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ANTENATAL CORTICOSTERIODS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: Synthesize available evidence on ACS effectiveness among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period.

Methods: A systemic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, Global Index Medicus was conducted for all comparative randomized or non-randomized interventional studies in the four subpopulations. Data were extracted independently by authors. Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was used to assess risk in non-randomized studies. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to assess the certainty of evidence.

Results: Twenty-three studies with 18003 pregnant women/neonates were included. All included articles were observational studies. Data on women with diabetes were limited and evidence on women undergoing planned CS was inconclusive. ACS was associated with possibly reduced odds of neonatal mortality (pooled OR 0.49, 95%CI 0.33-0.74, low certainty), severe intraventricular hemorrhage (IVH) (pooled OR 0.41, 95%CI 0.23-0.72, low), and IVH (pooled OR 0.41, 95%CI 0.19-0.87, low) in women with histological chorioamnionitis. Among women with clinical chorioamnionitis, IVH (pooled OR 0.39, 95%CI 0.15-0.99, low) and periventricular leukomalacia (pooled OR 0.30, 95%CI 0.11-0.86, low) odds were possibly reduced. Among women with FGR, surfactant use (pooled OR 0.38, 95%CI 0.23-0.62, moderate), mechanical ventilation (pooled OR 0.42, 95%CI 0.26-0.66, moderate), and oxygen therapy (pooled OR 0.48, 95%CI 0.30-0.77, moderate) were probably reduced, but hypoglycemia probably increased (pooled OR 2.06, 95%CI 1.27-3.32, moderate). Definitional differences for populations and outcomes complicated meta-analyses. Most studies were conducted in high-income countries.

Conclusions: Evidence is lacking for women with diabetes or undergoing planned CS. ACS might have benefits in women with chorioamnionitis. ACS is probably beneficial in FGR but can increase neonatal hypoglycemia. Well-designed studies with adequate follow-up are required.

Protocol registration:

PROSPERO (CRD42021267816; Supplementary File S1)

Strengths and limitations:

-This review included a broad search strategy.
-This review applied rigorous quality assessment and GRADE methodology.
-Definitional differences for population and outcomes complicated meta-analysis.
-Most studies were conducted in high-income countries.

INTRODUCTION

Antenatal corticosteroids (ACS), such as intramuscular dexamethasone or betamethasone, have been shown to cross the placenta and can induce fetal lung maturation.[1] When ACS is administered to women at risk of imminent preterm birth prior to 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly reduced.[2] ACS also probably decreases the risk of intraventricular hemorrhage (IVH) and reduces developmental delay in childhood.[2] As a result, the World Health Organization (WHO) and several obstetric and gynecological societies internationally recommend ACS therapy in women up to 34 weeks' gestation for improving preterm newborn outcomes.[3-6] Some national organizations have recommended the use of ACS in women at risk of preterm birth up to 36 weeks' gestation on the basis of the evidence that there may be some respiratory-related benefits for the newborn.[3,4]

However, the evidence regarding benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis or babies fetal growth restriction (FGR), is more controversial. Women with diabetes, chorioamnionitis, or babies with FGR are at higher risk of adverse perinatal outcomes, but they are generally excluded from ACS efficacy trials.[2] Consequently, any subgroup analyses to explore the effects of ACS in women with these complications is unlikely to provide direct evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycaemic effects; respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor maternal glycaemic control.[7-9] Chorioamnionitis is acute inflammation of the membranes and chorion of the placenta and is estimated to affect 3.9% of women giving birth.[10] Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS is avoided due to concerns that its immunosuppressive effects may worsen outcomes for the woman and her baby. However, the relative benefits and harms

of using ACS in this clinical situation are unclear. In many high-income countries, small for gestational age (SGA) neonates account for approximately 10% of all babies; this proportion is generally higher in low-to-middle income countries.[11-13] SGA is associated with an increased risk of neonatal morbidity and mortality than those babies born appropriate for gestational age (AGA).[14,15] The term SGA is often used as a proxy measure for FGR because most cases of SGA are caused by FGR.[16] Clarifying ACS effects in women at risk of imminent preterm birth with growth-restricted fetuses is necessary.

An additional clinical scenario where there is uncertainty regarding ACS efficacy is in women undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37 weeks' gestation). Babies born in late preterm have lower risks of mortality and morbidity compared with those born prior to 34 weeks' gestation; however, they have higher risks of adverse outcomes than babies born at term.[17-20] In many countries, the rate of provider-initiated late preterm birth is rising, which has been linked to the more generalised increase in CS use.[21] Regardless of gestational age, babies born via elective CS do not have the usual physical and hormonal stimuli of passage through the birth canal; thus, they tend to have higher rates of respiratory morbidity.[22-24] Some studies

have suggested that the risk of neonatal hypoglycaemia is greater following CS although this may be confounded by the underlying indication for CS.[25]

In 2016, members of our team published a systematic review to assess the effectiveness of ACS in these four clinical situations.[26] The review did not find any direct evidence on the effects of ACS in pregnant women with diabetes at risk of preterm birth or for those undergoing elective CS in the late preterm period. The review could not draw firm conclusions regarding the effects of ACS in women with growth-restricted fetuses although low-quality evidence suggested that ACS reduces neonatal IVH in women with chorioamnionitis.[26] Findings of the previous review informed WHO's 2015 ACS recommendations.[27] As part of WHO's living guidelines in maternal and perinatal health program, the ACS recommendations are currently being updated.[28] Hence, our aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians, and maternal and newborn health stakeholders on safe and effective clinical management in preterm birth.

METHODS

The specific review objectives are described in Box 1, comprising four related questions

on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA infants. The review protocol was registered on PROSPERO (CRD42021267816) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary File S1, S2).[29]

Box 1. Four Participant, Intervention, Comparison, Outcome (PICO) questions for the systematic review

P1: Effects of antenatal corticosteroid (ACS) in women with pregestational and/or gestational diabetes
P: Women at risk of imminent preterm birth with pregestational diabetes mellitus and/or gestational diabetes mellitus
I: ACS administration
C: Placebo or no treatment
O: World Health Organization (WHO) priority outcomes for preterm birth

P2: Effects of ACS in women undergoing elective cesarean section (CS) in the late preterm period
P: Women undergoing elective CS in the late preterm period
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P3: Effects of ACS in women with chorioamnionitis
P: Women at risk of imminent preterm birth with chorioamnionitis
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P4: Effects of ACS in women with growth-restricted fetuses and/or small-for-gestational age infants
P: Women at risk of imminent preterm birth with growth-restricted fetuses and/or small-for-gestational-age infants
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

Study eligibility criteria

Eligible studies were randomized or nonrandomized primary research studies that reported on the effects of ACS in the four subpopulations. This included published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-after studies, interrupted-time-series studies, historically controlled studies, cohort studies, and cross-sectional studies comparing any ACS administration (betamethasone, dexamethasone, or hydrocortisone) given either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis, and women with a FGR fetus or SGA infant.

Articles in any language and from any country were eligible for inclusion if they reported on one or more of the review outcomes of interest that reflected WHO's priority outcomes for preterm birth guideline development.[27] Maternal outcomes were death, maternal morbidity, and side effects of therapy. Newborn and child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity,

neurodevelopment, anthropometric status, and side effects of therapy (Supplementary File S3).

Data sources and search strategy

An information specialist was consulted for developing the search strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions. Controlled vocabularies supplemented with free keywords were used to search for the relevant concept areas, with duplicates removed in the process to yield a total number of abstracts for each database (Supplementary File S4). Reference lists of the included articles, including any recent systematic reviews, were also hand-searched for further potentially relevant studies. All citations were imported into a Rayyan (http://rayyan.qcri.org) library for eligibility assessment.

Study selection, data extraction, and quality assessment

Two reviewers (KS, EN) independently assessed titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies

were obtained and assessed in duplicate by two reviewers independently, with disagreements resolved through discussion or consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through discussion or consulting a third reviewer. Extracted data were entered into Review Manager version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS).[30] If we identified any randomized trials, we planned to use the Cochrane Risk of Bias tool.[31] We planned to assess for potential publication bias through visual inspection of funnel plots for asymmetry in situations where data for a single outcome were available from 10 or more studies.

Data synthesis and analysis

Aggregate odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals (CIs) were determined for dichotomous data using Mantel–Haenszel analysis (fixed-effects model). Where between-study clinical or methodological heterogeneity undermined the compatibility of the quantitative results, or if substantial statistical heterogeneity was detected, random-effects meta-analysis was used. Data were pooled

using ORs when the numbers of events were available and using logarithms of the ORs weighted by the inverse variance when events were not available. For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for heterogeneity. For the analysis on women with FGR fetuses and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only, SGA and FGR). Data from the three populations were combined and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%.

All statistical analyses were performed using RevMan5. Statistical significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) is an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines and was used in this review.

Patients and public involvement

As this paper is a systematic review of previously published data, there was no direct involvement from patients or the public.

RESULTS

Effects of ACS in women with pregestational and/or gestational diabetes mellitus

The search identified 179 citations, from which 11 potentially eligible studies were evaluated, and five studies met the eligibility criteria, providing data for 8,067 pregnant women/neonates (Figure 1).[32-36] All studies were conducted in high-income countries and collected data between 2006 and 2017 (Supplementary File S5). One study involved women with pregestational diabetes only, two studies involved women with gestational diabetes only, and two studies involved women with either pregestational or gestational diabetes. Three studies used betamethasone only, one study used dexamethasone or betamethasone, and in one study, the corticosteroid used was not specified. All included studies were judged as low risk of bias across all domains, except for two studies judged as high risk of selection bias (Figure 2; Supplementary File S6). Data were available for 5 outcomes (Table 1; Supplementary File S7). One retrospective cohort study found that in women with gestational diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (1 study, 2262 infants; OR 7.41, 95% CI 5.04

to 10.89, *low certainty evidence*)[32]; however, the effect of ACS on neonatal hypoglycemia was uncertain (3 studies, 2376 infants; pooled OR 1.74, 95% CI 0.96 to 3.16, *very low certainty evidence*). Certainty of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn (Supplementary File S8).

Table 1: Maternal and neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

Neonatal outcomes	No of studies	No of patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death within 48 h of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09–2.20)	14 fewer per 1000 (from 23 fewer to 29 more)	Very Low
RDS	3	179/695 (25.8%)	39/2242 (1.7%)	2.03 (0.60–6.85)	17more per 1000 (from 7 fewer to 91 more)	Very Low
Neonatal hypoglycemia	3	32/177 (18.1%)	77/2199 (3.5%)	1.74 (0.96–3.16)	24 more per 1000 (from 1 fewer to 68 more)	Very Low
Apgar score < 7 at 5 min	1	1/129 (0.8%)	21/2133 (1.0%)	0.79 (0.10–5.89)	2 fewer per 1000 (from 9 fewer to 45 more)	Very Low
Admission to NICU	1	51/129 (39.5%)	173/2133 (8.1%)	7.41 (5.04–10.89)	314 more per 1000 (from 227 more to 409 more)	Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome. *There is no maternal outcome.

Effects of ACS in women undergoing elective CS in the late preterm period

The search identified 211 citations, from which 17 potentially eligible studies were evaluated, and two studies were included (Figure 3).[37,38] These were observational studies (one case-control, one retrospective cohort) conducted in high-income countries between 2011 and 2017, providing data for 205 pregnant women/neonates (Supplementary File S5). In both studies, betamethasone was used. The case-control study was judged as low risk of bias for all domains(Figure 4; Supplementary File S6) . The retrospective cohort study was judged as high risk of bias for the selection of

participants and confounding variables. Data for 10 outcomes were available; however, all had very low certainty, so no meaningful conclusions could be drawn (Table 2; Supplementary Files S7, S8).

Table 2: Maternal and neonatal outcomes for women undergoing elective cesarean section in the late preterm period

Maternal outcomes	**No of studies**	**No of patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09–1.21)	89 fewer per 1000 (from 126 fewer to 25 more)	Very Low
Neonatal outcomes	**No of studies**	**No of patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29–2.24)	17 fewer per 1000 (from 65 fewer to 95 more)	Very Low
IVH	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Necrotizing enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Neonatal hypoglycemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81–2.78)	93 more per 1000 (from 44 fewer to 246 more)	Very Low
Use of mechanical ventilation	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.30–2.12)	17 fewer per 1000 (from 64 fewer to 86 more)	Very Low
Admission to NICU	2	10/88 (11.4%)	14/117 (12.0%)	0.73 (0.26–2.05)	29 fewer per 1000 (from 86 fewer to 98 more)	Very Low
Apgar score ≤ 7 at 5 min	1	2/58 (3.4%)	0/107 (0.0%)	9.51 (0.45–201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS in women with chorioamnionitis (histological or clinical)

The search identified 418 citations, from which 12 potentially eligible studies were evaluated, and eight studies met the eligibility criteria (Figure 5).[39-46] Two were prospective cohort studies and six were retrospective cohorts, providing data on 1460 pregnant women/neonates (Supplementary File S5). All studies were conducted in high-income countries and enrolled women between 1989 and 2014. One study evaluated dexamethasone, four studies evaluated betamethasone, and three studies evaluated

either betamethasone or dexamethasone. Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process.[39,42-44,47] All included studies were judged as low risk of bias overall although six studies were judged as high risk of bias for the domain regarding confounding variables as adjusted analyses were not reported (Figure 6; Supplementary File S6). Data for 25 outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3; Supplementary File S7). Amongst women with histological chorioamnionitis, ACS administration was associated with a possible reduction in the odds of neonatal mortality (6 studies, 1193 infants; pooled OR 0.49, 95% CI 0.33 to 0.74, *low certainty evidence*), IVH (5 studies, 658 infants; pooled OR 0.41, 95% CI 0.23 to 0.72, *low certainty evidence*), and severe IVH (4 studies, 528 infants; pooled OR 0.41, 95% CI 0.19 to 0.87, *low certainty evidence*). ACS might result in no difference in neonatal sepsis; however, evidence was uncertain (6 studies, 1193 infants: pooled OR 1.03, 95% CI 0.73 to 1.47, *very low certainty evidence*). The certainty of evidence was very low for other outcomes (Supplementary File S8). In women with clinical chorioamnionitis, ACS administration was associated with a possible reduction in the odds of IVH (3 studies, 318 infants, pooled OR 0.39, 95% CI 0.15 to 0.99, *low certainty evidence*), and

periventricular leukomalacia (3 studies, 318 infants, pooled OR 0.30, 95% CI 0.11 to 0.86, *low certainty evidence*). For neonatal sepsis, only very low certainty evidence was available (2 studies, 150 infants, pooled OR 0.96, 95% CI 0.40 to 2.29). The certainty of evidence was very low for all other outcomes (Supplementary File S8).

Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						
Preeclampsia or eclampsia	1	5/97 (5.2%)	1/12 (8.3%)	0.60 (0.06–5.59)	32 fewer per 1000 (from 78 fewer to 254 more)	Very Low
Neonatal outcomes (histological chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	0.49 (0.33–0.74)	78 fewer per 1000 (from 106 fewer to 38 more)	Low
Severe IVH	4	25/414 (6.0%)	13/114 (11.4%)	0.41 (0.19–0.87)	64 fewer per 1000 (from 90 fewer to 13 fewer)	Low
IVH	5	42/502 (8.4%)	26/156 (16.7%)	0.41 (0.23–0.72)	91 fewer per 1000 (from 123 fewer to 41 fewer)	Low
Sepsis	6	112/677 (16.5%)	83/516 (16.1%)	1.03 (0.73–1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very Low
Neonatal outcomes (clinical chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
IVH	3	13/163 (8.0%)	20/155 (12.9%)	0.39 (0.15–0.99)	74 fewer per 1000 (from 107 fewer to 1 fewer)	Low
PVL	3	8/163 (4.9%)	24/155 (15.5%)	0.30 (0.11–0.86)	103 fewer per 1000 (from 135 fewer to 19 fewer)	Low
Sepsis	2	26/104 (25.0%)	12/46 (26.1%)	0.96 (0.40–2.29)	8 fewer per 1000 (from 137 fewer to 186 more)	Very Low

*There is no maternal outcome in clinical chorioamnionitis.

*ACS: Antenatal corticosteroid, BPD/CLD: Bronchopulmonary dysplasia/chronic lung disease, CC: Clinical chorioamnionitis, CI: Confidence interval, HC: Histological chorioamnionitis, IVH: Intraventricular hemorrhage, OR: Odds ratio, PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia, RDS: Respiratory distress syndrome

Effects of ACS in women with growth-restricted fetuses and/or small for gestational age infants

The search identified 261 citations, from which 36 potentially eligible studies were assessed, and 18 studies were included (Figure 7).[42,48-64] Of these, 12 studies included women with SGA infants only, 4 studies included women with FGR or SGA infants, and 2 studies included women with FGR infants only (Supplementary File S5). All were observational studies conducted in high-income countries. Data were available from 8271 pregnant women/neonates enrolled between 1984 and 2019. Additional unpublished data from the study by Torrance et al. (2007) were extracted from a review paper published in 2009, which was identified through the search strategy.[54,65] Most of the included studies (17 of 18 studies) were judged as low risk of bias across all domains. Five studies were judged as high risk of bias for the domain regarding confounding variables. Four studies were judged as high risk of bias regarding incomplete outcome data (Figure 8; Supplementary File S6). For SGA infants only, 12 studies provided data on 27 outcomes (Supplementary File S7, S8). The administration of ACS for women with SGA was associated with the increasing odds of pregnancy-induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95% CI 1.08 to 2.07, *low certainty evidence*) although the odds of neonatal mortality (8 studies, 2710 infants; pooled OR: 0.61, 95% CI: 0.49 to 0.78, *low certainty evidence*) and severe IVH (6 studies, 3235 infants; pooled OR 0.60, 95% CI 0.45 to 0.80, *low certainty evidence)*

were possibly reduced (Table 4; Supplementary File S7, S8). Two studies involving FGR infants only provided data for 19 review outcomes; however, all outcomes were assessed as very low certainty evidence (Supplementary File S7, S8). Four studies involved SGA or FGR infants, providing data for 24 outcomes (Supplementary File S7, S8). The administration of ACS for women with SGA or FGR was associated with a possible reduction in the odds of surfactant use (3 studies, 599 infants; pooled OR 0.38, 95% CI 0.23 to 0.62, *moderate certainty evidence*), use of mechanical ventilation (2 studies, 508 infants; pooled OR 0.42, 95% CI 0.26 to 0.66, *moderate certainty evidence*), oxygen use (2 studies, 508 infants; pooled OR 0.48, 95% CI 0.30 to 0.77, *moderate certainty evidence*), and duration of hospital stay (1 study, 247 infants; MD −2.3 days, 95% CI −3.8 to −0.8, *low certainty evidence*) (Table 4; Supplementary File S7, S8). Pooled ORs involving women and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be determined for 18 outcomes (Supplementary File S7, S8). The administration of ACS for women with SGA and/or FGR was associated with a possible reduction in severe IVH (8 studies, 3450 infants; pooled OR 0.62, 95% CI 0.47 to 0.82, *low certainty evidence*) and in duration of hospital stay (2 studies, 396 infants; MD −2.23 days, 95% CI −3.81 to −0.83, *low certainty evidence*). However, the odds of PIH (3 studies, 775

women; pooled OR 1.47, 95% CI 1.07 to 2.01, *low certainty evidence*) and neonatal hypoglycemia (2 studies, 329 infants; pooled OR 2.06, 95% CI 1.27 to 3.32, *moderate certainty evidence*) were possibly increased (Table 4; Supplementary Files S7, S8).

Table 4: Maternal and neonatal outcomes for women with growth-restricted fetuses and/or small-for-gestational-age infants

Maternal outcomes	**No of study**	**No of patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
PIH						
Total	3	195/453 (43.0%)	99/322 (30.7%)	1.47 (1.07–2.01)	87 more per 1000 (from 15 more to 164 more)	Low
SGA	2	144/370 (38.9%)	94/314 (29.9%)	1.50 (1.08–2.07)	91 more per 1000 (from 16 more to 170 more)	Low
Neonatal outcomes	**No of study**	**No of patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death						
SGA	8	NS	NS	0.61 (0.49–0.78)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Low
Severe IVH						
Total	8	156/2341 (6.7%)	108/1109 (9.7%)	0.62 (0.47–0.82)	35 fewer per 1000 (from 49 fewer to 16 fewer)	Low
SGA	6	143/2196 (6.5%)	99/1039 (9.5%)	0.60 (0.45–0.80)	36 fewer per 1000 (from 50 fewer to 18 fewer)	Low
Neonatal hypoglycemia						
Total	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27–3.32)	155 more per 1000 (from 47 more to 273 more)	Moderate
Surfactant use						
FGR or SGA	3	61/358 (17.0%)	58/241 (24.1%)	0.38 (0.23–0.62)	133 fewer per 1000 (from 173 fewer to 76 fewer)	Moderate
Use of mechanical ventilation						
FGR or SGA	2	73/275 (26.5%)	94/233 (40.3%)	0.42 (0.26–0.66)	182 fewer per 1000 (from 254 fewer to 95 fewer)	Moderate
Oxygen therapy						
FGR or SGA	2	79/275 (28.7%)	94/233 (40.3%)	0.48 (0.30–0.77)	158 fewer per 1000 (from 235 fewer to 61 fewer)	Moderate
Duration of hospital stay (days)						
Total	2	223	173		MD 2.32 lower (3.81 lower to 0.83 lower)	Low
FGR or SGA	1	136	111		MD 2.3 lower (3.8 lower to 0.8 lower)	Low

*The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in total were calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH:

Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy induced hypertension, SGA: Small for gestational age

DISCUSSION

This systematic review identified 33 observational studies pertaining to the benefits and possible harms of using ACS in subgroups of women with specific complications of pregnancy. In women with diabetes and those undergoing elective late preterm CS, the available evidence on effects of ACS was largely very low certainty and conclusions could not be drawn. In women with histological and clinical chorioamnionitis, ACS was associated with some benefits. In women with FGR and/or SGA babies, ACS possibly has benefits for neonatal morbidity and mortality, as well as reduced use of respiratory support interventions for the newborn, although neonatal hypoglycemia might be increased.

Effects of ACS in women with pregestational and/or gestational diabetes

A clinical concern regarding the use of ACS in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycemia causing avoidable harm to the neonate. For example, in women with insulin-dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid administration.[66] A 2002 Danish study on 24 pregnant women with diabetes who received steroids suggested that insulin dose adjustment may be required for up to 5

days after ACS administration.[67] However, in the current review, there was insufficient evidence to assess whether ACS increased neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU admission[32]; however, the authors noted that neonatal birthweight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding. Further well-designed studies are needed on this clinical question and would ideally describe any adjustments to maternal diabetic regimens at the time of ACS therapy and the time from ACS administration to birth and report on important newborn health outcomes.

Effects of ACS in women undergoing elective CS in late preterm period

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, the subgroup analysis on gestational age at trial entry reported on findings from seven trials (4142 women) recruiting women at ≥34 weeks 0 days gestation.[2] This subgroup analysis suggested that ACS reduces RDS and increases neonatal hypoglycemia when used in the late preterm period. Two systematic reviews (2018 and 2021) on trials of ACS in the late preterm period drew similar conclusions.[68,69] However, the CS rate (only reported in five trials) was less than 30% in four of these trials[70-73]; hence, these findings cannot

be generalized to all women undergoing CS in the late preterm period. Our review demonstrates there is currently insufficient evidence to draw conclusions on the benefits and possible harms of ACS when used in this subpopulation although an ongoing randomized trial in New Zealand is assessing the effects of ACS in women with CS planned between 35 weeks 0 days and 39 weeks 6 days.[74]

Effects of ACS in women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to concerns that prolongation of pregnancy and/or immunosuppression may worsen outcomes for women and newborns. While ACS appears to be associated with reduced neonatal mortality, IVH, and severe IVH in women with histological chorioamnionitis, there was insufficient evidence for other important infection-related maternal and newborn outcomes. While these conclusions are broadly similar to a 2011 review by Been et al.,[47] we do not consider that the available evidence supports the routine use of ACS in women with chorioamnionitis as clinical trials comparing ACS therapy with no ACS in this population and reliable evidence for infection-related outcomes are still lacking. It is unlikely that such trials will be performed although well-conducted observational studies could provide useful additional evidence.

Effects of ACS in women with growth-restricted fetuses and/or small for gestational age infants

The totality of evidence identified in this review suggests that ACS should be used in the setting fetal growth restriction. While the evidence was largely low or very low certainty, benefits were observed for several outcomes (including neonatal death, severe IVH, and use of respiratory support interventions) and an absence of harms. The current review identified more substantive evidence (18 studies) than that identified in our 2016 systematic review (8 studies) that was unable to draw conclusions of the effects of ACS in this subpopulation.[26] It is also noteworthy that the largest trial of ACS in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected fetal growth restriction.[75] The current review did not identify benefits for the outcome RDS, which might be attributable to a single retrospective cohort study in Japan in which neonates in the ACS group were delivered significantly earlier than those in the control group.[57] A sensitivity analysis in which we excluded this study suggests that RDS is significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases neonatal hypoglycemia in this subpopulation, which

warrants further exploration in future research.

Strengths and limitations

Strengths of this review included a broad search strategy, which included studies published in languages other than English, rigorous quality assessment, and use of GRADE methodology to assess the reliability of the review findings. We thus consider the risk of missing potentially eligible studies to be low although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified, or diagnosed the subgroup conditions and outcomes and interest. These differences might have created bias in the review conclusions. However, we explored and reported heterogeneity for meta-analyses, as well as downgrading for imprecision. Another limitation is that most included studies were conducted in high-income countries although over 60% of all preterm births globally occur in African and South Asian countries.[76]

CONCLUSION

ACS has possible benefits in the setting of FGR and/or SGA; however, direct evidence on its effectiveness and safety for pregnant women with pregestational and/or

gestational diabetes mellitus and those undergoing elective CS in late preterm is lacking. While ACS might have some benefits in the context of histological chorioamnionitis, more evidence is required. Well-designed studies, ideally trials, with adequate follow-up for long-term child outcomes are needed to confirm the effects and harms of ACS use in these subpopulations.

Author contributions

Dr Saito participated in the conceptualization and design of the study; conducted title, abstract, and full-text screening; performed data extraction, analysis, and interpretation; assessed the risk of bias; drafted the initial manuscript; and critically revised the manuscript. Ms Nishimura conducted title, abstract, and full-text screening; performed data-extraction, analysis, and interpretation; assessed the risk of bias; and critically revised the manuscript. Dr Swa conceptualized and designed the search strategy, conducted a systematic search, and critically reviewed the manuscript for important intellectual content. Dr Ramson assisted in the interpretation of data and the assessment of risk of bias, and critically reviewed the manuscript for important intellectual content. Drs Namba, Cao and Lavin critically reviewed the protocol and manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel designed and

planned the study, assisted with developing the literature search strategy and resolving inclusion conflicts, critically revised the manuscript, and supervised the execution of the study. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

Data were obtained from published journal articles: extracts are available upon reasonable request.

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Competing interest

None declared.

Supplementary Files

Supplementary File S1: PROSPERO

Supplementary File S2: PRISMA 2020 Checklist

Supplementary File S3: Review outcomes

Supplementary File S4: Database-specific search terms and strategies

Supplementary File S5: Characteristic tables

Supplementary Fille S6: Risk of bias

Supplementary File S7: Forest plots

Supplementary File S8: GRADE tables

Ethics approval

As this study is a systematic review of published studies, ethical approval was not required.

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Figure 1. Flow diagram of search results and study selection for women with pregestaional and/or gestaional diabetes

Figure 2. Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes. Green=low risk of bias; red=high risk of bias; yellow=unclear risk of bias.

Figure 3. Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

Figure 4. Summary of risk of bias for each trial for women undergoing elective Cesarean section in late preterm period. Green=low risk of bias; red=high risk of bias; yellow=unclear risk of bias.

Figure 5. Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

Figure 6. Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical). Green=low risk of bias; red=high risk of bias; yellow=unclear risk of bias.

Figure 7. Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants

Figure 8. Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants. Green=low risk of bias; red=high risk of bias; yellow=unclear risk of bias.

Figure 1: Flow diagram of search results and study selection for women with pregestational and/or gestational diabetes

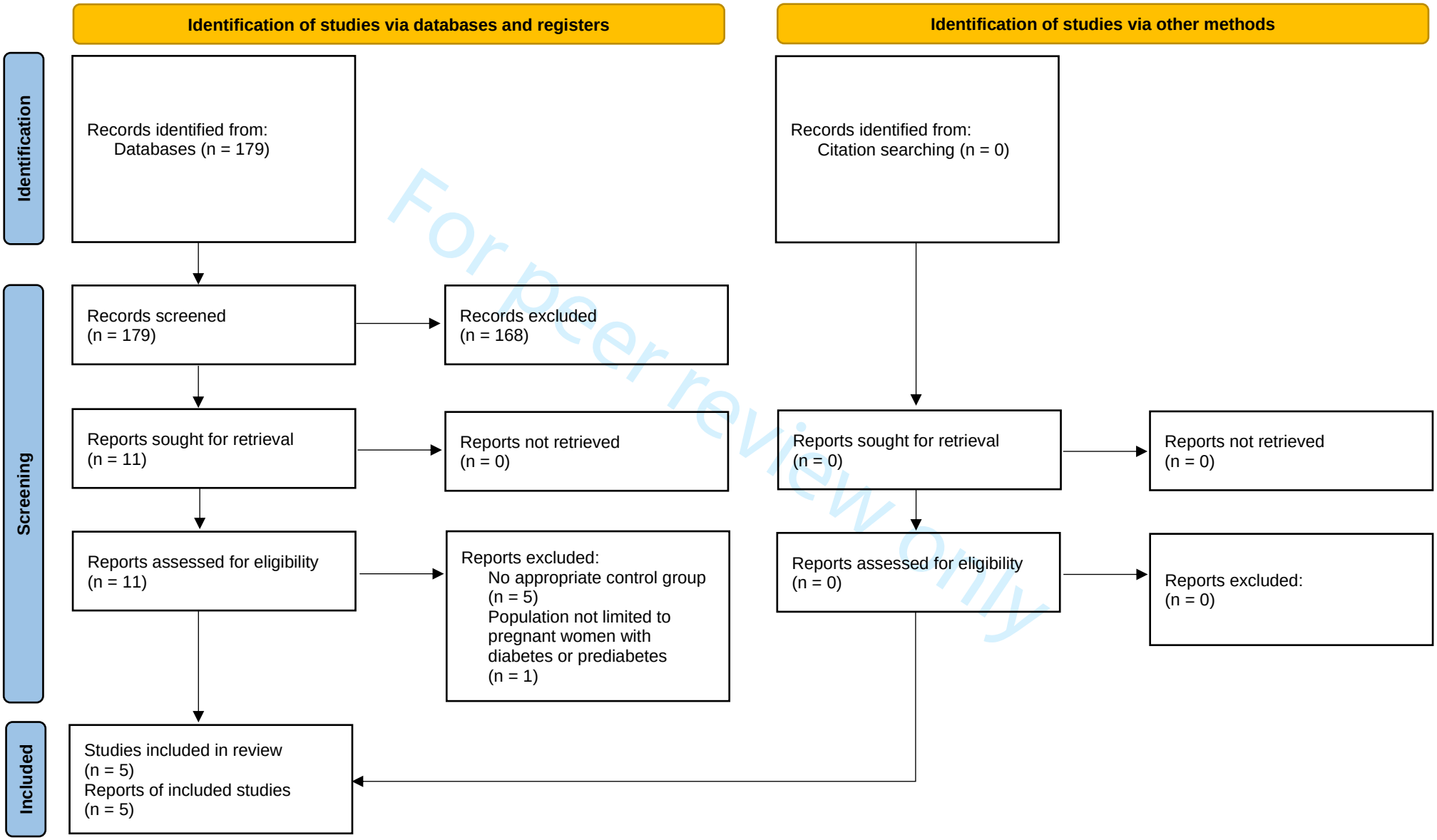


Figure 2: Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

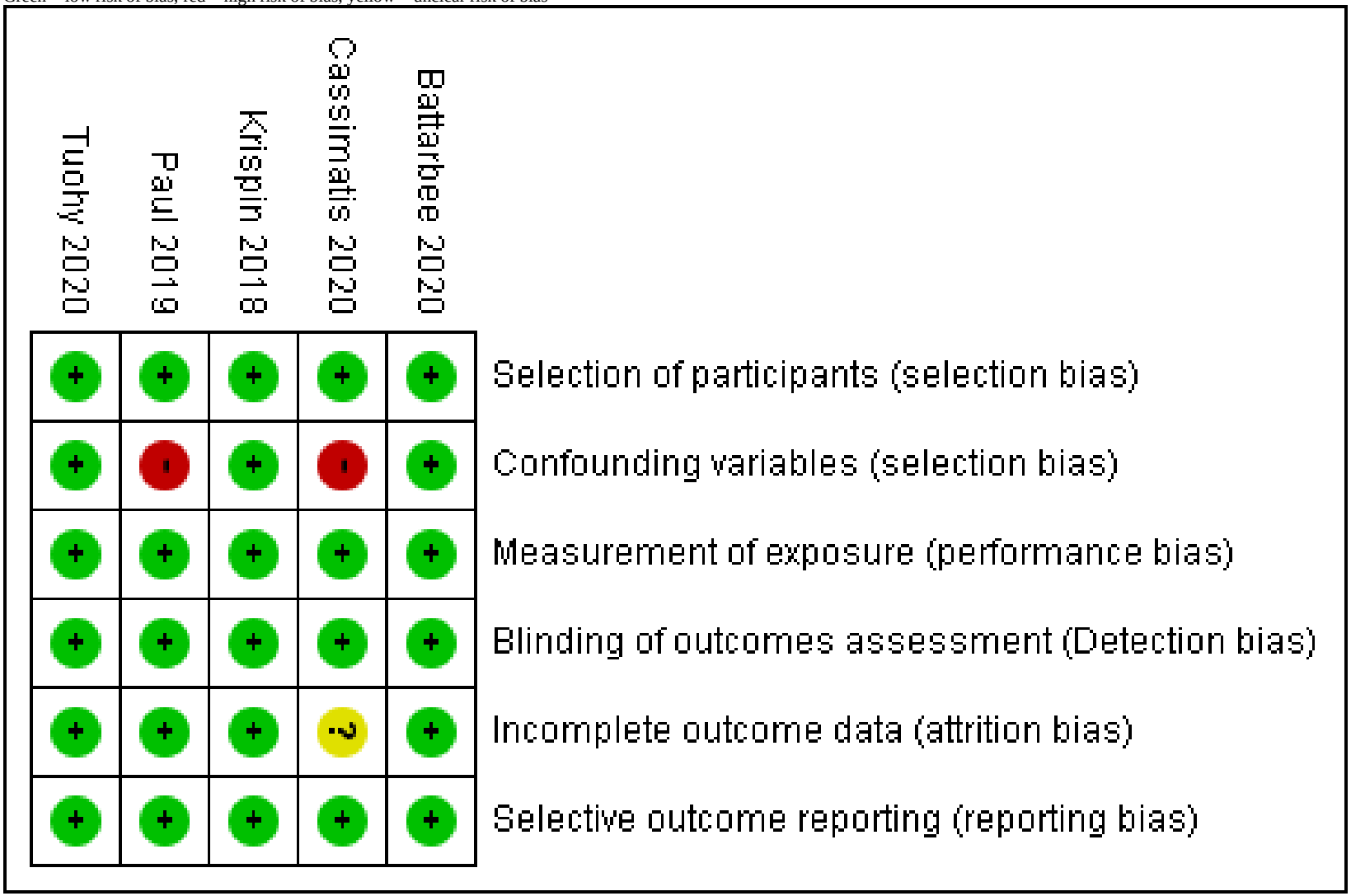


Figure 3: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

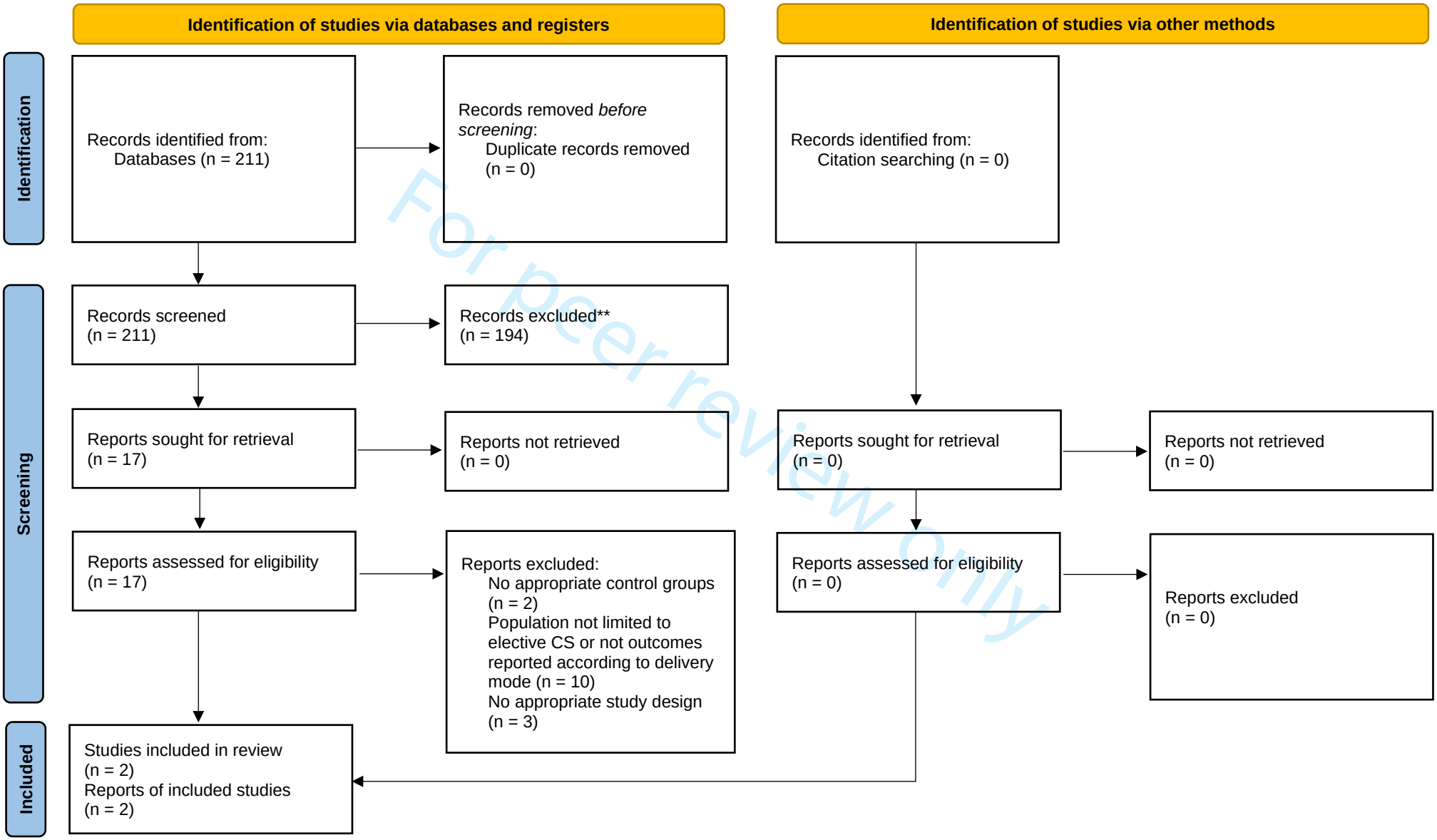


Figure 4: Summary of risk of bias for each trial for women undergoing elective Cesarean section in late preterm period
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

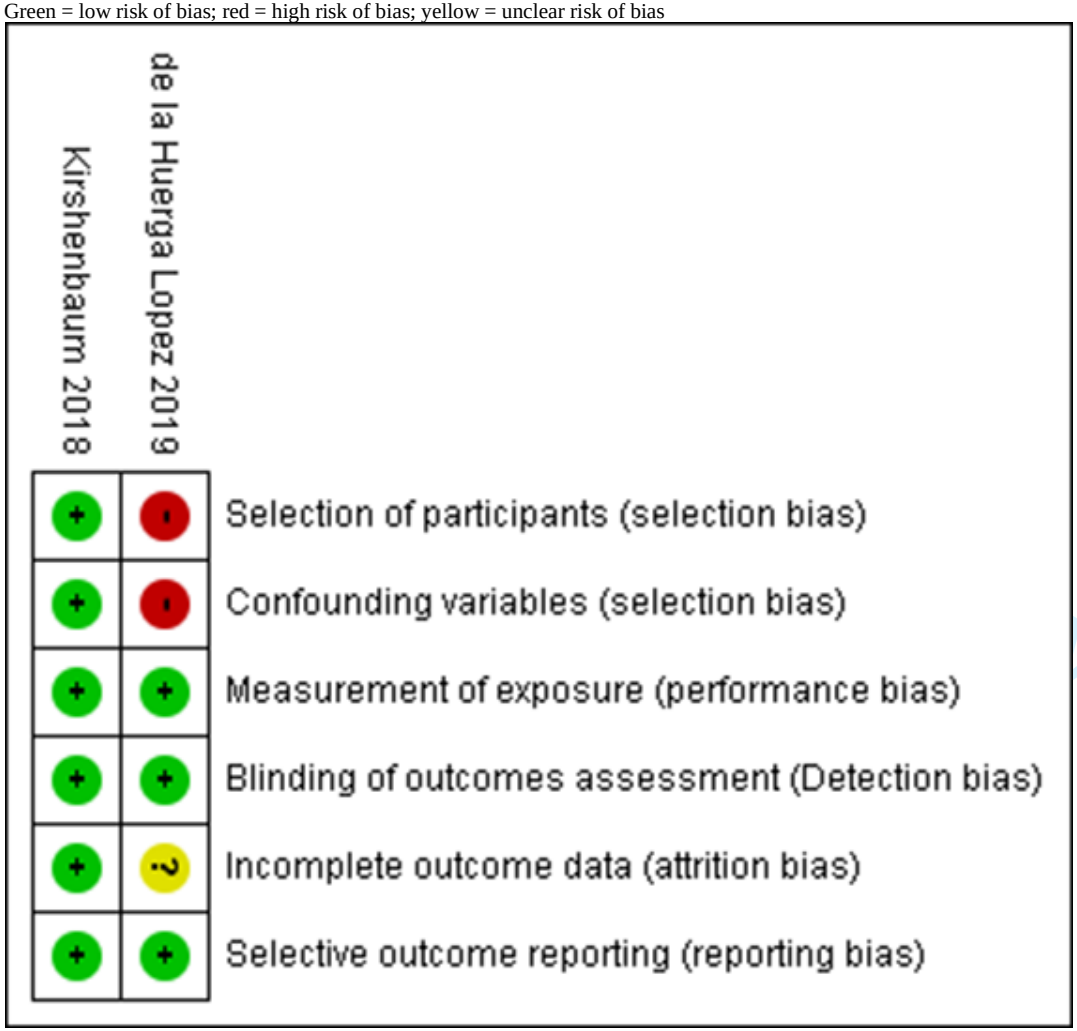


Figure 5: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

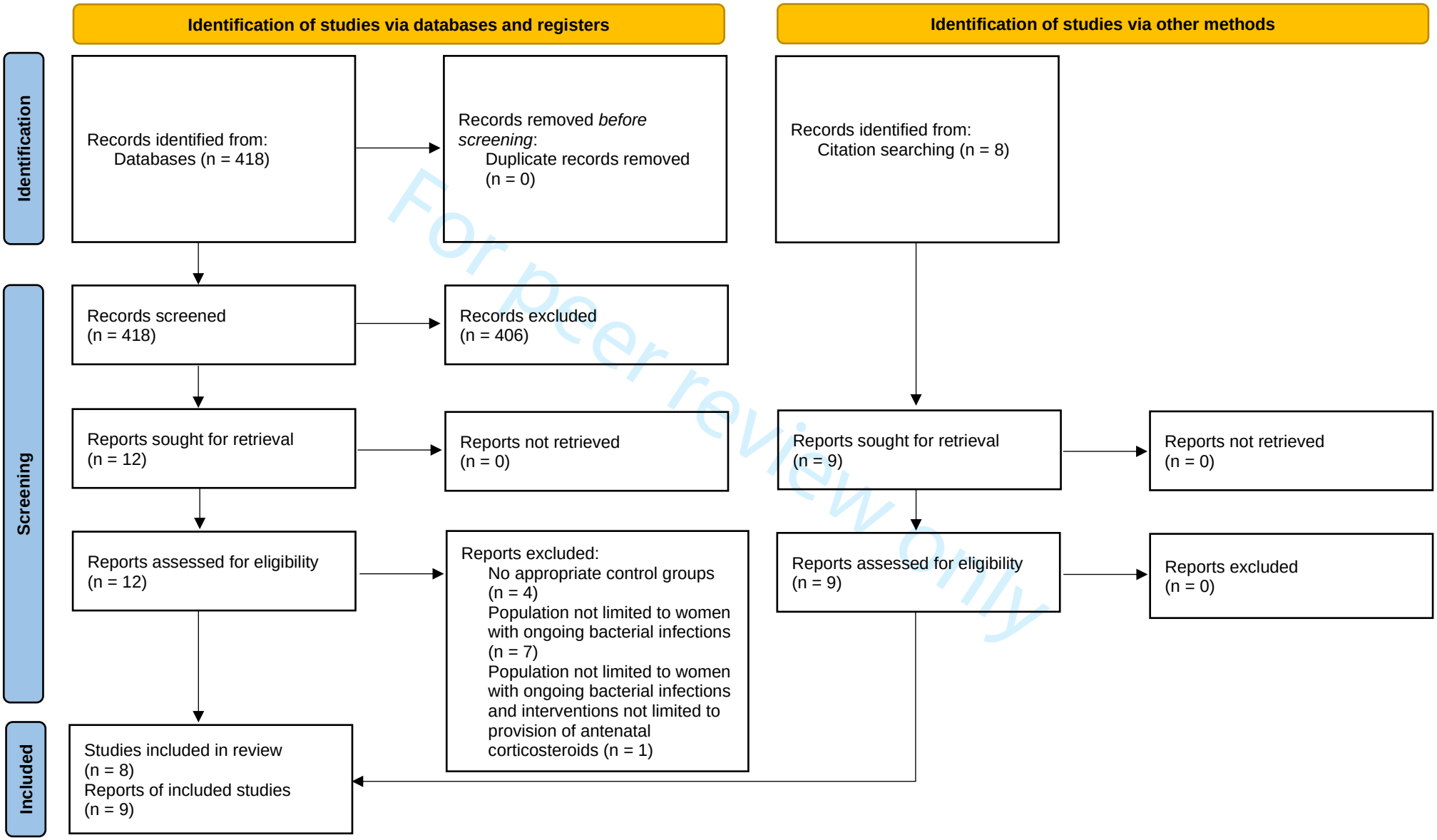


Figure 6: Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical)
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

