious	not serious	not serious	serious ^a	none	29/326 (8.9%)	9/122 (7.4%)	OR 1.33 (0.39 to 4.56)	22 more per 1,000 (from 44 fewer to 193 more)	⊕○○○ Very low	
Early-onset sepsis (CC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	6/64 (9.4%)	1/29 (3.4%)	OR 2.90 (0.33 to 25.23)	59 more per 1,000 (from 23 fewer to 439 more)	⊕○○○ Very low	
Sepsis (HC)												
6	observational studies	not serious	not serious	not serious	serious ^a	none	112/677 (16.5%)	83/516 (16.1%)	OR 1.03 (0.73 to 1.47)	4 more per 1,000 (from 38 fewer to 59 more)	⊕○○○ Very low	
Sepsis (CC)												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	26/104 (25.0%)	12/46 (26.1%)	OR 0.71 (0.13 to 3.89)	60 fewer per 1,000 (from 217 fewer to 318 more)	⊕○○○ Very low	
Patent ductus arteriosus (HC)												
4	observational studies	not serious	not serious	not serious	serious ^a	none	109/407 (26.8%)	112/438 (25.6%)	OR 0.70 (0.46 to 1.07)	62 fewer per 1,000 (from 119 fewer to 13 more)	⊕○○○ Very low	
Patent ductus arteriosus (CC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	22/64 (34.4%)	13/29 (44.8%)	OR 0.64 (0.26 to 1.58)	106 fewer per 1,000 (from 274 fewer to 114 more)	⊕○○○ Very low	
Chronic lung disease / bronchopulmonary dysplasia (HC)												

4	observational studies	not serious	not serious	not serious	serious ^a	none	75/420 (17.9%)	30/116 (25.9%)	OR 0.54 (0.27 to 1.10)	100 fewer per 1,000 (from 173 fewer to 19 more)	⊕○○○ Very low	
Chronic lung disease / bronchopulmonary dysplasia (CC)												
3	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	34/149 (22.8%)	24/98 (24.5%)	OR 0.91 (0.44 to 1.86)	17 fewer per 1,000 (from 120 fewer to 131 more)	⊕○○○ Very low	
Periventricular leukomalacia (HC)												
4	observational studies	not serious	not serious	not serious	serious ^a	none	18/414 (4.3%)	6/114 (5.3%)	OR 0.76 (0.27 to 2.12)	12 fewer per 1,000 (from 38 fewer to 53 more)	⊕○○○ Very low	
Periventricular leukomalacia (CC)												
3	observational studies	not serious	not serious	not serious	serious ^a	none	8/163 (4.9%)	24/155 (15.5%)	OR 0.39 (0.08 to 1.90)	88 fewer per 1,000 (from 140 fewer to 103 more)	⊕○○○ Very low	
Mean duration of mechanical ventilation, days (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	52	36	-	MD 2 lower (4.23 lower to 0.23 higher)	⊕○○○ Very low	
Necrotizing enterocolitis (HC)												
5	observational studies	not serious	not serious	not serious	serious ^a	none	64/625 (10.2%)	31/480 (6.5%)	OR 1.23 (0.72 to 2.10)	14 more per 1,000 (from 17 fewer to 62 more)	⊕○○○ Very low	
Necrotizing enterocolitis (CC)												
2	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	16/104 (15.4%)	3/46 (6.5%)	OR 2.58 (0.70 to 9.55)	87 more per 1,000 (from 19 fewer to 335 more)	⊕○○○ Very low	
Apgar score <7 at 5 minutes (HC)												
1	observational studies	not serious	not serious	not serious	serious ^{b,e}	none	31/169 (18.3%)	120/358 (33.5%)	OR 0.45 (0.28 to 0.70)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Use of mechanical ventilation (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	66/89 (74.2%)	29/32 (90.6%)	OR 0.30 (0.08 to 1.07)	163 fewer per 1,000 (from 470 fewer to 6 more)	⊕○○○ Very low	
Use of mechanical ventilation (CC)												
1	observational studies	not serious	not serious	not serious	serious ^a	none	49/64 (76.6%)	29/29 (100.0%)	OR 0.05 (0.00 to 0.94)	0 fewer per 1,000 (from 0 fewer to -)	⊕○○○ Very low	

Duration of oxygen use, days (HC)

1	observational studies	not serious	not serious	not serious	serious ^a	none	52	36	-	MD 9 higher (5.66 higher to 12.34 higher)	⊕○○○ Very low	
Hypotension within 7postnatal days (HC)												
1	observational studies	not serious	not serious	not serious	serious ^a	none	9/97 (9.3%)	6/12 (50.0%)	OR 0.08 (0.01 to 0.64)	426 fewer per 1,000 (from 490 fewer to 110 fewer)	⊕○○○ Very low	
Retinopathy of prematurity requiring treatment (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	9/97 (9.3%)	2/12 (16.7%)	OR 0.51 (0.10 to 2.71)	74 fewer per 1,000 (from 147 fewer to 185 more)	⊕○○○ Very low	
Discharge with respiratory support (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	23/97 (23.7%)	4/12 (33.3%)	OR 0.62 (0.17 to 2.25)	97 fewer per 1,000 (from 255 fewer to 196 more)	⊕○○○ Very low	
Systemic inflammatory response syndrome (HC)												
1	observational studies	not serious	not serious	not serious	serious ^a	none	72/182 (39.6%)	24/36 (66.7%)	OR 0.33 (0.15 to 0.70)	269 fewer per 1,000 (from 436 fewer to 83 fewer)	⊕○○○ Very low	
Systemic inflammatory response syndrome (CC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	25/40 (62.5%)	11/17 (64.7%)	OR 0.91 (0.28 to 2.97)	22 fewer per 1,000 (from 308 fewer to 198 more)	⊕○○○ Very low	
Severe RDS (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	16/89 (18.0%)	9/32 (28.1%)	OR 0.56 (0.22 to 1.44)	102 fewer per 1,000 (from 202 fewer to 79 more)	⊕○○○ Very low	
Meningitis (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	2/88 (2.3%)	0/42 (0.0%)	OR 2.46 (0.12 to 52.32)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Intrahepatic cholestasis (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	4/52 (7.7%)	6/36 (16.7%)	OR 0.42 (0.11 to 1.60)	89 fewer per 1,000 (from 145 fewer to 76 more)	⊕○○○ Very low	
Pneumonia (HC)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	23/88 (26.1%)	5/42 (11.9%)	OR 2.62 (0.92 to 7.47)	142 more per 1,000 (from 8 fewer to 383 more)	⊕○○○ Very low	

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Estimate based on wide confidence interval crossing the line of no effect.
- b. Estimate based on small sample size.
- c. Heterogeneity is high (I-square \geq 60%).
- d. Wide difference of denominators between ACS and control group.
- e. The data were extracted from one study.

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Is antenatal corticosteroid therapy effective and safe for reducing adverse maternal and child outcomes in women with growth-restricted fetuses and/or small-for-gestational age infants?

Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (SGA)												
3	observational studies	not serious	not serious	not serious	serious*	none	774/851 (91.0%)	1145/1309 (87.5%)	OR 1.35 (0.86 to 2.12)	29 more per 1,000 (from 17 fewer to 62 more)	⊕○○○ Very low	
Chorioamnionitis (histologic and /or clinical) (SGA)												
4	observational studies	not serious	not serious	not serious	serious*	none	63/702 (9.0%)	83/1094 (7.6%)	OR 1.27 (0.70 to 2.30)	19 more per 1,000 (from 22 fewer to 83 more)	⊕○○○ Very low	
Preeclampsia (SGA)												
2	observational studies	not serious	not serious	not serious	not serious	none	359/806 (44.5%)	640/1271 (50.4%)	OR 0.78 (0.66 to 0.94)	62 fewer per 1,000 (from 103 fewer to 15 fewer)	⊕○○○ Very low	
Gestational diabetes mellitus (SGA)												
2	observational studies	not serious	not serious	not serious	serious*	none	10/764 (1.3%)	27/1247 (2.2%)	OR 0.57 (0.27 to 1.19)	9 fewer per 1,000 (from 16 fewer to 4 more)	⊕○○○ Very low	
Pregnancy induced hypertension (SGA)												
2	observational studies	not serious	not serious	not serious	not serious	none	144/370 (38.9%)	94/314 (29.9%)	OR 1.50 (1.08 to 2.07)	91 more per 1,000 (from 16 more to 170 more)	⊕⊕○○ Low	
Neonatal death (SGA)												
8	observational studies	not serious	not serious	not serious	not serious	none	242/1544 (15.7%)	196/1116 (17.6%)	OR 0.68 (0.47 to 0.97)	49 fewer per 1,000 (from 85 fewer to 4 fewer)	⊕⊕○○ Low	
Death before discharge home (SGA)												
4	observational studies	not serious	serious*	not serious	not serious	none	390/2746 (14.2%)	386/2344 (16.5%)	OR 0.62 (0.43 to 0.90)	56 fewer per 1,000 (from 87 fewer to 14 fewer)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate / severe RDS (SGA)												
13	observational studies	not serious	not serious	not serious	not serious	none	-	-	OR 0.86 (0.72 to 1.03)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ Very low	
Surfactant use (SGA)												
2	observational studies	not serious	not serious	not serious	serious*	none	62/209 (29.7%)	34/176 (19.3%)	OR 1.66 (0.91 to 3.03)	91 more per 1,000 (from 14 fewer to 227 more)	⊕○○○ Very low	
Major brain lesion (IVH, ICH, PVH, PVL) (SGA)												

3	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	-	-	OR 0.52 (0.20 to 1.34)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	-----------------------------	------	---	---	---------------------------	--	------------------	--

Interventricular haemorrhage (SGA)

8	observational studies	not serious	serious ^a	not serious	serious ^a	none	386/3592 (10.7%)	378/2758 (13.7%)	OR 0.75 (0.53 to 1.06)	31 fewer per 1,000 (from 59 fewer to 7 more)	⊕○○○ Very low	
---	-----------------------	-------------	----------------------	-------------	----------------------	------	------------------	------------------	---------------------------	---	------------------	--

Severe interventricular haemorrhage (grade3-4) (SGA)

7	observational studies	not serious	serious ^a	not serious	not serious	none	177/2873 (6.2%)	162/1548 (10.5%)	OR 0.57 (0.37 to 0.86)	42 fewer per 1,000 (from 63 fewer to 13 fewer)	⊕○○○ Very low	
---	-----------------------	-------------	----------------------	-------------	-------------	------	-----------------	------------------	---------------------------	---	------------------	--

Periventricular leukomalacia (SGA)

4	observational studies	not serious	not serious	not serious	not serious	none	74/2219 (3.3%)	68/1736 (3.9%)	OR 0.54 (0.38 to 0.77)	18 fewer per 1,000 (from 24 fewer to 9 fewer)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	-------------	------	----------------	----------------	---------------------------	--	------------------	--

Neonatal sepsis (SGA)

5	observational studies	not serious	not serious	not serious	serious ^a	none	128/1239 (10.3%)	126/1743 (7.2%)	OR 1.28 (0.98 to 1.68)	18 more per 1,000 (from 1 fewer to 43 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	------------------	-----------------	---------------------------	--	------------------	--

Necrotizing enterocolitis (SGA)

8	observational studies	not serious	not serious	not serious	serious ^a	none	238/3753 (6.3%)	162/2961 (5.5%)	OR 0.84 (0.66 to 1.06)	8 fewer per 1,000 (from 18 fewer to 3 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	-----------------	-----------------	---------------------------	--	------------------	--

Patent ductus arteriosus (SGA)

4	observational studies	not serious	not serious	not serious	serious ^a	none	315/1194 (26.4%)	368/1706 (21.6%)	OR 1.22 (0.98 to 1.52)	36 more per 1,000 (from 3 fewer to 79 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	------------------	------------------	---------------------------	--	------------------	--

Chronic lung disease / bronchopulmonary dysplasia (SGA)

7	observational studies	not serious	not serious	not serious	not serious	none	596/2835 (21.0%)	389/2112 (18.4%)	OR 1.14 (0.89 to 1.46)	21 more per 1,000 (from 17 fewer to 64 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	-------------	------	------------------	------------------	---------------------------	---	------------------	--