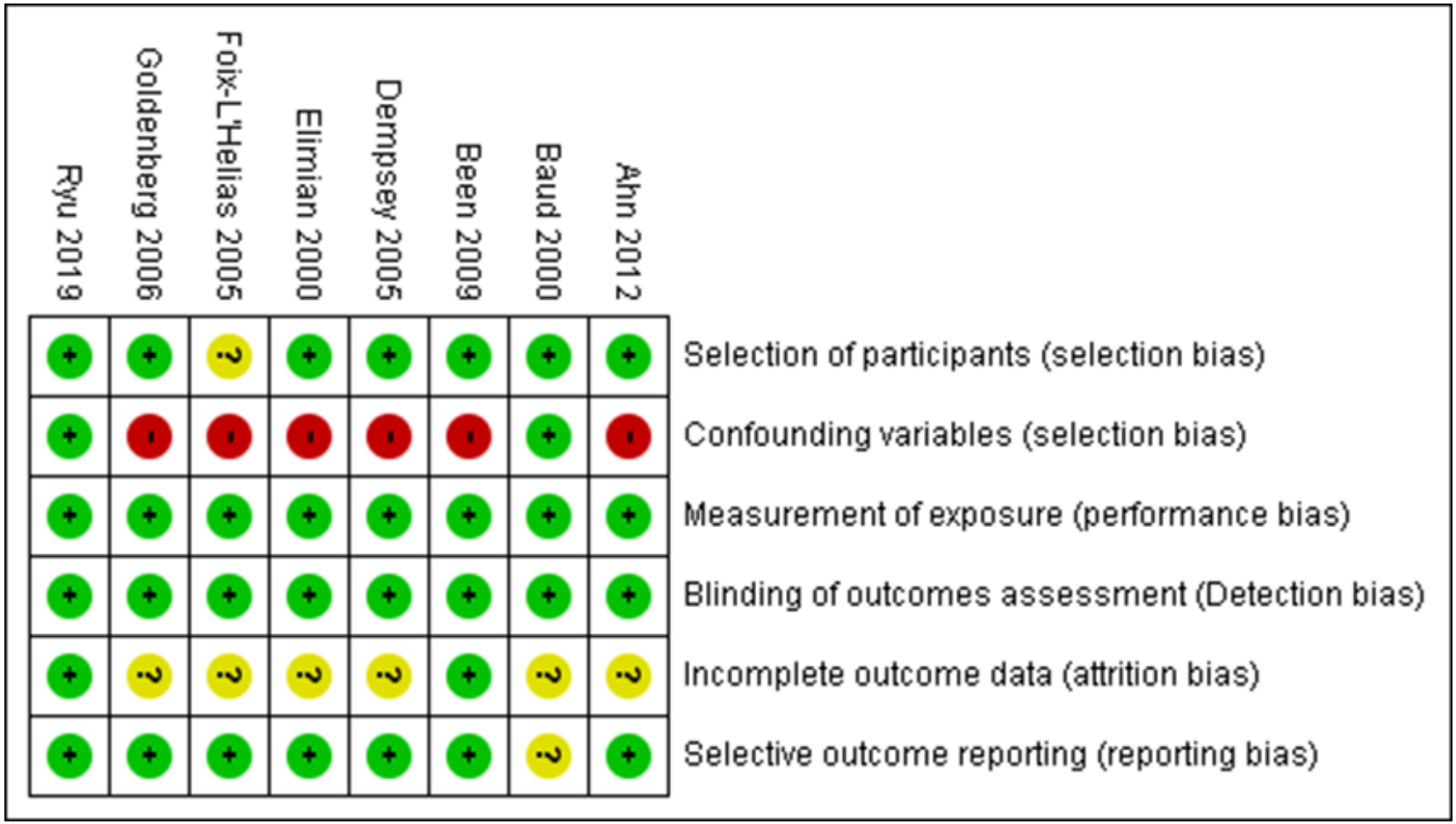


Figure 7: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants

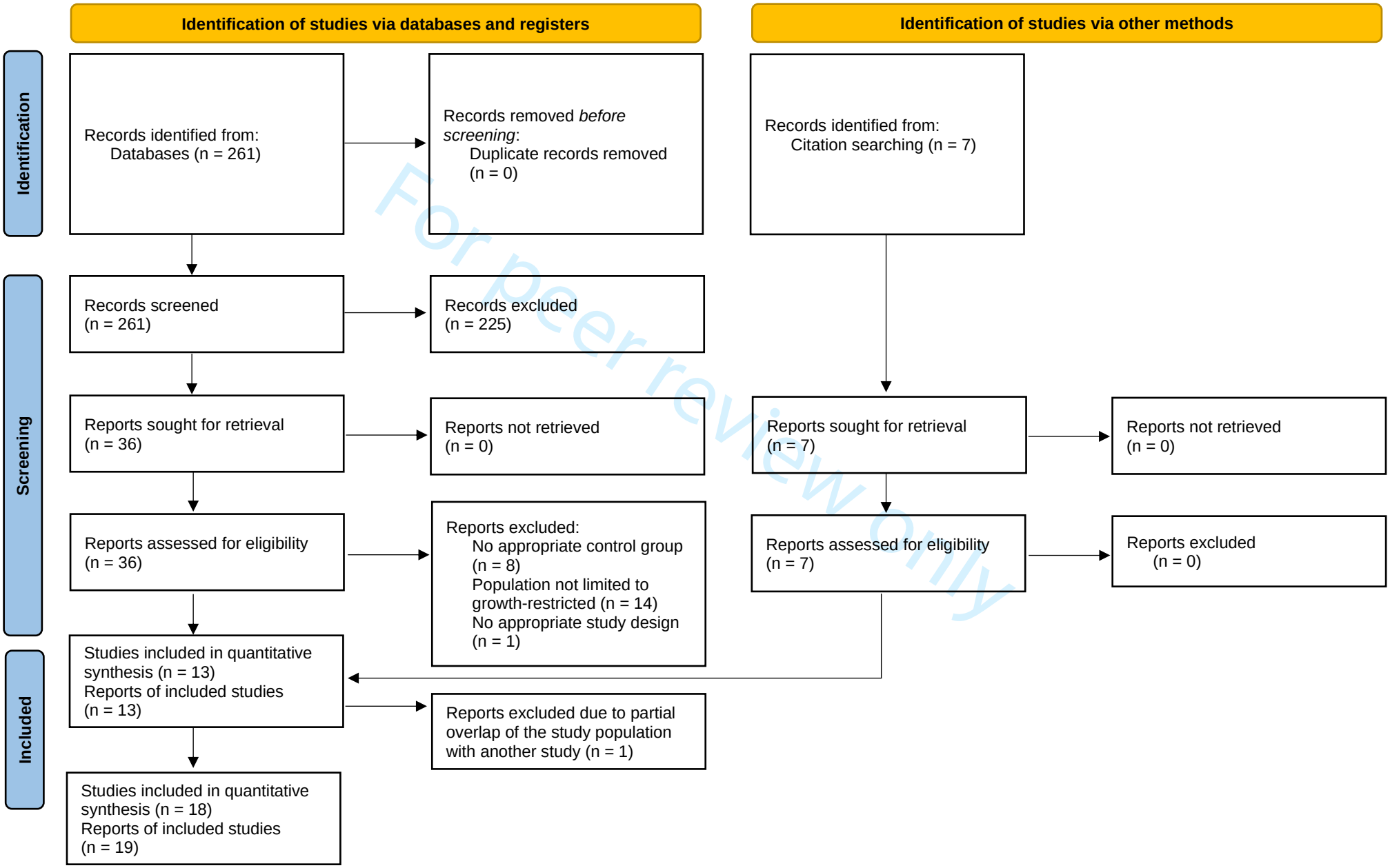
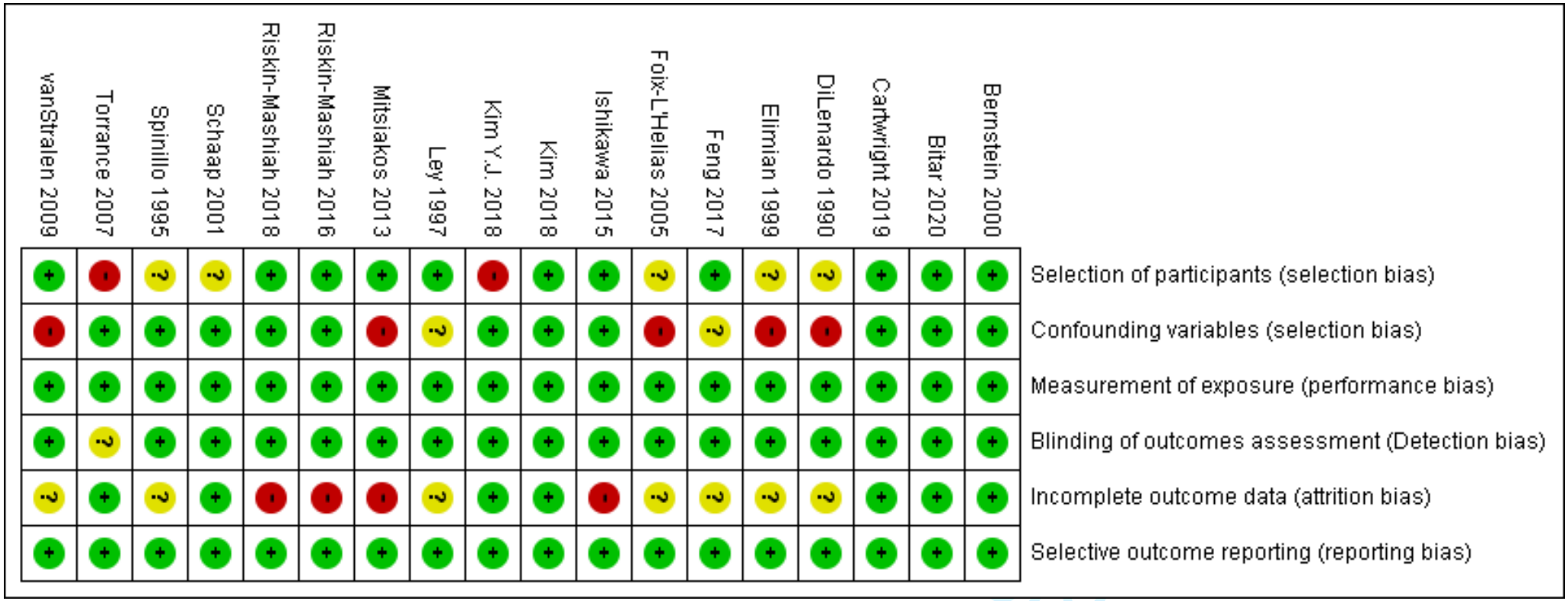


Figure 8: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

06/06/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2021

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

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National Institute for Health Research

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Kana Saito

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Kana Saito

7. * Named contact email.

Give the electronic email address of the named contact.

kana988@saitama-med.ac.jp

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

1981, Kamoda, Kawagoe-city, Saitama, Japan

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

81-49-228-3400

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Saitama Medical University

Organisation web address:

http://www.saitama-med.ac.jp/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr KANA SAITO. Saitama Medical University, Neonatology Department
Ms Etsuko Nishimura. St. Luke's International University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Non funded research

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Toshiyuki Swa. Osaka University Graduate School of Medicine
Dr Fumihiko Namba. Saitama Medical University
Dr Erika Ota. St. Luke's International University
Dr Joshua P. Vogel. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Ramson. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Cao. Child and Adolescent Health Program, Burnet Institute, Melbourne

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

This study aims to synthesize available evidence on antenatal corticosteroid (ACS) use among specific subgroups of women at risk of imminent preterm birth.

The primary objective is to determine the effects of ACS administration for four subgroups of pregnant women at risk of imminent preterm birth on maternal and child outcomes. These subgroups are as follows.

1) women with pregestational or gestational diabetes mellitus

2) women undergoing elective CS in the late preterm period (from 34 weeks 0 days to 36 weeks 6 days)

3) women with an intrapartum inflammation, infection, or both (eg: chorioamnionitis)

4) women with growth-restricted fetuses

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search electronic databases (e.g. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP).

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

We will search electronic databases (i.e. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP). Search terms include “adrenal cortex hormones”, “pregnancy”, “pregnancy outcome”, “fetal death”, “maternal death”, “obstetric labor complications”, “obstetric labor, premature”, “pregnancy, prolonged”, “fetus”, “infant, newborn”, “prenatal care”, “fetal development”, “birth weight”, “prenatal exposure delayed effects”, “diabetes mellitus”, “hyperglycemia”, “diabetes, gestational”, “pregnancy in diabetics”, “cesarean section”, “bacterial infections and mycoses”, “chorioamnionitis“, “pregnancy complications, infectious”, “fetal development”.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Pregnancy

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: We will not restrict the population to pregnant women less than 20 completed weeks gestation and their babies.
Exclusion: Pregnancy beyond 20 completed weeks gestation and their babies.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

We will include women who received at least one dose of antenatal corticosteroid, either betamethasone, dexamethasone, or hydrocortisone after 20 weeks of gestation.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Women and babies who did not receive antenatal corticosteroids.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-and-after studies, interrupted-time-series studies, historical controlled studies, cohort studies, and cross-sectional studies comparing ACS administration (betamethasone, dexamethasone, or hydrocortisone), given parenterally or enterally, compared with placebo or no treatment in women at risk of imminent preterm birth as a result of either spontaneous preterm labor, preterm rupture of the membranes, or elective preterm delivery, and where all (or at least a well-defined sub-sample) of the women under study also fulfilled one or more of the following conditions:

1. having pregestational or gestational diabetes mellitus;
2. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
3. having intrauterine inflammation, infection, or both; or
4. having a growth-restricted infant (or, more broadly, one that was at least small for gestational age).

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

We aim to establish the existing evidence that examines the implications of using or not using ACS in cases of imminent preterm birth in these subgroups of women. This evidence-based effort will be the source for the World Health Organization's (WHO) updated recommendations on interventions to improve preterm birth outcomes.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a) maternal outcomes

-maternal death or severe morbidity (e.g. organ dysfunction, intensive care unit admission, chorioamnionitis)

-maternal morbidity(e.g. puerperal sepsis, pregnancy-induced hypertension, gestational diabetes mellitus, placental abruption, postpartum haemorrhage, or as defined by the author)

-route of delivery

-side effects of therapy

b) neonatal outcomes

-perinatal mortality

-fetal mortality

-neonatal mortality

-respiratory distress syndrome (RDS) and moderate/severe RDS

-surfactant use

-interventricular haemorrhage (IVH)

-periventricular leukomalacia (PVL)

-sepsis; early onset sepsis

-necrotizing enterocolitis (NEC)

-mechanical ventilation use and mean duration

-patent ductus arteriosus (PDA)

-chronic lung disease (CLD)/ bronchopulmonary dysplasia (BPD)

-Apgar scores seven at 5 minutes

-neurodevelopment

-anthropometric status; birth weight, height, and head circumference

-NICU admission and mean duration

-side effects of therapy

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

We will conduct the sub-group analysis; extremely preterm (less than GA 28weeks), very preterm (GA28 to 32weeks) and moderate to late preterm (GA 32 to 37weeks) on each predetermined outcome.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

At least two researchers will work independently to assess each title and abstract for eligibility. Disagreement will yield automatic inclusion into the next level of screening. After the initial screening of titles and abstracts, full-text publications of studies with the potential for inclusion will be obtained and assessed. The same reviewers will independently evaluate studies under consideration for inclusion without consideration of their results. Any disagreement will be resolved through discussion to reach a consensus. Finally, the reviewers independently will extract baseline and outcome data and assess the quality of the included studies. Any discrepancies will be resolved through discussion to reach a consensus.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Study quality will be assessed independently by the aforementioned reviewers at the outcome level using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS). Randomized control trials will be assessed with Risk of Bias 2 (RoB2). Potential publication bias will be assessed by visual inspection of funnel plots for asymmetry, subject to a sufficient number of included studies. Any disagreement will be resolved by discussion to reach a consensus.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the

number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference with 95% CIs will be used.

The heterogeneity of studies will be assessed using both qualitative and quantitative measures. Statistical heterogeneity will be determined for each meta-analysis using T2, I², and ?² statistics.

Heterogeneity will be deemed substantial if T2 will be greater than zero and either I² will be greater than 50% or p0.10 in the ?² test for heterogeneity. To further assess potential heterogeneity, both fixed- and random-effects models will be compared for each outcome, where possible.

All statistical analyses will be performed using RevMan 5. Existing meta-analyses will be reviewed for relevance and completeness, and new meta-analyses will be performed where deemed necessary.

Statistical significance will be set at an alpha level of 0.05 for all analyses, except when testing study heterogeneity, where p0.10 will be regarded as significant.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat

No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
Yes

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Japan

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We will disseminate the finding with a relevant medical journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Antenatal corticosteroid

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. PLoS ONE. 2016; 11(2): e0147604.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Supplementary File S2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplementary file S2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7, 8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8, 9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8, 9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9, 10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9, 10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7, 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9, 10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 10, 11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 10, 11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10, 11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 10, 11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 10, 11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 10, 11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 10, 11
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9, 10

Supplementary File S2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 10, 11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 11-27
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 11-27
Study characteristics	17	Cite each included study and present its characteristics.	Page 11-27
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11-27
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 11-27
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 11-27
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11-27
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11-27
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11-27
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 11-27
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 11-27
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 28-32
	23b	Discuss any limitations of the evidence included in the review.	Page 32
	23c	Discuss any limitations of the review processes used.	Page 32
	23d	Discuss implications of the results for practice, policy, and future research.	Page 32, 33
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 6, 7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 34
Competing interests	26	Declare any competing interests of review authors.	Page 34, 35
Availability of	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from	Page 34

Supplementary File S2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
data, code and other materials		included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Supplementary File S2: PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary File S3: Review outcomes

Maternal outcomes	Neonatal outcomes
Preeclampsia or eclampsia	Neonatal death
Preeclampsia	Neonatal death within 48 h after birth
Hypertensive disorders	Death before discharge home
Pregnancy induced hypertension (PIH)	Apgar score ≤ 7 at 5 min after birth
Chorioamnionitis	Apgar score < 7 at 5 min after birth
	Apgar score < 5 at 1 min after birth
	Respiratory distress syndrome (RDS)
	Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)
	Pneumonia
	Use of mechanical ventilation
	Surfactant use
	Oxygen therapy
	Oxygen requirement for at least 4 h
	Mean duration of mechanical ventilations
	Duration of oxygen use
	Patent ductus arteriosus (PDA)
	Hypotension within 7 postnatal days
	Hypotension
	Intraventricular hemorrhage (IVH)
	Severe IVH

Periventricular leukomalacia (PVL)
Major brain lesion damage
Necrotizing enterocolitis (NEC)
Sepsis
Early onset sepsis
Systemic inflammatory response syndrome
Meningitis
Neonatal hypoglycemia
Neonatal adrenal insufficiency
Intrahepatic cholestasis
Retinopathy of prematurity (ROP)
ROP requiring treatment
Gestational age at birth
Birth weight
Small for gestational age
Neonatal intensive care unit (NICU) admission
Duration of hospital stay
Survival free from disability
Death at long-term follow up
Death or disability/handicap at 2 years
Cerebral palsy
Severe hearing impairment
Visual impairment

	Discharge with respiratory support
	Growth < 10%tile in early childhood
	Abnormal behavior at long-term follow up at school-age

Supplementary File S4: Database-specific search terms and strategies

MEDLINE (via Ovid) 2021/6/6

#	Searches	Annotations
1	exp *Adrenal Cortex Hormones/ad, tu	
2	exp *Adrenal Cortex Hormones/ and (ci or de or dt).fs.	
3	exp Adrenal Cortex Hormones/ae, po, to	
4	or/1-3	
5	exp Pregnancy/	
6	exp Pregnancy Outcome/	
7	Fetal Death/	
8	Maternal Death/	
9	Obstetric Labor Complications/	
10	exp Obstetric Labor, Premature/	
11	Pregnancy, Prolonged/	
12	Fetus/	
13	exp Infant, Newborn/	
14	Prenatal Care/	
15	exp Fetal Development/	
16	exp Birth Weight/	
17	Prenatal Exposure Delayed Effects/	
18	or/5-17	
19	4 and 18	
20	limit 19 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactivetutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
21	limit 20 to meta analysis	
22	20 not 21	
23	19 not 22	
24	limit 23 to humans	
25	("*corticosteroid" or "*corticoid").mp.	
26	(pregnan* or labor or labour or gestation* or delivery* or preterm* or fetus or fetal or baby or babies or newborn* or neonat* or antenat* or prenat* or birth*).mp.	
27	25 and 26	
28	MEDLINE.st.	
29	27 not 28	
30	(biograph* or case report* or comment or congress* or conference* or editor* or tutorial* or interview* or lecture* or news* or handout* or guideline* or (review* not (meta analys* or metaanalys*))).mp.	

31	29 not 30	
32	exp Diabetes Mellitus/	
33	exp Hyperglycemia/	
34	or/32-33	
35	34 and 18	
36	exp Diabetes, Gestational/	
37	Pregnancy in Diabetics/	
38	or/36-37	
39	or/5-17	
40	38 and 39	
41	or/35,40	
42	4 and 41	
43	limit 42 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
44	limit 43 to meta analysis	
45	43 not 44	
46	42 not 45	
47	limit 46 to humans	
48	diabet*.mp.	
49	31 and 48	
50	or/47,49	
51	remove duplicates from 50	
52	exp epidemiologic study/	
53	(trial* or comparative or meta analysis or metaanalysis or multicenter or observational or randomized or randomised or rct or cct or cohort or cross sectional or longitudinal or evaluation or prospective or retrospective or control*).mp.	
54	or/52-53	
55	51 and 54	P1-1
56	51 not 55	P1-2
57	exp Cesarean Section/	
58	(cesarean or cesarian or caesarean or caesarian).mp.	
59	or/57-58	
60	or/24,31	
61	60 and 59	
62	remove duplicates from 61	
63	62 and 54	P2-1
64	62 not 63	P2-2
65	exp "Bacterial Infections and Mycoses"/	
66	Pregnancy Complications, Infectious/	

67	or/65-66	
68	24 and 67	
69	(infect* or chorioamnionitis).mp.	
70	31 and 69	
71	or/68,70	
72	remove duplicates from 71	
73	72 and 54	P3-1
74	72 not 73	P3-2
75	exp *Fetal Development/	
76	(growth adj3 restrict*).mp.	
77	or/75-76	
78	24 and 77	
79	((fetal or fetus or baby or babies or restricted) adj3 (development or growth or maturity or weight)).mp.	
80	31 and 79	
81	or/78,80	
82	remove duplicates from 81	
83	82 and 54	P4-1
84	82 not 83	P4-2

Embase (via embase.com) 2021/6/6

set	query	Annotations
#1	'corticosteroid'/exp/mj/dd_do,dd_cm,dd_dt,dd_ad,dd_to,dd_ct,dd_it	
#2	'corticosteroid'/exp/dd_ae	
#3	#1 OR #2	
#4	#3 AND 'human'/de	
#5	#4 AND [embase]/lim NOT [medline]/lim	
#6	'parameters concerning the fetus, newborn and pregnancy'/exp	
#7	'fetus death'/exp	
#8	'labor complication'/exp	
#9	'prolonged pregnancy'/de	
#10	'fetus'/de	
#11	'newborn'/de	
#12	'prenatal care'/exp	
#13	'prenatal development'/exp	
#14	'prenatal exposure'/de	
#15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
#16	#5 AND #15	
#17	'editorial'/de OR 'erratum'/exp OR 'note'/de OR 'review'/de	
#18	'meta analysis'/exp	
#19	#17 NOT #18	
#20	#16 NOT #19	
#21	'case report'/exp	
#22	#20 NOT #21	

#23	'diabetes mellitus'/exp	
#24	'hyperglycemia'/de	
#25	#23 OR #24	
#26	#22 AND #25	P1
#27	'cesarean section'/de	
#28	#22 AND #27	P2
#29	'infection'/exp	
#30	'chorioamnionitis'/de	
#31	#29 OR #30	
#32	#22 AND #31	P3
#33	'prenatal development'/exp/mj	
#34	#22 AND #33	P4

Cochrane Library (via Wiley) 2021/6/8

ID	Search	Annotations
#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	
#2	*corticosteroid* or *corticoid*	
#3	#1 or #2	
#4	MeSH descriptor: [Pregnancy] explode all trees	
#5	pregnan* or labor or labour	
#6	MeSH descriptor: [Pregnancy Outcome] explode all trees	
#7	stillbirth or livebirth	
#8	MeSH descriptor: [Fetal Death] explode all trees	
#9	MeSH descriptor: [Maternal Death] explode all trees	
#10	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	
#11	MeSH descriptor: [Pregnancy, Prolonged] explode all trees	
#12	MeSH descriptor: [Obstetric Labor Complications] this term only	
#13	MeSH descriptor: [Fetus] this term only	
#14	fetus or fetal	
#15	MeSH descriptor: [Infant, Newborn] explode all trees	
#16	infant* or newborn* or neonate* or baby or babies	
#17	MeSH descriptor: [Prenatal Care] explode all trees	
#18	prenatal or antenatal or perinatal	
#19	MeSH descriptor: [Fetal Development] explode all trees	
#20	matur* or immatur* or prematur*	
#21	MeSH descriptor: [Birth Weight] explode all trees	
#22	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees	
#23	gestation* or birth* or offspring	
#24	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	
#25	#3 and #24	
#26	MeSH descriptor: [Diabetes Mellitus] explode all trees	P1
#27	diabet* or dm	

#28	MeSH descriptor: [Hyperglycemia] explode all trees	
#29	hyperglycem*	
#30	MeSH descriptor: [Diabetes, Gestational] explode all trees	
#31	MeSH descriptor: [Pregnancy in Diabetics] explode all trees	
#32	#26 or #27 or #28 or #29 or #30 or #31	
#33	#25 and #32	
#34	handsrch	
#35	#33 and #34	P1
#36	MeSH descriptor: [Cesarean Section] explode all trees	
#37	cesarean or cesarian or caesarean or caesarian	
#38	#36 or #37	
#39	#25 and #38	
#40	#39 and #34	P2
#41	MeSH descriptor: [Bacterial Infections and Mycoses] explode all trees	
#42	infect*	
#43	MeSH descriptor: [Pregnancy Complications, Infectious] explode all trees	
#44	chorioamnionitis	
#45	#41 or #42 or #43 or #44	
#46	#25 and #45	
#47	#46 and #34	P3
#48	growth near restrict*	
#49	#25 and #48	
#50	#49 and #34	P4

CINAHL (via EBSCOhost) 2021/6/6

ID#	Search Terms	Search Options	Annotations
S1	(MM "Adrenal Cortex Hormones+/AD/DE/TU")		
S2	(MH "Adrenal Cortex Hormones+/AE")		
S3	S1 or S2		
S4	(MH "Pregnancy+")		
S5	(MH "Expectant Mothers")		
S6	(MH "Pregnancy Outcomes")		
S7	(MH "Perinatal Death")		
S8	(MH "Maternal Mortality")		
S9	(MH "Labor Complications+")		
S10	(MH "Labor, Premature")		
S11	(MH "Pregnancy, Prolonged")		
S12	(MH "Fetus+")		
S13	(MH "Infant, Newborn+")		
S14	(MH "Prenatal Care")		
S15	(MH "Fetal Development+")		
S16	(MH "Birth Weight")		

S17	(MH "Prenatal Exposure Delayed Effects")		
S18	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17		
S19	S3 and S18		
S20	S19	Limiters - Human	
S21	S20	Limiters - Research Article; Exclude MEDLINE records	
S22	(MH "Metabolic Diseases") OR (MH "Diabetes Mellitus+")		
S23	(MH "Hyperglycemia")		
S24	(MH "Pregnancy in Diabetes+")		
S25	S22 or S23 or S24		
S26	S21 and S25		P1
S27	(MH "Cesarean Section+")		
S28	S21 and S27		P2
S29	(MH "Bacterial and Fungal Diseases+")		
S30	S21 and S29		P3
S31	(MM "Fetal Development+")		
S32	restrict* N3 (growth or development or matur*)		
S33	S31 or S32		
S34	S21 and S33		P4

WHO Global Index Medicus (via WHO-GIM site) 2021/6/8

	Search Terms	Annotations
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (diaebet* OR DM OR hyperglycem*)	P1
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (elective caesarean)	P2
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (infect*)	P3
	cortico AND restrict* AND growth	P4

Web of Science Core Collection (via Web of Science) 2021/6/8

Set	Searches	Annotations
# 1	CITED AUTHOR: (amiya r*) AND CITED YEAR: (2016)	Cited Reference Search

Supplementary File S5: Chracteristic tables

Table 1: Characteristics of included studies for women with pregestational and/or gestational diabetes mellitus

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	PGDM or GDM	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Battarbee et al., 2020 [34]	Retrospective cohort	510 (439, 71)	2008–2011	USA	Women giving birth at GA 23–33weeks	Stillborn, nonresuscitated cases	PGDM or GDM	NS	NS	NS	Yes
Cassimatis et al., 2020 [35]	Retrospective cohort	54 (18, 36)	2014–2017	USA	Women giving birth in late preterm	Congenital anomalies, multiple pregnancy	PGDM	Beta	12	24	No
Tuohy et al., 2020 [36]	Retrospective cohort	7282 (647, 6635)	2006–2016	New Zealand	Women giving birth after GA 22 weeks	Stillborn infant	PGDM or GDM	Beta /Dex	11.4/ NS	24	Yes
Paul et al., 2019 [33]	Retrospective cohort	60 (30, 30)	2011–2016	New Zealand	Women undergoing CS in term	None	GDM	Beta	11.4	24	No
Krispin et al., 2018 [32]	Retrospective cohort	161 (47, 114) [1)]	2012–2016	Israel	Women giving birth in late preterm period	Preterm PROM, multiple gestations, PGDM, fetal anomaly, fetal chromosomal abnormalities	GDM	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, Dex: Dexamethasone, GA: Gestational age, GDM: Gestational diabetes mellitus, NS: Not stated, PGDM: Pregestational diabetes mellitus, PROM: Premature rupture of the membranes

[1)] This study included 2262 women who gave birth in the late preterm and term period. Data were extracted and reported for women in the late-preterm delivery group (n = 161) only.

Table 2: Characteristics of included studies for women undergoing elective cesarean section in the late preterm period

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	Antenatal corticosteroid course			
							Drug	Dose (mg)	Interval (h)	Repeat ACS
de la Huerga et al., 2019 [38]	Retrospective cohort	40 (30, 10)	2013–2017	Spain	Women undergoing elective CS between 35 weeks 0 days and 36 weeks 6 days	Congenital anomalies, transferred to other hospitals	Beta	NS	NS	NS
Kirshenbaum et al., 2018 [37]	Case-control	165 (58, 107)	2011–2013	Israel	Women undergoing elective CS between GA 34 weeks 0 days and 37 weeks 0 days	Multiple pregnancy, congenital anomalies, chromosomal abnormalities, chorioamnionitis	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, GA: Gestational age, NS: Not stated

Table 3: Characteristics of included studies for women with chorioamnionitis (histological or clinical)

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	HC CC	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Ryu et al., 2019 [46]	Retrospective cohort	108 (97, 11)	2007–2014	Republic of Korea	Women giving birth between GA 23weeks 0 days and 33 weeks 6 days	Multiple gestations, congenital anomalies, SGA or LGA, transferred to other hospitals, incomplete information	HC	Beta /Dex	NS	NS	No

Ahn et al., 2012 [45]	Prospective cohort	89 (53, 36)	2005–2010	Republic of Korea	Women giving birth at GA < 34 weeks	Congenital anomalies, transferred from other hospitals	HC	Dex	5	12	No
Been et al., 2009 [44]	Prospective cohort	121 (89, 32)	2001–2003	Netherlands	Women giving birth at GA < 32 weeks	Congenital anomalies	HC CC	Beta	12	24	No
Goldernberg et al., 2006 [43]	Retrospective cohort	218 (182, 36)	1996–2001	USA	Women giving birth between GA 23 weeks 0 days and 32 weeks 6 days	Multiple gestations	HC CC	Beta	12	24	Yes
Dempsey et al., 2005 [41]	Retrospective cohort	130 (88, 42)	1989–1999	USA	Women giving birth at GA < 30 weeks	Multiple gestations	HC	Beta	12	24	NS
Foix-L'Helias et al., 2005 [42]	Retrospective cohort	97 (45, 52)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations	CC	Beta /Dex	12 6	24 12	Yes
Baud et al., 2000 [39]	Retrospective cohort	170 (60, 110)	1993–1997	France	Women giving birth at GA < 33 weeks	Multiple gestations, severe DM	CC	Beta /Dex	12 6	24 12	Yes
Elimian et al., 2000 [40]	Retrospective cohort	527 (169, 358)	1990–1997	USA	Birth weight: 500–1750 g	CC	HC	Beta	12	24	Yes

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CC: Clinical chorioamnionitis, Dex: Dexamethasone, DM: Diabetes mellitus, GA: Gestational age, HC: Histological

chorioamnionitis, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

Table 4: Characteristics of included studies for women with growth-restricted fetuses and/or small for gestational age infants

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	FGR SGA	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Bitar et al., 2020 [64]	Retrospective cohort	247 (136, 111)	2015–2019	USA	Women giving birth between GA 34 weeks 0 days and 36 weeks 6 days	Multiple gestations, mother age ≥ 18 years	SGA or FGR	Beta	NS	NS	NS
Cartwright et al., 2019 [63]	Retrospective cohort	261 (139, 122)	1998–2004	Australia New Zealand	Women giving birth at GA < 32 weeks, single, twin, and triplet pregnancy	Chorioamnionitis requiring urgent delivery, labor at the second stage, mature fetal lung development, and further steroid therapy	SGA or FGR	Beta	13.8	NS	Yes
Kim WJ et al., 2018 [60]	Retrospective cohort	82 (45, 37)	2009–2016	Republic of Korea	Women giving birth between GA 29 weeks 0 days and 34 weeks 6 days	Multiple gestations, still birth, major congenital abnormality, ACS administration within 24 h before births, ACS administration >7 days before birth	SGA	Dex	5	12	NS
Kim YJ et al., 2018 [62]	Retrospective cohort	91 (83, 3)	2007–2014	Republic of Korea	Women giving birth between GA 23 weeks 0 days and 33 weeks 6 days	Multiple gestations, major congenital abnormality, fetal hydrops, incomplete information, LGA, repeated ACS, transfer to other hospitals, SGA without fetal umbilical artery Doppler abnormalities	FGR or SGA	Beta/ Dex	NS	24 12	No

Riskin-Mashiah et al., 2018 [61]	Retrospective cohort	784 (585,199)	1995–2012	Israel	Women giving birth to twins between GA 24 weeks 0 days and 31 weeks 6 days	Congenital anomalies	SGA	NS	NS	NS	NS
Feng et al., 2017 [59]	Retrospective cohort	602 (325, 277)	2013–2014	China	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days	Major congenital abnormality, inherited metabolic disease	SGA	Beta/ Dex	12 5–6	24 12	No
Riskin-Mashiah et al., 2016 [58]	Retrospective cohort	1771 (1246, 525)	1995–2012	Israel	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital malformation, incomplete data	SGA	NS	NS	NS	NS
Ishikawa et al., 2015 [57]	Retrospective cohort	1929 (719, 1210)	2003–2007	Japan	Birth weight < 1500 g	Multiple gestations, Women giving birth ≥34 weeks, major congenital malformation, incomplete information, out-of-hospital birth	SGA	NS	NS	NS	NS
Mitsiakos et al., 2013 [56]	Retrospective cohort	149 (87, 62)	NS	Canada	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital anomalies	SGA	Beta	12	24	No
van Stralen et al, 2009 [55]	Retrospective cohort	88 (54,34)	2001–2005	Netherlands	Birth weight < 1500 g	Multiple gestations, major congenital malformation or infection, incomplete information	FGR	Beta	11.4	24	NS
Torrance et al., 2007 [54]	Retrospective cohort	FGR140 (112,28), SGA165 (146, 19)	1999–2003	Netherlands	Women giving birth at GA < 34 weeks	Congenital, chromosomal or syndromic abnormalities	SGA	Beta	12	24	NS
Foix-L'Helias et al, 2005 [42]	Retrospective cohort	151 (96,55)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	NS	SGA	NS	NS	NS	NS

Schaap et al, 2001 [53]	Case-control	124 (62,62)	1984–1991	Netherlands	Women giving birth between GA 26 weeks 0 days and 31 weeks 6 days	ACS < 24 h before delivery, fetal death or fetal distress at admission to the hospital, abruptio placentae, lethal congenital abnormalities or infections	FGR	Beta	12.5	24	NS
Bernstein et al, 2000 [52]	Retrospective cohort	1258 (703,555)	1991–1996	USA, Canada	Women giving birth between GA 25 weeks 0 days and 30 weeks 6 days, white and African-American infants	Multiple gestations, major anomalies	SGA	NS	NS	NS	NS
Elimian et al, 1999 [51]	Retrospective cohort	220 (63,157)	1990–1997	USA	Birth weight ≤ 1750 g	NS	SGA	Beta	12	24	Yes
Ley et al, 1997 [50]	Retrospective cohort	234 (117, 117)	1984–1985	Sweden	Women giving birth at GA < 33 weeks	NS	SGA	NS	NS	NS	NS
Spinillo et al, 1995 [49]	Prospective cohort	96 (32,64)	1988–1993	Italy	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days, indetermined or immature lecithin/sphingomyelin ratio, planned delivery with medication complications, liveborn	Congenital anomalies	SGA	Beta/Dex	12 12	NS	NS

Lenardo et al, 1990 [48]	Retrospective cohort	72 (15,57)	NS	Italy	Women giving birth at GA ≤ 35 weeks	Twin gestations	SGA	Beta	12	24	NS

*ACS: Antenatal corticosteroid, Beta: Betamethasone, Dex: Dexamethasone, FGR: Fetal growth restriction, GA: Gestational age, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

Supplementary File S6: Risk of bias

Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cassimatis 2020 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from three institutions had PGDM (type 1 or type 2) with singleton pregnancies and delivered in late preterm between April 2014 and May 2017.	**High.** No confirmation or consideration in either design or analysis phases.	**Low.** Data obtained from an obstetric electronic database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Paul 2019 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from a single hospital had GDM and delivered via cesarean section at ≥37 weeks gestation between 2011 and 2016.	**High.** No confirmation or consideration in either design or analysis phases.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low.** No missing data.	**Low.** All predefined outcomes reported.	-
Krispin 2018 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from a single, university-affiliated, tertiary medical center had GDM and delivered after 34 weeks of gestation between 2012 and 2016.	**Low.** The following potential confounders were controlled for: birth weight, gestational age at delivery, gravidity, parity, hypertensive disorders, body mass index, and ACS treatment.	**Low.** Data obtained from a comprehensive computerized perinatal database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low.** No missing data.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Tuohy 2020 (Retrospective cohort study)	NA	N/A	**Low.** All participants from a single tertiary hospital who were diagnosed with diabetes in pregnancy and gave birth after 22 weeks of gestation between 2006 and 2016.	**Low.** Multiple logistic regression performed.	**Low.** Data obtained from the hospital database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low.** No missing data.	**Low.** All predefined outcomes reported.	-
Battarbee 2020 (Retrospective cohort study)	N/A	N/A	**Low.** A cohort study that included 115,502 participants from 25 hospitals in the United States between March 2008 and February 2011. To avoid overrepresentation of participants from larger hospitals, participants were selected for up to one-third of days at hospitals with annual delivery volumes from 2,000 to 7,000 and up to one-sixth of days at hospitals with annual deliveries > 7,000.	**Low.** The following potential confounders were controlled for: maternal age, body mass index, race and ethnicity, nulliparity, labor prior to delivery, gestational age, neonatal sex, multiple gestation, congenital malformation, GDM or PGDM, and study site.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low.** Eleven sets of missing data (11 women and 12 neonates) were excluded from the data for steroids, but the proportion of the missing data was very small (less than 1%).	**Low.** All predefined outcomes reported.	-

PGDM: Pregestational diabetes mellitus; **GDM:** gestational diabetes mellitus; **ACS:** Antenatal corticosteroid

Risk of bias assessments for studies of antenatal corticosteroids in women undergoing elective cesarean section in the late preterm period

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kirshenbaum 2018 (Case-control study)	N/A	N/A	**Low.** All participants from a single tertiary medical center who delivered by elective cesarean section at 34 + 0–37 + 0 weeks of gestation between January 2011 and December 2013.	**Low.** Multiple logistic regression performed, and inclusion of confounding factors specified: birth weight, gestational diabetes mellitus, medical indication for cesarean section, gestational age at delivery, and neonatal gender.	**Low.** Data obtained from obstetric electronic database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low.** No missing data.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
de la Huerga López 2019 (Retrospective cohort study)	N/A	N/A	**High.** All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017). Newborns with congenital malformations or those transferred to another hospital were excluded from the study. Cases and controls were selected from the same gestational age. However, the control group was defined only by no-steroid treatment without further specification. The percentage of planned cesarean sections was higher in SGA newborns, with statistical significance (34/38 89% vs. 174/245 71%; p = 0.016). It was statistically significant that more corticosteroids were administered in preterm delivery compared to term delivery with indication (30/40 75% PTNBs vs. 67/168 39.9% NTBs; p < 0.001).	**High.** No confirmation or consideration in either design or analysis phase.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	

SGA: Small for gestational age; **PTNB:** Preterm newborns; **NTB:** Normal term birth

Risk of bias assessments for studies of antenatal corticosteroids in women with chorioamnionitis (histological or clinical)

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Ahn 2012 (Prospective cohort study)	N/A	N/A	**Low.** All participants admitted/born at Ewha Women's University between 2005 and 2010.	**Low/High** (depending on outcome). Multiple logistic regression models used, controlled for gestational age; however, did not control for NEC, PDA, or neonatal death in analyses.	**Low**. Data obtained from direct measurements /clinical assessments.	**Low**. No statement to indicate blinding, but unlikely to affect outcome measurements .	**Unclear.** The problem of missing data was deduced from the results; no statement on the reason for missing data.	**Low**. All expected outcomes reported.	-
Been 2009 (Prospective cohort study)	N/A	N/A	**Low**. All participants admitted/born at the Erasmus University Medical Center-Sophia Children's Hospital between May 2001 and February 2003.	**High**. Adjusted analyses not available for separate HC/CC results.	**Low**. Data obtained from direct measurements /clinical assessments.	**Low**. No statement to indicate blinding, but unlikely to affect outcome. measurements .	**Low**. No missing data.	**Low**. All expected outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Goldenberg 2006 (Retrospective cohort study)	N/A	N/A	**Low**. All participants admitted/delivered at the same institution during the same period (December 5, 1996–June 13, 2001).	**High**. Adjusted analyses for results stratified by corticosteroid administration not available.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear**. No reasons are given for the missing data.	**Low.** All expected outcomes were reported.	-
Dempsey 2005 (Retrospective cohort study)	N/A	N/A	**Low**. All participants admitted/delivered at the same institution between January 1989 and January 1999.	**High**. Adjusted analyses for results stratified by corticosteroid administration not available.	**Low**. Data obtained from medical records (obstetrical and neonatal database and pathology database, cross-referenced with data from pathology database and from maternal and neonatal chart review).	**Low**. No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear**. No missing data.	**Low**. All expected outcomes were reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Unclear.** Participants drawn from different institutions between 1993 and 1996. However, other participant information was scarce.	**High.** Adjusted analyses for results stratified by IUGR not available.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential ACS underestimation.
Baud 2000 (Retrospective cohort study)	N/A	N/A	**Low**. All participants admitted to Antoine Beclere University Hospital between 1993 and 1997.	**Low**. Multiple logistic regression models used, controlling for antenatal antibiotic administration, mode of delivery, gestational age, and origin (inborn or out born).	**Low**. Data obtained from computerized database.	**Low**. No statement to indicate blinding, but unlikely to affect outcome measurements.	**Unclear**. Unclear whether incomplete outcome data resulted in low or high risk because the number and reasons for missing data are given without specifying to which group they belong (intervention or control).	**Unclear**. Unclear whether selective outcome reporting resulted in high or low risk.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 2000 (Retrospective cohort study)	N/A	N/A	**Low.** All participants admitted/delivered at the same institution between January 1990 and December 1997.	**High**. Adjusted analyses for results stratified by corticosteroid administration not available.	**Low**. Data obtained from medical records.	**Low**. No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low**. All expected outcomes were reported.	-
Ryu 2019 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from a single university hospital, admitted to the same institution (Seoul National University Hospital) between 2007 and 2014.	**Low.** Multiple logistic regression performed, and inclusion of confounding factors specified (e.g., GA, genders, and CS).	**Low.** Data obtained from obstetric electronic database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** At the beginning of the study incomplete information was excluded.	**Low.** All predefined outcomes reported.	-

NEC: Necrotizing enterocolitis; **PDA:** Patent ductus arteriosus; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis; **IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **GA:** Gestational age; **CS:** Cesarean section

Risk of bias assessments for of studies of antenatal corticosteroids in women with growth-restricted fetuses and/or small-for-gestational-age infants

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
van Stralen 2009 (Retrospective cohort study)	N/A	N/A	**Low.** All participants admitted/delivered and treated at the same institution (Leiden University Medical Center) over the same period (January 2001–December 2005).	**High.** No confirmation or consideration in either design or analysis phase.	**Low.** Data obtained from obstetric electronic database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** One child died during an emergency cesarean section after eclampsia; it is unclear how it was handled.	**Low.** All predefined outcomes reported.	Although equally divided, the difference in origin, i.e., referral pattern, may also have influenced the results.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Torrance 2007 (Retrospective cohort study)	N/A	N/A	**High.** All participants from a single tertiary referral center admitted to the same institution (neonatal intensive care unit at the University Medical Centre Utrecht, the Netherlands) over the same period (from January 1, 1999, to December 31, 2003). Cases and controls were selected from same pool (e.g., same gestational age, same birth weight). However, the control group was defined only by no-steroid treatment without further specification, so it is conceivable that fetal conditions on hospitalizations differed. Further, because babies were not delivered at the study site, there was an absence of outcomes not confirmed at the start of the study.	**Low.** Partial correlation performed for scale data to correct for potential confounding factors: for nominal data, binary logistic regression was used for this purpose. Variables were considered potential confounders when the Chi-square test or independent t-test identified a significant difference.	**Low** Data was obtained from an electronic database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** No loss to follow-up.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Unclear.** Participants drawn from different institutions during the same period (1993–1996) although the distribution of treatment and control groups was unclear.	**High.** Adjusted analyses for results stratified by IUGR not available.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential underestimation.
Schaap 2001 (Case-control study)	N/A	N/A	**Unclear.** Participants drawn from different institutions during the same period (1984–1991) although the distribution of treatment and control groups was unclear. Possibility of selection bias cannot be excluded due to retrospective design.	**Low.** Treated group matched with control group by random electronic selection based on birth weight (difference < 175 g), sex, and year of birth (difference < 2 years).	**Low.** Data obtained from medical records. Because all mothers had been admitted at least 24 h before delivery, a difference in fetal condition on admission was unlikely.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** Nine losses at school age follow-up (4 in steroid group, 5 in control group) but no significant difference in sociodemographic details between those lost and retained at follow-up.	**Low.** All predefined outcomes reported.	Hypertensive mothers less often treated with corticosteroids. Further, matching notwithstanding, birth weight and gestational age were significantly lower in the AGA group although magnitude of the difference is small.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 1999 (Retrospective cohort study)	N/A	N/A	**Unclear.** All participants from the same institution during the same period (January 1990–July 1997) but control group defined only by no-steroid treatment without further specification, so it is conceivable that fetal condition on hospitalization differed.	**High.** Consideration in design but there is no adjusted stratified analysis for sub-sample of interest.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-
Ley 1997 (Retrospective cohort study)	N/A	N/A	**Low.** All participants admitted/delivered and treated at the same institution (University Hospital of Lund) during the same period (1985–1994).	**Unclear.** Multiple logistic regressions performed, but inclusion of confounding factors not specified.	**Low.** Data obtained from hospital records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-
Spinillo 1995 (Prospective cohort study)	N/A	N/A	**Unclear.** All participants from the same institution during the same period (1988–1993) but the control group was defined only by	**Low.** Multivariate models used to account for potential confounders (age, birth weight, and sex of the infant).	**Low.** Data obtained from hospital records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
			no-steroid treatment without further specification, so it is conceivable that fetal condition on hospitalization differed.						
Di Lenardo 1990 (Retrospective cohort study)	N/A	N/A	**Unclear.** All participants admitted/delivered and treated at the same institution (Prenatal Care Ward of Univ. of Padua's Gynecology & Obstetrics Institution) but unclear whether over the same period.	**High.** No confirmation or consideration in either design or analysis phase.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-
Bitar 2020 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from a single hospital who delivered at 34.0–36.6 weeks of gestation, with small-for-gestational-age or fetal-growth-restriction infants between January 2015 and December 2019.	**Low.** Multiple logistic regression performed and the inclusion of confounding factors specified: birth weight, gestational diabetes mellitus, indication for cesarean section, gestational age at delivery, and neonatal gender.	**Low.** Data obtained from electronic medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** There are missing data, but this is unlikely to have affected the study outcome.	**Low.** All predefined outcomes were reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cartwright 2019 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from 23 collaborating hospitals, 16 in Australia and 7 in New Zealand, with a single, twin, or triplet pregnancy at less than 32 weeks of gestational age from April 1998 to July 2004.	**Low.** Major confounding variables: gestational age at trial entry, antepartum hemorrhage, preterm prelabor rupture of membranes, and country of birth were adjusted.	**Low.** Data obtained from case notes.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** The numbers and causes of missing data developments are similar.	**Low.** The predefined outcomes were described as planned.	-
Riskin-Mashiah 2018 (Retrospective cohort study)	NA	N/A	**Low.** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012.	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from the national network.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High.** There are some missing data, but the causes are not given. The missing data could affect the study outcome.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim 2018 (Retrospective cohort study)	N/A	N/A	**Low.** All participants from a single hospital between 2009 and 2016.	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from medical records and perinatal database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** No statement of missing data, but the possibility of data loss is low.	**Low.** All predefined outcomes reported.	-
Ishikawa 2015 (Retrospective cohort study)	N/A	N/A	**Low.** The data of all participants from the National Research Network Database in Japan between 2003 and 2007.	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from national network.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High.** For long-term outcome, the missing data could affect the study outcome.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Riskin-Mashiah 2016 (Retrospective cohort study)	N/A	N/A	**Low.** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012.	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from national network.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High.** There are some missing data, but the causes are not given. The missing data could affect the study outcome.	**Low.** All predefined outcomes reported.	-
Mitsiakos 2013 (Retrospective cohort study)	N/A	N/A	**Low.** All participants between 24 and 31 6/7 weeks of gestational age from a single hospital. The study period was not specifically mentioned, but intervention and control groups seem to be selected from the same population groups.	**High.** No consideration in either design or analysis phase.	**Low.** Data obtained from obstetric and neonatal database.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High.** For long-term outcome, the missing data could affect the study outcome.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim YJ 2018 (Retrospective cohort study)	N/A	N/A	**High.** All participants born at 23 + 0 to 33 + 6 weeks of gestation between January 2007 and December 2014 in a single university hospital in South Korea. However, the difference in proportion between the two groups is large (intervention: 91.2% vs. control: 8.8%).	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from medical records and perinatal databases.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** No statement of missing data, but the possibility of data loss is low.	**Low.** All predefined outcomes reported.	-
The collaborative study group for respiratory distress syndrome in preterm infants 2017 (Retrospective cohort study)	N/A	N/A	**Low.** Participants drawn from 14 hospitals during the same period (2013–2014).	**Unclear.** Multiple logistic regression performed, but inclusion of confounding factors not specified.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Unclear.** No information about missing data.	**Low.** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Bernstein 2000 (Retrospective cohort study)	N/A	N/A	**Low.** Participants drawn from North American hospitals during the same period (1991–1996).	**Low.** Major confounding variables were adjusted.	**Low.** Data obtained from medical records.	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low.** No statement of missing data, but the possibility of data loss is low.	**Low.** All predefined outcomes reported.	-

IUGR: Intrauterine growth restriction; **ACS:** Antenatal corticosteroid

Supplementary File S7: Forest plots

Maternal outcomes for women with pregestational and/or gestational diabetes mellitus

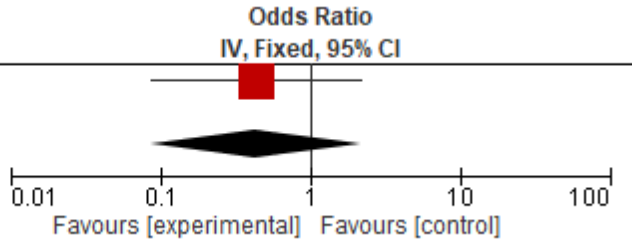
*There is no maternal outcome.

Neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

1) Neonatal death within 48 h of birth

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Battarbee 2020	-0.8305	0.8256	536	79	100.0%	0.44 [0.09, 2.20]
Total (95% CI)			**536**	**79**	**100.0%**	**0.44 [0.09, 2.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

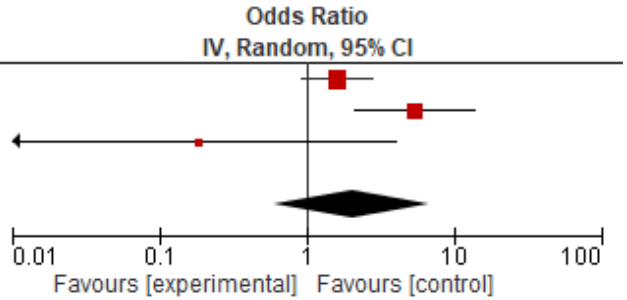


SE: Standard error; **CI:** Confidence interval

2) Respiratory distress syndrome (RDS)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Battarbee 2020	0.4794	0.2837	536	79	47.6%	1.62 [0.93, 2.82]
Krispin 2018	1.6915	0.4774	129	2133	40.3%	5.43 [2.13, 13.83]
Paul 2019	-1.6773	1.5709	30	30	12.1%	0.19 [0.01, 4.06]
Total (95% CI)			**695**	**2242**	**100.0%**	**2.03 [0.60, 6.85]**

Heterogeneity: $Tau^2 = 0.73$; $Chi^2 = 7.18$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 1.14 (P = 0.25)

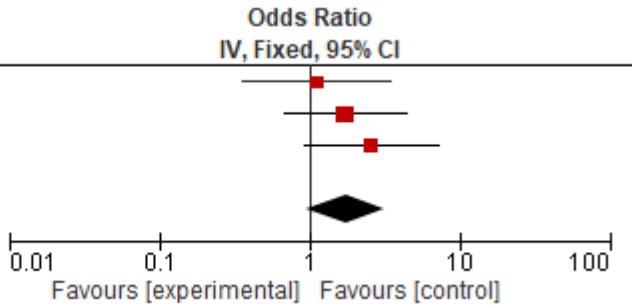


SE: Standard error; **CI:** Confidence interval

3) Neonatal hypoglycemia

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Cassimatis 2020.	0.1112	0.5776	18	36	27.5%	1.12 [0.36, 3.47]
Krispin 2018	0.5394	0.4785	129	2133	40.0%	1.71 [0.67, 4.38]
Paul 2019	0.952	0.5314	30	30	32.5%	2.59 [0.91, 7.34]
Total (95% CI)			**177**	**2199**	**100.0%**	**1.74 [0.96, 3.16]**

Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)

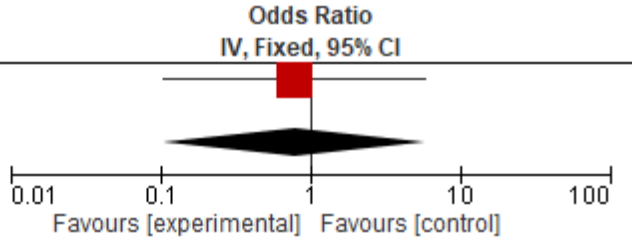


SE: Standard error; **CI:** Confidence interval

4) Apgar score < 7 at 5 min

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Krispin 2018	-0.2412	1.0276	129	2133	100.0%	0.79 [0.10, 5.89]
Total (95% CI)			**129**	**2133**	**100.0%**	**0.79 [0.10, 5.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)

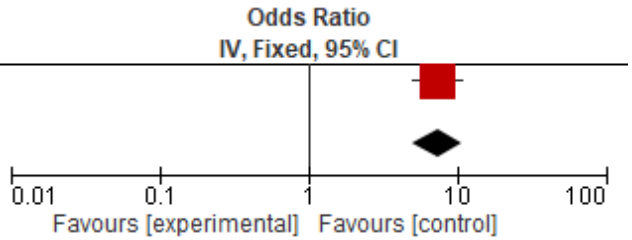


SE: Standard error; **CI:** Confidence interval

5) Admission to neonatal intensive care unit (NICU)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Krispin 2018	2.0025	0.1968	129	2133	100.0%	7.41 [5.04, 10.89]
Total (95% CI)			**129**	**2133**	**100.0%**	**7.41 [5.04, 10.89]**

Heterogeneity: Not applicable
Test for overall effect: Z = 10.18 (P < 0.00001)



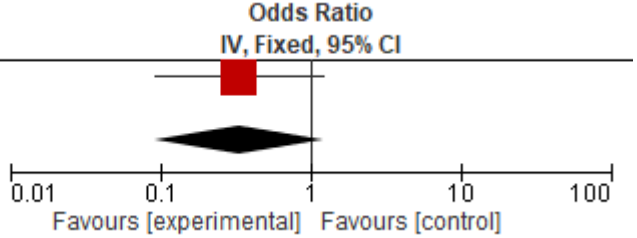
SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kirshenbaum 2018	-1.095	0.655	58	107	100.0%	0.33 [0.09, 1.21]
Total (95% CI)			**58**	**107**	**100.0%**	**0.33 [0.09, 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)



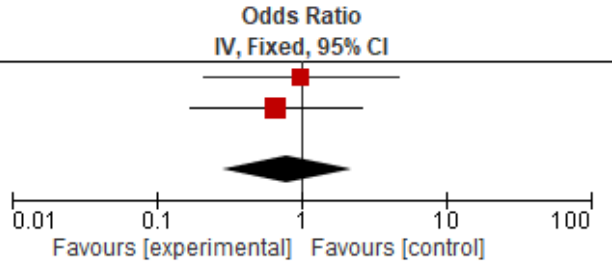
SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women undergoing elective cesarean section in late preterm period

1) Respiratory distress syndrome (RDS)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
de la Huerga Lopez 2019	0	0.7968	30	10	43.4%	1.00 [0.21, 4.77]
Kirshenbaum 2018	-0.393	0.6976	58	107	56.6%	0.68 [0.17, 2.65]
Total (95% CI)			**88**	**117**	**100.0%**	**0.80 [0.29, 2.24]**

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

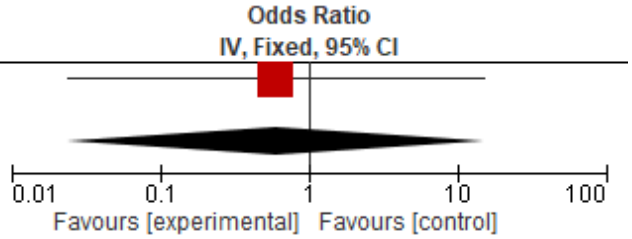


SE: Standard error; **CI:** Confidence interval

2) Intraventricular hemorrhage (IVH)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kirshenbaum 2018	-0.4995	1.6411	58	107	100.0%	0.61 [0.02, 15.13]
Total (95% CI)			**58**	**107**	**100.0%**	**0.61 [0.02, 15.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)

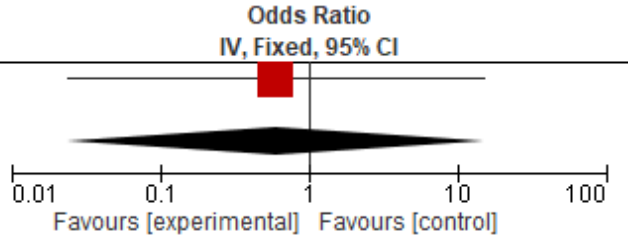


SE: Standard error; **CI:** Confidence interval

3) Necrotizing enterocolitis (NEC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kirshenbaum 2018	-0.4995	1.6411	58	107	100.0%	0.61 [0.02, 15.13]
Total (95% CI)			**58**	**107**	**100.0%**	**0.61 [0.02, 15.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)

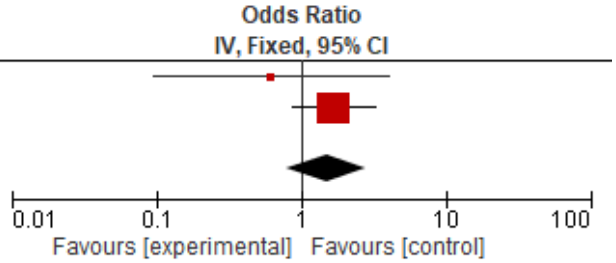


SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
de la Huerga Lopez 2019	-0.4855	0.9558	30	10	10.9%	0.62 [0.09, 4.01]
Kirshenbaum 2018	0.5137	0.3349	58	107	89.1%	1.67 [0.87, 3.22]
Total (95% CI)			**88**	**117**	**100.0%**	**1.50 [0.81, 2.78]**

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)

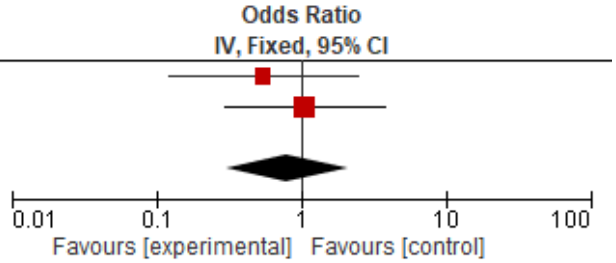


SE: Standard error; **CI:** Confidence interval

5) Use of mechanical ventilation

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
de la Huerga Lopez 2019	-0.6061	0.7662	30	10	41.8%	0.55 [0.12, 2.45]
Kirshenbaum 2018	0.0566	0.6491	58	107	58.2%	1.06 [0.30, 3.78]
Total (95% CI)			**88**	**117**	**100.0%**	**0.80 [0.30, 2.12]**

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

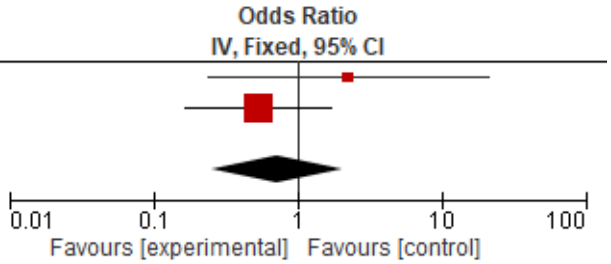


SE: Standard error; **CI:** Confidence interval

6) Admission to neonatal intensive care unit (NICU)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
de la Huerga Lopez 2019	0.8109	1.1487	30	10	21.2%	2.25 [0.24, 21.38]
Kirshenbaum 2018	-0.6243	0.5967	58	107	78.8%	0.54 [0.17, 1.72]
Total (95% CI)			**88**	**117**	**100.0%**	**0.73 [0.26, 2.05]**

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.60 (P = 0.55)

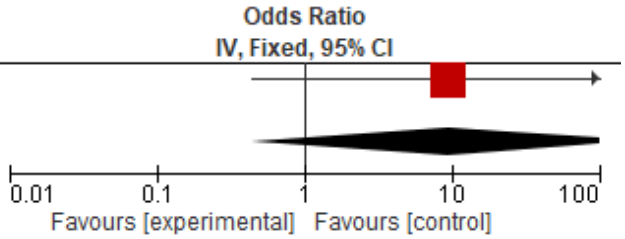


SE: Standard error; **CI:** Confidence interval

7) Apgar score ≤ 7 at 5min

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kirshenbaum 2018	2.2527	1.5579	58	107	100.0%	9.51 [0.45, 201.57]
Total (95% CI)			**58**	**107**	**100.0%**	**9.51 [0.45, 201.57]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

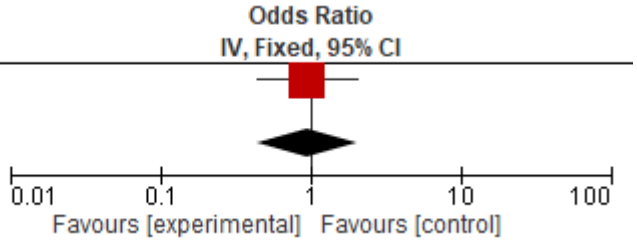


SE: Standard error; **CI:** Confidence interval

8) Oxygen requirement for at least 4 hours

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kirshenbaum 2018	-0.0539	0.389	58	107	100.0%	0.95 [0.44, 2.03]
Total (95% CI)			**58**	**107**	**100.0%**	**0.95 [0.44, 2.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)

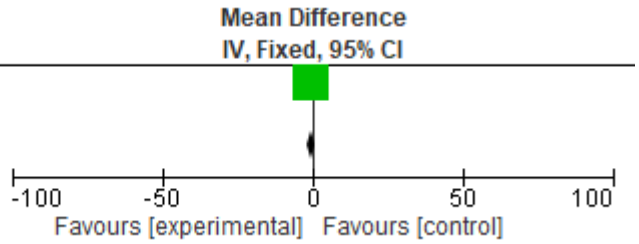


SE: Standard error; **CI:** Confidence interval

9) Mean duration of mechanical ventilation, days

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
de la Huerga Lopez 2019	0.51	1.56	30	0.71	1.63	10	100.0%	-0.20 [-1.35, 0.95]
Total (95% CI)			**30**			**10**	**100.0%**	**-0.20 [-1.35, 0.95]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)



SD: Standard Deviation; **CI:** Confidence interval

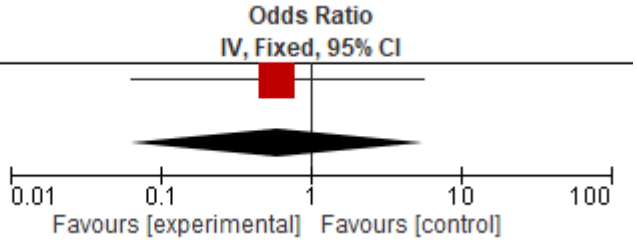
Maternal outcomes for women with histological chorioamnionitis

*There is no maternal outcome in clinical chorioamnionitis.

1) Preeclampsia or eclampsia (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ryu 2019	-0.5145	1.141	97	12	100.0%	0.60 [0.06, 5.59]
Total (95% CI)			**97**	**12**	**100.0%**	**0.60 [0.06, 5.59]**

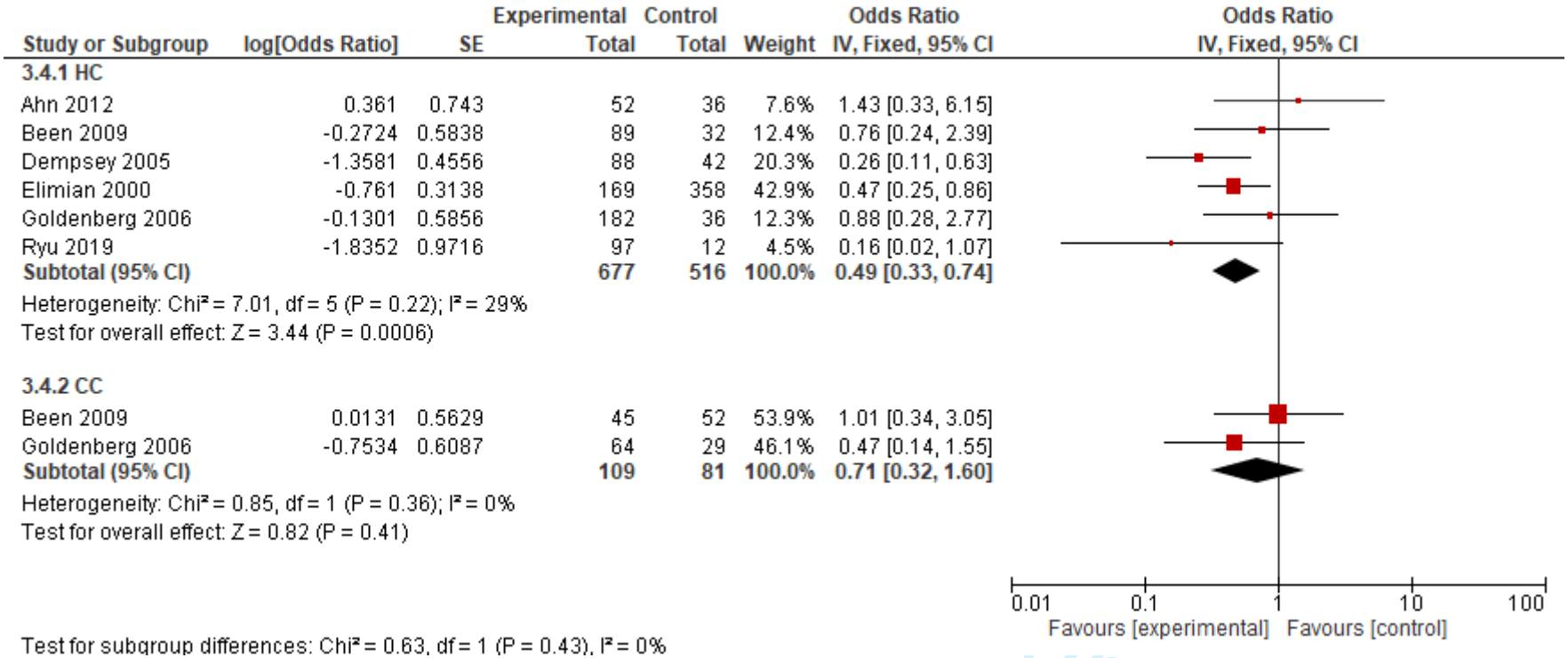
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

Neonatal outcomes for women with histological chorioamnionitis (HC) and clinical chorioamnionitis (CC)

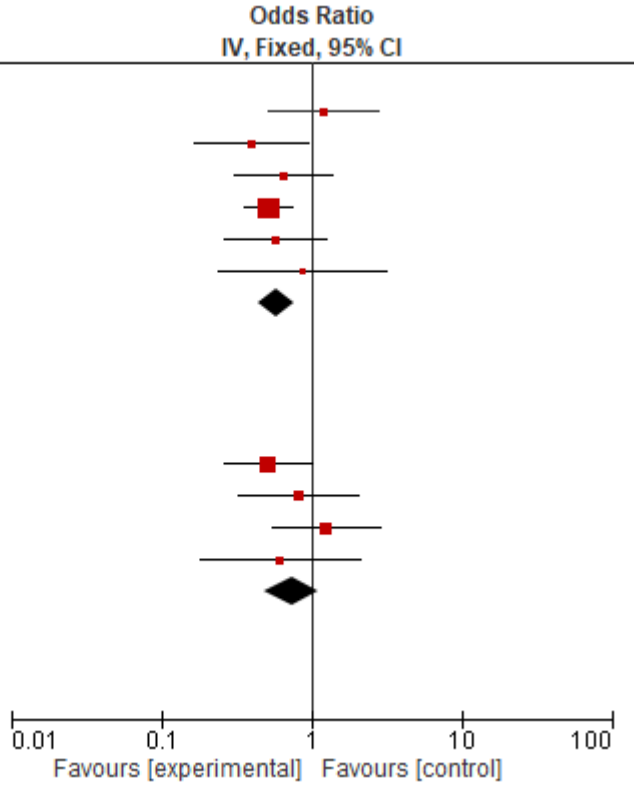
1) Neonatal death



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

2) Respiratory distress syndrome (RDS)

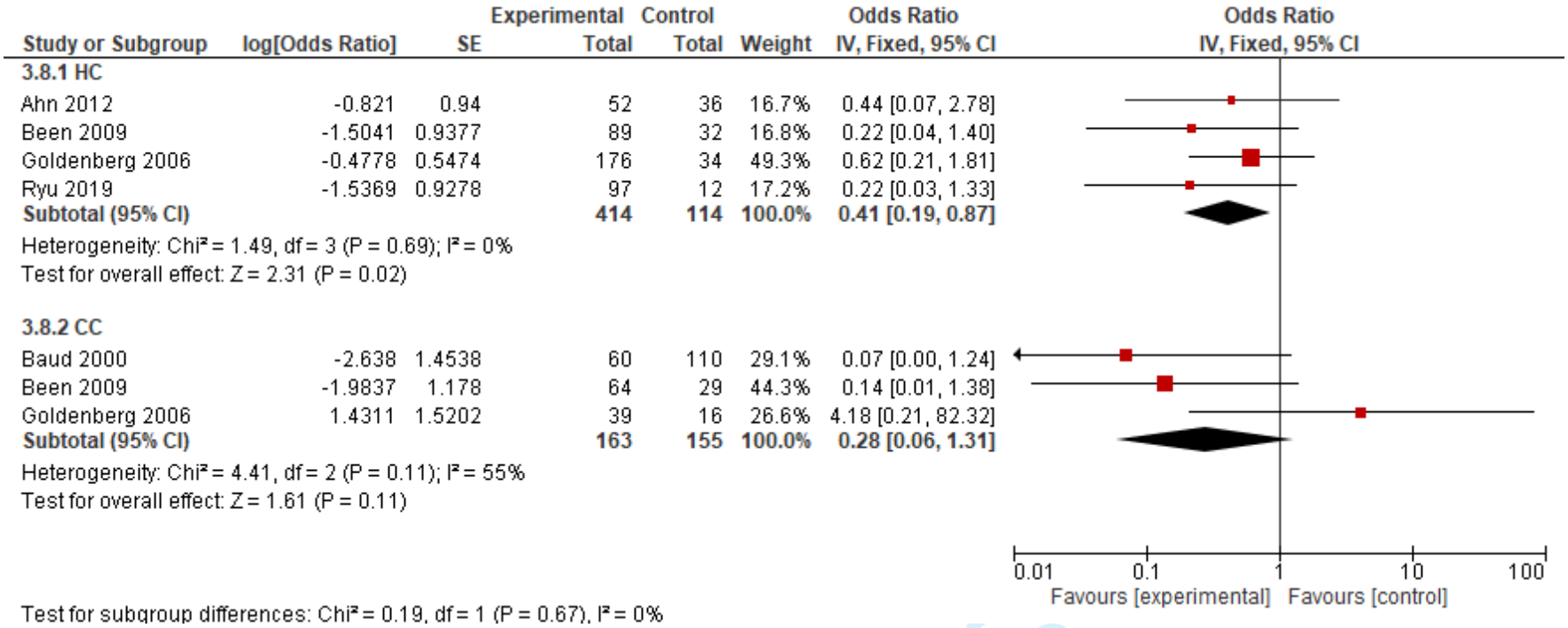
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.6.1 HC						
Ahn 2012	0.1882	0.4342	52	36	9.9%	1.21 [0.52, 2.83]
Been 2009	-0.9158	0.4467	89	32	9.4%	0.40 [0.17, 0.96]
Dempsey 2005	-0.418	0.382	88	42	12.8%	0.66 [0.31, 1.39]
Elimian 2000	-0.656	0.1899	169	358	51.9%	0.52 [0.36, 0.75]
Goldenberg 2006	-0.5546	0.4017	182	36	11.6%	0.57 [0.26, 1.26]
Ryu 2019	-0.1393	0.6571	97	12	4.3%	0.87 [0.24, 3.15]
Subtotal (95% CI)			**677**	**516**	**100.0%**	**0.59 [0.45, 0.77]**
Heterogeneity: Chi² = 4.37, df = 5 (P = 0.50); I² = 0%						
Test for overall effect: Z = 3.89 (P = 0.0001)						
3.6.2 CC						
Baud 2000	-0.665	0.3406	60	110	40.3%	0.51 [0.26, 1.00]
Been 2009	-0.1972	0.4672	64	29	21.4%	0.82 [0.33, 2.05]
Foix-L'Helias 2005	0.2305	0.4214	45	52	26.3%	1.26 [0.55, 2.88]
Goldenberg 2006	-0.47	0.6225	40	17	12.1%	0.63 [0.18, 2.12]
Subtotal (95% CI)			**209**	**208**	**100.0%**	**0.74 [0.48, 1.12]**
Heterogeneity: Chi² = 2.86, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						



Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

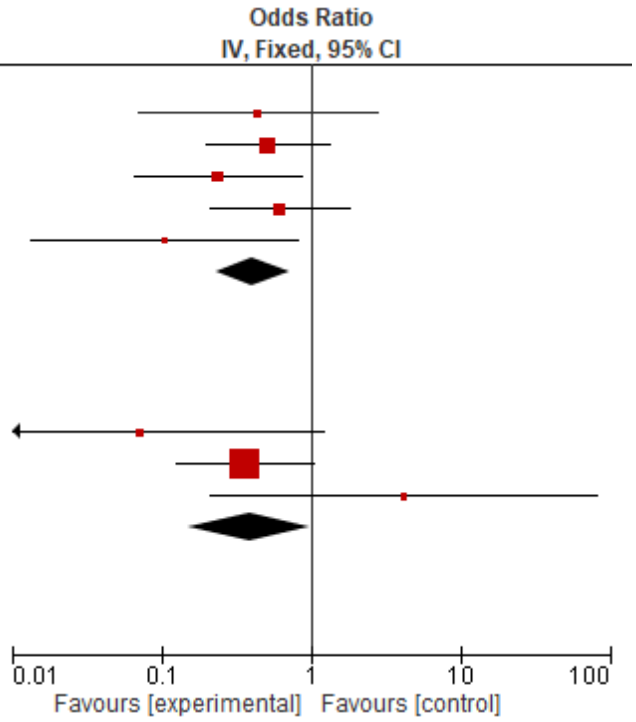
3) Severe intraventricular hemorrhage (IVH)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

4) Intraventricular hemorrhage (IVH)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.9.1 HC						
Ahn 2012	-0.821	0.94	52	36	9.5%	0.44 [0.07, 2.78]
Been 2009	-0.6577	0.4845	89	32	35.7%	0.52 [0.20, 1.34]
Dempsey 2005	-1.4351	0.6583	88	42	19.3%	0.24 [0.07, 0.87]
Goldenberg 2006	-0.4778	0.5474	176	34	28.0%	0.62 [0.21, 1.81]
Ryu 2019	-2.2513	1.0538	97	12	7.5%	0.11 [0.01, 0.83]
Subtotal (95% CI)			**502**	**156**	**100.0%**	**0.41 [0.23, 0.72]**
Heterogeneity: Chi² = 3.16, df = 4 (P = 0.53); I² = 0%						
Test for overall effect: Z = 3.09 (P = 0.002)						
3.9.2 CC						
Baud 2000	-2.638	1.4538	60	110	10.9%	0.07 [0.00, 1.24]
Been 2009	-1.0116	0.5389	64	29	79.2%	0.36 [0.13, 1.05]
Goldenberg 2006	1.4311	1.5202	39	16	9.9%	4.18 [0.21, 82.32]
Subtotal (95% CI)			**163**	**155**	**100.0%**	**0.39 [0.15, 0.99]**
Heterogeneity: Chi² = 3.81, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 1.97 (P = 0.05)						

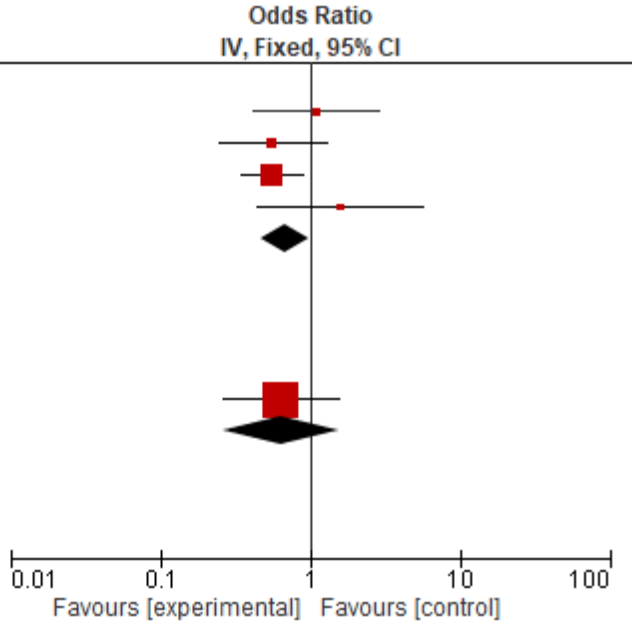


Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

5) Patent ductus arteriosus (PDA)

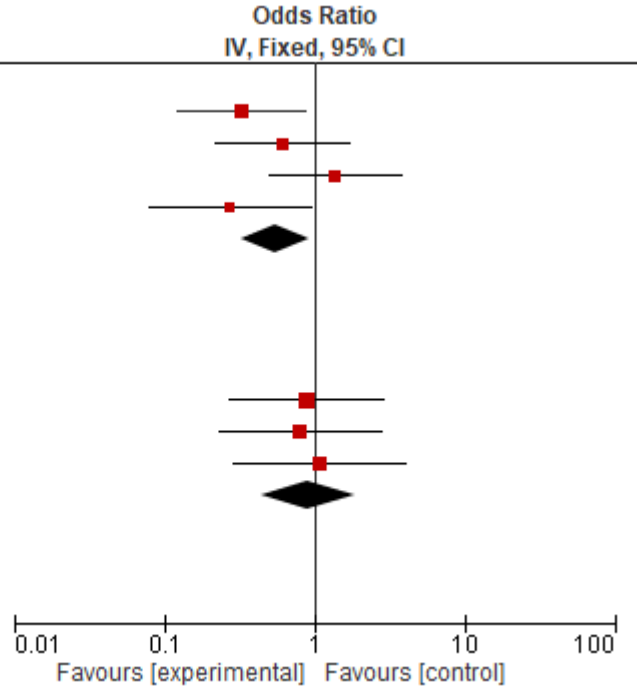
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.12.1 HC						
Ahn 2012	0.1001	0.4959	52	36	14.5%	1.11 [0.42, 2.92]
Been 2009	-0.58	0.4244	89	32	19.8%	0.56 [0.24, 1.29]
Elimian 2000	-0.5841	0.2497	169	358	57.2%	0.56 [0.34, 0.91]
Ryu 2019	0.4654	0.6456	97	12	8.6%	1.59 [0.45, 5.64]
Subtotal (95% CI)			**407**	**438**	**100.0%**	**0.67 [0.47, 0.98]**
Heterogeneity: Chi² = 3.54, df = 3 (P = 0.32); I² = 15%						
Test for overall effect: Z = 2.09 (P = 0.04)						
3.12.2 CC						
Been 2009	-0.439	0.4568	64	29	100.0%	0.64 [0.26, 1.58]
Subtotal (95% CI)			**64**	**29**	**100.0%**	**0.64 [0.26, 1.58]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

6) Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)

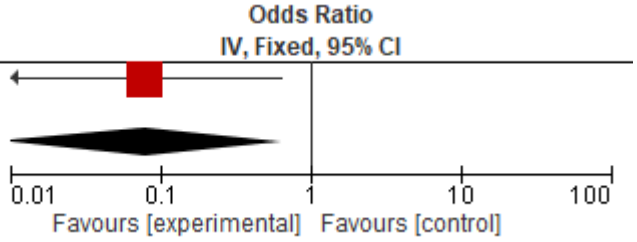
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.13.1 HC						
Ahn 2012	-1.112	0.5012	52	36	28.6%	0.33 [0.12, 0.88]
Been 2009	-0.4928	0.5224	89	32	26.4%	0.61 [0.22, 1.70]
Goldenberg 2006	0.3171	0.5189	182	36	26.7%	1.37 [0.50, 3.80]
Ryu 2019	-1.2891	0.6278	97	12	18.3%	0.28 [0.08, 0.94]
Subtotal (95% CI)			**420**	**116**	**100.0%**	**0.55 [0.32, 0.93]**
Heterogeneity: Chi² = 5.41, df = 3 (P = 0.14); I² = 45%						
Test for overall effect: Z = 2.23 (P = 0.03)						
3.13.2 CC						
Been 2009	-0.1178	0.6002	64	29	37.3%	0.89 [0.27, 2.88]
Foix-L'Helias 2005	-0.2221	0.6326	38	44	33.6%	0.80 [0.23, 2.77]
Goldenberg 2006	0.08	0.6784	40	17	29.2%	1.08 [0.29, 4.09]
Subtotal (95% CI)			**142**	**90**	**100.0%**	**0.91 [0.44, 1.86]**
Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.8%						



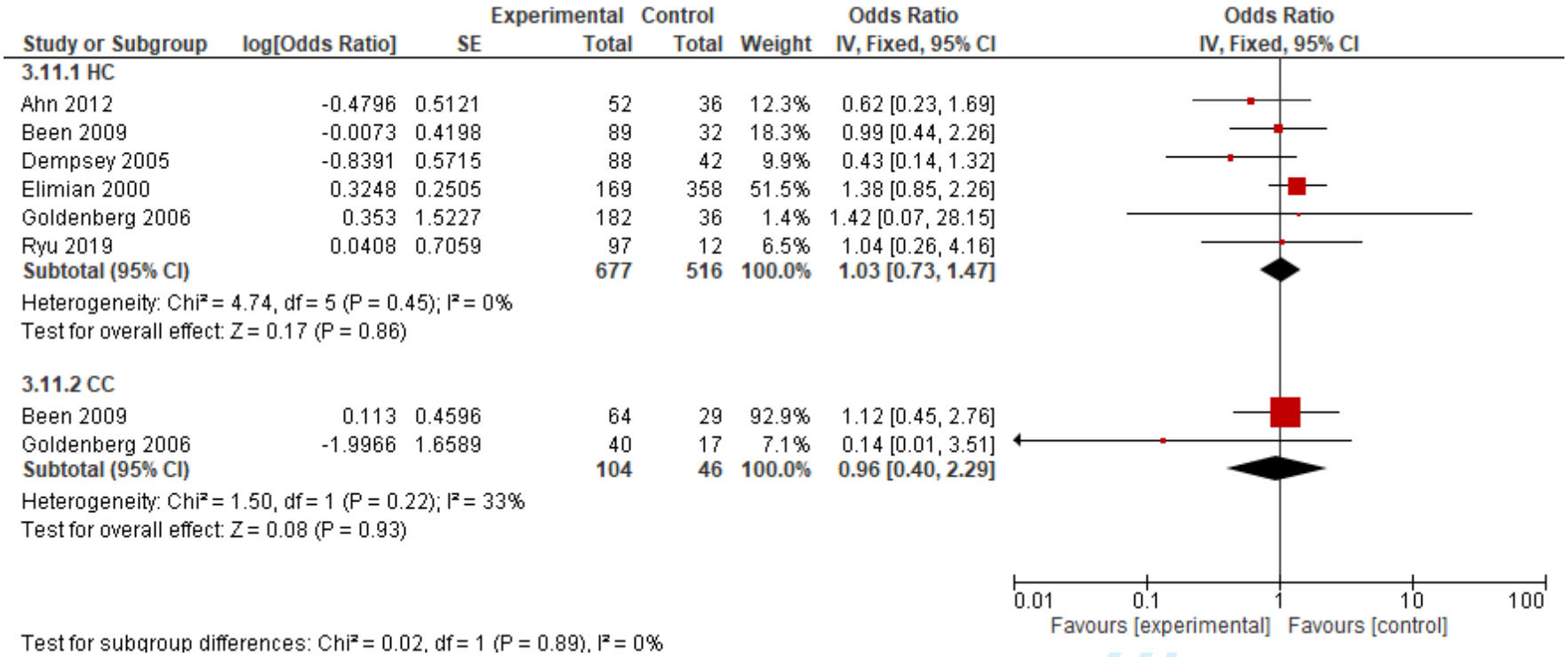
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

7) Hypotension within 7 days postnatal

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ryu 2019	-2.5257	1.061	97	12	100.0%	0.08 [0.01, 0.64]
Total (95% CI)			**97**	**12**	**100.0%**	**0.08 [0.01, 0.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.38 (P = 0.02)						



8) Sepsis

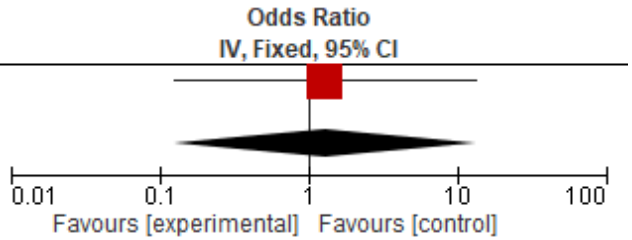


SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

9) Death before discharge home (CC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Foix-L'Helias 2005	0.2603	1.1928	40	17	100.0%	1.30 [0.13, 13.44]
Total (95% CI)			**40**	**17**	**100.0%**	**1.30 [0.13, 13.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

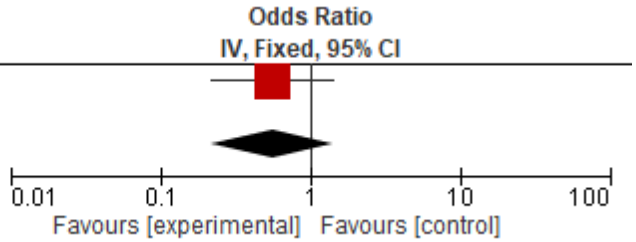


SE: Standard error; **CI:** Confidence interval; **CC:** Clinical chorioamnionitis

10) Severe respiratory distress syndrome (RDS) (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Been 2009	-0.5796	0.4804	89	32	100.0%	0.56 [0.22, 1.44]
Total (95% CI)			**89**	**32**	**100.0%**	**0.56 [0.22, 1.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)

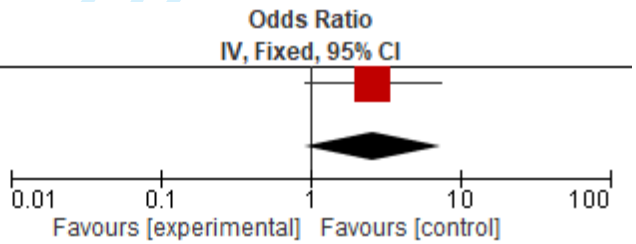


SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

11) Pneumonia (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Dempsey 2005	0.9626	0.5347	88	42	100.0%	2.62 [0.92, 7.47]
Total (95% CI)			**88**	**42**	**100.0%**	**2.62 [0.92, 7.47]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)



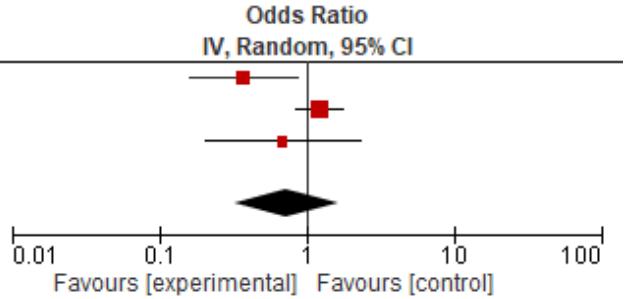
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

12) Surfactant use (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Been 2009	-0.987	0.4299	89	32	32.2%	0.37 [0.16, 0.87]
Elimian 2000	0.1958	0.1923	169	358	44.4%	1.22 [0.83, 1.77]
Ryu 2019	-0.3722	0.6241	97	12	23.3%	0.69 [0.20, 2.34]
Total (95% CI)			**355**	**402**	**100.0%**	**0.73 [0.32, 1.65]**

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 6.63$, df = 2 (P = 0.04); $I^2 = 70\%$

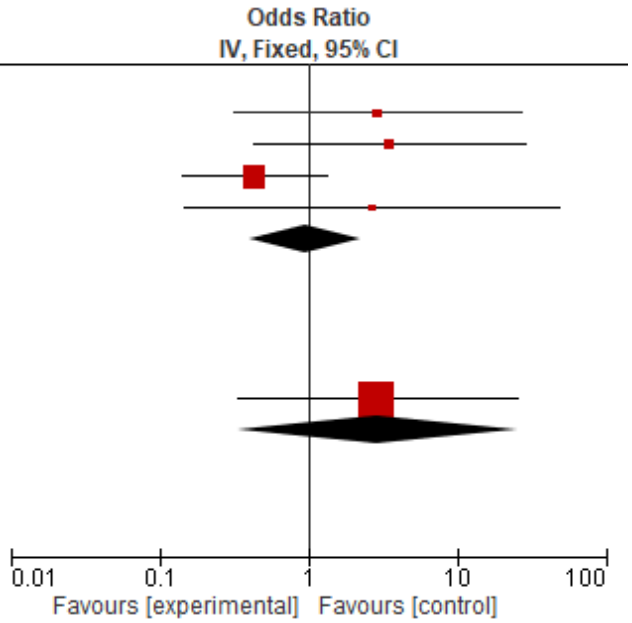
Test for overall effect: Z = 0.76 (P = 0.45)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

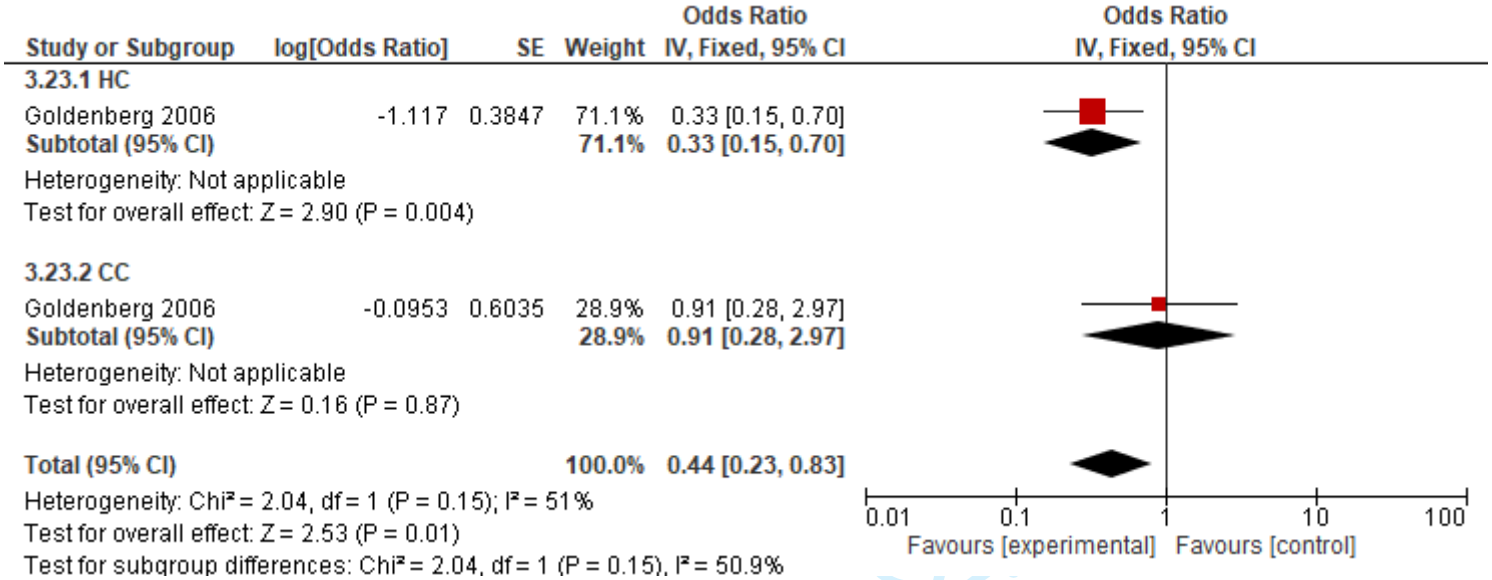
13) Early-onset sepsis

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.10.1 HC						
Ahn 2012	1.0704	1.1399	52	36	14.9%	2.92 [0.31, 27.24]
Been 2009	1.2492	1.0751	89	32	16.8%	3.49 [0.42, 28.68]
Dempsey 2005	-0.8391	0.5715	88	42	59.4%	0.43 [0.14, 1.32]
Ryu 2019	0.9872	1.4821	97	12	8.8%	2.68 [0.15, 49.01]
Subtotal (95% CI)			**326**	**122**	**100.0%**	**0.96 [0.40, 2.27]**
Heterogeneity: Chi² = 4.82, df = 3 (P = 0.19); I² = 38%						
Test for overall effect: Z = 0.09 (P = 0.92)						
3.10.2 CC						
Been 2009	1.0635	1.1044	64	29	100.0%	2.90 [0.33, 25.23]
Subtotal (95% CI)			**64**	**29**	**100.0%**	**2.90 [0.33, 25.23]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%						