Use of mechanical ventilation (SGA)

2	observational studies	not serious	serious ^a	not serious	very serious ^{a,b}	none	89/191 (46.6%)	25/56 (44.6%)	OR 1.03 (0.37 to 2.90)	7 more per 1,000 (from 217 fewer to 254 more)	⊕○○○ Very low	
---	-----------------------	-------------	----------------------	-------------	-----------------------------	------	----------------	---------------	---------------------------	--	------------------	--

Apgar score < 7 at 5 minutes (SGA)

3	observational studies	not serious	not serious	not serious	serious ^a	none	52/433 (12.0%)	62/471 (13.2%)	OR 0.74 (0.51 to 1.09)	31 fewer per 1,000 (from 60 fewer to 10 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	----------------	----------------	---------------------------	--	------------------	--

Apgar score < 5 at 1 minute (SGA)

2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	49/191 (25.7%)	15/56 (26.8%)	OR 1.37 (0.63 to 2.97)	66 more per 1,000 (from 81 fewer to 253 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	----------------	---------------	---------------------------	--	------------------	--

Neonatal hypoglycemia (SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	17/45 (37.8%)	8/37 (21.6%)	OR 2.20 (0.82 to 5.91)	161 more per 1,000 (from 32 fewer to 404 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	---------------	--------------	---------------------------	---	------------------	--

Gestational age at birth (SGA)

2	observational studies	not serious	not serious	not serious	serious ^d	none	806	1272	-	MD 0.58 lower (0.81 lower to 0.34 lower)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	-----	------	---	---	------------------	--

Small for gestational age (< 2.3rd percentile for gestational age) (SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	63/146 (43.2%)	12/19 (63.2%)	OR 0.44 (0.16 to 1.19)	202 fewer per 1,000 (from 416 fewer to 39 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	----------------	---------------	---------------------------	--	------------------	--

Neonatal adrenal insufficiency (SGA)

1	observational studies	not serious	not serious	not serious	serious ^a	none	53/719 (7.4%)	67/1210 (5.5%)	OR 1.36 (0.94 to 1.97)	18 more per 1,000 (from 3 fewer to 48 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	---------------	----------------	---------------------------	--	------------------	--

Cerebral palsy (SGA)

1	observational studies	not serious	not serious	not serious	serious ^a	none	19/278 (6.8%)	25/498 (5.0%)	OR 1.39 (0.75 to 2.57)	18 more per 1,000 (from 12 fewer to 69 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	---------------	---------------	---------------------------	---	------------------	--

Severe hearing impairment (SGA)

1	observational studies	not serious	not serious	not serious	serious ^a	none	0/277 (0.0%)	5/502 (1.0%)	OR 0.16 (0.01 to 2.96)	8 fewer per 1,000 (from 10 fewer to 19 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	--------------	--------------	---------------------------	---	------------------	--

Visual impairment (SGA)

1	observational studies	not serious	not serious	not serious	serious ^a	none	1/275 (0.4%)	3/490 (0.6%)	OR 0.59 (0.06 to 5.72)	3 fewer per 1,000 (from 6 fewer to 28 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------	------	--------------	--------------	---------------------------	--	------------------	--

Birth weight (SGA)

2	observational studies	not serious	serious ^a	not serious	serious ^a	none	806	1272	-	MD 49.1 lower (110.53 lower to 12.32 higher)	⊕○○○ Very low	
---	-----------------------	-------------	----------------------	-------------	----------------------	------	-----	------	---	---	------------------	--

Duration of hospital stay (SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	87	62	-	MD 4 lower (17.43 lower to 9.43 higher)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	----	----	---	--	------------------	--

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Estimate based on wide confidence interval crossing the line of no effect.
- b. Estimate based on small sample size.
- c. Heterogeneity is high (I-square=>60%).
- d. Estimate based on the risk of selection bias.

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Women with growth-restricted fetuses compared to placebo for [health problem]

Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	20/165 (12.1%)	6/62 (9.7%)	OR 0.69 (0.26 to 1.81)	28 fewer per 1,000 (from 70 fewer to 66 more)	⊕○○○ Very low	
Death before discharge home (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	9/62 (14.5%)	15/62 (24.2%)	OR 0.53 (0.21 to 1.33)	97 fewer per 1,000 (from 179 fewer to 56 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR)												
3	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	-	-	OR 0.85 (0.57 to 1.26)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ Very low	
Surfactant use (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	19/53 (35.8%)	13/34 (38.2%)	OR 0.90 (0.37 to 2.20)	25 fewer per 1,000 (from 196 fewer to 194 more)	⊕○○○ Very low	
Major brain lesion (IVH, ICH, PVH, PVL) (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	12/116 (10.3%)	10/96 (10.4%)	OR 0.86 (0.35 to 2.10)	13 fewer per 1,000 (from 65 fewer to 92 fewer)	⊕○○○ Very low	
Interventricular haemorrhage (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Severe interventricular haemorrhage (grade3-4) (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Neonatal sepsis (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	45/115 (39.1%)	36/96 (37.5%)	OR 0.83 (0.44 to 1.58)	43 fewer per 1,000 (from 166 fewer to 112 more)	⊕○○○ Very low	
Necrotizing enterocolitis (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	3/53 (5.7%)	2/34 (5.9%)	OR 0.96 (0.15 to 6.07)	2 fewer per 1,000 (from 50 fewer to 216 more)	⊕○○○ Very low	
Patent ductus arteriosus (FGR)												

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	10/53 (18.9%)	6/34 (17.6%)	OR 1.09 (0.35 to 3.32)	13 more per 1,000 (from 107 fewer to 239 more)	⊕○○○ Very low	
Chronic lung disease / bronchopulmonary dysplasia (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	22/115 (19.1%)	23/96 (24.0%)	OR 0.83 (0.42 to 1.63)	32 fewer per 1,000 (from 123 fewer to 100 more)	⊕○○○ Very low	
Duration of mechanical ventilation (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	115	96	-	MD 1.09 higher (0.86 lower to 3.05 higher)	⊕○○○ Very low	
Use of mechanical ventilation (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	61/115 (53.0%)	45/96 (46.9%)	OR 1.24 (0.72 to 2.14)	54 more per 1,000 (from 80 fewer to 185 more)	⊕○○○ Very low	
Hypotension (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	15/53 (28.3%)	5/34 (14.7%)	OR 2.29 (0.75 to 7.03)	136 more per 1,000 (from 33 fewer to 401 more)	⊕○○○ Very low	
Growth <10th percentile in early childhood (FGR)												
1	observational studies	not serious	not serious	not serious	serious ^b	none	14/49 (28.6%)	3/42 (7.1%)	OR 5.20 (1.38 to 19.62)	214 more per 1,000 (from 25 more to 530 more)	⊕○○○ Very low	
Abnormal behavior at long-term follow-up at school age (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	21/49 (42.9%)	19/42 (45.2%)	OR 0.91 (0.40 to 2.08)	23 fewer per 1,000 (from 204 fewer to 180 more)	⊕○○○ Very low	
Death at long-term follow-up (school age) (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	4/62 (6.5%)	5/62 (8.1%)	OR 0.79 (0.20 to 3.08)	16 fewer per 1,000 (from 63 fewer to 132 more)	⊕○○○ Very low	
Death or disability/handicap at 2yrs' corrected age (FGR)												
1	observational studies	not serious	not serious	not serious	serious ^a	strong association	11/62 (17.7%)	22/62 (35.5%)	OR 0.39 (0.17 to 0.90)	178 fewer per 1,000 (from 269 fewer to 24 fewer)	⊕⊕○○ Low	

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Estimate based on wide confidence interval crossing the line of no effect.
b. Estimate based on small sample size.