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

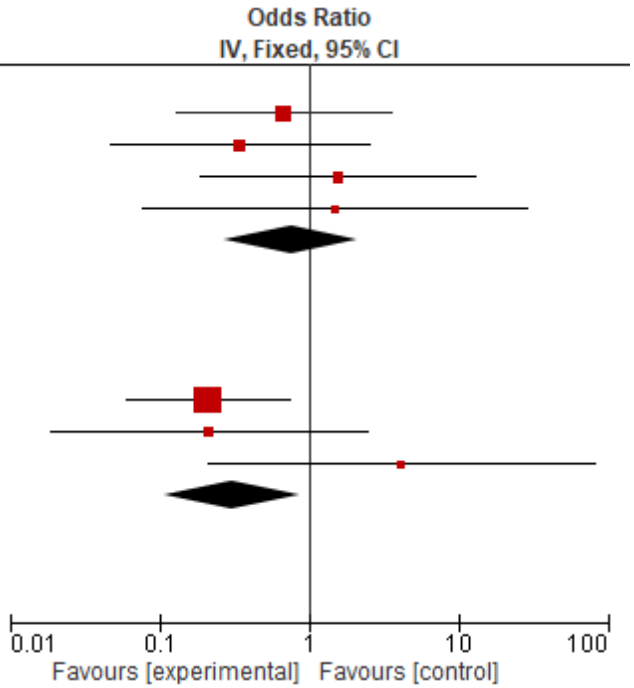
14) Systemic inflammatory response syndrome



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

15) Periventricular leukomalacia (PVL)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.14.1 HC						
Ahn 2012	-0.3953	0.847	52	36	38.2%	0.67 [0.13, 3.54]
Been 2009	-1.0647	1.0222	89	32	26.2%	0.34 [0.05, 2.56]
Goldenberg 2006	0.452	1.0776	176	34	23.6%	1.57 [0.19, 12.99]
Ryu 2019	0.3964	1.5075	97	12	12.0%	1.49 [0.08, 28.53]
Subtotal (95% CI)			**414**	**114**	**100.0%**	**0.76 [0.27, 2.12]**
Heterogeneity: Chi² = 1.27, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
3.14.2 CC						
Baud 2000	-1.5581	0.6385	60	110	69.5%	0.21 [0.06, 0.74]
Been 2009	-1.5404	1.2462	64	29	18.2%	0.21 [0.02, 2.46]
Goldenberg 2006	1.4311	1.5202	39	16	12.3%	4.18 [0.21, 82.32]
Subtotal (95% CI)			**163**	**155**	**100.0%**	**0.30 [0.11, 0.86]**
Heterogeneity: Chi² = 3.38, df = 2 (P = 0.18); I² = 41%						
Test for overall effect: Z = 2.23 (P = 0.03)						

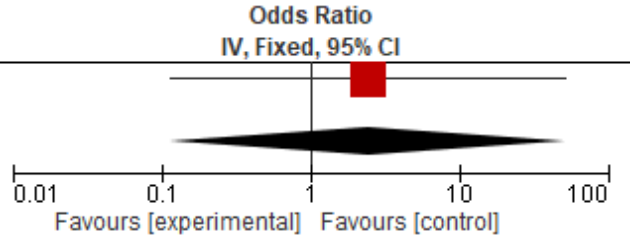


Test for subgroup differences: Chi² = 1.50, df = 1 (P = 0.22), I² = 33.1%

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

16) Meningitis (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Dempsey 2005	0.8988	1.5605	88	42	100.0%	2.46 [0.12, 52.32]
Total (95% CI)			**88**	**42**	**100.0%**	**2.46 [0.12, 52.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						



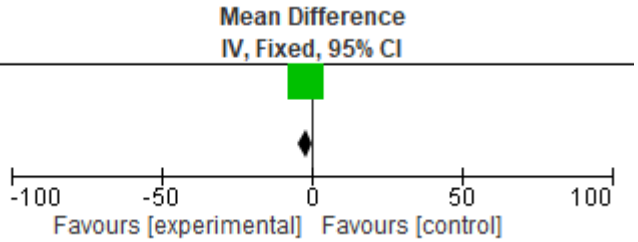
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

17) Mean duration of mechanical ventilation, days (HC)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ahn 2012	1	1.25	52	3	6.75	36	100.0%	-2.00 [-4.23, 0.23]
Total (95% CI)			**52**			**36**	**100.0%**	**-2.00 [-4.23, 0.23]**

Heterogeneity: Not applicable

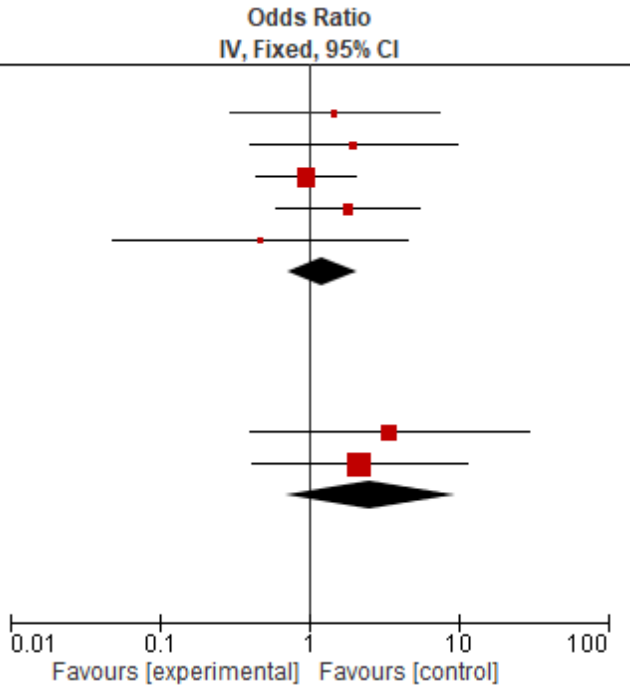
Test for overall effect: Z = 1.76 (P = 0.08)



SD: Standard Deviation; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Necrotizing enterocolitis (NEC)

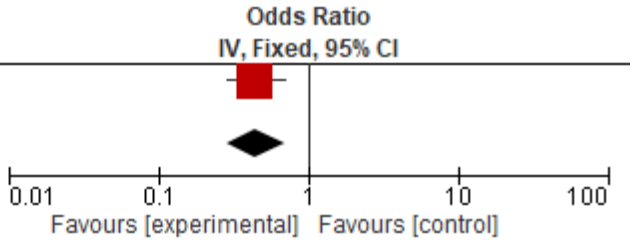
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
3.16.1 HC						
Been 2009	0.393	0.8189	89	32	11.2%	1.48 [0.30, 7.37]
Dempsey 2005	0.6931	0.8139	88	42	11.3%	2.00 [0.41, 9.86]
Elimian 2000	-0.0403	0.3933	169	358	48.4%	0.96 [0.44, 2.08]
Goldenberg 2006	0.6086	0.5634	182	36	23.6%	1.84 [0.61, 5.54]
Ryu 2019	-0.7484	1.1626	97	12	5.5%	0.47 [0.05, 4.62]
Subtotal (95% CI)			**625**	**480**	**100.0%**	**1.23 [0.72, 2.10]**
Heterogeneity: Chi² = 1.99, df = 4 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						
3.16.2 CC						
Been 2009	1.2351	1.0937	64	29	37.2%	3.44 [0.40, 29.33]
Goldenberg 2006	0.7781	0.8426	40	17	62.8%	2.18 [0.42, 11.35]
Subtotal (95% CI)			**104**	**46**	**100.0%**	**2.58 [0.70, 9.55]**
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.9%						



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

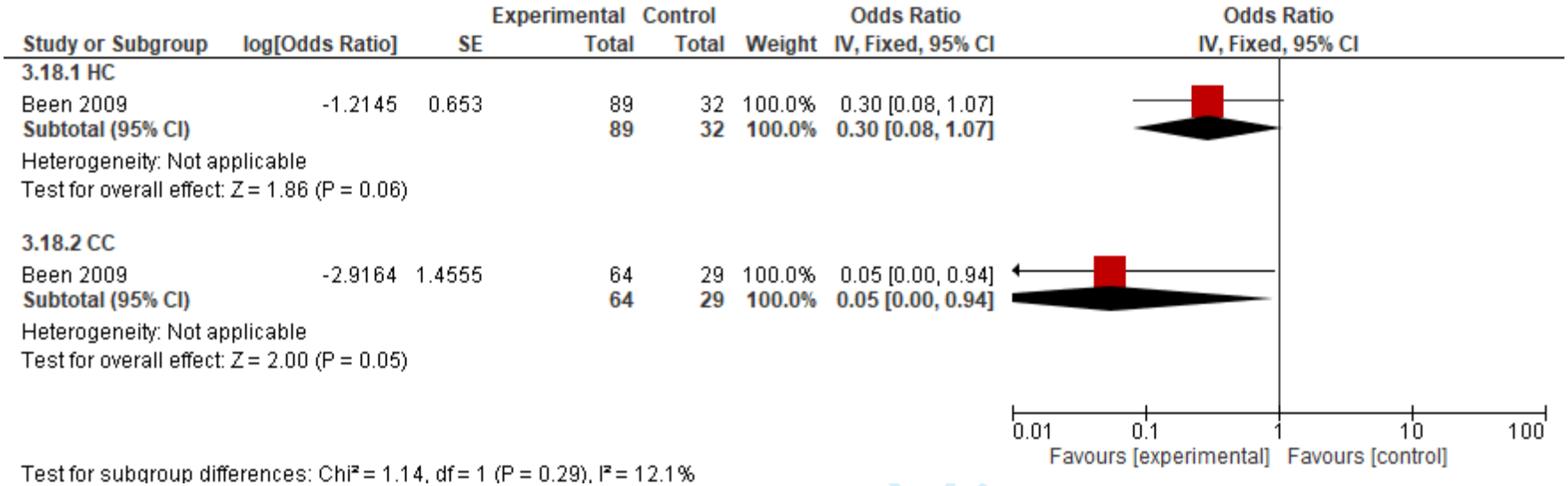
19) Apgar score < 7 at 5 minutes (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Elimian 2000	-0.8085	0.2281	169	358	100.0%	0.45 [0.28, 0.70]
Total (95% CI)			**169**	**358**	**100.0%**	**0.45 [0.28, 0.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.54 (P = 0.0004)						



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

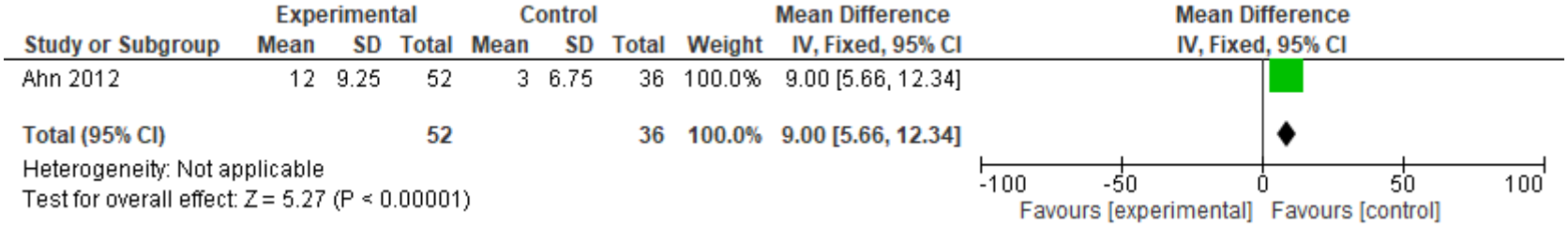
20) Use of mechanical ventilation



Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.1%

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

21) Duration of oxygen use, days (HC)

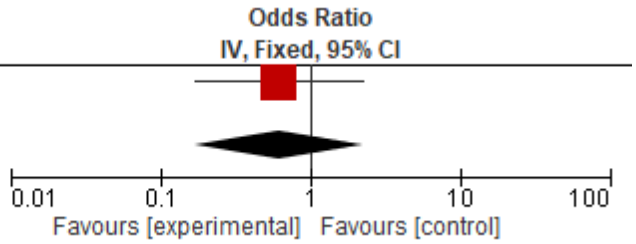


SD: Standard Deviation; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

22) Discharge with respiratory support (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ryu 2019	-0.4754	0.6573	97	12	100.0%	0.62 [0.17, 2.25]
Total (95% CI)			**97**	**12**	**100.0%**	**0.62 [0.17, 2.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

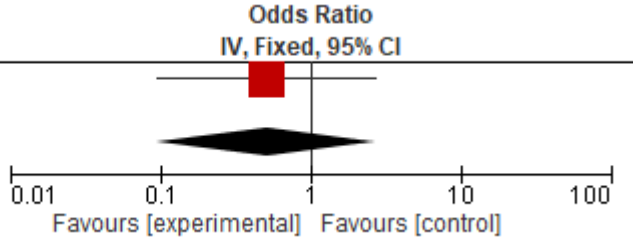


SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

23) Retinopathy of prematurity requiring treatment (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ryu 2019	-0.6707	0.85	97	12	100.0%	0.51 [0.10, 2.71]
Total (95% CI)			**97**	**12**	**100.0%**	**0.51 [0.10, 2.71]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

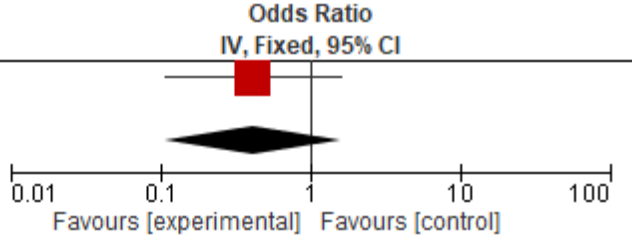


SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

24) Intrahepatic cholestasis (HC)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ahn 2012	-0.8755	0.6862	52	36	100.0%	0.42 [0.11, 1.60]
Total (95% CI)			**52**	**36**	**100.0%**	**0.42 [0.11, 1.60]**

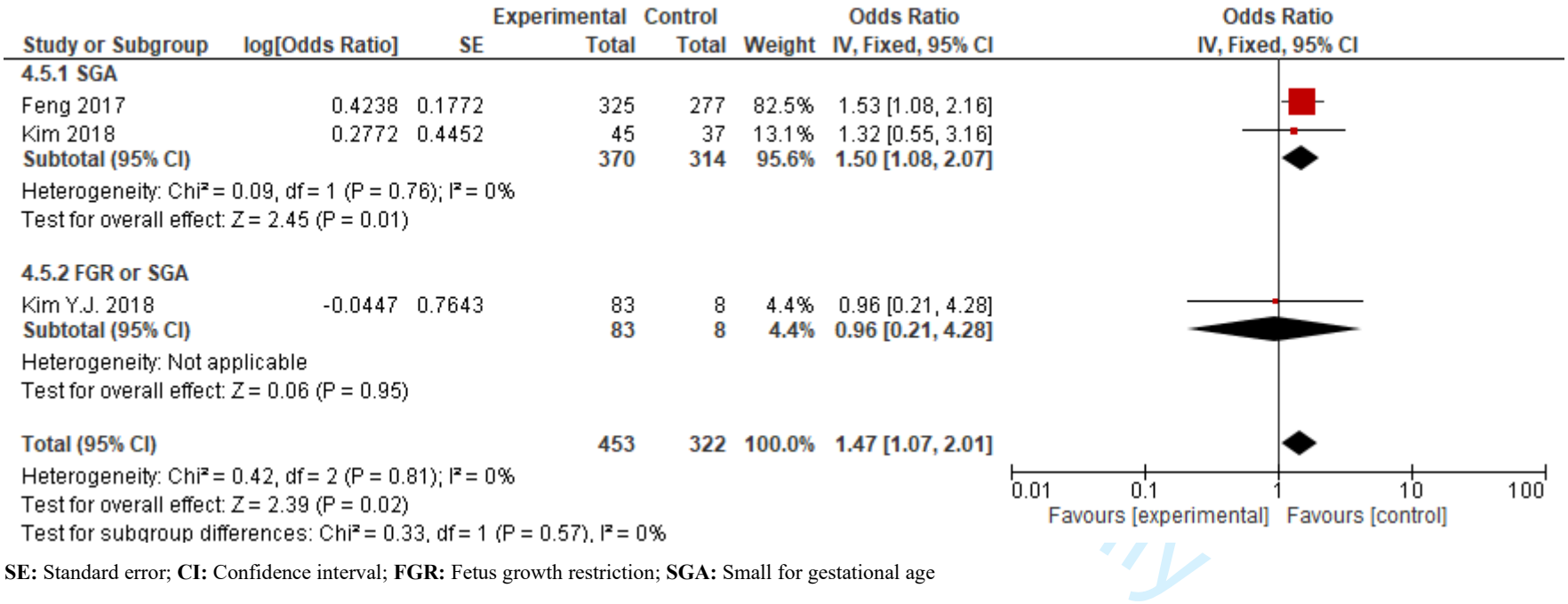
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

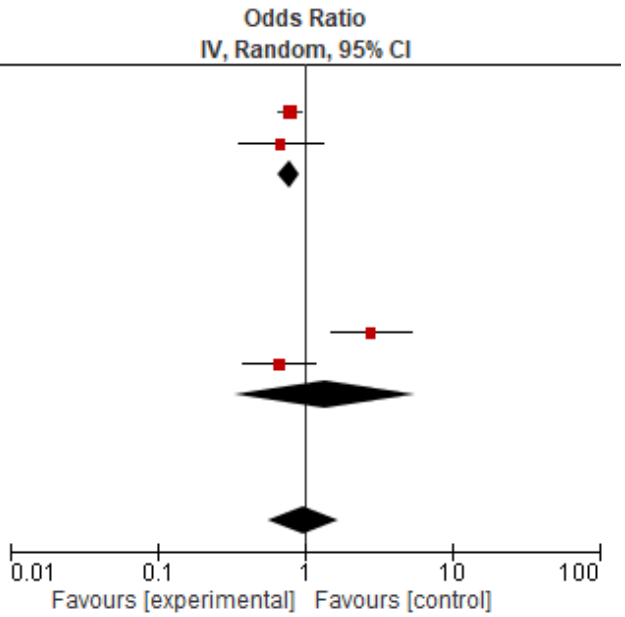
1) Pregnancy-induced hypertension (PIH)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Preeclampsia

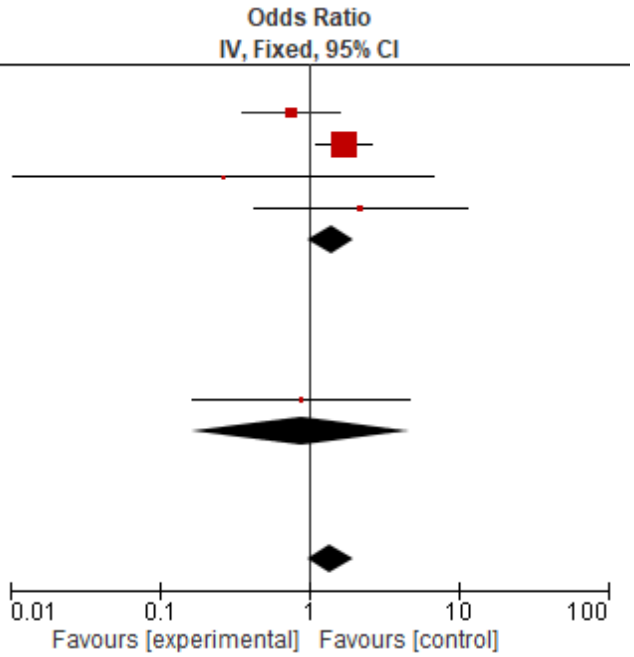
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
4.3.1 SGA						
Ishikawa 2015	-0.2336	0.0946	719	1209	31.2%	0.79 [0.66, 0.95]
Mitsiakos 2013	-0.3746	0.3343	87	62	22.2%	0.69 [0.36, 1.32]
Subtotal (95% CI)			**806**	**1271**	**53.4%**	**0.78 [0.66, 0.94]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.68 (P = 0.007)						
4.3.2 FGR or SGA						
Bitar 2020	1.0389	0.3199	136	111	22.8%	2.83 [1.51, 5.29]
Cartwright 2019	-0.4008	0.2955	118	98	23.8%	0.67 [0.38, 1.20]
Subtotal (95% CI)			**254**	**209**	**46.6%**	**1.37 [0.33, 5.61]**
Heterogeneity: Tau² = 0.94; Chi² = 10.93, df = 1 (P = 0.0009); I² = 91%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)			**1060**	**1480**	**100.0%**	**0.99 [0.57, 1.71]**
Heterogeneity: Tau² = 0.25; Chi² = 15.72, df = 3 (P = 0.001); I² = 81%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%						



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Chorioamnionitis

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.2.1 SGA						
Elimian 1999	-0.2675	0.3843	63	157	21.7%	0.77 [0.36, 1.63]
Ishikawa 2015	0.5412	0.2166	507	838	68.2%	1.72 [1.12, 2.63]
Kim 2018	-1.319	1.648	45	37	1.2%	0.27 [0.01, 6.76]
Mitsiakos 2013	0.7985	0.8341	87	62	4.6%	2.22 [0.43, 11.40]
Subtotal (95% CI)			**702**	**1094**	**95.6%**	**1.42 [0.99, 2.03]**
Heterogeneity: Chi² = 4.68, df = 3 (P = 0.20); I² = 36%						
Test for overall effect: Z = 1.90 (P = 0.06)						
4.2.2 FGR or SGA						
Kim Y.J. 2018	-0.1158	0.8573	83	8	4.4%	0.89 [0.17, 4.78]
Subtotal (95% CI)			**83**	**8**	**4.4%**	**0.89 [0.17, 4.78]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)			**785**	**1102**	**100.0%**	**1.39 [0.98, 1.97]**
Heterogeneity: Chi² = 4.95, df = 4 (P = 0.29); I² = 19%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						

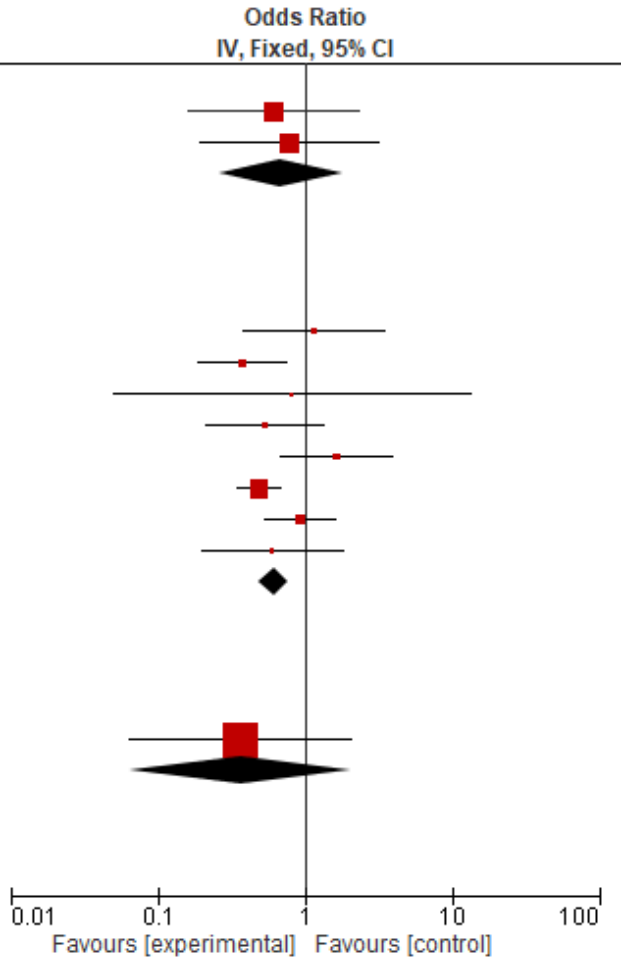


SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

Neonatal outcomes for women with growth-restricted fetuses

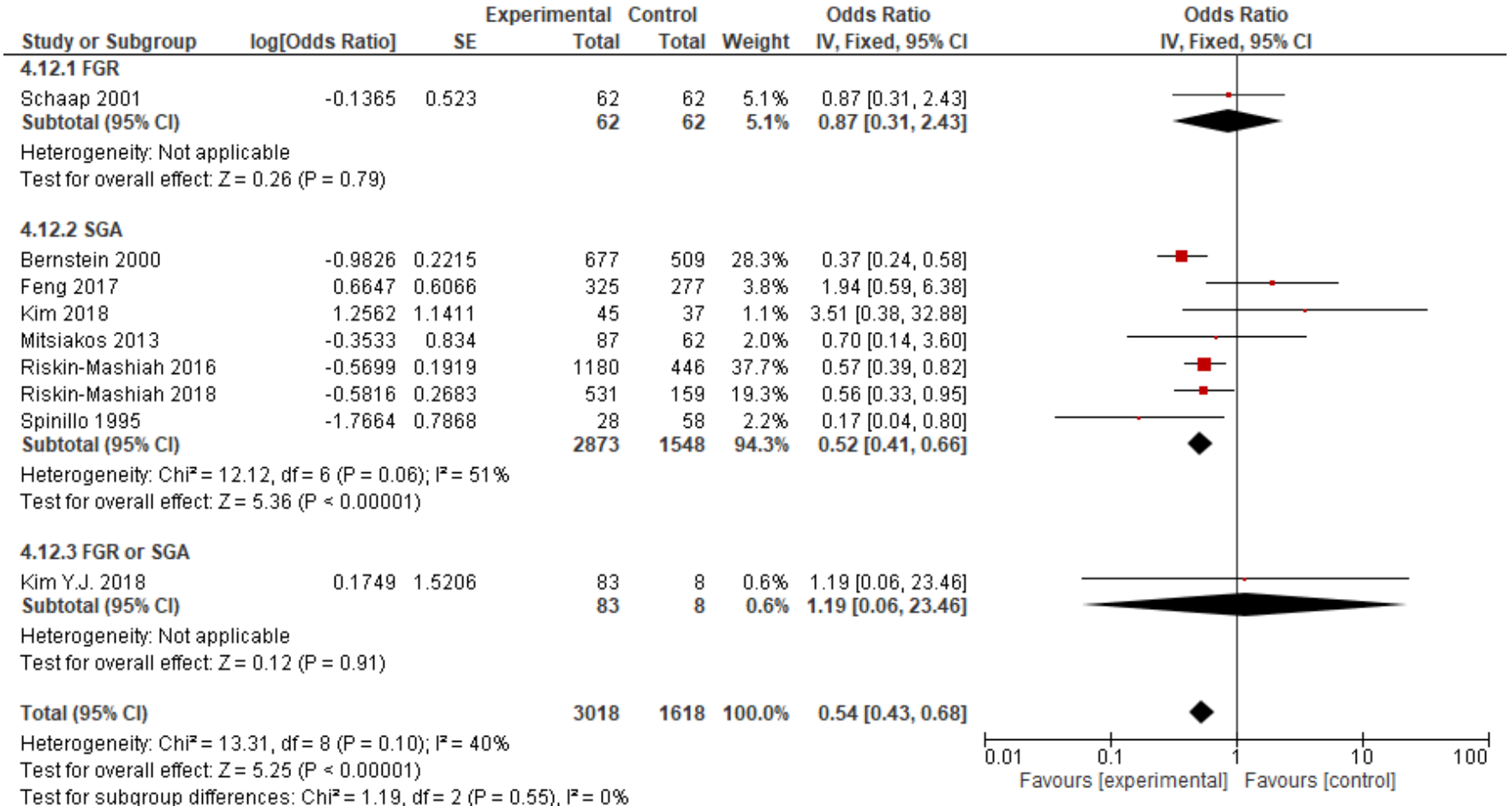
1) Neonatal death

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.6.1 FGR						
Torrance 2007	-0.4932	0.6857	146	19	51.7%	0.61 [0.16, 2.34]
vanStralen 2009	-0.2469	0.71	53	34	48.3%	0.78 [0.19, 3.14]
Subtotal (95% CI)			**199**	**53**	**100.0%**	**0.69 [0.26, 1.81]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
4.6.2 SGA						
Elimian 1999	0.1347	0.5612	63	157	4.6%	1.14 [0.38, 3.44]
Feng 2017	-0.9808	0.3523	325	277	11.6%	0.38 [0.19, 0.75]
Kim 2018	-0.2007	1.432	45	37	0.7%	0.82 [0.05, 13.54]
Ley 1997	-0.6349	0.4723	117	117	6.4%	0.53 [0.21, 1.34]
Mitsiakos 2013	0.498	0.4442	87	62	7.3%	1.65 [0.69, 3.93]
Riskin-Mashiah 2018	-0.7174	0.1746	585	199	47.1%	0.49 [0.35, 0.69]
Spinillo 1995	-0.0728	0.2841	176	248	17.8%	0.93 [0.53, 1.62]
Torrance 2007	-0.5108	0.5605	146	19	4.6%	0.60 [0.20, 1.80]
Subtotal (95% CI)			**1544**	**1116**	**100.0%**	**0.61 [0.49, 0.78]**
Heterogeneity: Chi² = 12.12, df = 7 (P = 0.10); I² = 42%						
Test for overall effect: Z = 4.07 (P < 0.0001)						
4.6.3 FGR or SGA						
Kim Y.J. 2018	-1.0082	0.8895	83	8	100.0%	0.36 [0.06, 2.09]
Subtotal (95% CI)			**83**	**8**	**100.0%**	**0.36 [0.06, 2.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%						



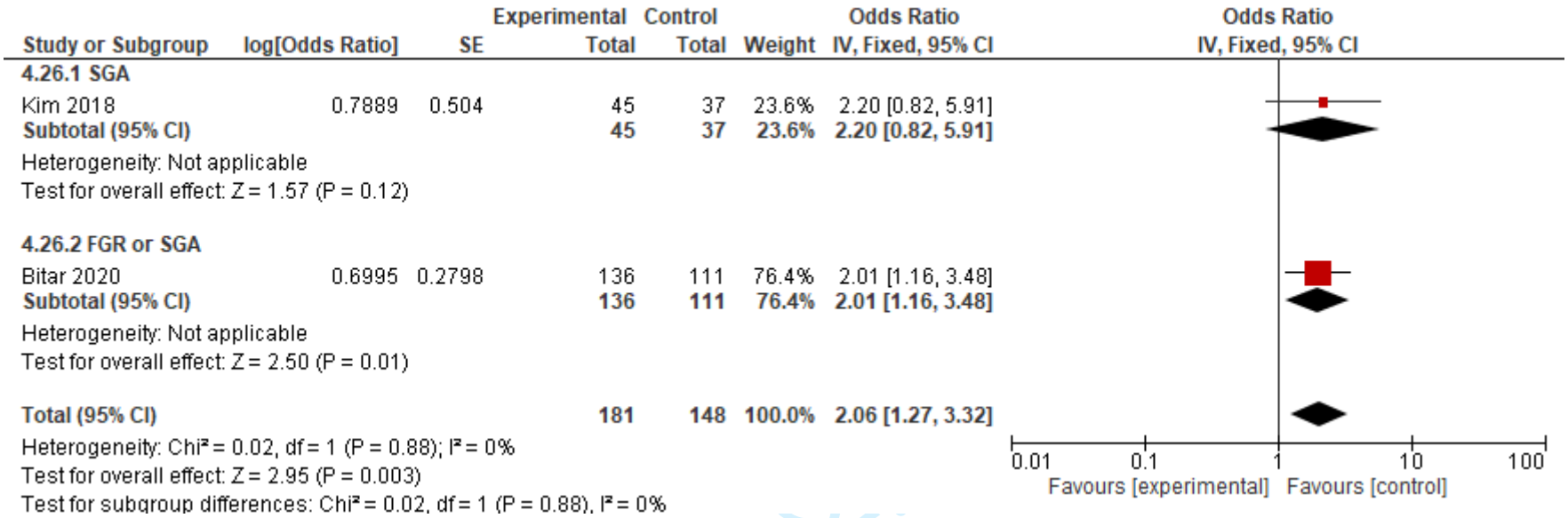
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Severe intraventricular hemorrhage (IVH)



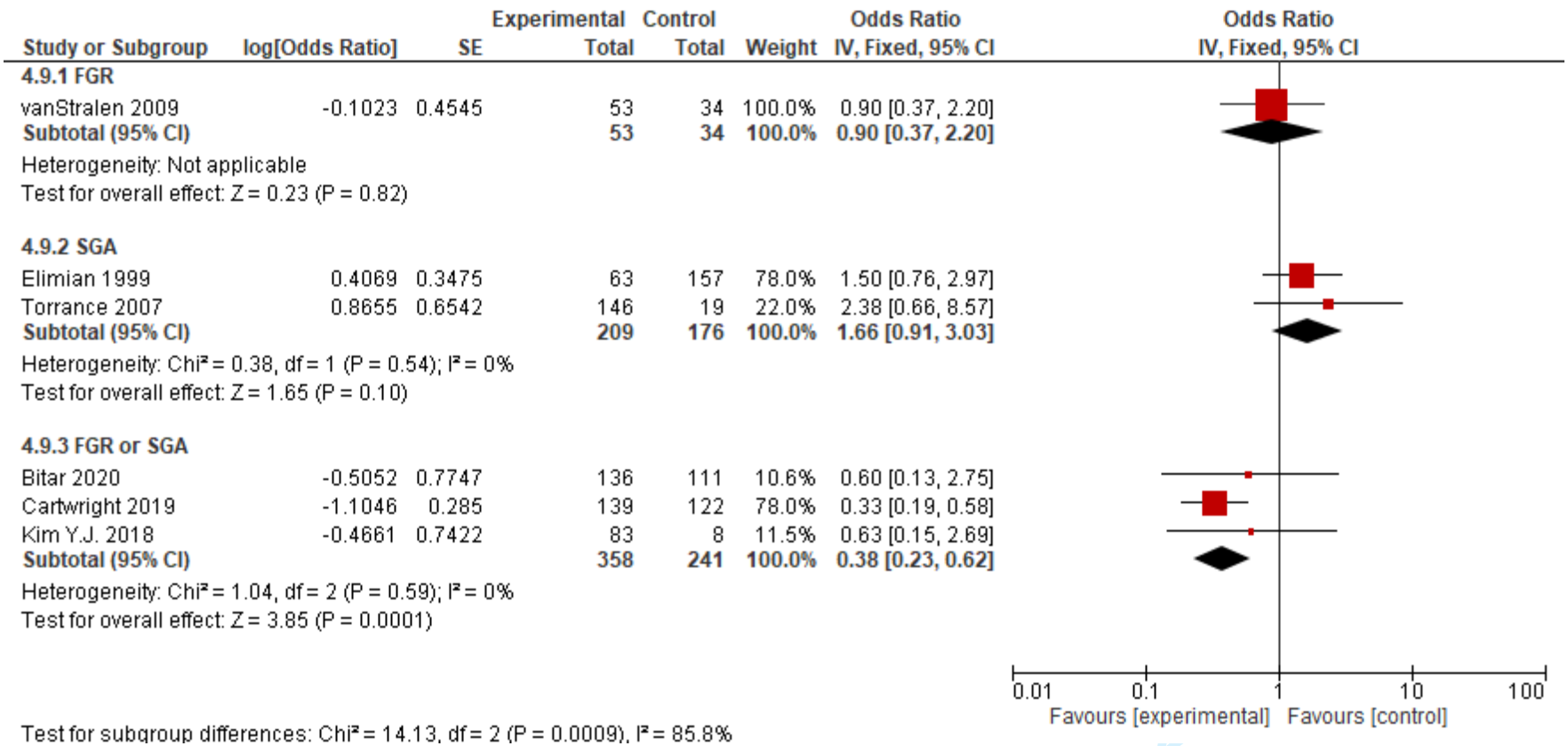
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Neonatal hypoglycemia



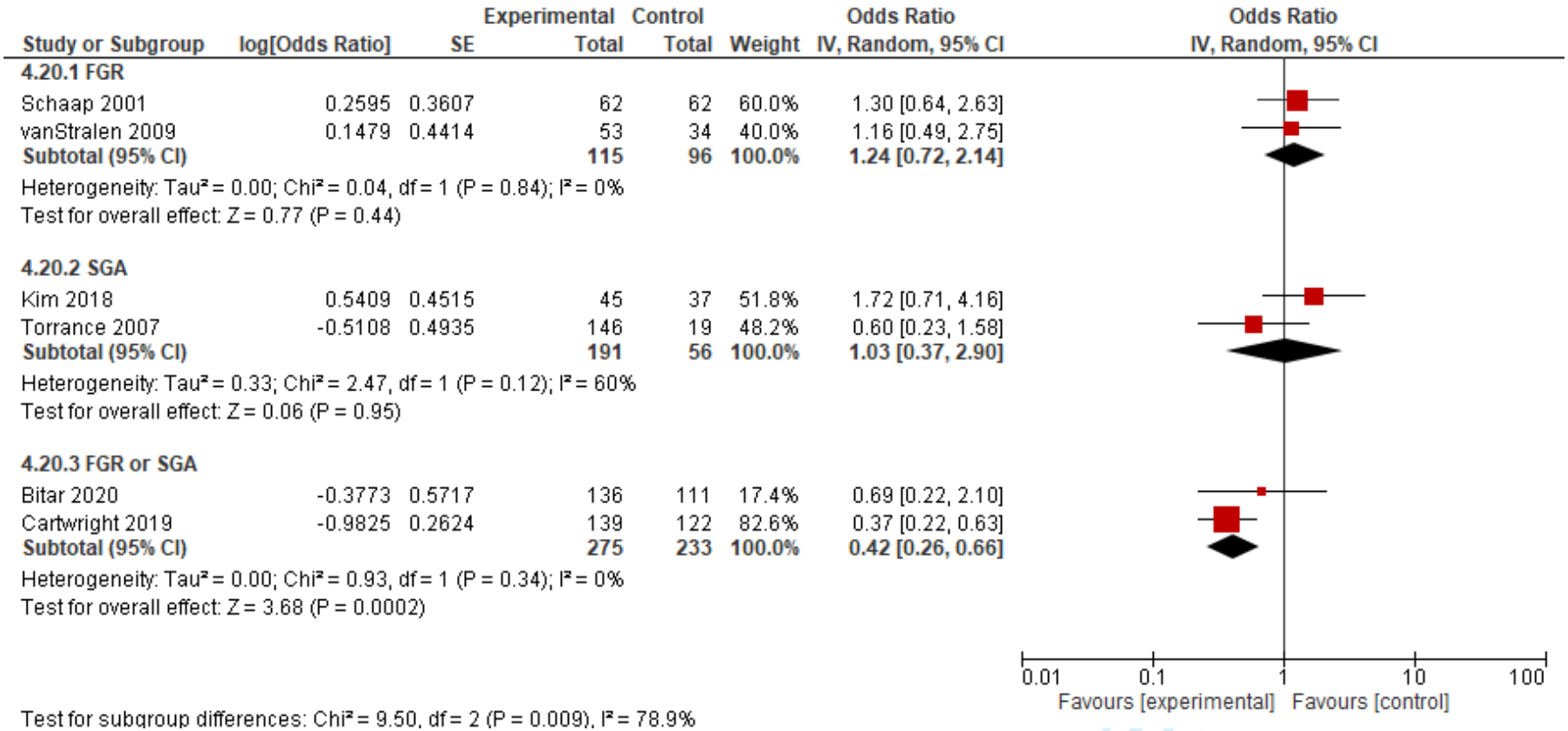
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Surfactant use



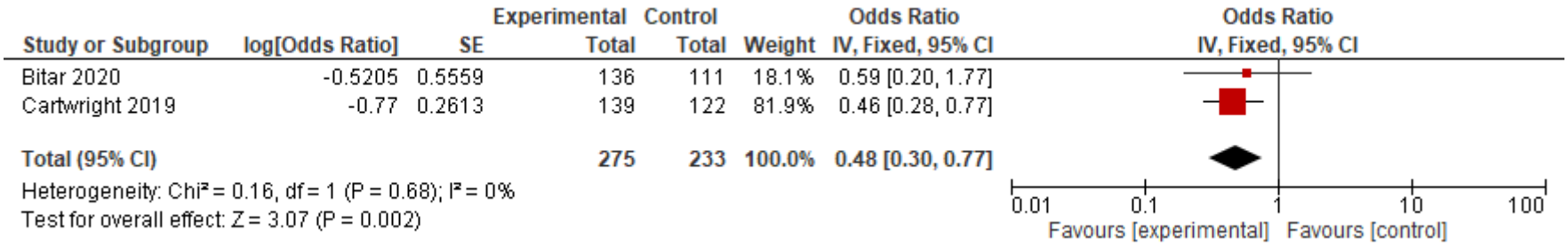
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

5) Use of mechanical ventilation



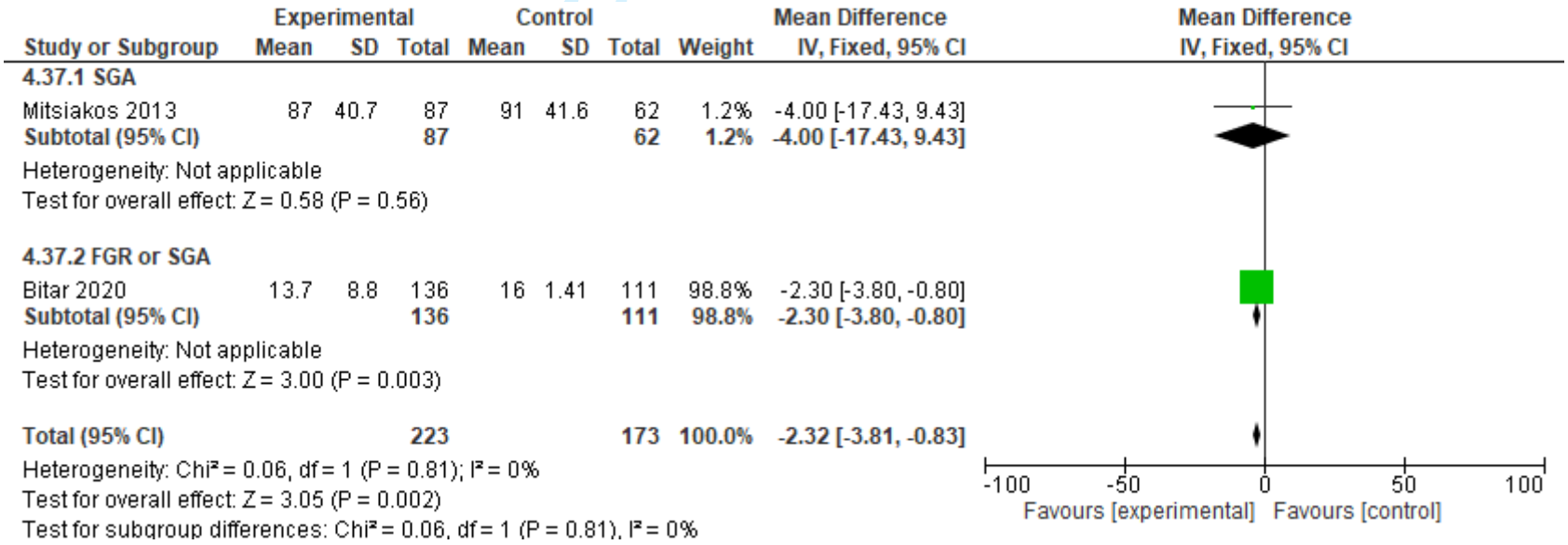
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

6) Oxygen therapy (FGR or SGA)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

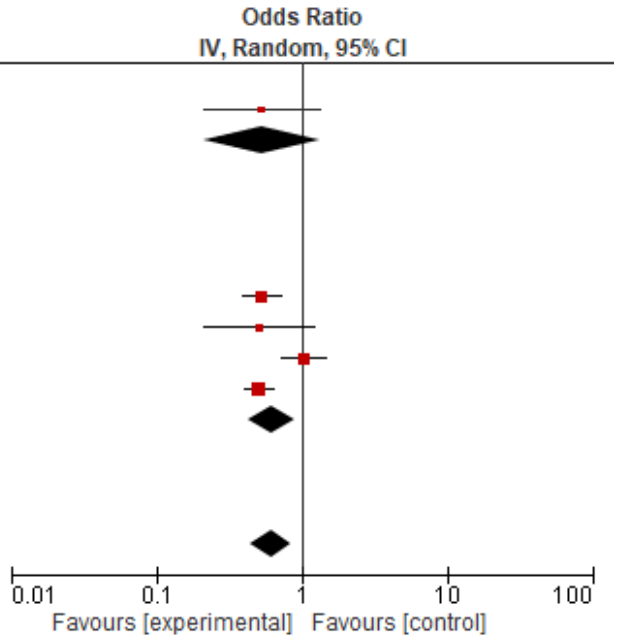
7) Duration of hospital stay (days)



SD: Standard Deviation; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

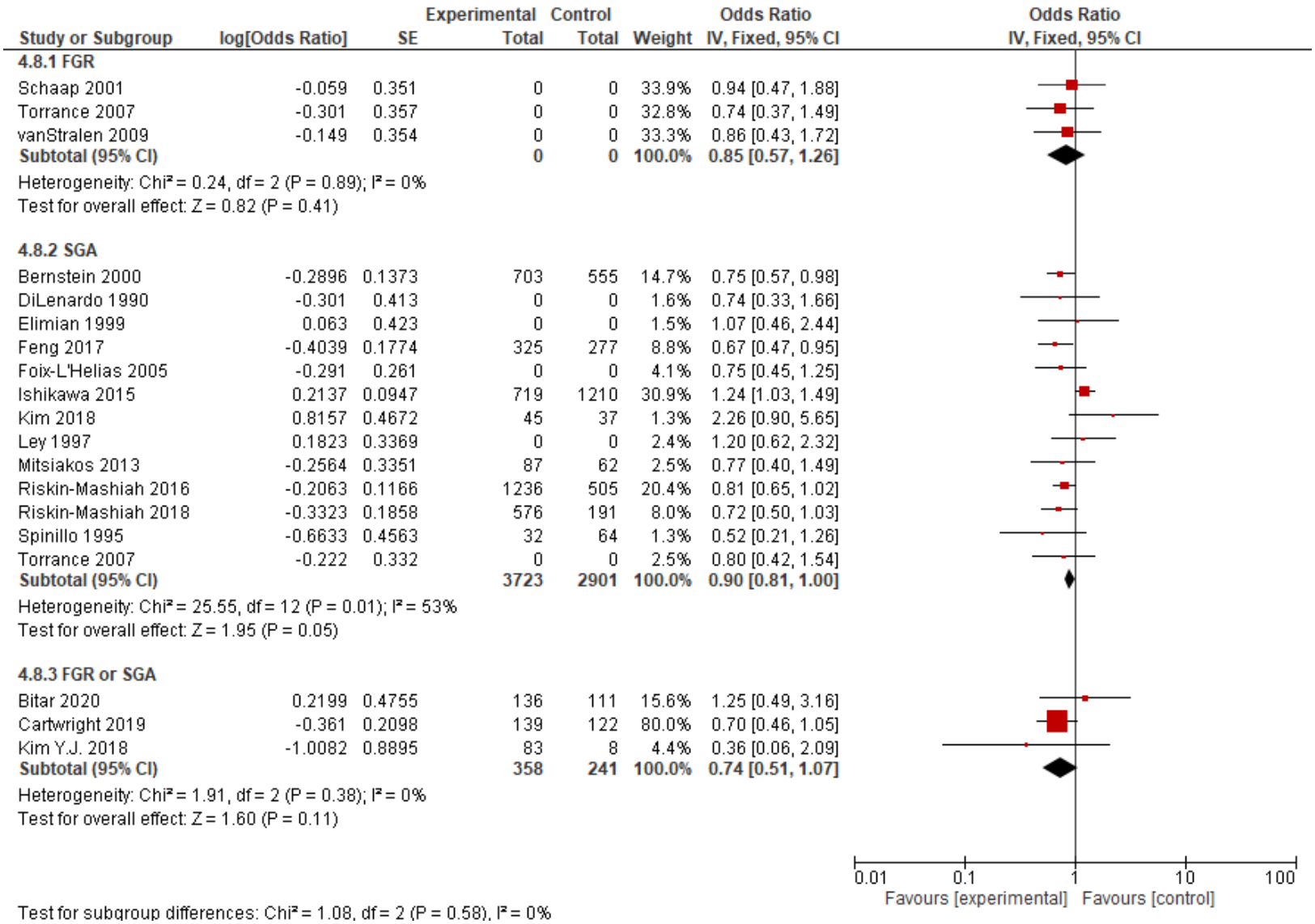
8) Death before discharge home

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
4.7.1 FGR						
Schaap 2001	-0.631	0.4668	62	62	9.3%	0.53 [0.21, 1.33]
Subtotal (95% CI)			**62**	**62**	**9.3%**	**0.53 [0.21, 1.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
4.7.2 SGA						
Bernstein 2000	-0.6335	0.158	685	554	26.4%	0.53 [0.39, 0.72]
Foix-L'Helias 2005	-0.6696	0.4493	96	55	9.9%	0.51 [0.21, 1.23]
Ishikawa 2015	0.0261	0.1764	719	1210	24.9%	1.03 [0.73, 1.45]
Riskin-Mashiah 2016	-0.6881	0.1178	1246	525	29.5%	0.50 [0.40, 0.63]
Subtotal (95% CI)			**2746**	**2344**	**90.7%**	**0.62 [0.43, 0.90]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.25$, df = 3 (P = 0.007); $I^2 = 76\%$						
Test for overall effect: Z = 2.54 (P = 0.01)						
Total (95% CI)			**2808**	**2406**	**100.0%**	**0.61 [0.44, 0.85]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 12.30$, df = 4 (P = 0.02); $I^2 = 67\%$						
Test for overall effect: Z = 2.92 (P = 0.003)						
Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$						



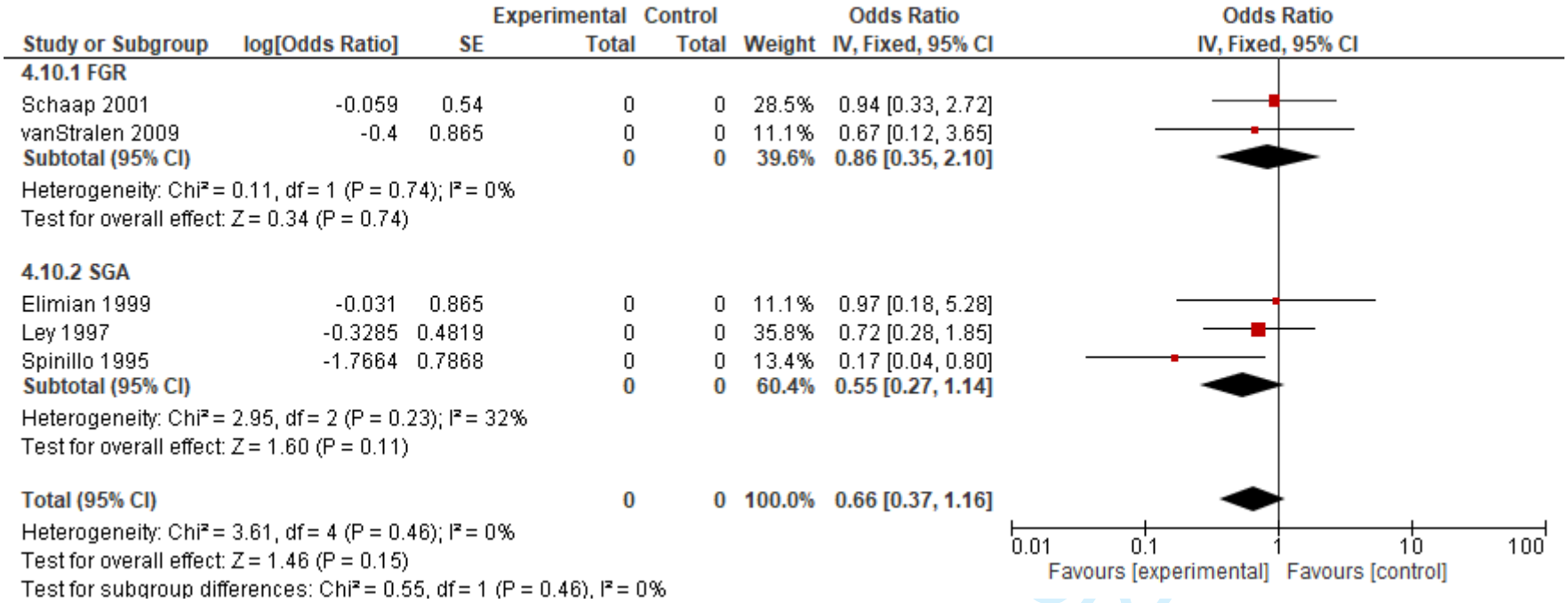
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

9) Respiratory distress syndrome (RDS)


Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup
log[Odds Ratio]
SE
Total
Total
Weight
IV, Fixed, 95% CI
IV, Fixed, 95% CI
4.8.1 FGR
Schaap 2001 -0.059 0.351 0 0 33.9% 0.94 [0.47, 1.88]
Torrance 2007 -0.301 0.357 0 0 32.8% 0.74 [0.37, 1.49]
vanStralen 2009 -0.149 0.354 0 0 33.3% 0.86 [0.43, 1.72]
Subtotal (95% CI) 0 0 100.0% 0.85 [0.57, 1.26]
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
4.8.2 SGA
Bernstein 2000 -0.2896 0.1373 703 555 14.7% 0.75 [0.57, 0.98]
DiLenardo 1990 -0.301 0.413 0 0 1.6% 0.74 [0.33, 1.66]
Elimian 1999 0.063 0.423 0 0 1.5% 1.07 [0.46, 2.44]
Feng 2017 -0.4039 0.1774 325 277 8.8% 0.67 [0.47, 0.95]
Foix-L'Helias 2005 -0.291 0.261 0 0 4.1% 0.75 [0.45, 1.25]
Ishikawa 2015 0.2137 0.0947 719 1210 30.9% 1.24 [1.03, 1.49]
Kim 2018 0.8157 0.4672 45 37 1.3% 2.26 [0.90, 5.65]
Ley 1997 0.1823 0.3369 0 0 2.4% 1.20 [0.62, 2.32]
Mitsiakos 2013 -0.2564 0.3351 87 62 2.5% 0.77 [0.40, 1.49]
Riskin-Mashiah 2016 -0.2063 0.1166 1236 505 20.4% 0.81 [0.65, 1.02]
Riskin-Mashiah 2018 -0.3323 0.1858 576 191 8.0% 0.72 [0.50, 1.03]
Spinillo 1995 -0.6633 0.4563 32 64 1.3% 0.52 [0.21, 1.26]
Torrance 2007 -0.222 0.332 0 0 2.5% 0.80 [0.42, 1.54]
Subtotal (95% CI) 3723 2901 100.0% 0.90 [0.81, 1.00]
Heterogeneity: Chi² = 25.55, df = 12 (P = 0.01); I² = 53%
Test for overall effect: Z = 1.95 (P = 0.05)
4.8.3 FGR or SGA
Bitar 2020 0.2199 0.4755 136 111 15.6% 1.25 [0.49, 3.16]
Cartwright 2019 -0.361 0.2098 139 122 80.0% 0.70 [0.46, 1.05]
Kim Y.J. 2018 -1.0082 0.8895 83 8 4.4% 0.36 [0.06, 2.09]
Subtotal (95% CI) 358 241 100.0% 0.74 [0.51, 1.07]
Heterogeneity: Chi² = 1.91, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Chi² = 1.08, df = 2 (P = 0.58), I² = 0%
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

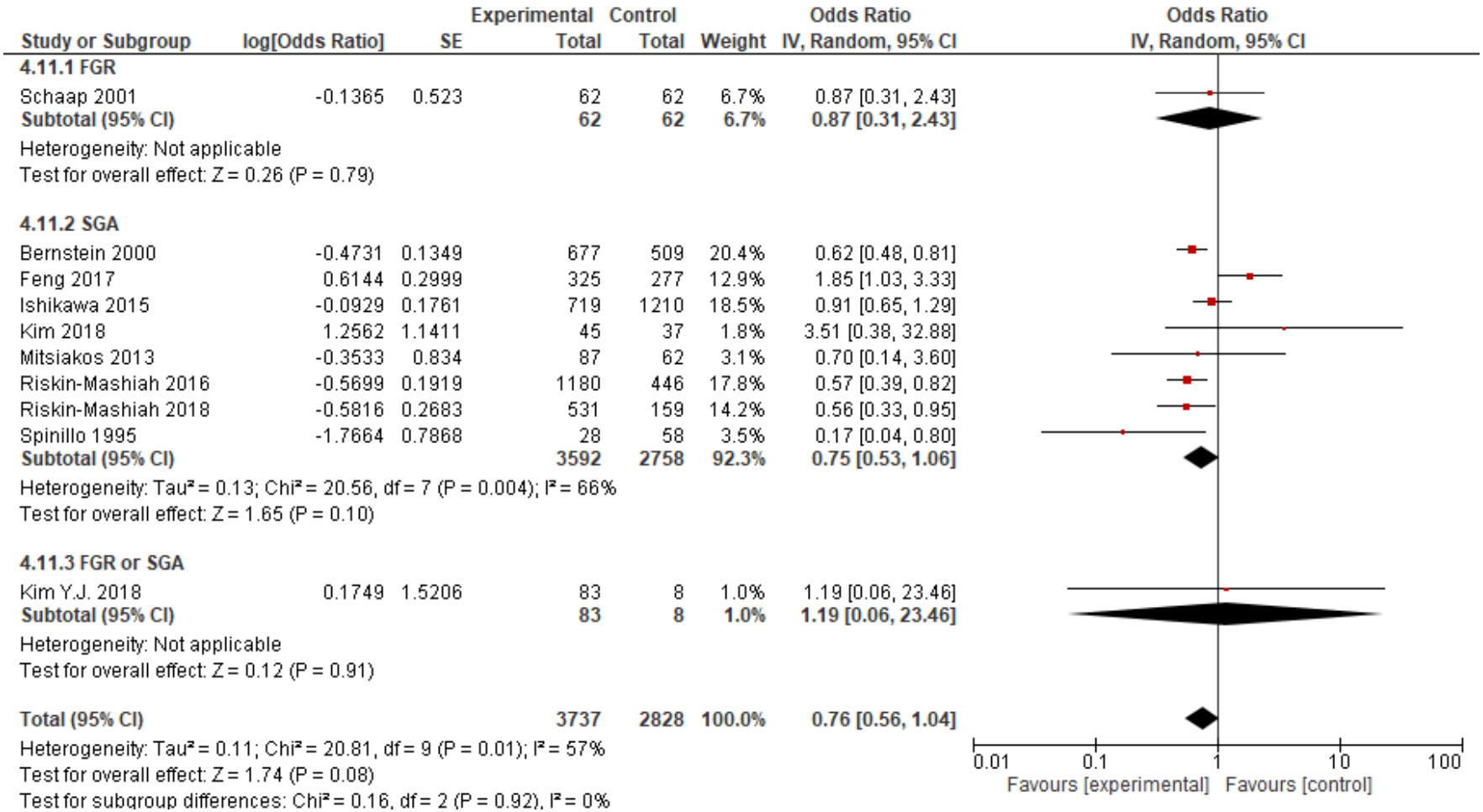
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

10) Major brain lesion (IVH, ICH, PVH, PVL)



IVH: Intraventricular hemorrhage; **ICH**: Intracranial hemorrhage; **PVH**: Periventricular hemorrhage; **PVL**: Periventricular leukomalacia; **SE:** Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

11) Intraventricular hemorrhage (IVH)

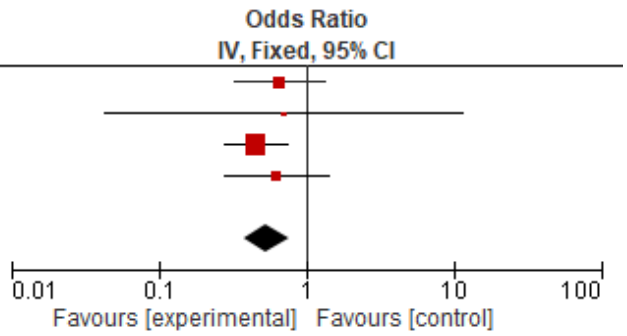


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

12) Periventricular leukomalacia (PVL) (SGA)

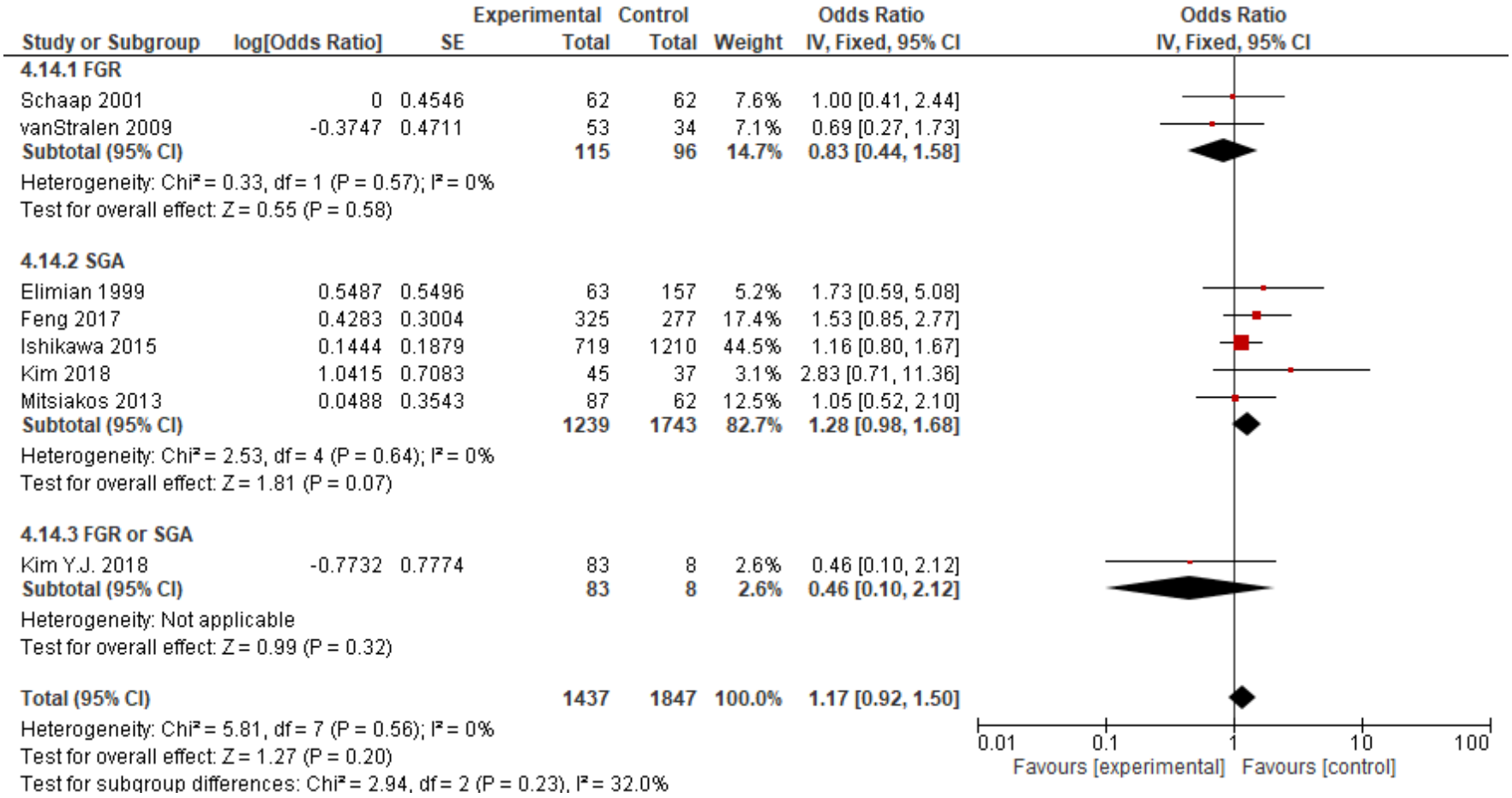
Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ishikawa 2015	-0.4218	0.359	719	1210	25.6%	0.66 [0.32, 1.33]
Mitsiakos 2013	-0.3435	1.4241	87	62	1.6%	0.71 [0.04, 11.56]
Riskin-Mashiah 2016	-0.7862	0.2489	992	347	53.3%	0.46 [0.28, 0.74]
Riskin-Mashiah 2018	-0.462	0.4129	421	117	19.4%	0.63 [0.28, 1.42]
Total (95% CI)			**2219**	**1736**	**100.0%**	**0.54 [0.38, 0.77]**

Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)



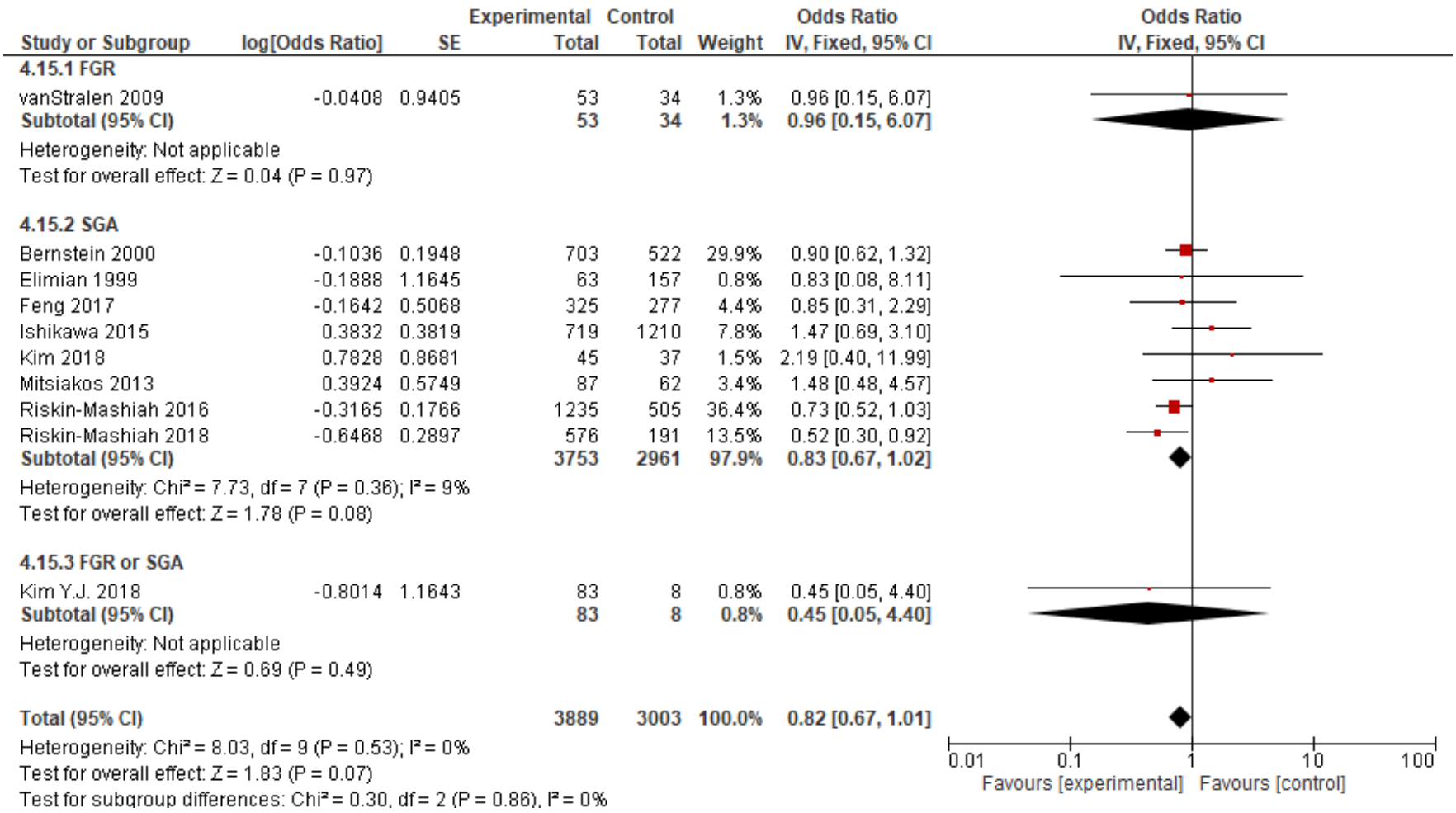
SE: Standard error; **CI**: Confidence interval; **SGA**: Small for gestational age

13) Neonatal sepsis



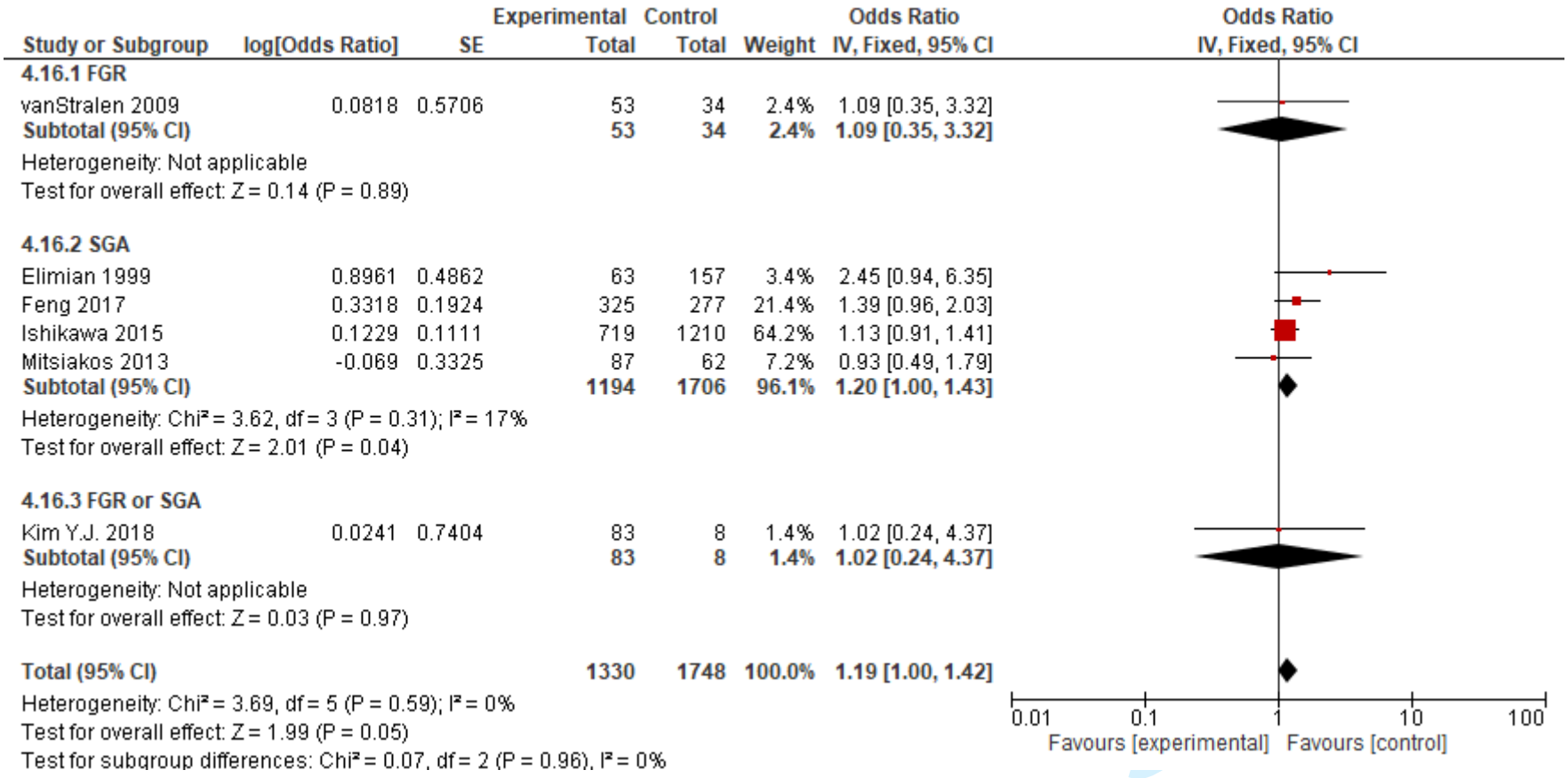
SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

14) Necrotizing enterocolitis (NEC)



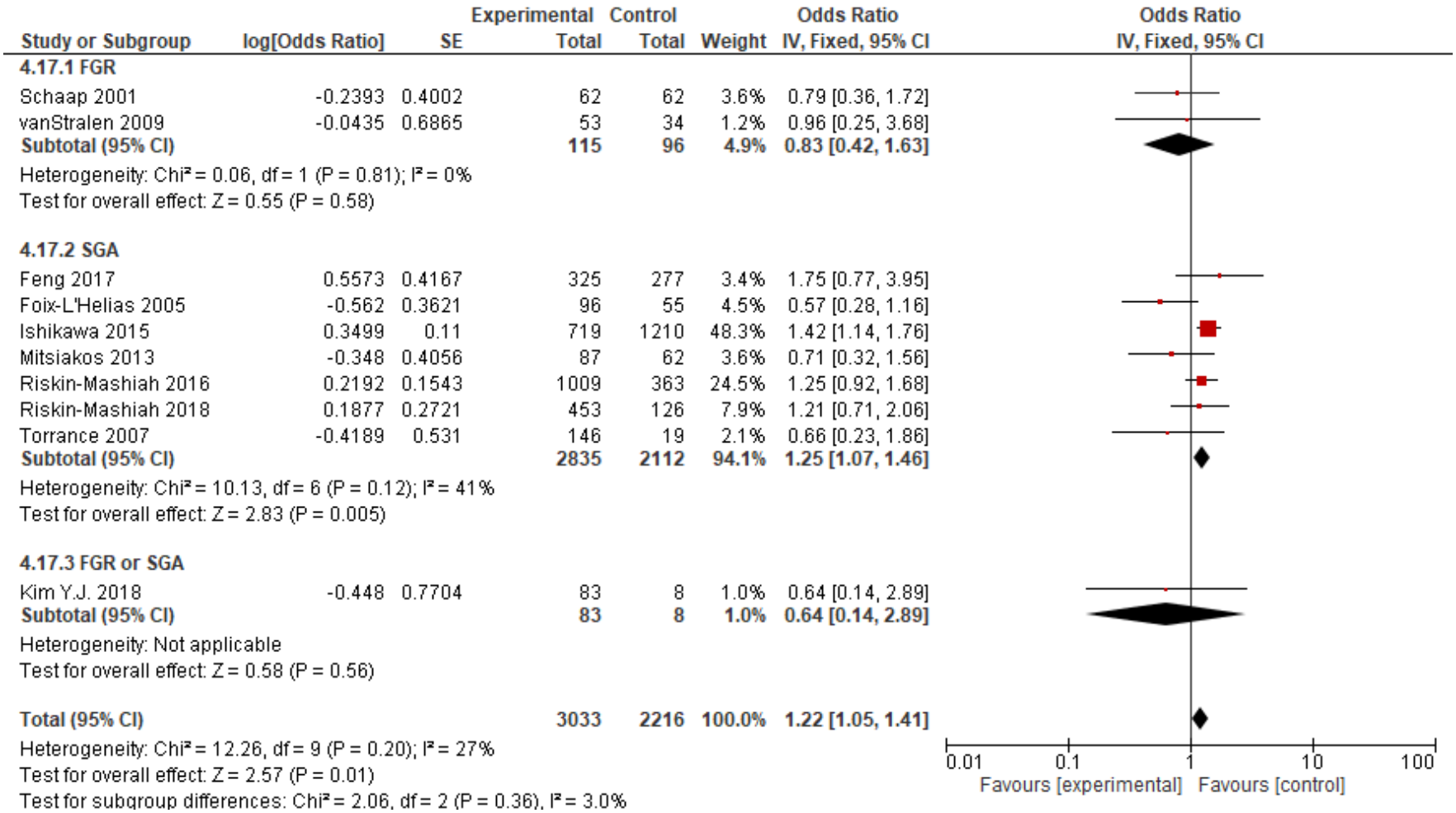
SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

15) Patent ductus arteriosus (PDA)



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

16) Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)

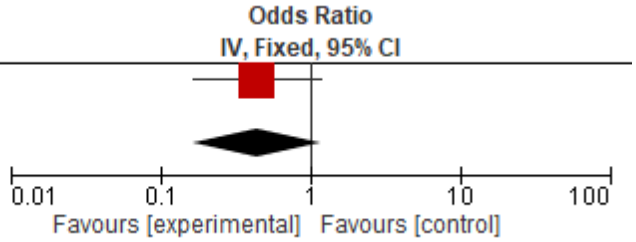


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

17) Small for Gestational age (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Torrance 2007	-0.8147	0.5041	146	19	100.0%	0.44 [0.16, 1.19]
Total (95% CI)			**146**	**19**	**100.0%**	**0.44 [0.16, 1.19]**

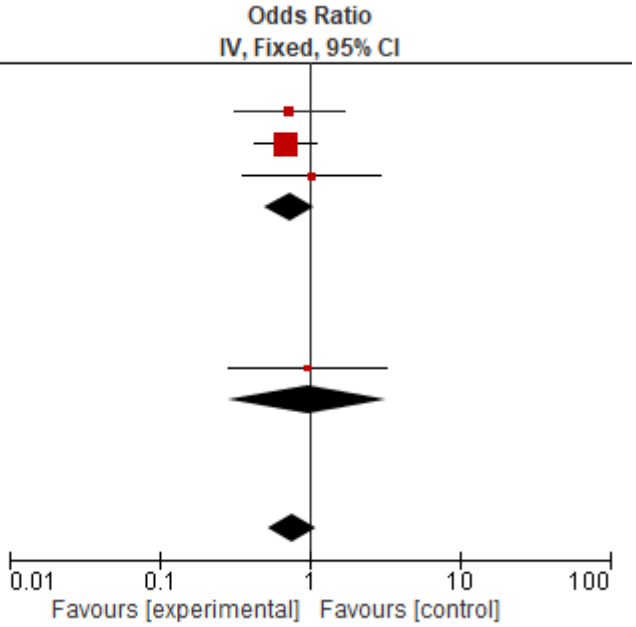
Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.11)



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

18) Apgar score < 7 at 5 minutes

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.21.1 SGA						
Elimian 1999	-0.3108	0.4351	63	157	18.5%	0.73 [0.31, 1.72]
Feng 2017	-0.3579	0.2409	325	277	60.3%	0.70 [0.44, 1.12]
Kim 2018	0.0351	0.5367	45	37	12.1%	1.04 [0.36, 2.97]
Subtotal (95% CI)			**433**	**471**	**90.9%**	**0.74 [0.51, 1.09]**
Heterogeneity: Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.51 (P = 0.13)						
4.21.2 FGR or SGA						
Bitar 2020	-0.0218	0.6195	136	111	9.1%	0.98 [0.29, 3.29]
Subtotal (95% CI)			**136**	**111**	**9.1%**	**0.98 [0.29, 3.29]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
Total (95% CI)			**569**	**582**	**100.0%**	**0.76 [0.53, 1.10]**
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						

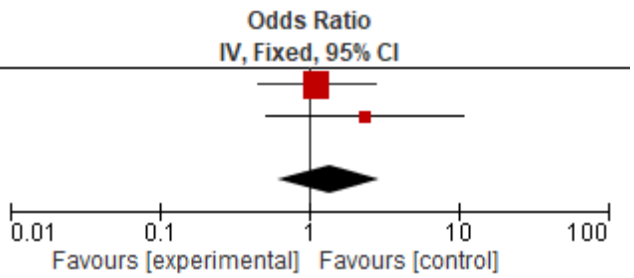


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

19) Apgar score < 5 at 1 minute (SGA)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Kim 2018	0.1141	0.4617	45	37	73.8%	1.12 [0.45, 2.77]
Torrance 2007	0.8696	0.7739	146	19	26.2%	2.39 [0.52, 10.87]
Total (95% CI)			**191**	**56**	**100.0%**	**1.37 [0.63, 2.97]**

Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.79 (P = 0.43)

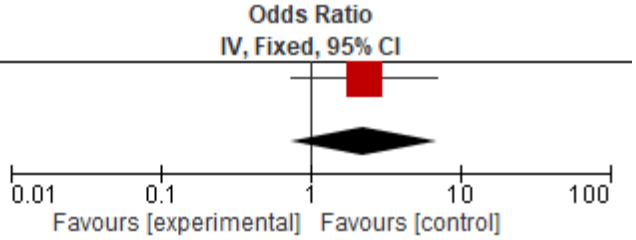


SE: Standard error; **CI**: Confidence interval; **SGA**: Small for gestational age

20) Hypotension (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
vanStralen 2009	0.8283	0.5722	53	34	100.0%	2.29 [0.75, 7.03]
Total (95% CI)			**53**	**34**	**100.0%**	**2.29 [0.75, 7.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

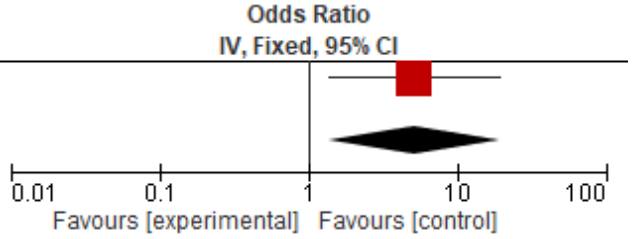


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

21) Growth < 10th percentile in early childhood (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Schaap 2001	1.6487	0.6775	49	42	100.0%	5.20 [1.38, 19.62]
Total (95% CI)			**49**	**42**	**100.0%**	**5.20 [1.38, 19.62]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.01)

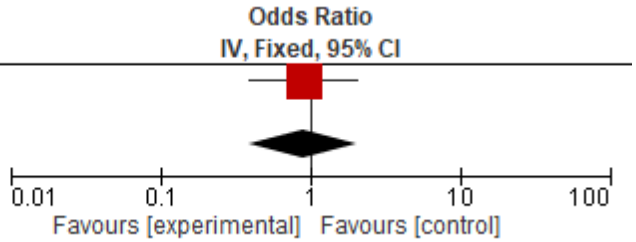


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

22) Abnormal behavior at long-term follow-up at school age (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Schaap 2001	-0.0966	0.4236	49	42	100.0%	0.91 [0.40, 2.08]
Total (95% CI)			**49**	**42**	**100.0%**	**0.91 [0.40, 2.08]**

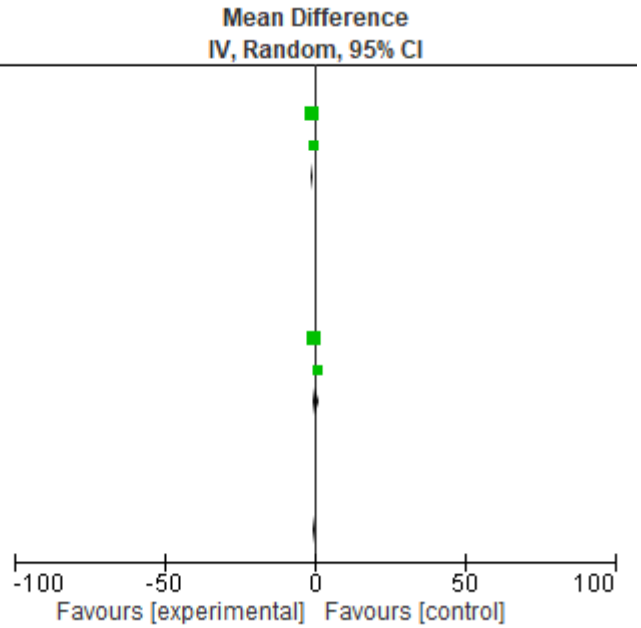
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

23) Gestational age at birth

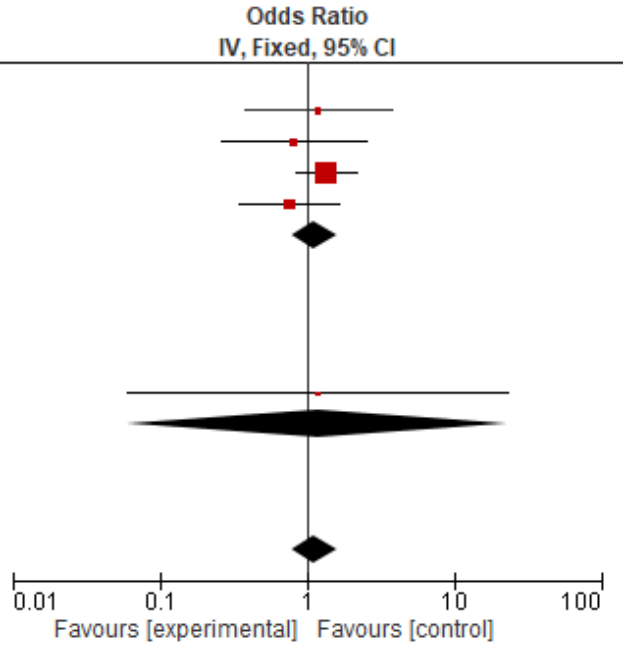
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.28.1 SGA								
Ishikawa 2015	29.1	2.6	719	29.7	2.7	1210	30.7%	-0.60 [-0.84, -0.36]
Mitsiakos 2013	27.5	2.5	87	27.8	2.5	62	18.3%	-0.30 [-1.11, 0.51]
Subtotal (95% CI)			**806**			**1272**	**49.0%**	**-0.58 [-0.81, -0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%								
Test for overall effect: Z = 4.84 (P < 0.00001)								
4.28.2 FGR or SGA								
Bitar 2020	35.4	0.71	136	35.4	0.79	111	31.5%	0.00 [-0.19, 0.19]
Cartwright 2019	32.2	3.2	139	31.2	3	122	19.5%	1.00 [0.25, 1.75]
Subtotal (95% CI)			**275**			**233**	**51.0%**	**0.43 [-0.54, 1.40]**
Heterogeneity: Tau² = 0.42; Chi² = 6.38, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Total (95% CI)			**1081**			**1505**	**100.0%**	**-0.04 [-0.57, 0.48]**
Heterogeneity: Tau² = 0.22; Chi² = 24.43, df = 3 (P < 0.0001); I² = 88%								
Test for overall effect: Z = 0.16 (P = 0.87)								
Test for subgroup differences: Chi² = 3.90, df = 1 (P = 0.05), I² = 74.4%								



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

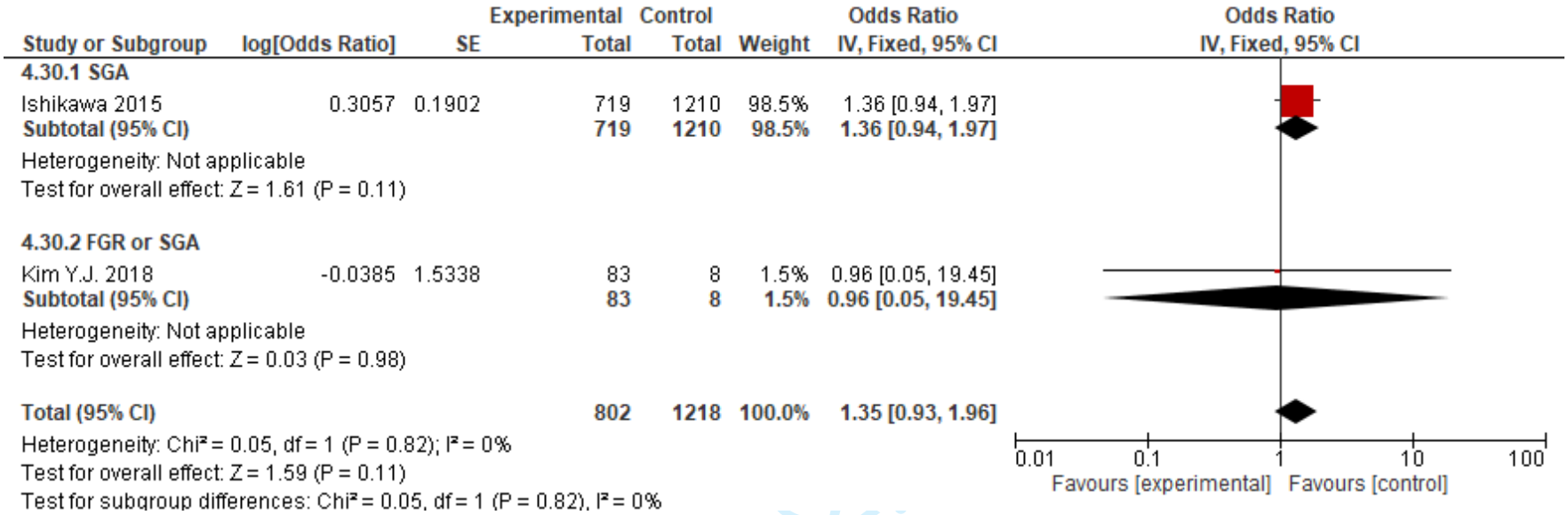
24) Retinopathy of prematurity

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
4.29.1 SGA						
Feng 2017	0.1802	0.5913	325	277	9.5%	1.20 [0.38, 3.82]
Mitsiakos 2013	-0.2025	0.583	87	62	9.8%	0.82 [0.26, 2.56]
Riskin-Mashiah 2016	0.3019	0.2383	1030	363	58.6%	1.35 [0.85, 2.16]
Riskin-Mashiah 2018	-0.2685	0.401	453	122	20.7%	0.76 [0.35, 1.68]
Subtotal (95% CI)			**1895**	**824**	**98.6%**	**1.13 [0.79, 1.62]**
Heterogeneity: Chi² = 1.84, df = 3 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
4.29.2 FGR or SGA						
Kim Y.J. 2018	0.1749	1.5206	83	8	1.4%	1.19 [0.06, 23.46]
Subtotal (95% CI)			**83**	**8**	**1.4%**	**1.19 [0.06, 23.46]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.91)						
Total (95% CI)			**1978**	**832**	**100.0%**	**1.13 [0.79, 1.61]**
Heterogeneity: Chi² = 1.84, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						



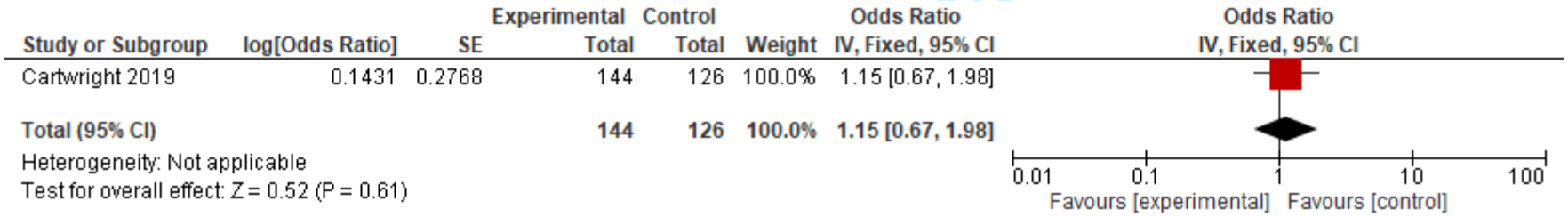
SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

25) Neonatal adrenal insufficiency



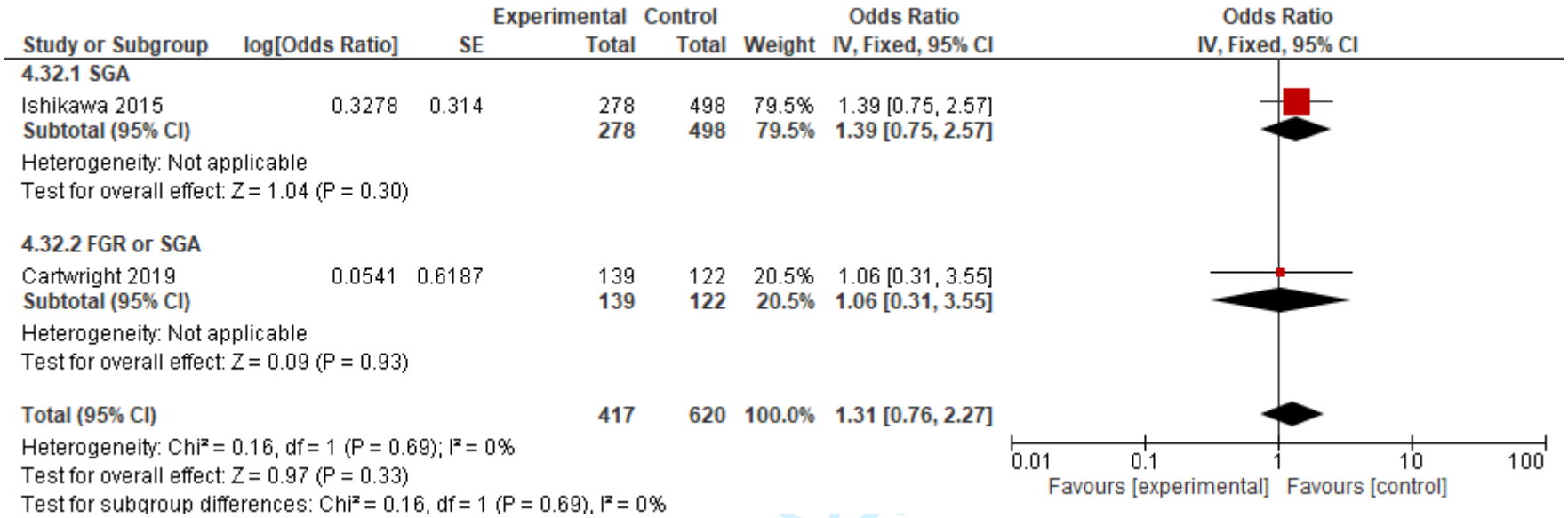
SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

26) Survival free of disability (FGR or SGA)



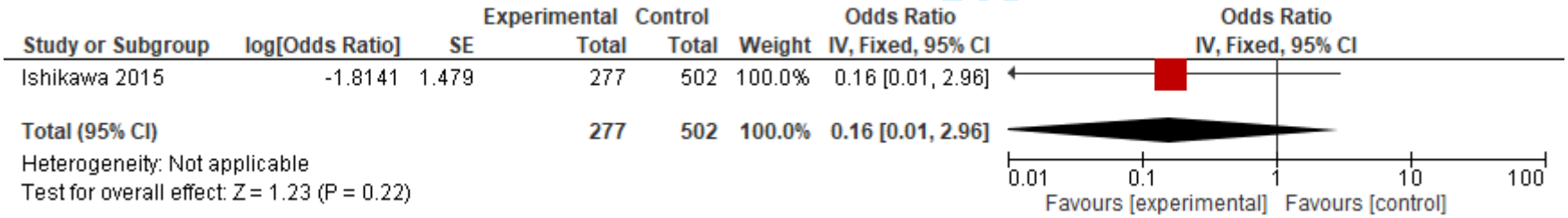
SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

27) Cerebral palsy



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

28) Severe hearing impairment (SGA)

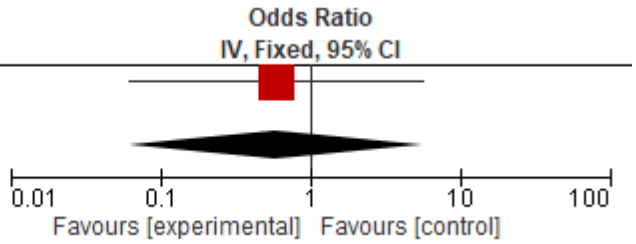


SE: Standard error; **CI**: Confidence interval; **SGA**: Small for gestational age

29) Visual impairment (SGA)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Ishikawa 2015	-0.5235	1.1572	275	490	100.0%	0.59 [0.06, 5.72]
Total (95% CI)			**275**	**490**	**100.0%**	**0.59 [0.06, 5.72]**