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Women with growth-restricted fetuses compared to placebo for [health problem]

Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	136/219 (62.1%)	56/119 (47.1%)	OR 1.02 (0.62 to 1.68)	5 more per 1,000 (from 115 fewer to 128 more)	⊕○○○ Very low	
Chorioamnionitis (histologic and /or clinical) (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	19/83 (22.9%)	2/8 (25.0%)	OR 0.89 (0.17 to 4.78)	21 fewer per 1,000 (from 196 fewer to 364 more)	⊕○○○ Very low	
Preeclampsia (FGR or SGA)												
2	observational studies	<u>not serious</u>	serious ^c	not serious	serious ^a	none	78/254 (30.7%)	52/209 (24.9%)	OR 1.37 (0.33 to 5.61)	63 more per 1,000 (from 150 fewer to 401 more)	⊕○○○ Very low	
Gestational diabetes mellitus (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	14/219 (6.4%)	7/119 (5.9%)	OR 1.06 (0.36 to 3.08)	3 more per 1,000 (from 37 fewer to 103 more)	⊕○○○ Very low	
Pregnancy induced hypertension (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	51/83 (61.4%)	5/8 (62.5%)	OR 0.96 (0.21 to 4.28)	10 fewer per 1,000 (from 366 fewer to 252 more)	⊕○○○ Very low	
Neonatal death (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	9/83 (10.8%)	2/8 (25.0%)	OR 0.36 (0.06 to 2.09)	143 fewer per 1,000 (from 230 fewer to 161 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR or SGA)												
3	observational studies	not serious	not serious	not serious	serious ^a	none	77/358 (21.5%)	74/241 (30.7%)	OR 0.74 (0.51 to 1.07)	60 fewer per 1,000 (from 123 fewer to 15 more)	⊕○○○ Very low	
Surfactant use (FGR or SGA)												
3	observational studies	not serious	not serious	not serious	not serious	strong association	61/358 (17.0%)	58/241 (24.1%)	OR 0.38 (0.23 to 0.62)	133 fewer per 1,000 (from 173 fewer to 76 fewer)	⊕⊕⊕○ Moderate	
Interventricular haemorrhage (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	

Severe interventricular haemorrhage (grade3-4) (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	-------------	------------	-----------------------------------	---	------------------	--

Neonatal sepsis (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	18/83 (21.7%)	3/8 (37.5%)	OR 0.46 (0.10 to 2.12)	159 fewer per 1,000 (from 318 fewer to 185 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	---------------	-------------	----------------------------------	--	------------------	--

Necrotizing enterocolitis (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	1/8 (12.5%)	OR 0.45 (0.05 to 4.40)	65 fewer per 1,000 (from 118 fewer to 261 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	-------------	-------------	----------------------------------	---	------------------	--

Patent ductus arteriosus (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	42/83 (50.6%)	4/8 (50.0%)	OR 1.02 (0.24 to 4.37)	5 more per 1,000 (from 306 fewer to 314 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	---------------	-------------	----------------------------------	---	------------------	--

Chronic lung disease / bronchopulmonary dysplasia (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	23/83 (27.7%)	3/8 (37.5%)	OR 0.64 (0.14 to 2.89)	98 fewer per 1,000 (from 298 fewer to 259 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	---------------	-------------	----------------------------------	---	------------------	--

Use of mechanical ventilation (FGR or SGA)

2	observational studies	not serious	not serious	not serious	not serious	strong association	73/275 (26.5%)	94/233 (40.3%)	OR 0.42 (0.26 to 0.66)	182 fewer per 1,000 (from 254 fewer to 95 fewer)	⊕⊕⊕○ Moderate	
---	-----------------------	-------------	-------------	-------------	-------------	--------------------	----------------	----------------	----------------------------------	--	------------------	--

Apgar score < 7 at 5 minutes (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	6/136 (4.4%)	5/111 (4.5%)	OR 0.98 (0.29 to 3.29)	1 fewer per 1,000 (from 32 fewer to 89 more)	⊕○○○ Very low	
---	-----------------------	-------------	-------------	-------------	----------------------------	------	--------------	--------------	----------------------------------	--	------------------	--

Neonatal hypoglycemia (FGR or SGA)

1	observational studies	not serious	not serious	not serious	serious ^a	strong association	55/136 (40.4%)	28/111 (25.2%)	OR 2.01 (1.16 to 3.48)	152 more per 1,000 (from 29 more to 288 more)	⊕⊕○○ Low	
---	-----------------------	-------------	-------------	-------------	----------------------	--------------------	----------------	----------------	----------------------------------	---	-------------	--