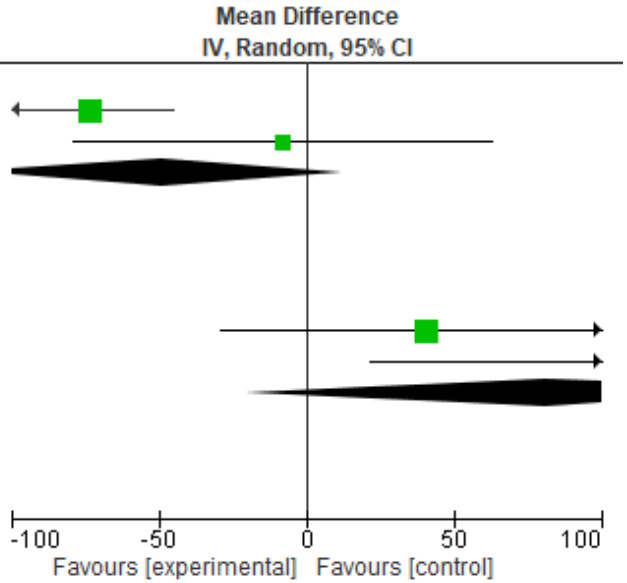
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)



SE: Standard error; **CI**: Confidence interval; **SGA**: Small for gestational age

30) Birth weight

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.35.1 SGA								
Ishikawa 2015	886	298	719	959	313	1210	63.2%	-73.00 [-101.03, -44.97]
Mitsiakos 2013	779	220	87	787	218	62	36.8%	-8.00 [-79.29, 63.29]
Subtotal (95% CI)			**806**			**1272**	**100.0%**	**-49.10 [-110.53, 12.32]**
Heterogeneity: Tau² = 1348.84; Chi² = 2.77, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 1.57 (P = 0.12)								
4.35.2 FGR or SGA								
Bitar 2020	2,061.7	273.9	136	2,020.7	281.7	111	62.6%	41.00 [-28.75, 110.75]
Cartwright 2019	1,476	519	139	1,328	521	122	37.4%	148.00 [21.54, 274.46]
Subtotal (95% CI)			**275**			**233**	**100.0%**	**80.97 [-20.48, 182.41]**
Heterogeneity: Tau² = 3009.84; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%								
Test for overall effect: Z = 1.56 (P = 0.12)								
Test for subgroup differences: Chi² = 4.62, df = 1 (P = 0.03), I² = 78.4%								

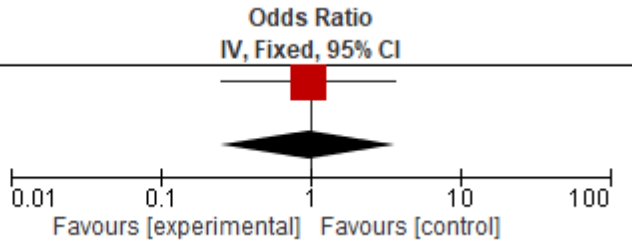


SD: Standard Deviation; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

31) Admission to neonatal intensive care unit (NICU) (FGR or SGA)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Bitar 2020	-0.0208	0.6834	136	111	100.0%	0.98 [0.26, 3.74]
Total (95% CI)			**136**	**111**	**100.0%**	**0.98 [0.26, 3.74]**

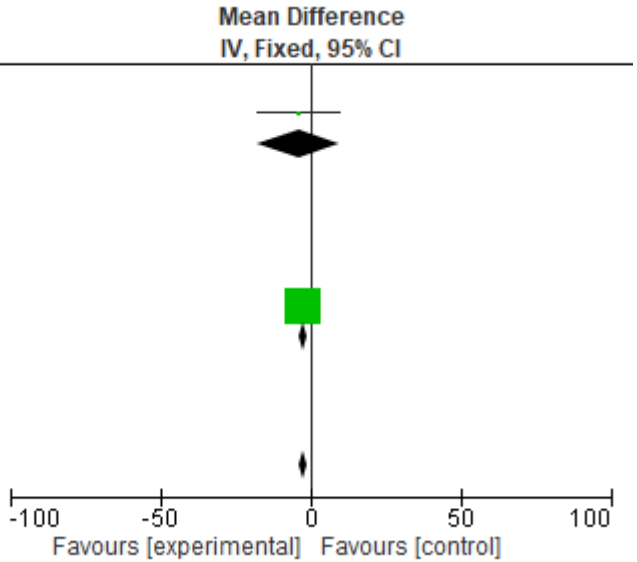
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction; **SGA**: Small for gestational age

32) Duration to hospital stay, days

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.37.1 SGA								
Mitsiakos 2013	87	40.7	87	91	41.6	62	1.2%	-4.00 [-17.43, 9.43]
Subtotal (95% CI)			**87**			**62**	**1.2%**	**-4.00 [-17.43, 9.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.58 (P = 0.56)								
4.37.2 FGR or SGA								
Bitar 2020	13.7	8.8	136	16	1.41	111	98.8%	-2.30 [-3.80, -0.80]
Subtotal (95% CI)			**136**			**111**	**98.8%**	**-2.30 [-3.80, -0.80]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.00 (P = 0.003)								
Total (95% CI)			**223**			**173**	**100.0%**	**-2.32 [-3.81, -0.83]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%								
Test for overall effect: Z = 3.05 (P = 0.002)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								

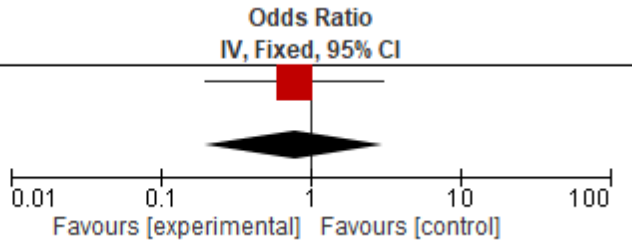


SD: Standard Deviation; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

33) Death at long-term follow-up (School age) (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Schaap 2001	-0.2405	0.6963	62	62	100.0%	0.79 [0.20, 3.08]
Total (95% CI)			**62**	**62**	**100.0%**	**0.79 [0.20, 3.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

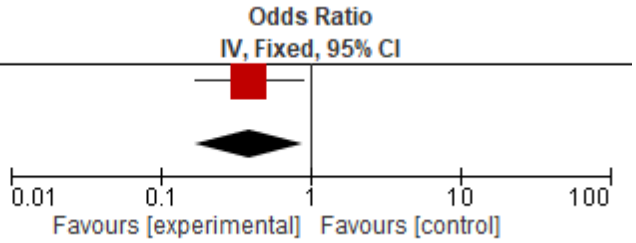


SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

34) Death or disability/handicap at 2years collected age (FGR)

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Schaap 2001	-0.9361	0.4254	62	62	100.0%	0.39 [0.17, 0.90]
Total (95% CI)			**62**	**62**	**100.0%**	**0.39 [0.17, 0.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)



SE: Standard error; **CI**: Confidence interval; **FGR**: Fetus growth restriction

Supplementary File S8: 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: 5 studies: 2 in the USA, 2 in New Zealand, 1 in Israel

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with PGDM	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death within 48 hours of birth												
1	observational studies	not serious	not serious	not serious	serious [c]	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 < 7 at 5 minutes												
1	observational studies	not serious	not serious	not serious	serious [c]	none	1/129 (0.8%)	21/2133 (1.0%)	**OR 0.79** (0.10 to 5.89)	**2 fewer per 1,000** (from 9 fewer to 45 more)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (RDS) and moderate/severe RDS												
3	observational studies	not serious	serious [b]	not serious	serious [c]	none	179/695 (25.8%)	39/2242 (1.7%)	**OR 2.03** (0.60 to 6.85)	**17 more per 1,000** (from 7 fewer to 91 more)	⨁◯◯◯ VERY LOW	
Neonatal hypoglycemia												
3	observational studies	serious [a]	not serious	not serious	serious [c]	none	32/177 (18.1%)	77/2199 (3.5%)	**OR 1.74** (0.96 to 3.16)	**24 more per 1,000** (from 1 fewer to 68 more)	⨁◯◯◯ VERY LOW	
Admission to neonatal intensive care unit												
1	observational studies	not serious	not serious	not serious	not serious	none	51/129 (39.5%)	173/2133 (8.1%)	**OR 7.41** (5.04 to 10.89)	**314 more per 1,000** (from 227 more to 409 more)	⨁⨁◯◯ LOW	
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

CI: Confidence interval; **OR:** Odds ratio; **PGDM:** Pregestational diabetes mellitus

Explanations

a. Confounding factors are high risk of bias.
b. Heterogeneity is high (I-square ≥ 60%).
c. Estimate based on wide confidence interval crossing the line of no effect.

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							№ of patients		Effect		Certainty	Importance
№ 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	serious [a]	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	
Respiratory distress syndrome												
2	observational studies	not serious	not serious	not serious	very serious [a]	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	
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Use of mechanical ventilation												
2	observational studies	not serious	not serious	not serious	very serious [a]	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	
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Admission to neonatal intensive care unit												
2	observational studies	not serious	not serious	not serious	very serious	none	10/88 (11.4%)	14/117 (12.0%)	**OR 0.73** (0.26 to 2.05)	**29 fewer per 1,000** (from 86 fewer to 98 more)	⨁◯◯◯ VERY LOW	
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Neonatal hypoglycemia												
2	observational studies	not serious	not serious	not serious	very serious [a]	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 hemorrhage												
1	observational studies	not serious	not serious	not serious	very serious [a]	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	
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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)		
Necrotizing enterocolitis												
1	observational studies	not serious	not serious	not serious	very serious [a]	none	0/58 (0.0%)	1/107 (0.9%) 0.0%	**OR 0.61** (0.02 to 15.13)	**4 fewer per 1,000** (from 9 fewer to 116 more) **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Apgar score ≥ 7 at 5 minutes												
1	observational studies	not serious	not serious	not serious	very serious [a]	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, days												
1	observational studies	serious [c]	not serious	not serious	very serious [a]	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]	none	13/58 (22.4%)	25/107 (23.4%) 0.0%	**OR 0.95** (0.44 to 2.03)	**9 fewer per 1,000** (from 115 fewer to 149 more) **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **CS:** Cesarean section

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 study contributing data had design limitations.

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							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
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	serious [c]	not serious	not serious	not serious	Strong association	63/677 (9.3%)	87/516 (16.9%)	**OR 0.49** (0.33 to 0.74)	**78 fewer per 1,000** (from 106 fewer to 38 fewer)	⨁⨁◯◯ LOW	
Neonatal death (CC)												
2	observational studies	serious [c]	not serious	not serious	very serious [a,b]	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	serious [c]	not serious	not serious	very serious [a,b]	none	3/40 (7.5%)	1/17 (5.9%)	**OR 1.30** (0.13 to 13.44)	**16 more per 1,000** (from 51 fewer to 398 more)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (HC)												
6	observational studies	serious [c]	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)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (CC)												
4	observational studies	serious [c]	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	
Severe respiratory distress syndrome (HC)												
1	observational studies	serious [c]	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	
Pneumonia (HC)												
1	observational studies	serious [c]	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	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Surfactant use (HC)												
3	observational studies	serious [c]	serious [d]	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 hemorrhage (grades 3–4) (HC)												
4	observational studies	serious [c]	not serious	not serious	not serious	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)	⨁⨁◯◯ LOW	
Severe interventricular hemorrhage (grades 3–4) (CC)												
3	observational studies	serious [c]	not serious	not serious	serious [a]	none	5/163 (3.1%)	14/155 (9.0%)	**OR 0.28** (0.06 to 1.31)	**63 fewer per 1,000** (from 84 fewer to 25 more)	⨁◯◯◯ VERY LOW	
Intraventricular hemorrhage (HC)												
5	observational studies	serious [c]	not serious	not serious	not serious	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 hemorrhage (CC)												
3	observational studies	serious [c]	not serious	not serious	not serious	Strong association	13/163 (8.0%)	20/155 (12.9%)	**OR 0.39** (0.15 to 0.99)	**74 fewer per 1,000** (from 107 fewer to 1 fewer)	⨁⨁◯◯ LOW	
Early-onset sepsis (HC)												
4	observational studies	serious [c]	not serious	not serious	serious [a]	none	29/326 (8.9%)	9/122 (7.4%)	**OR 0.96** (0.40 to 2.27)	**3 fewer per 1,000** (from 43 fewer to 79 more)	⨁◯◯◯ VERY LOW	
Early-onset sepsis (CC)												
1	observational studies	serious [c]	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	serious [c]	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	serious [c]	not serious	not serious	very serious [a,b]	none	26/104 (25.0%)	12/46 (26.1%)	**OR 0.96** (0.40 to 2.29)	**8 fewer per 1,000** (from 137 fewer to 186 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Systemic inflammatory response syndrome (HC)												
1	observational studies	serious [c]	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	serious [c]	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	
Patent ductus arteriosus (HC)												
4	observational studies	serious [c]	not serious	not serious	not serious	none	109/407 (26.8%)	112/438 (25.6%)	**OR 0.67** (0.47 to 0.98)	**69 fewer per 1,000** (from 117 fewer to 4 fewer)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus (CC)												
1	observational studies	serious [c]	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	serious [c]	not serious	not serious	not serious	none	75/420 (17.9%)	30/116 (25.9%)	**OR 0.55** (0.32 to 0.93)	**98 fewer per 1,000** (from 158 fewer to 14 fewer)	⨁◯◯◯ VERY LOW	
Chronic lung disease/Bronchopulmonary dysplasia (CC)												
3	observational studies	serious [c]	not serious	not serious	very serious [a,b]	none	25/142 (17.6%)	16/90 (17.8%)	**OR 0.91** (0.44 to 1.86)	**13 fewer per 1,000** (from 91 fewer to 109 more)	⨁◯◯◯ VERY LOW	
Periventricular leukomalacia (HC)												
4	observational studies	serious [c]	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	serious [c]	not serious	not serious	not serious	Strong association	8/163 (4.9%)	24/155 (15.5%)	**OR 0.30** (0.11 to 0.86)	**103 fewer per 1,000** (from 135 fewer to 19 fewer)	⨁⨁◯◯ LOW	
Meningitis (HC)												
1	observational studies	serious [c]	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	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean duration of mechanical ventilation, days (HC)												
1	observational studies	serious [c]	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	serious [c]	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	serious [c]	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	serious [c]	not serious	not serious	not serious	none	31/169 (18.3%)	120/358 (33.5%)	**OR 0.45** (0.28 to 0.70)	**150 fewer per 1,000** (from 211 fewer to 74 fewer)	⨁◯◯◯ VERY LOW	
Use of mechanical ventilation (HC)												
1	observational studies	serious [c]	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	serious [c]	not serious	not serious	serious [b]	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 0 fewer)	⨁◯◯◯ VERY LOW	
Duration of oxygen use, days (HC)												
1	observational studies	serious [c]	not serious	not serious	serious [b]	none	52	36	-	MD **9 higher** (5.66 higher to 12.34 higher)	⨁◯◯◯ VERY LOW	
Hypotension within 7 postnatal days (HC)												
1	observational studies	not serious	not serious	not serious	serious [b]	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	
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	
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	
Intrahepatic cholestasis (HC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with chorioamnionitis	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [c]	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	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

Explanations

a. Estimate based on wide confidence interval crossing the line of no effect.
b. Estimate based on small sample size.
c. Confounding factors are high risk of bias.
d. 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: 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							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis (histologic and/or clinical) (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	63/702 (9.0%)	83/1094 (7.6%)	**OR 1.42** (0.99 to 2.03)	**29 more per 1,000** (from 1 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Preeclampsia (SGA)												
2	observational studies	serious [a]	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	
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	[e]	[e]	**OR 0.61** (0.49 to 0.78)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	
Death before discharge home (SGA)												
3	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	308/2061 (14.9%)	273/1790 (15.3%)	**OR 0.66** (0.38 to 1.16)	**46 fewer per 1,000** (from 89 fewer to 20 more)	⨁◯◯◯ VERY LOW	
Respiratory distress syndrome (RDS) and moderate/severe RDS (SGA)												
12	observational studies	serious [a]	not serious	not serious	not serious	none	[e]	[e]	**OR 0.93** (0.83 to 1.04)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	
Surfactant use (SGA)												
2	observational studies	serious [a]	not serious	not serious	serious [b]	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, or PVL) (SGA)												
3	observational studies	not serious	not serious	not serious	very serious [b,c]	none	[e]	[e]	**OR 0.55** (0.27 to 1.14)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Interventricular hemorrhage (SGA)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
7	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	241/2915 (8.3%)	225/2249 (10.0%)	**OR 0.78** (0.50 to 1.23)	**20 fewer per 1,000** (from 47 fewer to 20 more)	⨁◯◯◯ VERY LOW	
Severe interventricular hemorrhage (grades 3–4) (SGA)												
6	observational studies	not serious	not serious	not serious	not serious	none	143/2196 (6.5%)	99/1039 (9.5%)	**OR 0.60** (0.45 to 0.80)	**36 fewer per 1,000** (from 50 fewer to 18 fewer)	⨁⨁◯◯ LOW	
Periventricular leukomalacia (SGA)												
4	observational studies	serious [a]	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	serious [a]	not serious	not serious	serious [b]	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)												
7	observational studies	serious [a]	not serious	not serious	serious [b]	none	173/3050 (5.7%)	109/2439 (4.5%)	**OR 0.79** (0.62 to 1.02)	**9 fewer per 1,000** (from 17 fewer to 1 more)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	315/1194 (26.4%)	368/1706 (21.6%)	**OR 1.20** (1.00 to 1.43)	**32 more per 1,000** (from 0 fewer to 67 more)	⨁◯◯◯ VERY LOW	
Chronic lung disease/bronchopulmonary dysplasia (SGA)												
7	observational studies	serious [a]	not serious	not serious	not serious	none	596/2835 (21.0%)	389/2112 (18.4%)	**OR 1.25** (1.07 to 1.46)	**36 more per 1,000** (from 10 more to 64 more)	⨁◯◯◯ VERY LOW	
Use of mechanical ventilation (SGA)												
2	observational studies	not serious	serious [d]	not serious	very serious [b,c]	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)												
4	observational studies	not serious	not serious	not serious	serious [b]	none	59/579 (10.2%)	77/490 (15.7%)	**OR 0.75** (0.51 to 1.10)	**34 fewer per 1,000** (from 70 fewer to 13 more)	⨁◯◯◯ VERY LOW	
Apgar score < 5 at 1 minute (SGA)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	not serious	not serious	not serious	very serious [b,c]	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 [b,c]	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	serious [a]	not serious	not serious	not serious	none	806	1272	-	MD **0.58 lower** (0.81 lower to 0.34 lower)	⨁◯◯◯ VERY LOW	
Retinopathy of prematurity (SGA)												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	130/1895 (6.9%)	44/824 (5.3%)	**OR 1.13** (0.79 to 1.62)	**7 more per 1,000** (from 11 fewer to 30 more)	⨁◯◯◯ VERY LOW	
Neonatal adrenal insufficiency (SGA)												
1	observational studies	serious [a]	not serious	not serious	serious [b]	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	serious [a]	not serious	not serious	serious [b]	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	serious [a]	not serious	not serious	serious [b]	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	serious [a]	not serious	not serious	serious [b]	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 (g) (SGA)												
2	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	806	1272	-	MD **49.1 lower** (110.53 lower to 12.32 higher)	⨁◯◯◯ VERY LOW	
Duration of hospital stay (SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	none	87	62	-	MD **4 lower** (17.43 lower to 9.43 higher)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **SGA:** Small for gestational age; **IVH:** Intraventricular hemorrhage; **ICH;** Intracranial hemorrhage; **PVH:** Periventricular hemorrhage; **PVL:** Periventricular leukomalacia

Explanations

a. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
d. Heterogeneity is high (I-square ≥ 60%.).
e. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

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							№ of patients		Effect		Certainty	Importance
№ 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	serious [a]	not serious	not serious	very serious [b,c]	none	15/199 (7.5%)	20/53 (37.7%)	**OR 0.69** (0.26 to 1.81)	**82 fewer per 1,000** (from 241 fewer to 146 more)	⨁◯◯◯ VERY LOW	
Death before discharge home (FGR)												
1	observational studies	not serious	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	none	[e]	[e]	**OR 0.85** (0.57 to 1.26)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Surfactant use (FGR)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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, or PVL) (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [b,c]	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 more)	⨁◯◯◯ VERY LOW	
Interventricular hemorrhage (FGR)												
1	observational studies	not serious	not serious	not serious	very serious [b,c]	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 hemorrhage (grades 3–4) (FGR)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	very serious [b,c]	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 [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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 [b,c]	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	
Small for gestational age (<2.3rd percentile for gestational age) (FGR)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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	
Duration of mechanical ventilation (FGR)												
2	observational studies	not serious	not serious	not serious	very serious [b,c]	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 [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious [c]	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 [b,c]	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 [b,c]	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 2 years (FGR)												
1	observational studies	not serious	not serious	not serious	serious [c]	none	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 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **FGR:** Fetus growth restriction; **IVH:** Intraventricular hemorrhage; **ICH;** Intracranial hemorrhage; **PVH:** Periventricular hemorrhage; **PVL:** Periventricular leukomalacia

Explanations

a. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
d. Heterogeneity is high (I-square ≥ 60%.).
e. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel
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Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis (histologic and/or clinical) (FGR or SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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	
Gestational diabetes mellitus (FGR or SGA)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	not serious	not serious	not serious	serious [b]	none	14/219 (6.4%)	7/119 (5.9%)	**OR 1.10** (0.43 to 2.86)	**6 more per 1,000** (from 33 fewer to 93 more)	⨁◯◯◯ VERY LOW	
Pregnancy induced hypertension (FGR or SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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 (FGR or SGA)												
3	observational studies	not serious	not serious	not serious	serious [b]	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 hemorrhage (FGR or SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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 hemorrhage (grades 3–4) (FGR or SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patent ductus arteriosus (FGR or SGA)												
1	observational studies	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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 [b,c]	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	serious [a]	not serious	not serious	serious [c]	none	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)	⨁◯◯◯ VERY 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 [d]	not serious	serious [b]	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	serious [a]	not serious	not serious	very serious [b,c]	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	serious [a]	not serious	not serious	very serious [b,c]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	very serious [b,c]	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 [b,c]	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 [b]	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 [b,c]	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 [c]	none	136	111	-	MD **2.3 lower** (3.8 lower to 0.8 lower)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

Explanations

a. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
d. Heterogeneity is high (I-square ≥ 60%.).
e. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Chorioamnionitis (histologic and/or clinical) (total)												
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	82/785 (10.4%)	85/1102 (7.7%)	**OR 1.39** (0.98 to 1.97)	**27 more per 1,000** (from 1 fewer to 64 more)	⨁◯◯◯ VERY LOW	
Preeclampsia (total)												
4	observational studies	not serious	serious [d]	not serious	serious [b]	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	
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)												
4	observational studies	serious [a]	serious [d]	not serious	serious [b]	none	317/2123 (14.9%)	288/1852 (15.6%)	**OR 0.64** (0.40 to 1.02)	**50 fewer per 1,000** (from 87 fewer to 3 more)	⨁◯◯◯ VERY LOW	
Major brain lesion (IVH, ICH, PVH, or PVL) (total)												
5	observational studies	not serious	not serious	not serious	very serious [b,c]	none	[e]	[e]	**OR 0.66** (0.37 to 1.16)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Interventricular hemorrhage (total)												
9	observational studies	serious [a]	not serious	not serious	serious [b]	none	254/3060 (8.3%)	234/2319 (10.1%)	**OR 0.80** (0.54 to 1.19)	**19 fewer per 1,000** (from 44 fewer to 17 more)	⨁◯◯◯ VERY LOW	
Severe interventricular hemorrhage (grade3-4) (total)												
8	observational studies	not serious	not serious	not serious	not serious	none	156/2341 (6.7%)	108/1109 (9.7%)	**OR 0.62** (0.47 to 0.82)	**35 fewer per 1,000** (from 49 fewer to 16 fewer)	⨁⨁◯◯ LOW	
Neonatal sepsis (total)												
8	observational studies	serious [a]	not serious	not serious	serious [b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
9	observational studies	serious [a]	not serious	not serious	serious [b]	none	181/3186 (5.7%)	112/2481 (4.5%)	**OR 0.79** (0.62 to 1.02)	**9 fewer per 1,000** (from 17 fewer to 1 more)	⨁◯◯◯ VERY LOW	
Patent ductus arteriosus (total)												
6	observational studies	serious [a]	not serious	not serious	serious [b]	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	serious [a]	not serious	not serious	not serious	none	641/3033 (21.1%)	415/2216 (18.7%)	**OR 1.22** (1.05 to 1.41)	**32 more per 1,000** (from 8 more to 58 more)	⨁◯◯◯ VERY LOW	
Apgar score < 7 at 5 minutes (total)												
5	observational studies	not serious	not serious	not serious	serious [b]	none	65/715 (9.1%)	82/601 (13.6%)	**OR 0.77** (0.53 to 1.11)	**28 fewer per 1,000** (from 59 fewer to 13 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 [d]	not serious	serious [b]	none	1081	1505	-	MD **0.04 lower** (0.57 lower to 0.48 higher)	⨁◯◯◯ VERY LOW	
Retinopathy of prematurity (total)												
5	observational studies	serious [a]	not serious	not serious	serious [b]	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	serious [a]	not serious	not serious	serious [b]	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 [b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	not serious	not serious	not serious	not serious	none	223	173	-	MD **2.32 lower** (3.81 lower to 0.83 lower)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **IVH:** Intraventricular hemorrhage; **ICH;** Intracranial hemorrhage; **PVH:** Periventricular hemorrhage; **PVL:** Periventricular leukomalacia

Explanations

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ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This study aimed to synthesize available evidence on the efficacy of antenatal corticosteroid (ACS) therapy among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period.

Methods: A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted for all comparative randomized or non-randomized interventional studies in the four subpopulations. The authors extracted data individually. Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was used to assess the risk of bias in non-randomized studies. Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool was also used to assess the certainty of evidence.

Results: Thirty-one studies involving 5018 pregnant women and 10819 neonates were included. All the included articles were observational studies in high-income countries. Data on women with diabetes were limited, and evidence on women undergoing planned CS was inconclusive. ACS use was associated with possibly reduced odds of severe intraventricular hemorrhage (IVH) (pooled OR: 0.41; 95%CI: 0.19–0.87, low certainty), and IVH (pooled OR: 0.41; 95%CI: 0.23–0.72, low certainty) in women with histological chorioamnionitis. Among women with FGR, the rates of surfactant use (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate certainty), mechanical ventilation (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate certainty), and oxygen therapy (pooled OR: 0.48; 95%CI: 0.30–0.77, moderate certainty) were probably reduced; however, the rate of hypoglycemia probably increased (pooled OR: 2.06; 95%CI: 1.27–3.32, moderate certainty). Definitional differences in populations and outcomes complicated meta-analyses.

Conclusions: There is a paucity of evidence for women who have diabetes or are undergoing planned CS. ACS therapy may have benefits in women with chorioamnionitis and is probably beneficial in FGR; however, it can increase neonatal hypoglycemia. Well-designed studies with adequate follow-up are required.

Protocol registration:
PROSPERO (CRD42021267816)

Strengths and limitations of this study:
-This review included a broad search strategy.
-This review applied rigorous quality assessment and GRADE methodology.
-All included studies were observational studies.
-Definitional differences between populations and outcomes complicated the meta-analysis.
-Most studies were conducted in high-income countries.

INTRODUCTION

Previous studies demonstrated that antenatal corticosteroids (ACS), such as intramuscular dexamethasone or betamethasone, cross the placenta and can induce fetal lung maturation [1]. When administered to women at risk of imminent preterm birth before 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly reduced [2]. ACS therapy also probably decreases the risk of intraventricular hemorrhage (IVH) and reduces the rate of developmental delay in childhood [2]. Therefore, the World Health Organization (WHO) and several international obstetric and gynecological societies recommend ACS therapy in women before or up to 34 weeks' gestation for improving preterm newborns' outcomes [3-6]. Some national organizations have recommended ACS use in women at risk of preterm birth up to 36 weeks' gestation based on evidence of the existence of possible respiratory-related benefits for the newborn [3,5].

However, current evidence regarding the benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis, or fetal growth restriction (FGR), is controversial. Women with diabetes, chorioamnionitis, or FGR are at a higher risk of adverse perinatal outcomes; however, they are generally excluded from ACS efficacy trials [2]. Consequently, any subgroup analysis to explore the effects of ACS on women with these complications is unlikely to yield concrete evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycemic effects, and respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor

maternal glycemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women giving birth, causing 22.6–36.9% of total stillbirths [9-11]. Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided due to concerns that its immunosuppressive effects may worsen outcomes for women and their babies. However, the relative benefits and harms of using ACS in clinical settings are unclear. FGR is associated with an increased risk of morbidity and mortality [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as SGA neonates include constitutionally small ones [16]. In most cases, FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant women with both FGR fetuses and SGA neonates.

One clinical scenario with uncertainty regarding ACS efficacy is women undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37 weeks' gestation). Babies born in the late preterm period have lower risks of mortality and morbidity than those born before 34 weeks' gestation; however, they have higher risks of adverse outcomes than those born at term [18-21]. In many countries, the rising rate of provider-initiated late preterm birth has been linked to the generalized increase in the CS rate [22]. Regardless of the gestational age, babies born via elective CS do not have the usual physical and hormonal stimuli of passage through the birth canal; thus, they tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested that the risk of neonatal hypoglycemia is greater following CS; however, this may be confounded by the underlying indication for CS [26].

In 2016, members of our team published a systematic review assessing the effectiveness of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for

those undergoing elective CS in the late preterm period was found. The review could not draw firm conclusions regarding the effects of ACS on women with growth-restricted fetuses, although low-quality evidence suggested that ACS reduces neonatal IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015 ACS recommendations [28]. ACS recommendations are currently being updated as part of the WHO's living guidelines in maternal and perinatal health programs [29]. Our aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians, and maternal and newborn health stakeholders on safe, effective clinical management in preterm birth.

METHODS

The specific review objectives are presented in Box 1, comprising four related questions on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are explained in Supplementary table 1. SGA infants are all neonates with birth weights below the 10th percentile. In this survey, FGR fetuses were defined with each study inclusion criterion (Supplementary table 1). The review protocol was registered on PROSPERO (CRD42021267816) and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary file 1, Supplementary table 2) [30].

Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a

systematic review

P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes
P: Women at risk of imminent preterm birth less than 37 weeks with pregestational diabetes mellitus and/or gestational diabetes mellitus
I: ACS administration
C: Placebo or no treatment
O: World Health Organization (WHO) priority outcomes for preterm birth

P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period
P: Women undergoing elective CS in the late preterm period between 34 weeks and 0 days and 36 weeks and 6 days
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P3: Effects of ACS therapy on women with chorioamnionitis
P: Women at risk of imminent preterm birth less than 37 weeks with chorioamnionitis
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants
P: Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or small-for-gestational-age infants
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

Study eligibility criteria

Eligible studies were randomized or non-randomized primary studies that reported on the effects of ACS therapy in the four subpopulations. This included published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-after studies, interrupted-time-series studies, historically controlled studies, cohort studies, and cross-sectional studies comparing any ACS (betamethasone, dexamethasone, or hydrocortisone) administered either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational

diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis, and women with FGR fetuses or SGA infants.

Articles in any language and from any country were eligible for inclusion if they reported on one or more of WHO's priority outcomes for preterm birth guideline development [28]. Maternal outcomes were death, maternal morbidity, and therapy side effects. Newborn and child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric status, and therapy side effects (Supplementary table 3).

Data sources and search strategy

An information specialist was consulted for the development of the search strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions on June 6, 2021. Controlled vocabularies supplemented with free keywords were used to search for the relevant concept areas, with duplicates removed in the process to yield a total number of abstracts for each database (Supplementary table 4). Reference lists of the included articles, including any recent systematic reviews, were also hand-searched for further potentially relevant studies. All citations were imported into a Rayyan (http://rayyan.qcri.org) library for eligibility assessment.

Study selection, data extraction, and quality assessment

Two reviewers (KS, EN) independently assessed the titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies

were obtained and assessed in duplicate by two reviewers working independently, with disagreements resolved through discussions or by consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through discussions or by consulting a third reviewer. Extracted data were entered into the Review Manager version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [31]. If we identified any randomized trials, we planned to use the Cochrane Risk of Bias tool [32]. Potential publication bias was inspected visually using funnel plots for asymmetry in situations where data for a single outcome were available from at least ten studies.

Data synthesis and analysis

Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs) were determined for dichotomous data using the Mantel–Haenszel analysis (fixed-effects model). Where between-study clinical or methodological heterogeneity undermined the compatibility of the quantitative results, or if substantial statistical heterogeneity was detected, the random-effects meta-analysis was used. Data were pooled using ORs when the numbers of events were available and using logarithms of the ORs weighted by the inverse variance when events were not available. For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for heterogeneity. For the analysis of women with FGR fetuses and/or SGA babies,

we reported results for three subpopulations (SGA only, FGR only, and SGA with FGR). Data from the three populations were combined, and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%.

All statistical analyses were performed using RevMan5. The threshold for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development, and Evaluation (GRADE), an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines, was used in this review.

Patients and public involvement

Since this is a systematic review of previously published data, there was no direct involvement of patients or the public.

RESULTS

Effects of ACS therapy on women with pregestational and/or gestational diabetes mellitus

The search identified 179 citations: 11 potentially eligible studies were evaluated, and three studies met the eligibility criteria, providing data on 725 pregnant women and 830 neonates (Supplementary file 2) [33-35]. All studies were conducted in high-income countries and data collection was performed between 2008 and 2017 (Supplementary table 1). One study involved women with pregestational diabetes only, one study involved women with gestational diabetes only, and one study involved women with either pregestational or gestational diabetes. All included studies were judged as having

a low risk of bias across all domains (Supplementary file 3, Supplementary table 5). Data were available for six outcomes (Table 1). One retrospective cohort study found that in women with gestational diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (one study, 162 infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty evidence*); however, the effect of ACS therapy on neonatal hypoglycemia was uncertain (two studies, 215 infants; pooled OR: 1.44; 95%CI: 0.702.97, *very-low-certainty evidence*) [33]. The certainty of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn.

Table 1: Maternal and neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

Neonatal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Caesarean section	2	31/65 (47.7%)	58/150 (38.7%)	1.75 (0.63–4.82)	138 more per 1,000 (from 102 fewer to 366 more)	Very Low
Neonatal death within 48 h of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09–2.20)	14 fewer per 1000 (from 23 fewer to 29 more)	Very Low
RDS	2	179/583 (30.7%)	37/193 (19.2%)	2.79 (0.85–9.08)	207 more per 1000 (from 24 fewer to4 91 more)	Very Low
Neonatal hypoglycemia	2	14/65 (21.5%)	66/150 (44.0%)	1.44 (0.70–2.97)	91 more per 1000 (from 85 fewer to 260 more)	Very Low
Apgar score < 7 at 5 min	1	1/47 (2.1%)	21/114 (18.4%)	0.79 (0.10–5.89)	33 fewer per 1000 (from 162 fewer to 387 more)	Very Low
Admission to NICU	1	19/47 (40.4%)	36/114 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome.

Effects of ACS therapy on women undergoing elective CS in the late preterm period

The search identified 211 citations:17 potentially eligible studies were evaluated, and two studies were included (Supplementary file 2) [36,37]. The two studies were observational studies conducted in high-income countries between 2011 and 2017, providing data on 205 pregnant women/neonates (Supplementary table 1). The two studies were judged as having a high risk of bias for confounding variables (Supplementary file 3, Supplementary table 5). Data on eleven outcomes were available but all had very low certainty; so, no meaningful conclusions could be drawn (Table 2).

Table 2: Maternal and neonatal outcomes for women undergoing elective cesarean section in the late preterm period

Maternal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09–1.21)	89 fewer per 1000 (from 126 fewer to 25 more)	Very Low
Gestational diabetes mellitus	1	3/30 (10.0%)	4/10 (40.0%)	0.17 (0.03-0.95)	298 fewer per 1000 (from 380 to 12 fewer)	Very Low
Neonatal outcomes	**No of studies**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29–2.24)	17 fewer per 1000 (from 65 fewer to 95 more)	Very Low
IVH	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Necrotizing enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Neonatal hypoglycemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81–2.78)	93 more per 1000 (from 44 fewer to 246 more)	Very Low
Use of mechanical ventilation	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.30–2.12)	17 fewer per 1000 (from 64 fewer to 86 more)	Very Low
Admission to NICU	2	10/88 (11.4%)	14/117 (12.0%)	0.78 (0.23–2.72)	24 fewer per 1000 (from 89 fewer to 150 more)	Very Low
Apgar score ≤ 7 at 5 min	1	2/58 (3.4%)	0/107 (0.0%)	9.51 (0.45–201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very Low
Mean duration of mechanical ventilation	1	30	10	-	MD 0.2 lower (1.35 lower to 0.95 higher)	Very Low
Oxygen requirement for at least 4 hours	1	13/58 (22.4%)	25/107 (23.4%)	0.95 (0.44-2.03)	9 fewer per 1000 (from 115 fewer to 149 more)	Very Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS therapy on women with chorioamnionitis (histological or clinical)

The search identified 418 citations: 12 potentially eligible studies were evaluated, and eight were found to be eligible (Supplementary file 2) [38-45]. Two were prospective cohort studies and six were retrospective, providing data on 1372 pregnant women and 1460 neonates (Supplementary table 1). Four studies included pregnant women with clinical chorioamnionitis, and there were variations in the diagnostic criteria (Supplementary table 1). All studies were conducted in high-income countries between 1989 and 2014. Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process [38,41-43,46]. All included studies were judged as having a low risk of bias overall, although six studies were judged as having a high risk of bias regarding confounding variables as adjusted analyses were not reported (Supplementary file 3, Supplementary table 5). Data for 27 outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3;

Supplementary file 4). Among women with histological chorioamnionitis, ACS administration was associated with a possible reduction in the odds of severe intraventricular hemorrhage (IVH) (four studies, 528 infants; pooled OR: 0.41; 95%CI: 0.19–0.87, *low-certainty evidence*), IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*). ACS might result in no difference in neonatal sepsis; however, the evidence was uncertain (six studies, 1193 infants: pooled OR: 1.03; 95%CI: 0.73–1.47, *very-low-certainty evidence*). The certainty of evidence was very low for other outcomes (Supplementary table 6). In women with clinical chorioamnionitis, only very-low-certainty evidence was available for neonatal sepsis (two studies, 150 infants, pooled OR: 0.71; 95%CI: 0.13–3.89). The certainty of evidence was very low for all other outcomes (Supplementary table 6).

Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						
Caesarean section	1	42/97 (43.3%)	2/12 (16.7%)	3.82 (0.79–18.36)	266 fewer per 1000 (from 30 fewer to 619 more)	Very Low
Gestational diabetes mellitus	1	6/97 (6.2%)	2/12 (16.7%)	0.33 (0.06-1.86)	105 fewer per 1000 (from 155 fewer to 104 more)	Very Low
Preeclampsia or eclampsia	1	5/97 (5.2%)	1/12 (8.3%)	0.60 (0.06–5.59)	32 fewer per 1000 (from 78 fewer to 254 more)	Very Low
Neonatal outcomes (histological chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	0.51 (0.31–0.85)	75 fewer per 1000 (from 109 fewer to 22 fewer)	Very Low
Severe IVH	4	25/414 (6.0%)	13/114 (11.4%)	0.41 (0.19–0.87)	64 fewer per 1000 (from 90 fewer to 13 fewer)	Low
IVH	5	42/502 (8.4%)	26/156 (16.7%)	0.41 (0.23–0.72)	91 fewer per 1000 (from 123 fewer to 41 fewer)	Low
RDS	6	305/677 (45.1%)	289/516 (56.0%)	0.59 (0.45-0.77)	131fewer per 1000 (from 196 fewer to 65 fewer)	Very Low
Sepsis	6	112/677 (16.5%)	83/516 (16.1%)	1.03 (0.73–1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very Low
Neonatal outcomes (clinical chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	2	14/109 (12.8%)	14/81 (17.3%)	0.71 (0.32-1.60)	44 fewer per 1000 (from 110 fewer to 78 more)	Very Low
Severe IVH	3	5/163 (3.1%)	14/155 (9/0%)	0.32 (0.03–3.19)	60 fewer per 1000 (from 87 fewer to 150 more)	Very Low
IVH	3	13/163 (8.0%)	20/155 (12.9%)	0.43 (0.07–2.44)	69 fewer per 1000 (from 119 fewer to 136 more)	Very Low
RDS	4	99/209 (47.45)	99/208 (47.6%)	0.74 (0.48-1.12)	74 fewer per 1000 (from 172 fewer to 28 more)	Very Low
Sepsis	2	26/104 (25.0%)	12/46 (26.1%)	0.71 (0.13–3.89)	60 fewer per 1000 (from 271 fewer to 318 more)	Very Low

*There was no maternal outcome in clinical chorioamnionitis.
*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-

gestational-age infants

The search identified 261 citations: 36 potentially eligible studies were assessed, and 18 studies were included (Supplementary file 2) [41,47-63]. Of these, twelve studies included women with SGA infants only, four studies included women with FGR or SGA infants, and two studies included women with FGR infants only (Supplementary table 1). Among the studies that included FGR fetuses, the definitions of FGR varied widely (Supplementary table 1). Since SGA status is insufficient to determine FGR, we separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three populations were combined, and the pooled OR in total was calculated. Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 [50,53,58]. These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event. All were observational studies conducted in high-income countries. Additional unpublished data from the study by Torrance et al. (2007) were extracted from a review paper published in 2009 identified through the search strategy [53,64]. Most included studies were judged as having a low risk of bias across all domains. Seven studies had a high risk of bias for the domain regarding confounding variables. Three studies had a high risk of bias regarding incomplete outcome data (Supplementary file 3, Supplementary table 5). For SGA infants only, 12 studies provided data on 30 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the

odds of neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–0.97, *low-certainty evidence*) were possibly reduced (Table 4). Two studies involving FGR infants only provided data for 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17–0.90, *low-certainty evidence*) were possibly reduced (Table 4). Four studies involved SGA or FGR infants, providing data for 25 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA or FGR was associated with a possible reduction in the odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62, *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants; pooled OR: 0.42; 95%CI: 0.26–0.66, *moderate-certainty evidence*), oxygen use (two studies, 508 infants; pooled OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*) although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01; 95%CI: 1.16–3.48, *low-certainty evidence*) (Table 4). Pooled ORs involving women and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be determined for 20 outcomes (Supplementary file 4, Supplementary table 6). ACS administration for women with SGA and/or FGR was associated with a possible reduction in severe IVH (nine studies, 4636 infants; pooled OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital stay (two studies, 396 infants; MD −2.23 days; 95%CI: −3.81–−0.83, *low-certainty evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were possibly increased (Table 4).

Table 4: Maternal and neonatal outcomes for women with growth-restricted fetuses and/or small-for-gestational-age infants

Maternal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Pregnancy induced hypertension						
Total	3	195/453 (43.0%)	99/322 (30.7%)	1.47 (1.07–2.01)	87 more per 1000 (from 15 more to 164 more)	Low
SGA	2	144/370 (38.9%)	94/314 (29.9%)	1.50 (1.08–2.07)	91 more per 1000 (from 16 more to 170 more)	Low
Neonatal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death [a)]						
SGA	8	242/1544 (15.7%)	196/1116 (17.6%)	0.68 (0.47-0.97)	49 fewer per 1000 (from 85 fewer to 4 fewer)	Low
Severe IVH						
Total	9	190/3018 (6.3%)	171/1618 (10.6%)	0.59 (0.41-0.85)	41 fewer per 1000 (from 59 fewer to 14 fewer)	Low
Neonatal hypoglycemia						
Total	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27–3.32)	155 more per 1000 (from 47 more to 273 more)	Moderate
FGR or SGA	1	55/136 (40.4%)	28/111 (25.2%)	2.01 (1.16-3.48)	152 more per 1000 (from 29 more to 288 more)	Low
Surfactants use						
FGR or SGA	3	61/358 (17.0%)	58/241 (24.1%)	0.38 (0.23–0.62)	133 fewer per 1000 (from 173 fewer to 76 fewer)	Moderate
Use of mechanical ventilation						
FGR or SGA	2	73/275 (26.5%)	94/233 (40.3%)	0.42 (0.26–0.66)	182 fewer per 1000 (from 254 fewer to 95 fewer)	Moderate
Oxygen therapy						
FGR or SGA	2	79/275 (28.7%)	94/233 (40.3%)	0.48 (0.30–0.77)	158 fewer per 1000 (from 235 fewer to 61 fewer)	Moderate
Duration of hospital stay (days)						
Total	2	223	173		MD 2.32 lower (3.81 lower to 0.83 lower)	Low
Death or disability/handicap at 2years' corrected age						
FGR	1	11/62 (17.7%)	22/62 (35.5%)	0.39 (0.17-0.90)	178 fewer per 1000 (from 269 fewer to 24 fewer)	Low

*The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in total and calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH: Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, SGA: Small for gestational age. [a)] We calculated the numerators using the crude OR in the study by Ley et al. (1997).

DISCUSSION

This systematic review identified 31 observational studies on the benefits and drawbacks of using ACS in subgroups of women with specific pregnancy complications. In women with diabetes and those undergoing elective late preterm CS, the available evidence on the effects of ACS therapy was largely very-low-certainty; thus, conclusions could not be drawn. In women with histological and clinical chorioamnionitis, ACS therapy was associated with the benefit of IVH reduction. In women with FGR and/or SGA babies, ACS therapy possibly has benefits regarding neonatal morbidity and mortality, as well as the reduced use of respiratory support interventions for the newborn; however, neonatal hypoglycemia might be increased.

Effects of ACS therapy on women with pregestational and/or gestational diabetes

A clinical concern regarding ACS use in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycemia, which causes avoidable harm to the neonate. For example, in women with insulin-dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid administration [65]. A 2002 Danish study conducted on 24 pregnant women with diabetes who received steroids suggested that insulin dose adjustment may be required

for up to five days after ACS administration [66]. However, in the current review, there was insufficient evidence to determine whether ACS increased neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU admission; however, the authors noted that the birthweight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding [33]. Well-designed studies are needed that describe adjustments to maternal diabetic regimens at the time of ACS therapy and from the time of ACS administration to birth and report on important newborn health outcomes.

Effects of ACS therapy on women undergoing elective CS in the late preterm period

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from seven trials recruiting women in the late preterm period [2]. This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh M et al. reported that ACS reduced the need for respiratory support and increased the risk of hypoglycemia with moderate certainty in late preterm [67]. However, no subgroup

analyses were conducted on CS [67]. Hence, these findings cannot be generalized to all women undergoing CS in the late preterm period. The RCT by Gyamfi-Bannerman CEA et al. reported that ACS in the late preterm period reduced the risk of transient tachypnea of the newborn, surfactant use, and BPD [68]. Their subgroup analysis of planned CS showed ACS resulted in no significant difference in their primary outcome and severe respiratory complication [68]. Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, mechanical ventilation, stillbirth, neonatal death, or the need for extracorporeal membrane oxygenation (ECMO) [68]. Their severe respiratory complications were defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death, or the need for ECMO [68]. Their outcomes did not adequately fit our outcomes, and the study was not included in this review. Our review demonstrates that there is currently insufficient evidence to draw conclusions on the benefits and possible harms of ACS when used in this subpopulation, although an ongoing randomized trial in New

Zealand is assessing the effects of ACS therapy on women with CS planned between 35 weeks 0 days and 39 weeks 6 days [69].

Effects of ACS on women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to concerns that the prolongation of pregnancy and/or immunosuppression may worsen outcomes for these women and their newborns. Although ACS appears to be associated with reduced IVH and severe IVH rates in women with histological chorioamnionitis, there was insufficient evidence of other important infection-related maternal and neonatal outcomes in this review. While these conclusions are similar to those of a 2011 review by Been et al., we do not consider that the available evidence supports the routine use of ACS therapy in women with chorioamnionitis, as clinical trials comparing ACS therapy to no ACS therapy in this population and reliable evidence regarding infection-related outcomes are still lacking [46]. Significant overlap exists between clinical and histological chorioamnionitis [70]. Histological chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis [71]. However, since physicians must decide the indications for ACS therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant

women with clinical chorioamnionitis should be encouraged.

Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The totality of the evidence identified in this review suggests that ACS therapy should be used in the fetal growth restriction setting. Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes, and no harm was reported. The current review identified more substantial evidence than that identified in our 2016 systematic review, which was unable to draw solid conclusions about the effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected fetal growth restriction [72]. The current review did not identify the benefits regarding the outcome RDS, which might be attributable to a single retrospective cohort study in Japan in which neonates in the ACS group were delivered significantly earlier than those in the control group [56]. A sensitivity analysis in which we excluded this study suggested that RDS is significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal

hypoglycemia in this subpopulation, which warrants further exploration in future research. In this meta-analysis, only two studies targeted pregnant women with FGR. Since the SGA status does not accurately represent FGR, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.

Strengths and limitations

The strengths of this review were its broad search strategy, which included studies published in languages other than English, rigorous quality assessments, and the use of the GRADE methodology to assess the reliability of the review's findings. Thus, we consider the risk of missing potentially eligible studies to be low, although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified, or diagnosed the subgroup conditions and outcomes of interest. These differences might have created a bias in the review conclusions. However, we explored and reported heterogeneity for meta-analyses. Another limitation is that most of the included studies were conducted in high-income countries, although over 60% of all preterm births globally occur in African and South Asian countries [73]. This review did not lead to any evidence of high certainty, and one reason for this observation is that all studies were observational. In 1990,

Crowley P et al. reported a structured review of ACS for preterm birth [74]. The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity [74]. In 1995, the National Institutes of Health developed a consensus on recommending ACS treatment for preterm birth [75]. In our review, only one study targeting women with chorioamnionitis and two studies targeting women with FGR started before 1990 [40,49,52]. It would be challenging to conduct the RCTs on ACS efficacy even in these special populations after the review by Crowley P et al. [74]. The latest Cochrane review on ACS treatment for preterm birth involved a subgroup analysis in the seven special conditions [2]. However, the review did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis, and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery [67]. Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes.

CONCLUSION

ACS has possible benefits in the setting of FGR and/or SGA; however, direct evidence of its efficacy and safety for pregnant women with pregestational and/or gestational diabetes mellitus and those undergoing elective CS in the late preterm period is still lacking. Although ACS may have some benefits in the context of histological chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with adequate follow-up for long-term child outcomes are needed to confirm the upsides and downsides of ACS use in these subpopulations.

AUTHOR CONTRIBUTIONS

Dr. Saito participated in the conceptualization and design of the study, conducted title, abstract, and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, drafted the initial manuscript, and critically reviewed the manuscript. Ms. Nishimura conducted the title abstract and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, and critically reviewed the manuscript. Dr. Swa conceptualized and designed the search strategy, conducted a systematic search, and critically reviewed the manuscript for

important intellectual content. Dr. Ramson assisted in the interpretation of data and the assessment of the risk of bias and critically reviewed the manuscript for important intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel designed and planned the study, assisted with developing the literature search strategy and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the execution of the study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DATA SHARING STATEMENT

Data were obtained from the published journal article, and extracts are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

None declared.

SUPPLEMENTARY FILES

Supplementary table 1: Characteristic tables

Supplementary table 2: PRISMA 2020 Checklist

Supplementary table 3: Review outcomes

Supplementary table 4: Database-specific search terms and strategies

Supplementary table 5: Risk of bias tables

Supplementary table 6: GRADE tables

Supplementary file 1: PROSPERO

Supplementary file 2: PRISMA flow diagrams

Supplementary file 3: Risk of bias figures

Supplementary file 4: Forest plots

ETHICS APPROVAL

As this study is a systematic review of published studies; thus, ethical approval was not required.

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11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr KANA SAITO. Saitama Medical University, Neonatology Department
Ms Etsuko Nishimura. St. Luke's International University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Non funded research

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Toshiyuki Swa. Osaka University Graduate School of Medicine
Dr Fumihiko Namba. Saitama Medical University
Dr Erika Ota. St. Luke's International University
Dr Joshua P. Vogel. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Ramson. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Cao. Child and Adolescent Health Program, Burnet Institute, Melbourne

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

This study aims to synthesize available evidence on antenatal corticosteroid (ACS) use among specific subgroups of women at risk of imminent preterm birth.

The primary objective is to determine the effects of ACS administration for four subgroups of pregnant women at risk of imminent preterm birth on maternal and child outcomes. These subgroups are as follows.

1) women with pregestational or gestational diabetes mellitus

2) women undergoing elective CS in the late preterm period (from 34 weeks 0 days to 36 weeks 6 days)

3) women with an intrapartum inflammation, infection, or both (eg: chorioamnionitis)

4) women with growth-restricted fetuses

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search electronic databases (e.g. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP).

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

We will search electronic databases (i.e. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP). Search terms include “adrenal cortex hormones”, “pregnancy”, “pregnancy outcome”, “fetal death”, “maternal death”, “obstetric labor complications”, “obstetric labor, premature”, “pregnancy, prolonged”, “fetus”, “infant, newborn”, “prenatal care”, “fetal development”, “birth weight”, “prenatal exposure delayed effects”, “diabetes mellitus”, “hyperglycemia”, “diabetes, gestational”, “pregnancy in diabetics”, “cesarean section”, “bacterial infections and mycoses”, “chorioamnionitis“, “pregnancy complications, infectious”, “fetal development”.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Pregnancy

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: We will not restrict the population to pregnant women less than 20 completed weeks gestation and their babies.
Exclusion: Pregnant women with a live birth after 20 completed weeks gestation and their babies.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

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International prospective register of systematic reviews

We will include women who received at least one dose of antenatal corticosteroid, either betamethasone, dexamethasone, or hydrocortisone after 20 weeks of gestation.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Women and babies who did not receive antenatal corticosteroids.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-and-after studies, interrupted-time-series studies, historical controlled studies, cohort studies, and cross-sectional studies comparing ACS administration (betamethasone, dexamethasone, or hydrocortisone), given parenterally or enterally, compared with placebo or no treatment in women at risk of imminent preterm birth as a result of either spontaneous preterm labor, preterm rupture of the membranes, or elective preterm delivery, and where all (or at least a well-defined sub-sample) of the women under study also fulfilled one or more of the following conditions:

1. having pre-gestational or gestational diabetes mellitus;
2. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
3. having intrauterine inflammation, infection, or both; or
4. having a growth-restricted infant (or, more broadly, one that was at least small for gestational age).

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

We aim to establish the existing evidence that examines the implications of using or not using ACS in cases of imminent preterm birth in these subgroups of women. This evidence-based effort will be the source for the World Health Organization's (WHO) updated recommendations on interventions to improve preterm birth outcomes.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a)maternal outcomes

-maternal death or severe morbidity (e.g. organ dysfunction, intensive care unit admission, chorioamnionitis)

-maternal morbidity(e.g. puerperal sepsis, pregnancy-induced hypertension, gestational diabetes mellitus, placental abruption, postpartum haemorrhage, or as defined by the author)

-route of delivery

-side effects of therapy

b) neonatal outcomes

-perinatal mortality

-fetal mortality

-neonatal mortality

-respiratory distress syndrome (RDS) and moderate/severe RDS

-surfactant use

-interventricular haemorrhage (IVH)

-periventricular leukomalacia (PVL)

-sepsis; early onset sepsis

-necrotizing enterocolitis (NEC)

-mechanical ventilation use and mean duration

-patent ductus arteriosus (PDA)

-chronic lung disease (CLD)/ bronchopulmonary dysplasia (BPD)

-Apgar scores seven at 5 minutes

-neurodevelopment

-anthropometric status; birth weight, height, and head circumference

-NICU admission and mean duration

-side effects of therapy

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

We will conduct the sub-group analysis; extremely preterm (less than GA 28weeks), very preterm (GA28 to 32weeks) and moderate to late preterm (GA 32 to 37weeks) on each predetermined outcome.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

At least two researchers will work independently to assess each title and abstract for eligibility. Disagreement will yield automatic inclusion into the next level of screening. After the initial screening of titles and abstracts, full-text publications of studies with the potential for inclusion will be obtained and assessed. The same reviewers will independently evaluate studies under consideration for inclusion without consideration of their results. Any disagreement will be resolved through discussion to reach a consensus. Finally, the reviewers independently will extract baseline and outcome data and assess the quality of the included studies. Any discrepancies will be resolved through discussion to reach a consensus.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Study quality will be assessed independently by the aforementioned reviewers at the outcome level using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS). Randomized control trials will be assessed with Risk of Bias 2 (RoB2). Potential publication bias will be assessed by visual inspection of funnel plots for asymmetry, subject to a sufficient number of included studies. Any disagreement will be resolved by discussion to reach a consensus.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the

number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference with 95% CIs will be used.

The heterogeneity of studies will be assessed using both qualitative and quantitative measures. Statistical heterogeneity will be determined for each meta-analysis using T2, I², and ?² statistics.

Heterogeneity will be deemed substantial if T2 will be greater than zero and either I² will be greater than 50% or p0.10 in the ?² test for heterogeneity. To further assess potential heterogeneity, both fixed- and random-effects models will be compared for each outcome, where possible.

All statistical analyses will be performed using RevMan 5. Existing meta-analyses will be reviewed for relevance and completeness, and new meta-analyses will be performed where deemed necessary.

Statistical significance will be set at an alpha level of 0.05 for all analyses, except when testing study heterogeneity, where p0.10 will be regarded as significant.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat

No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
Yes

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Japan

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We will disseminate the finding with a relevant medical journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Antenatal corticosteroid

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. PLoS ONE. 2016; 11(2): e0147604.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Supplementary file 2: PRISMA flow diagrams

Figure 1: Flow diagram of search results and study selection for women with pregestational and/or gestational diabetes

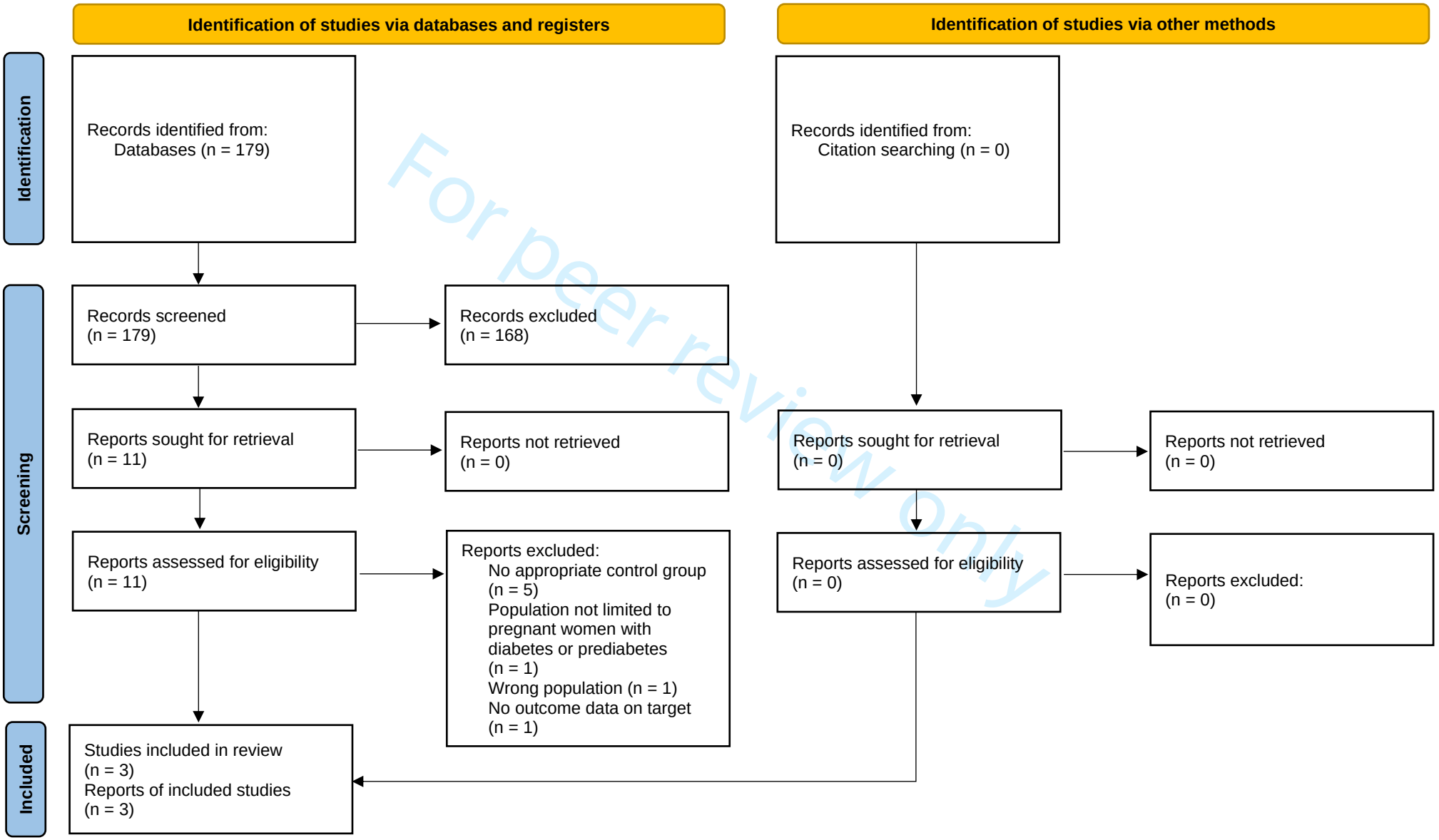


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

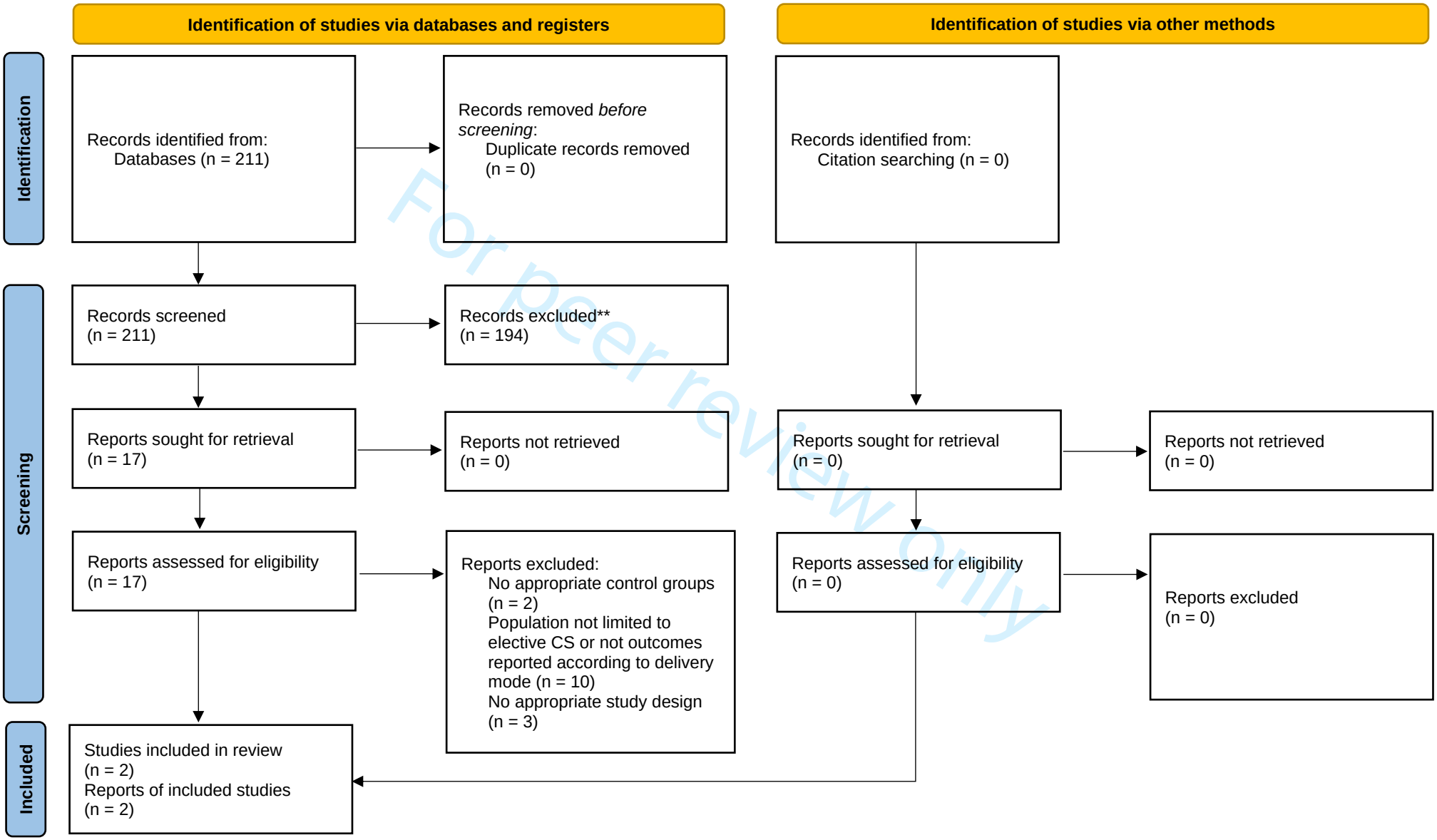


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

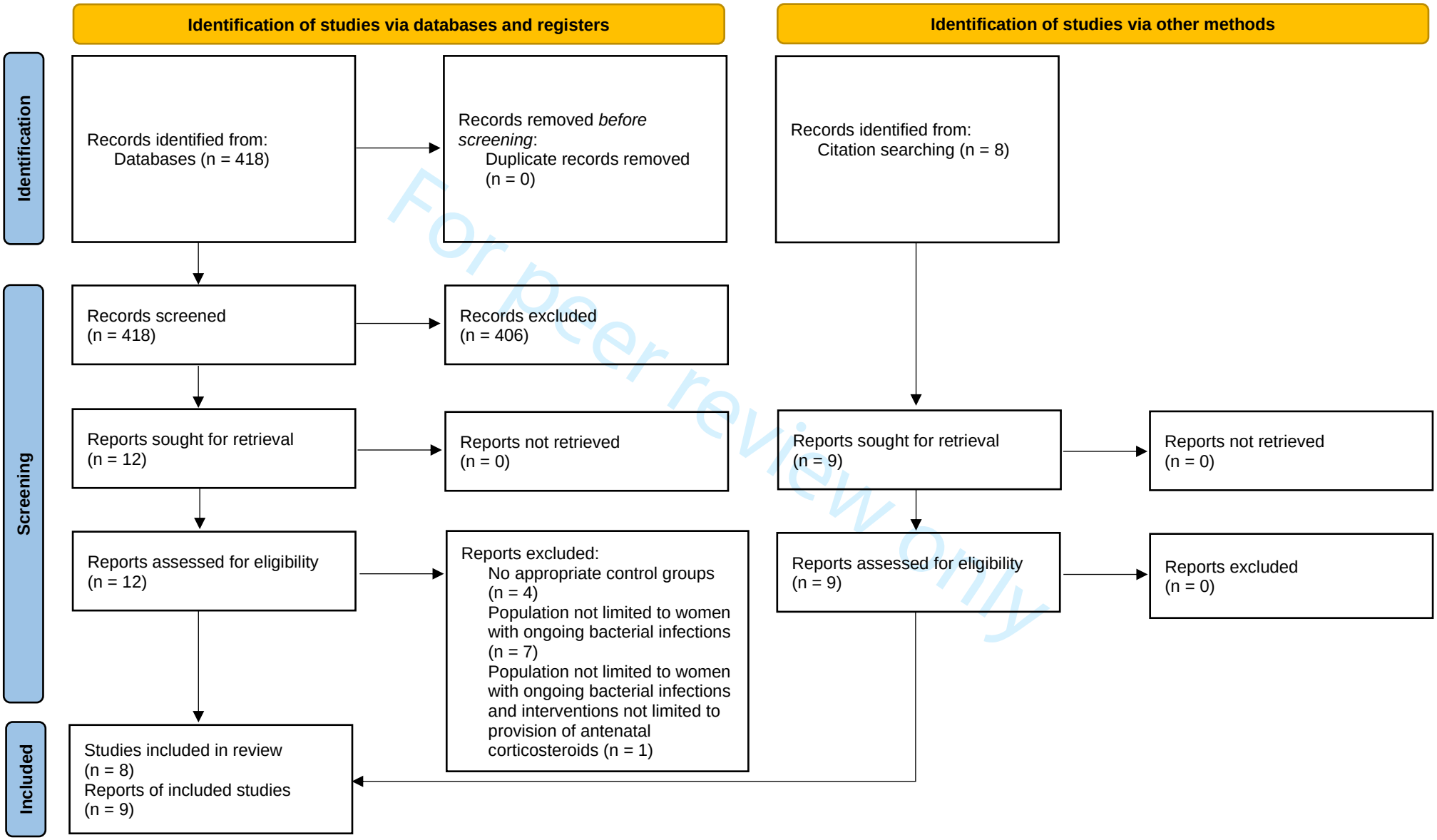
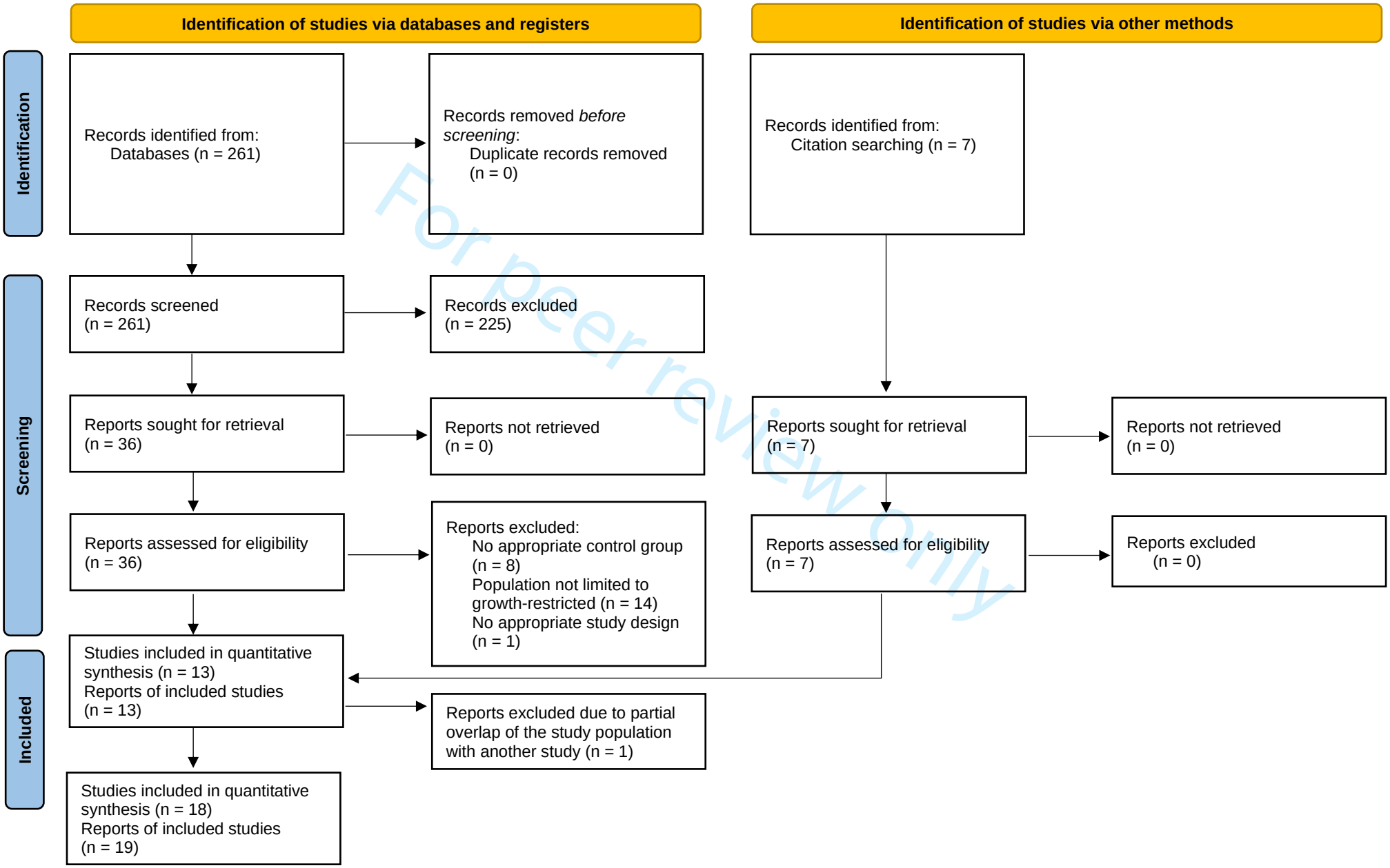


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure1: Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

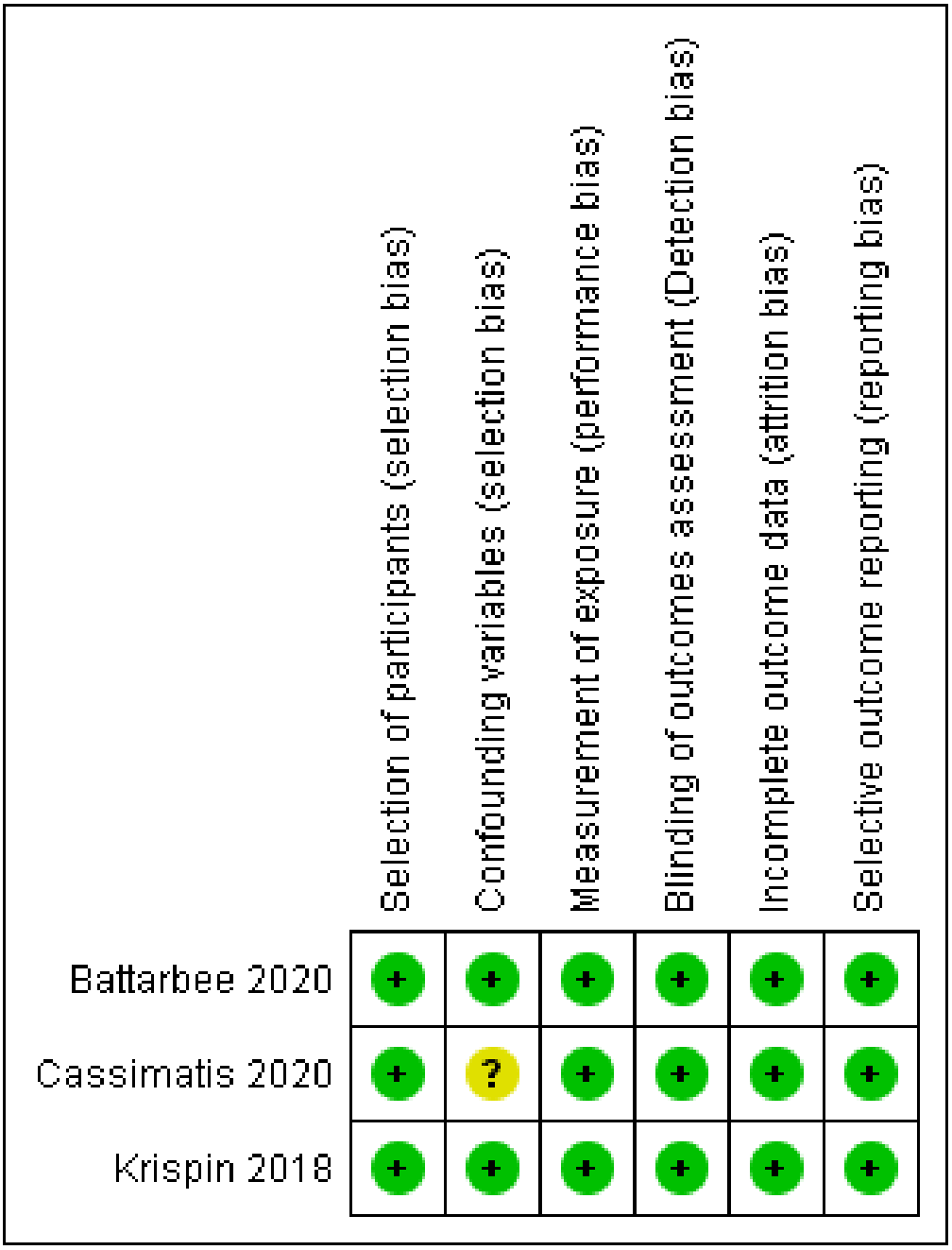


Figure 2: Summary of risk of bias for each trial for women undergoing elective Cesarean section in late preterm period
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

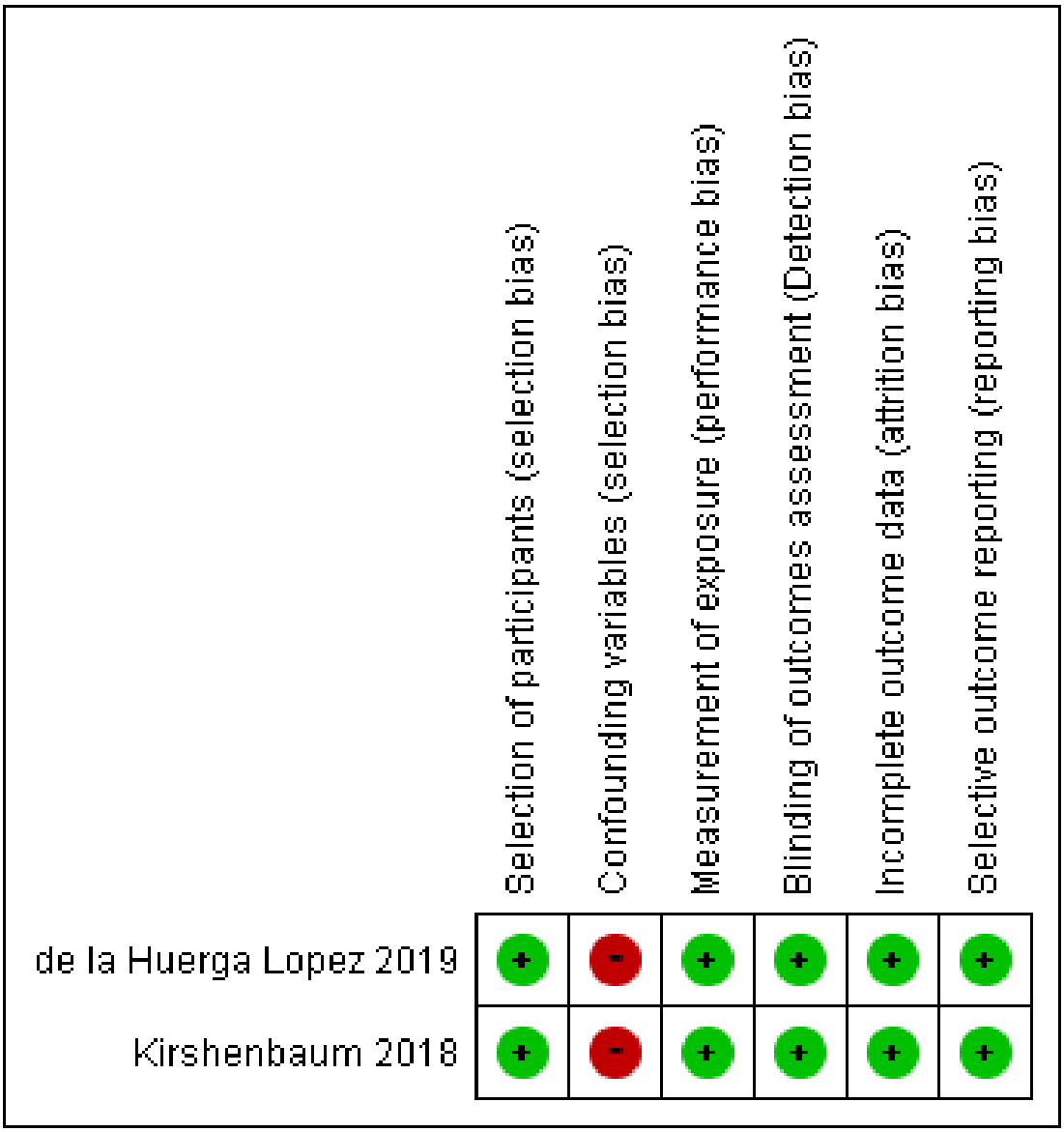


Figure 3: Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical)
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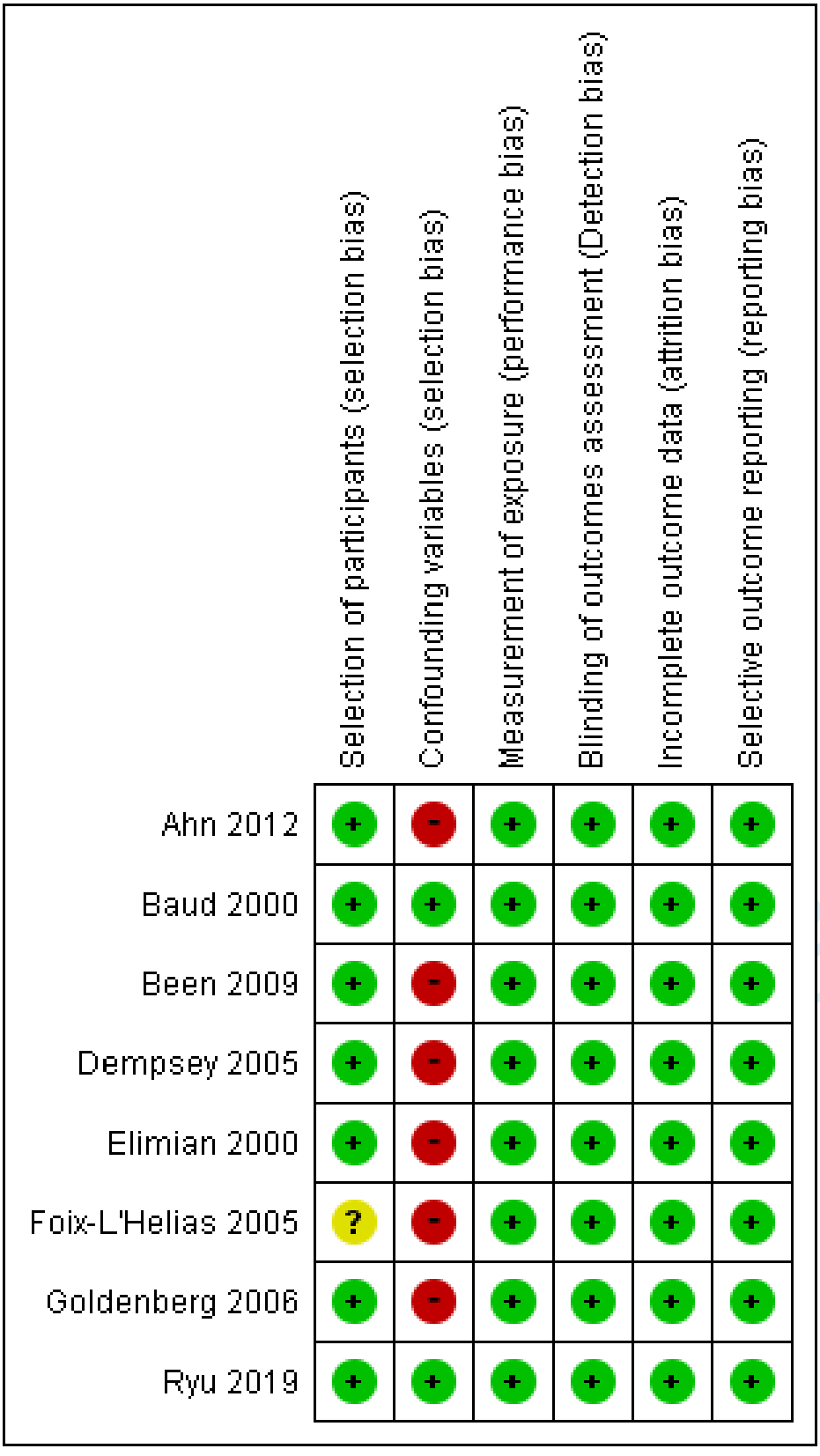
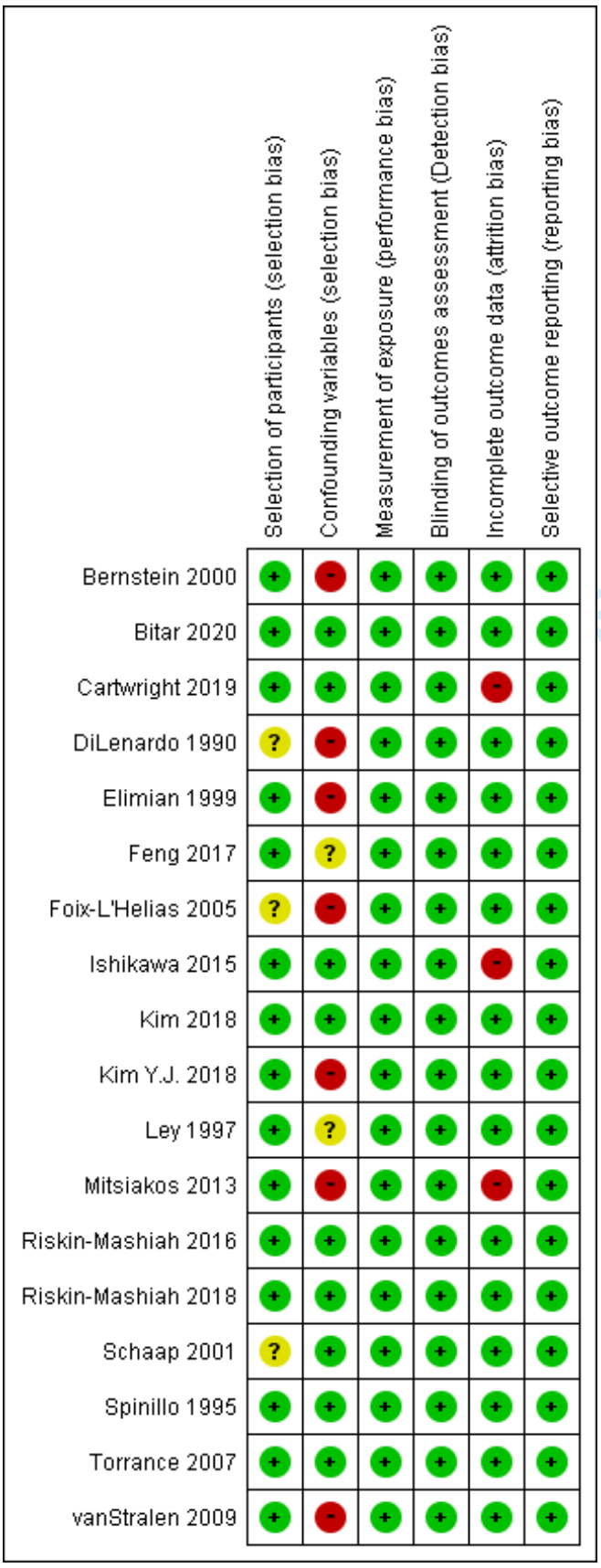


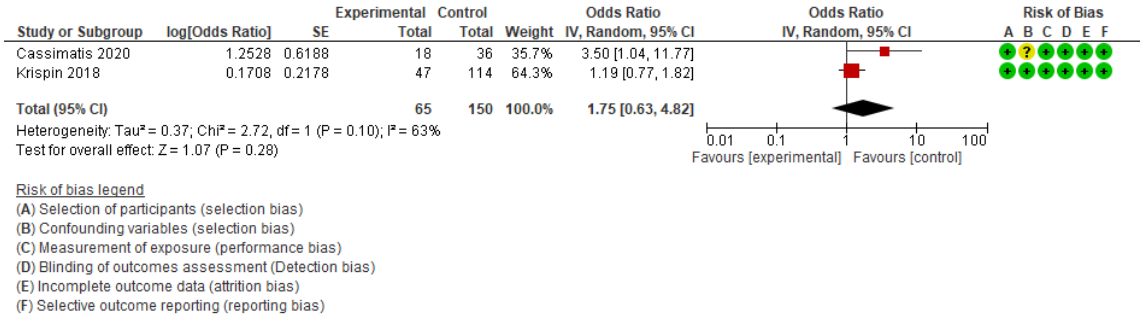
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



Supplementary file 4: Forest plots

Maternal outcomes for women with pregestational and/or gestational diabetes mellitus

1) Caesarean section

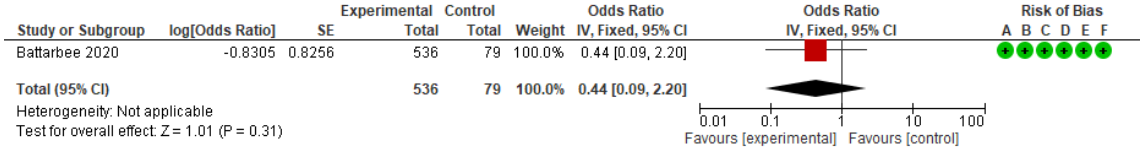


Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

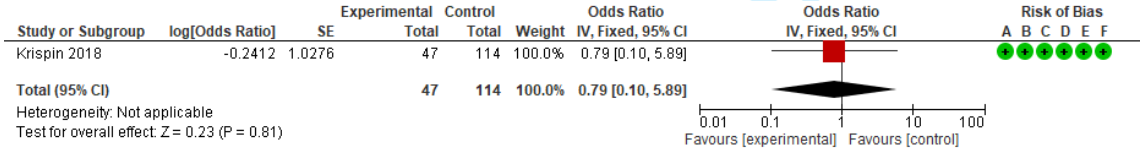
1) Neonatal death within 48 h of birth



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

2) Apgar score < 7 at 5 min



Risk of bias legend
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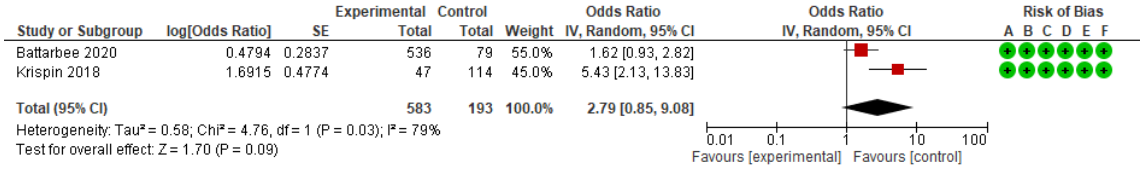
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

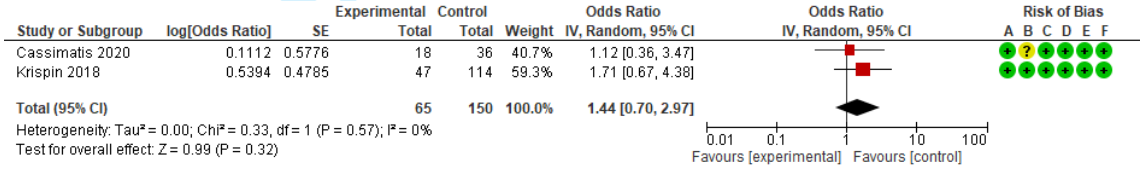
3) Respiratory distress syndrome (RDS)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia



Risk of bias legend
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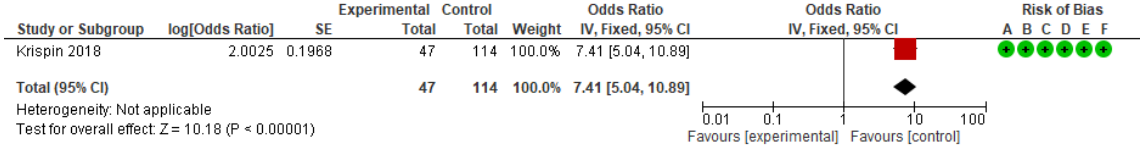
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

5) Admission to neonatal intensive care unit (NICU)



Risk of bias legend
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(D) Blinding of outcomes assessment (Detection bias)
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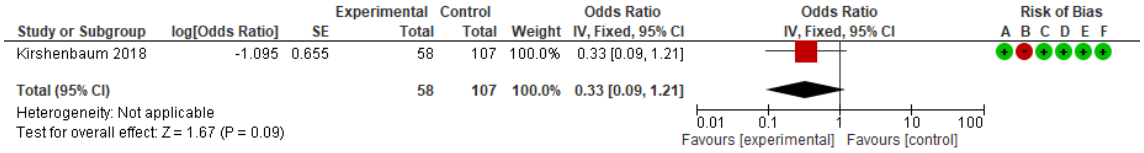
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders



Risk of bias legend
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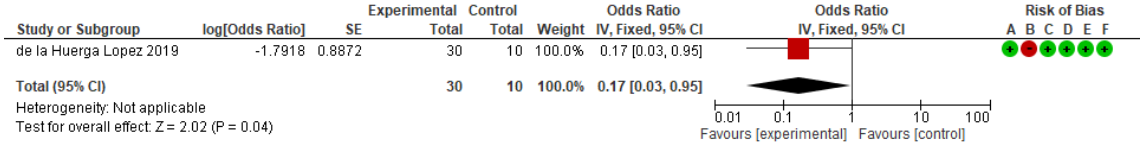
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

2) Gestational diabetes mellitus

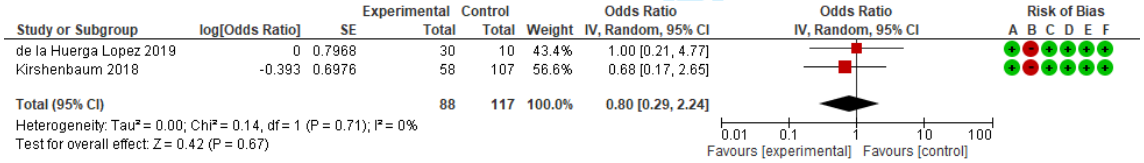


Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women undergoing elective cesarean section in late preterm period

1) Respiratory distress syndrome (RDS)



Risk of bias legend
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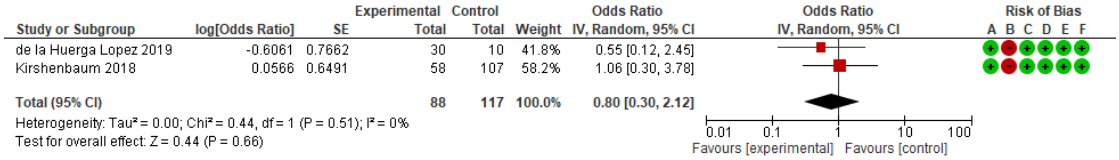
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

2) Use of mechanical ventilation



Risk of bias legend
(A) Selection of participants (selection bias)
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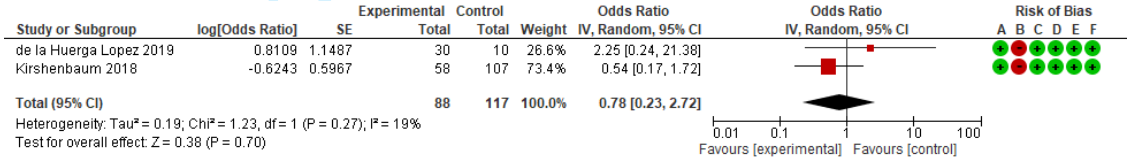
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

3) Admission to neonatal intensive care unit (NICU)



Risk of bias legend
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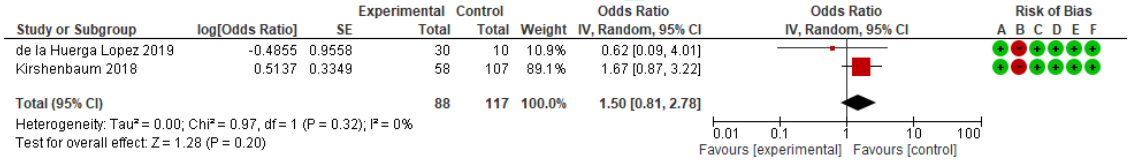
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia



Risk of bias legend
(A) Selection of participants (selection bias)
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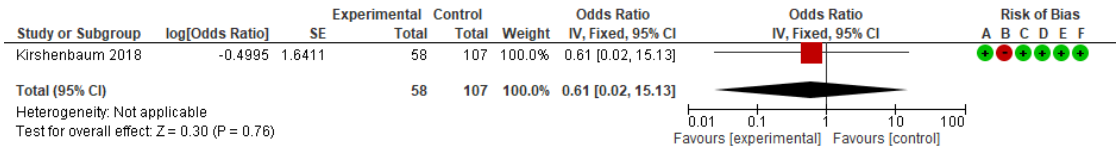
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

5) Intraventricular hemorrhage (IVH)



Risk of bias legend
(A) Selection of participants (selection bias)
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(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
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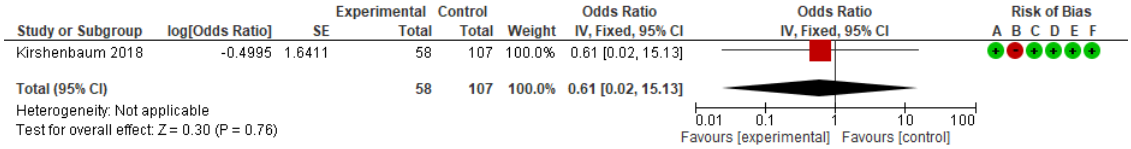
SE: Standard error; **CI:** Confidence interval

6) Necrotizing enterocolitis (NEC)



Risk of bias legend
(A) Selection of participants (selection bias)
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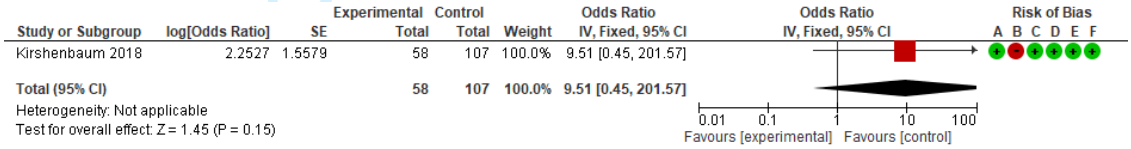
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

7) Apgar score ≤ 7 at 5min



Risk of bias legend
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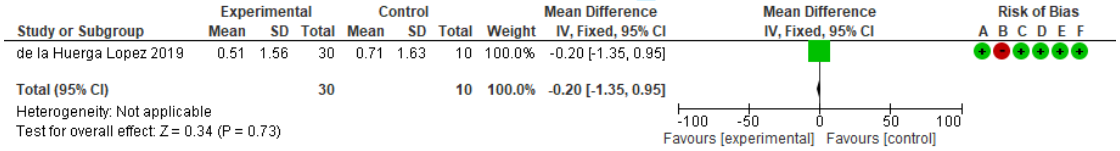
SE: Standard error; **CI:** Confidence interval

8) Mean duration of mechanical ventilation, days



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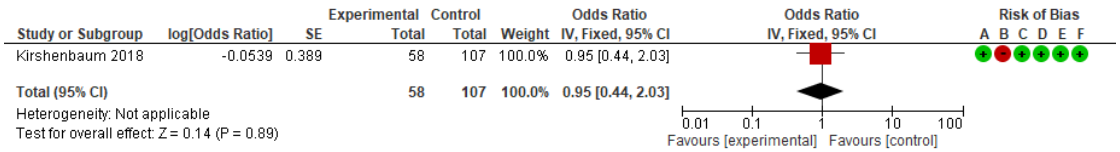
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

9) Oxygen requirement for at least 4 hours



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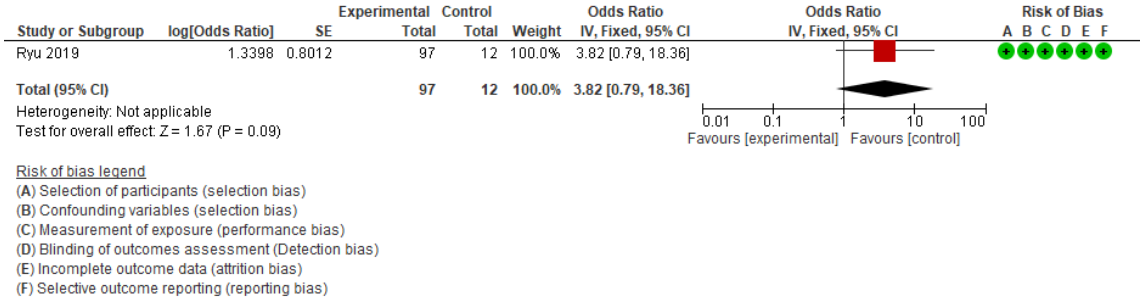
SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women with histological chorioamnionitis

*There is no maternal outcome in clinical chorioamnionitis.