Oxygen therapy (FGR or SGA)

2	observational studies	not serious	not serious	not serious	not serious	strong association	79/275 (28.7%)	94/233 (40.3%)	OR 0.48 (0.30 to 0.77)	158 fewer per 1,000 (from 235 fewer to 61 fewer)	⊕⊕⊕○ Moderate	
---	-----------------------	-------------	-------------	-------------	-------------	--------------------	----------------	----------------	----------------------------------	--	------------------	--

Gestational age at birth (FGR or SGA)

2	observational studies	not serious	serious ^a	not serious	serious ^a	none	275	233	-	MD 0.43 higher (0.54 lower to 1.4 higher)	⊕○○○ Very low	
---	-----------------------	-------------	----------------------	-------------	----------------------	------	-----	-----	---	---	------------------	--

Retinopathy of prematurity (FGR or SGA)

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Neonatal adrenal insufficiency (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	4/83 (4.8%)	0/8 (0.0%)	OR 0.96 (0.05 to 19.45)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Survival free from disability (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	108/144 (75.0%)	91/126 (72.2%)	OR 1.15 (0.67 to 1.98)	27 more per 1,000 (from 87 fewer to 115 more)	⊕○○○ Very low	
Cerebral palsy (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	6/139 (4.3%)	5/122 (4.1%)	OR 1.06 (0.31 to 3.55)	2 more per 1,000 (from 28 fewer to 91 more)	⊕○○○ Very low	
Birth weight (g) (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	275	233	-	MD 80.97 higher (20.48 lower to 182.41 higher)	⊕○○○ Very low	
Admission to neonatal intensive care unit (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	131/136 (96.3%)	107/111 (96.4%)	OR 0.98 (0.26 to 3.74)	1 fewer per 1,000 (from 90 fewer to 26 more)	⊕○○○ Very low	
Duration of hospital stay (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	serious ^a	none	136	111	-	MD 2.3 lower (3.8 lower to 0.8 lower)	⊕○○○ Very low	

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- Estimate based on wide confidence interval crossing the line of no effect.
- Estimate based on small sample size.
- Heterogeneity is high (I-square=>60%).

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel

Question: Women with growth-restricted fetuses compared to placebo for [health problem]

Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (total)												
5	observational studies	not serious	not serious	not serious	serious ^a	none	910/1070 (85.0%)	1201/1428 (84.1%)	OR 1.31 (0.99 to 1.74)	33 more per 1,000 (from 1 fewer to 61 more)	⊕○○○ Very low	
Chorioamnionitis (histologic and /or clinical) (total)												
5	observational studies	not serious	not serious	not serious	serious ^a	none	82/785 (10.4%)	85/1102 (7.7%)	OR 1.28 (0.79 to 2.06)	20 more per 1,000 (from 15 fewer to 70 more)	⊕○○○ Very low	
Preeclampsia (total)												
4	observational studies	not serious	serious ^a	not serious	serious ^a	none	437/1060 (41.2%)	692/1480 (46.8%)	OR 0.99 (0.57 to 1.71)	3 fewer per 1,000 (from 134 fewer to 133 more)	⊕○○○ Very low	
Gestational diabetes mellitus (total)												
4	observational studies	not serious	not serious	not serious	serious ^a	none	24/983 (2.4%)	34/1366 (2.5%)	OR 0.73 (0.41 to 1.31)	7 fewer per 1,000 (from 15 fewer to 7 more)	⊕○○○ Very low	
Pregnancy induced hypertension (total)												
3	observational studies	not serious	not serious	not serious	not serious	none	195/453 (43.0%)	99/322 (30.7%)	OR 1.47 (1.07 to 2.01)	87 more per 1,000 (from 15 more to 164 more)	⊕⊕○○ Low	
Death before discharge home (total)												
5	observational studies	not serious	serious ^a	not serious	not serious	none	399/2808 (14.2%)	401/2406 (16.7%)	OR 0.61 (0.44 to 0.85)	58 fewer per 1,000 (from 86 fewer to 21 fewer)	⊕○○○ Very low	
Major brain lesion (IVH, ICH, PVH, PVL) (total)												
5	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	-	-	OR 0.66 (0.37 to 1.16)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕○○○ Very low	
Interventricular haemorrhage (total)												
10	observational studies	not serious	not serious	not serious	serious ^a	none	399/3737 (10.7%)	387/2828 (13.7%)	OR 0.76 (0.56 to 1.04)	29 fewer per 1,000 (from 55 fewer to 5 more)	⊕○○○ Very low	
Severe interventricular haemorrhage (grade3-4) (total)												
9	observational studies	not serious	not serious	not serious	not serious	none	190/3018 (6.3%)	171/1618 (10.6%)	OR 0.59 (0.41 to 0.85)	41 fewer per 1,000 (from 59 fewer to 14 fewer)	⊕⊕○○ Low	
Neonatal sepsis (total)												

8	observational studies	not serious	not serious	not serious	serious*	none	191/1437 (13.3%)	165/1847 (8.9%)	OR 1.17 (0.92 to 1.50)	14 more per 1,000 (from 7 fewer to 39 more)	⊕○○○ Very low	
Necrotizing enterocolitis (total)												
10	observational studies	not serious	not serious	not serious	serious*	none	246/3889 (6.3%)	165/3003 (5.5%)	OR 0.82 (0.67 to 1.01)	9 fewer per 1,000 (from 17 fewer to 1 more)	⊕○○○ Very low	
Patent ductus arteriosus (total)												
6	observational studies	not serious	not serious	not serious	not serious	none	367/1330 (27.6%)	378/1748 (21.6%)	OR 1.19 (1.00 to 1.42)	31 more per 1,000 (from 0 fewer to 65 more)	⊕○○○ Very low	
Chronic lung disease / bronchopulmonary dysplasia (total)												
10	observational studies	not serious	not serious	not serious	not serious	none	641/3033 (21.1%)	415/2216 (18.7%)	OR 1.11 (0.90 to 1.38)	16 more per 1,000 (from 16 fewer to 54 more)	⊕○○○ Very low	
Apgar score < 7 at 5 minutes (total)												
4	observational studies	not serious	not serious	not serious	serious*	none	58/569 (10.2%)	67/582 (11.5%)	OR 0.76 (0.53 to 1.10)	25 fewer per 1,000 (from 51 fewer to 10 more)	⊕○○○ Very low	
Neonatal hypoglycemia (total)												
2	observational studies	not serious	not serious	not serious	not serious	strong association	72/181 (39.8%)	36/148 (24.3%)	OR 2.06 (1.27 to 3.32)	155 more per 1,000 (from 47 more to 273 more)	⊕⊕⊕○ Moderate	
Gestational age at birth (total)												
4	observational studies	not serious	serious*	not serious	serious*	none	1081	1505	-	MD 0.04 lower (0.57 lower to 0.48 higher)	⊕○○○ Very low	
Retinopathy of prematurity (total)												
5	observational studies	not serious	not serious	not serious	serious*	none	135/1978 (6.8%)	44/832 (5.3%)	OR 1.13 (0.79 to 1.61)	6 more per 1,000 (from 11 fewer to 30 more)	⊕○○○ Very low	
Neonatal adrenal insufficiency (total)												
2	observational studies	not serious	not serious	not serious	serious*	none	57/802 (7.1%)	67/1218 (5.5%)	OR 1.35 (0.93 to 1.96)	18 more per 1,000 (from 4 fewer to 47 more)	⊕○○○ Very low	
Cerebral palsy (total)												
2	observational studies	not serious	not serious	not serious	serious*	none	25/417 (6.0%)	30/620 (4.8%)	OR 1.31 (0.76 to 2.27)	14 more per 1,000 (from 11 fewer to 55 more)	⊕○○○ Very low	
Duration of hospital stay (total)												
2	observational studies	not serious	not serious	not serious	not serious	none	223	173	-	MD 2.23 lower (3.81 lower to 0.83 lower)	⊕○○○ Very low	

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Estimate based on wide confidence interval crossing the line of no effect.
- b. Estimate based on small sample size.
- c. Heterogeneity is high (I-square=>60%).