1) Caesarean section (HC)



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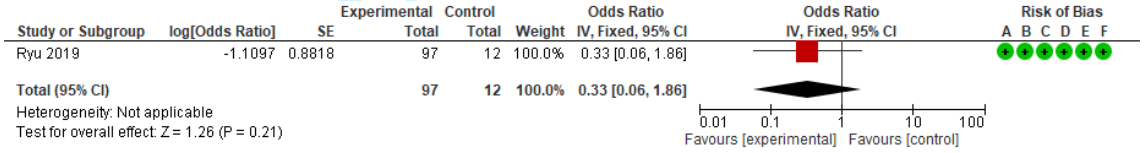
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

2) Gestational diabetes mellitus (HC)



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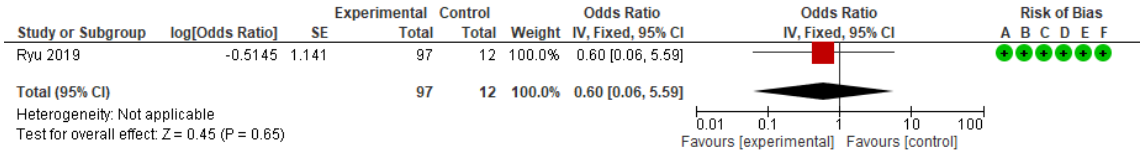
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

3) Preeclampsia or eclampsia (HC)



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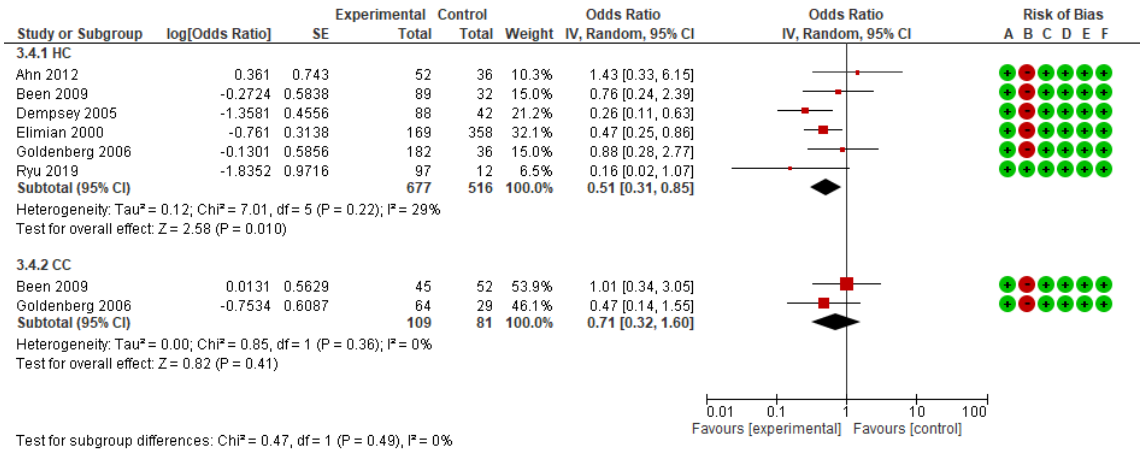
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

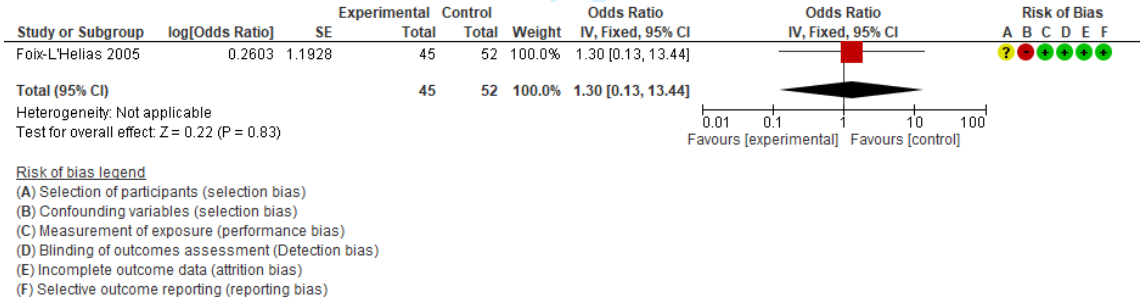
Neonatal outcomes for women with histological chorioamnionitis (HC) and clinical chorioamnionitis (CC)

1) Neonatal death



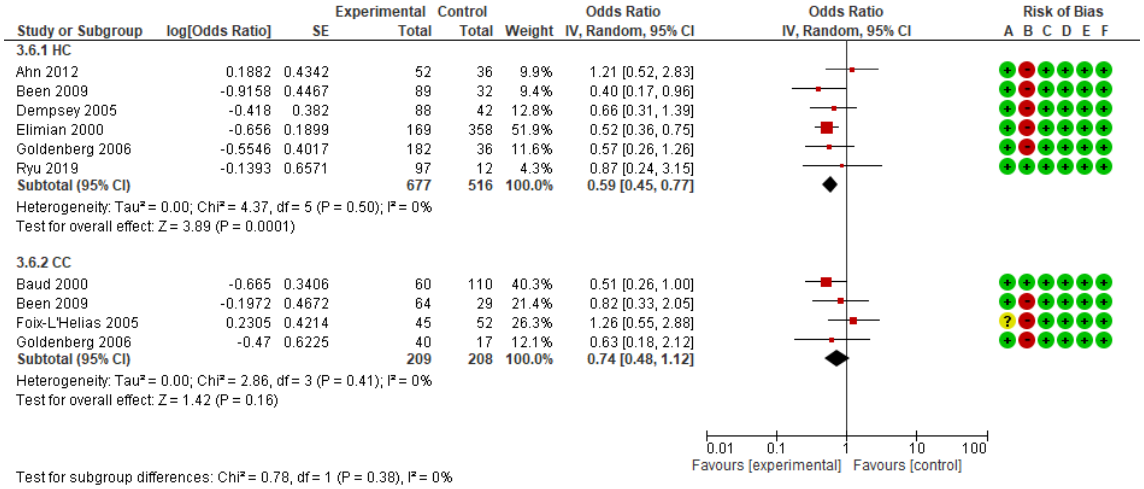
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

2) Death before discharge home (CC)



SE: Standard error; **CI:** Confidence interval; **CC:** Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%

Risk of bias legend
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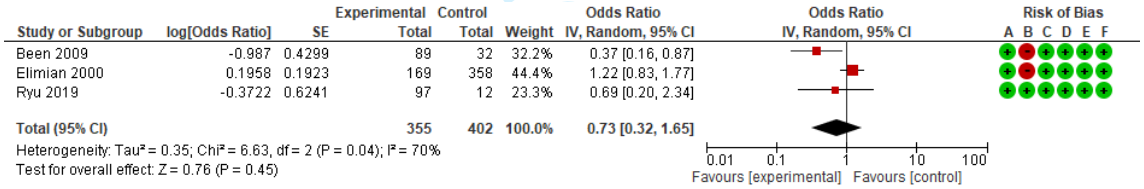
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

4) Surfactant use (HC)



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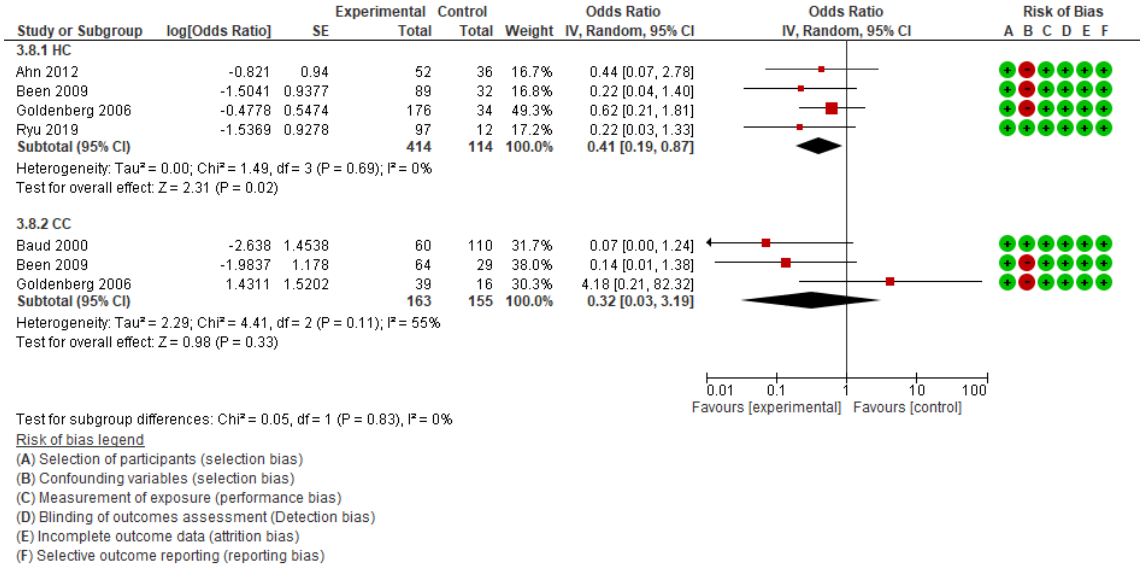
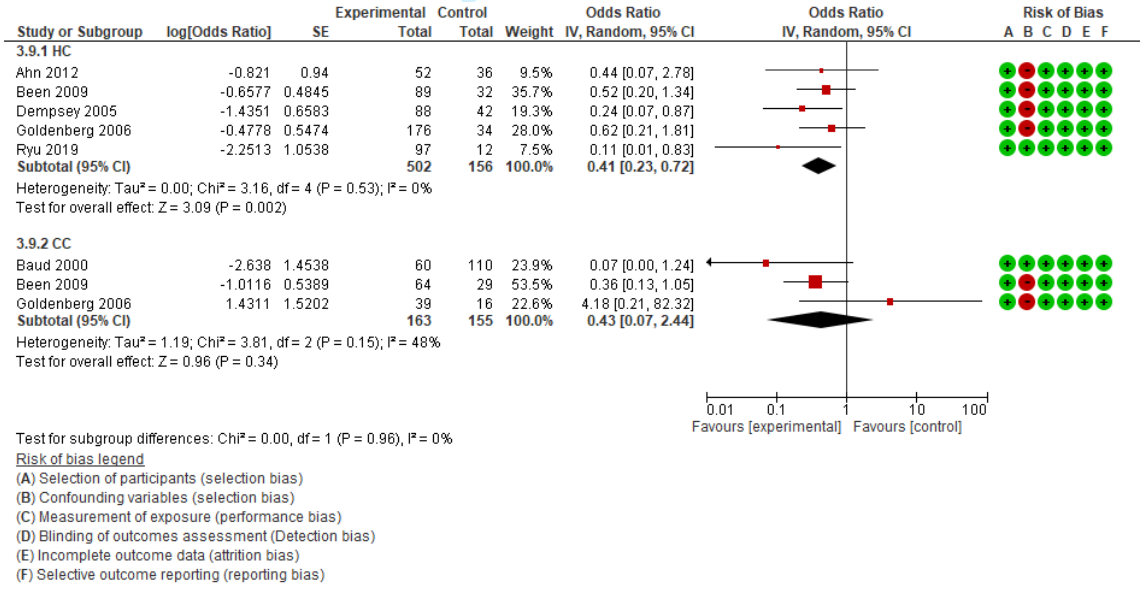
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

5) Severe intraventricular hemorrhage (IVH)



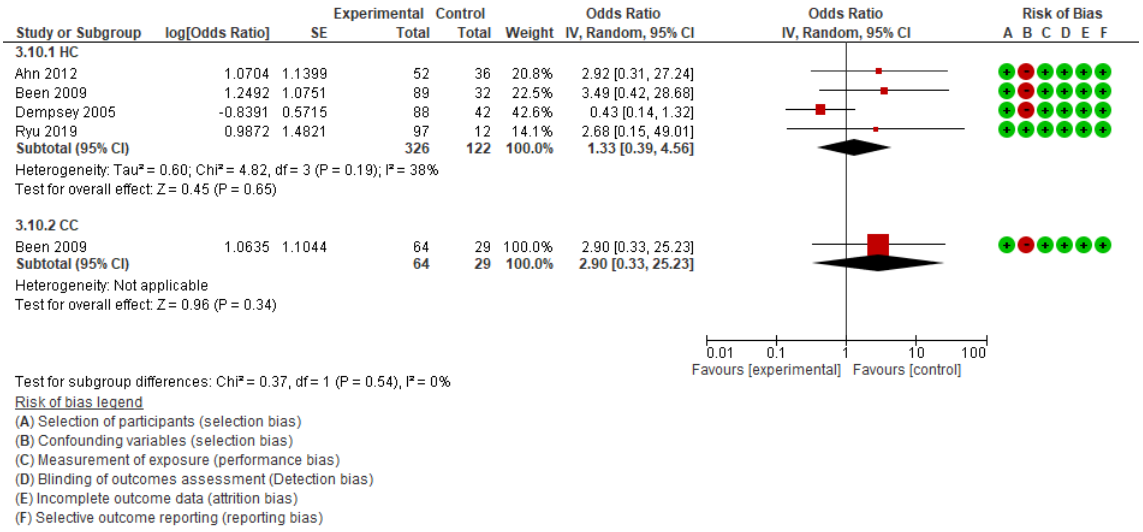
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



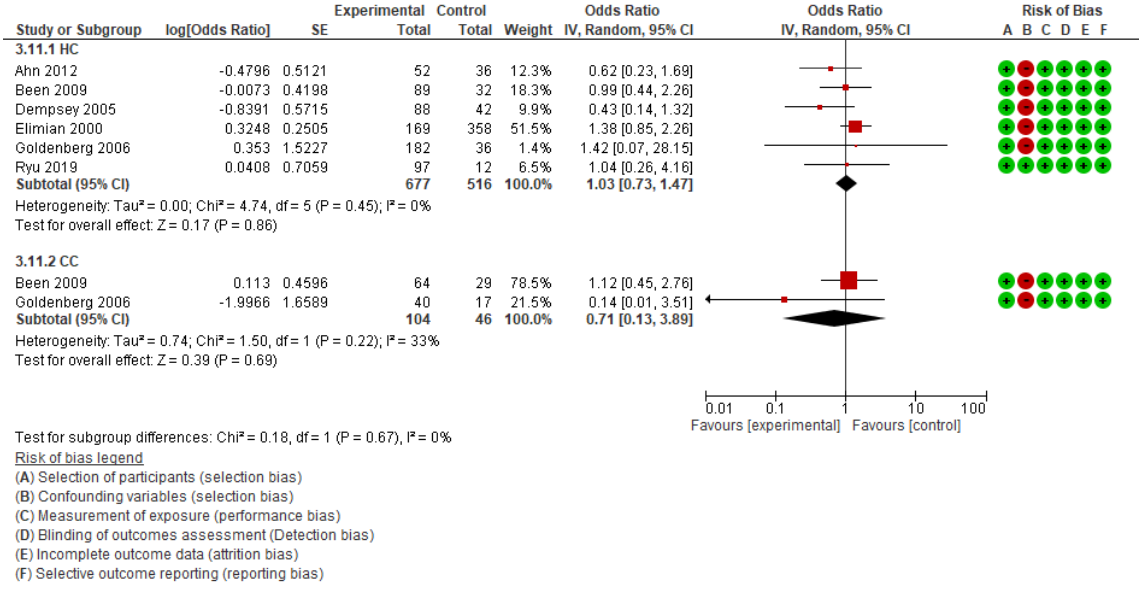
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

7) Early-onset sepsis



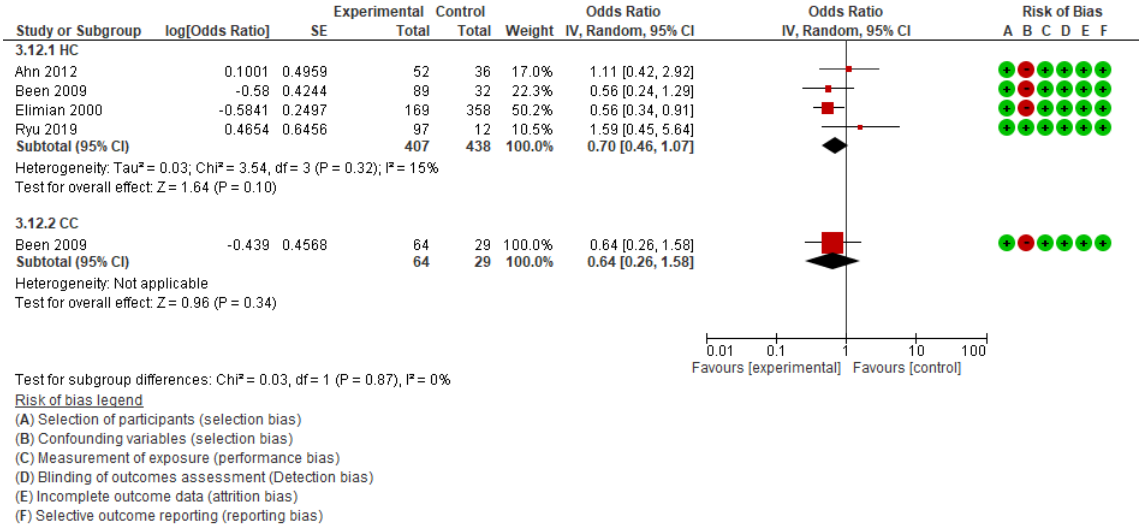
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

8) Sepsis



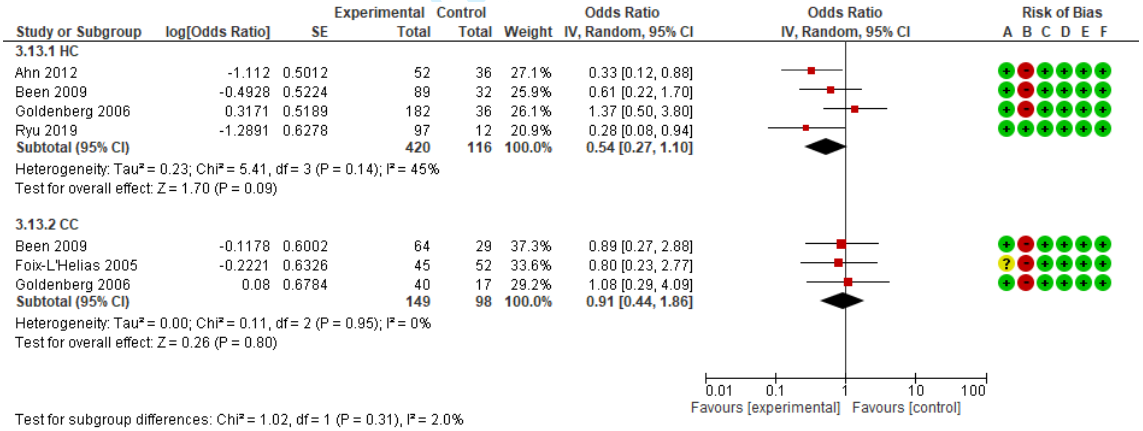
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



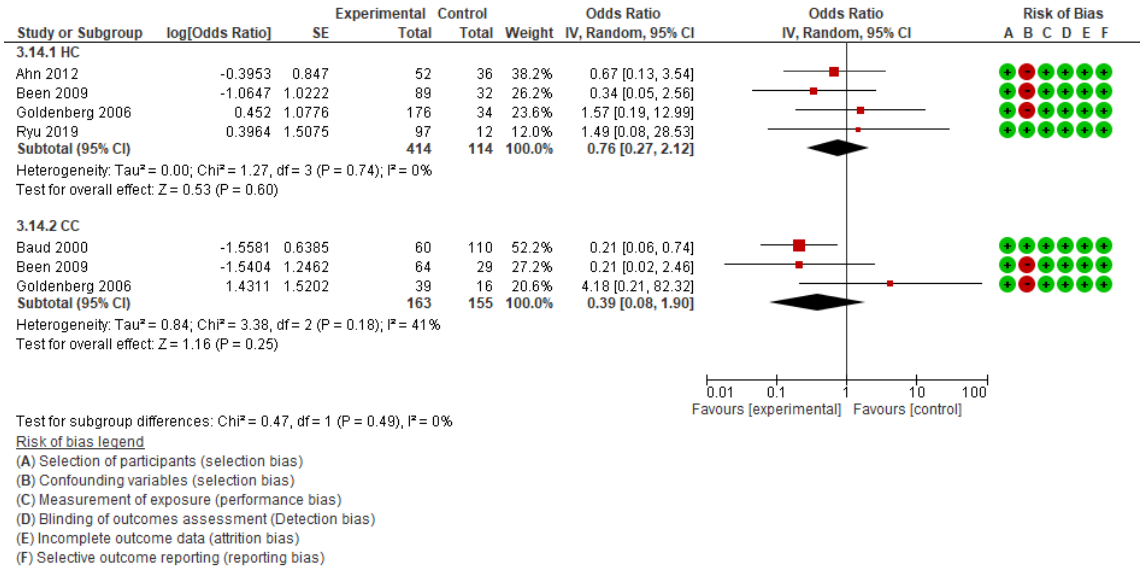
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

10) Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)



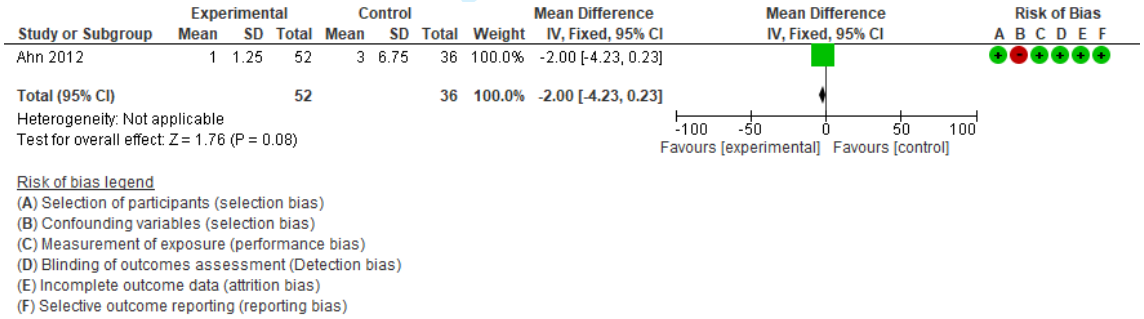
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

11) Periventricular leukomalacia (PVL)



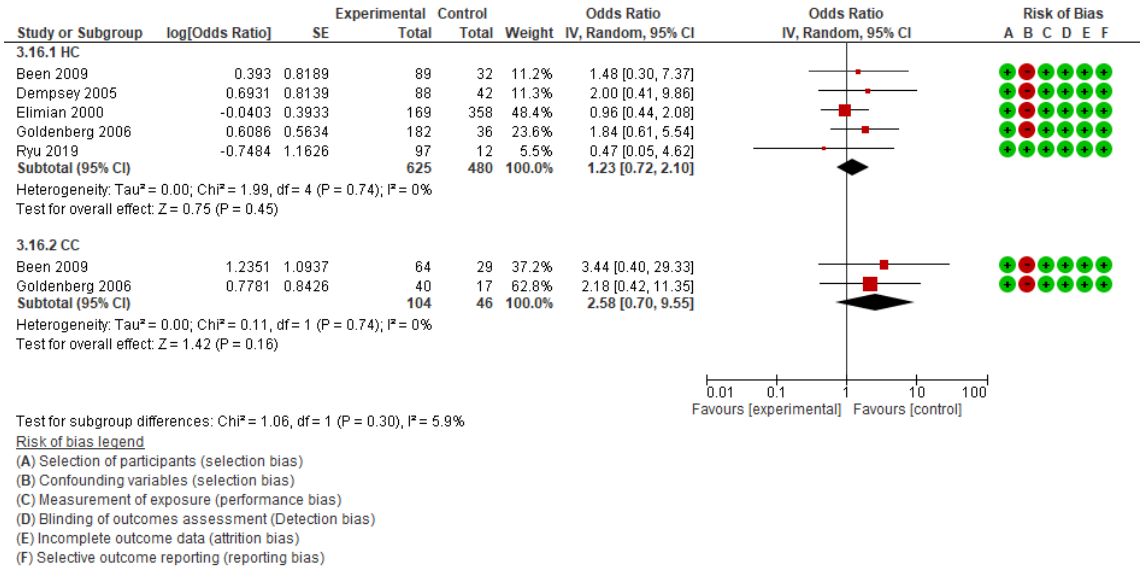
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

12) Mean duration of mechanical ventilation, days (HC)



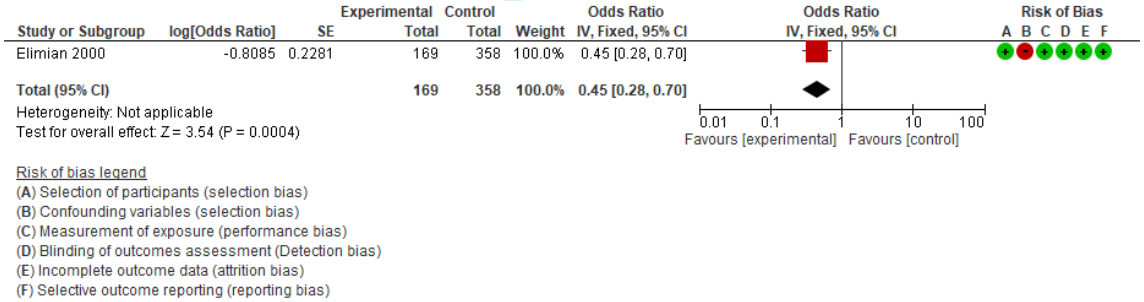
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

13) Necrotizing enterocolitis (NEC)



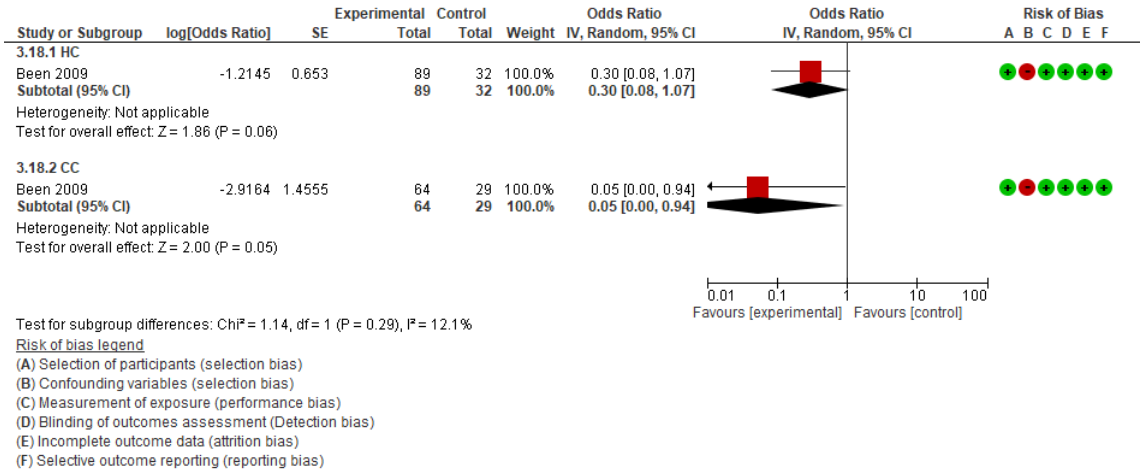
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

14) Apgar score < 7 at 5 minutes (HC)



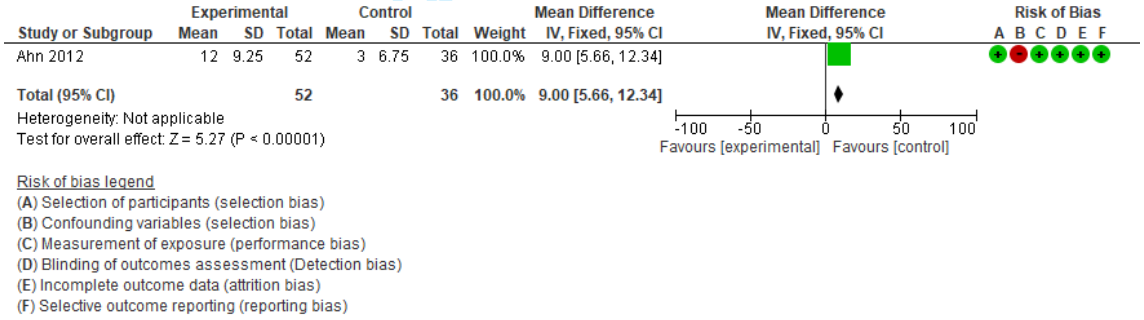
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

15) Use of mechanical ventilation



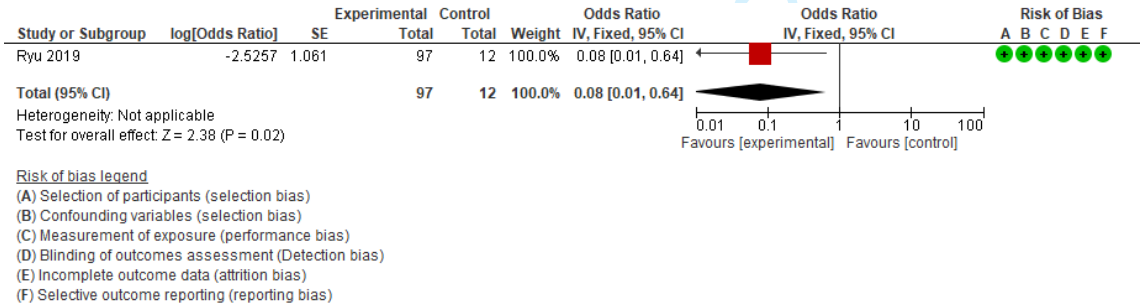
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)



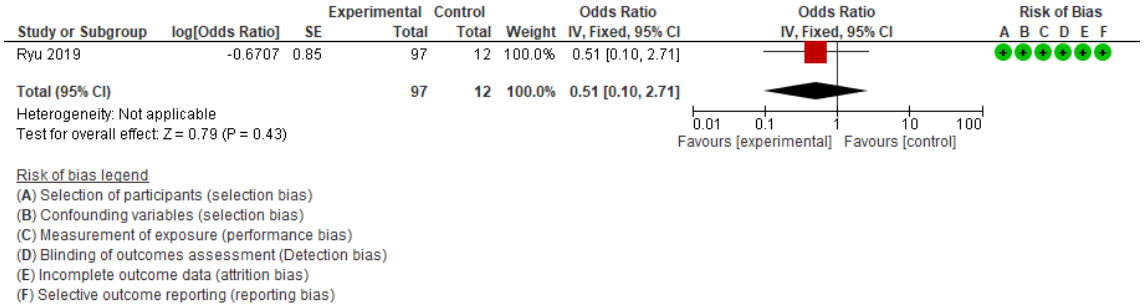
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

17) Hypotension within 7 postnatal days (HC)



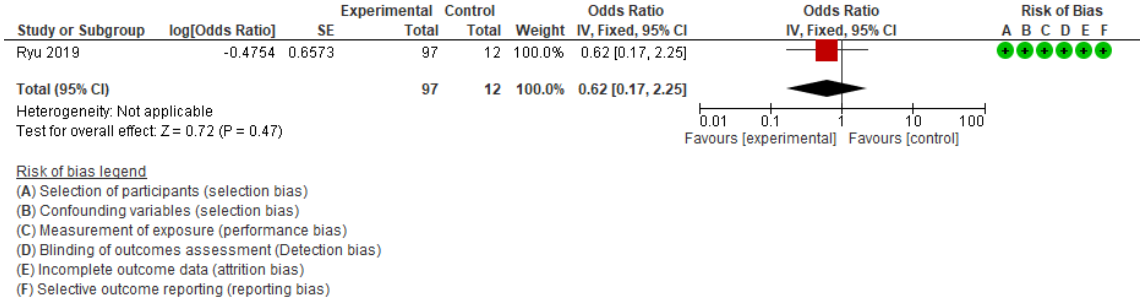
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Retinopathy of prematurity requiring treatment (HC)



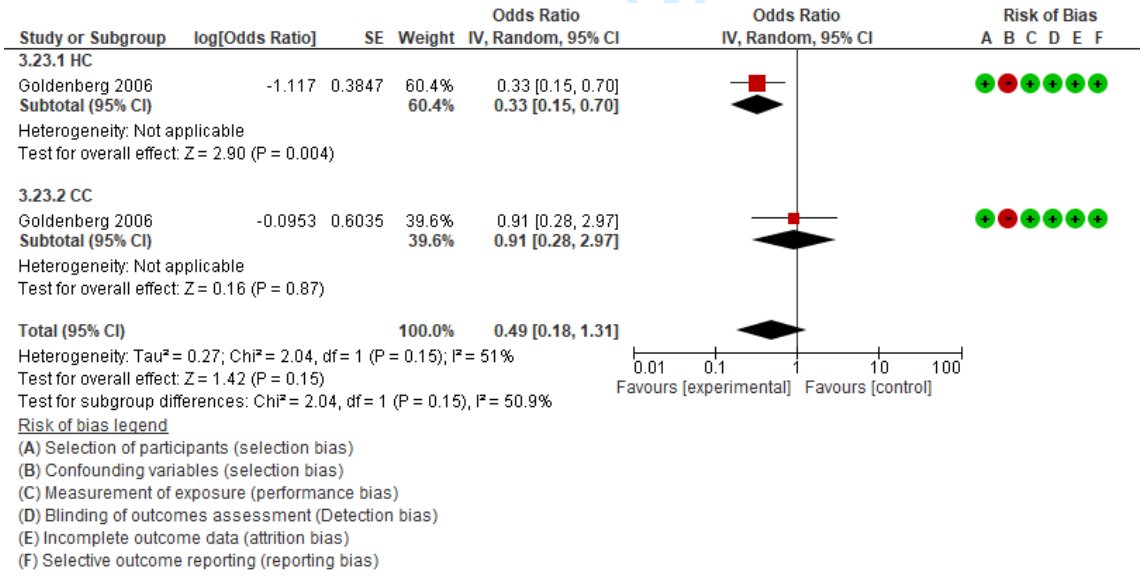
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

19) Discharge with respiratory support (HC)



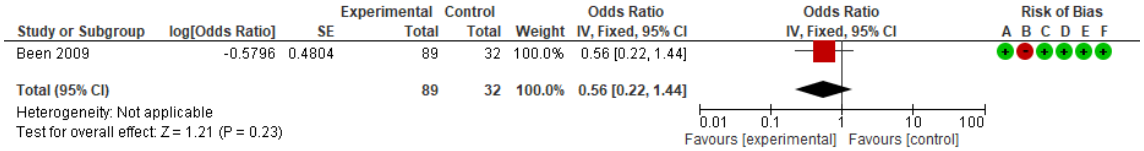
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

20) Systemic inflammatory response syndrome



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

21) Severe respiratory distress syndrome (RDS) (HC)



Risk of bias legend
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(D) Blinding of outcomes assessment (Detection bias)
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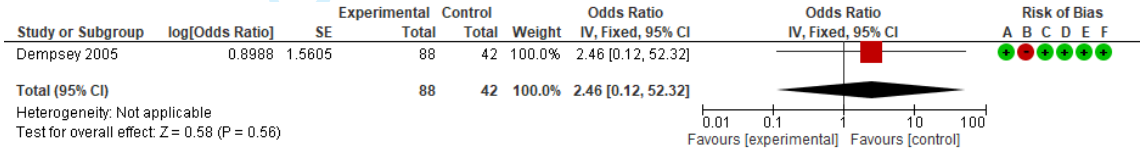
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

22) Meningitis (HC)



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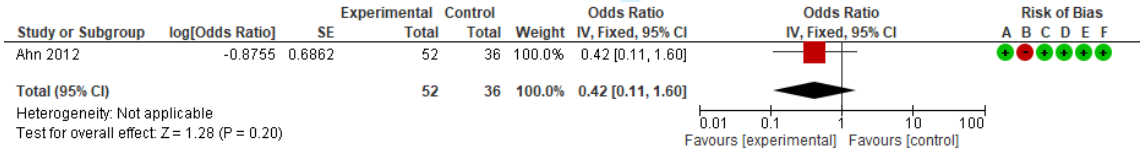
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

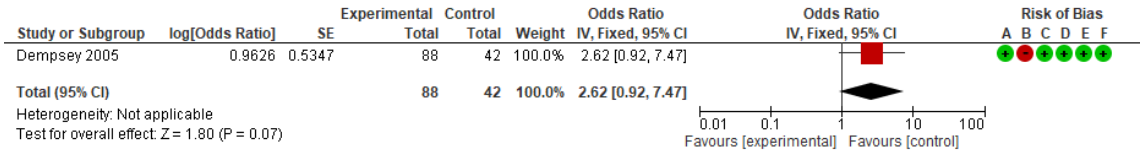
23) Intrahepatic cholestasis (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

24) Pneumonia (HC)



Risk of bias legend
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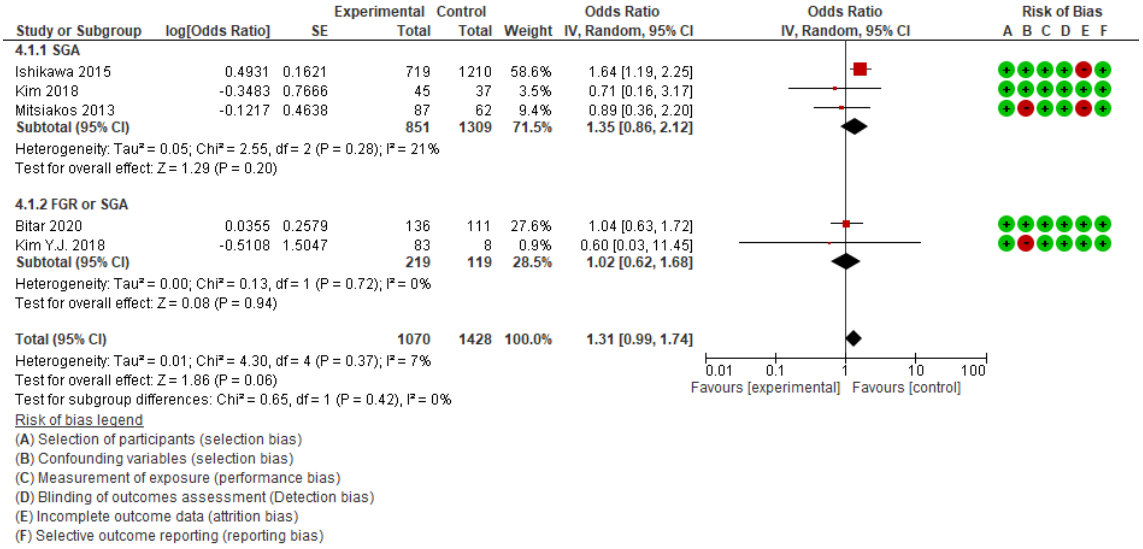
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

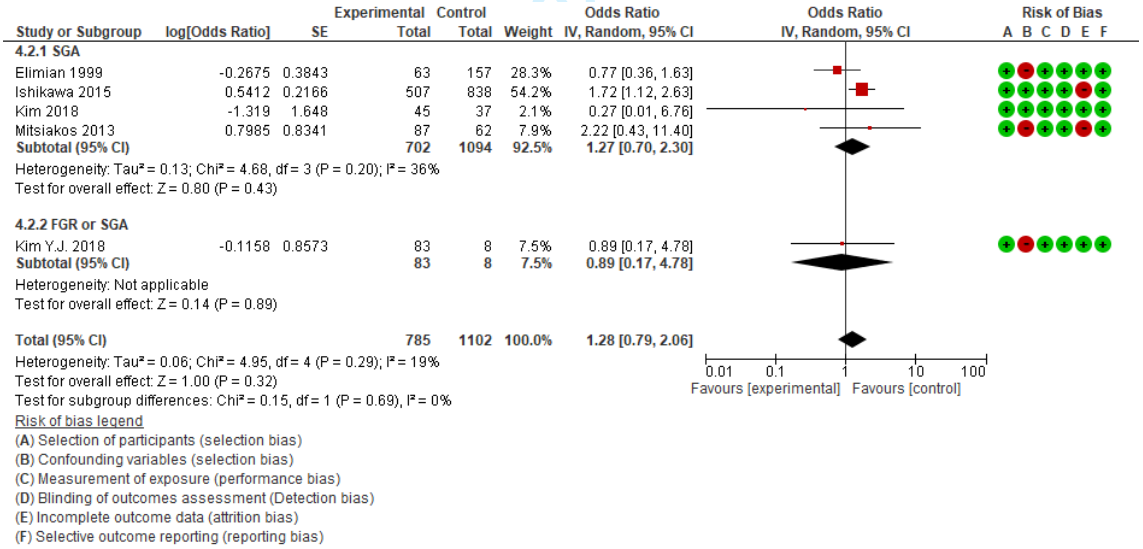
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



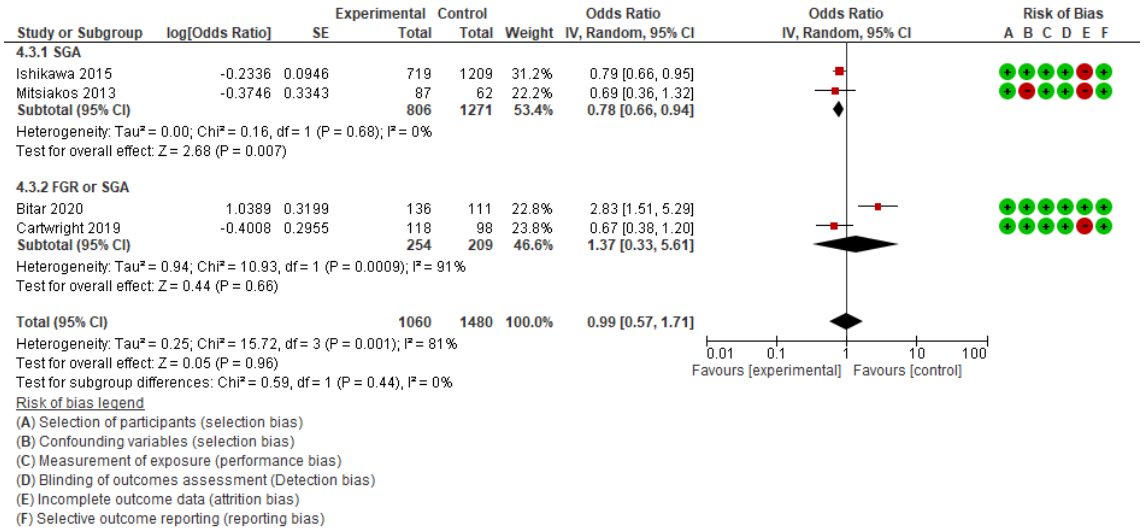
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Chorioamnionitis (histologic and /or clinical)



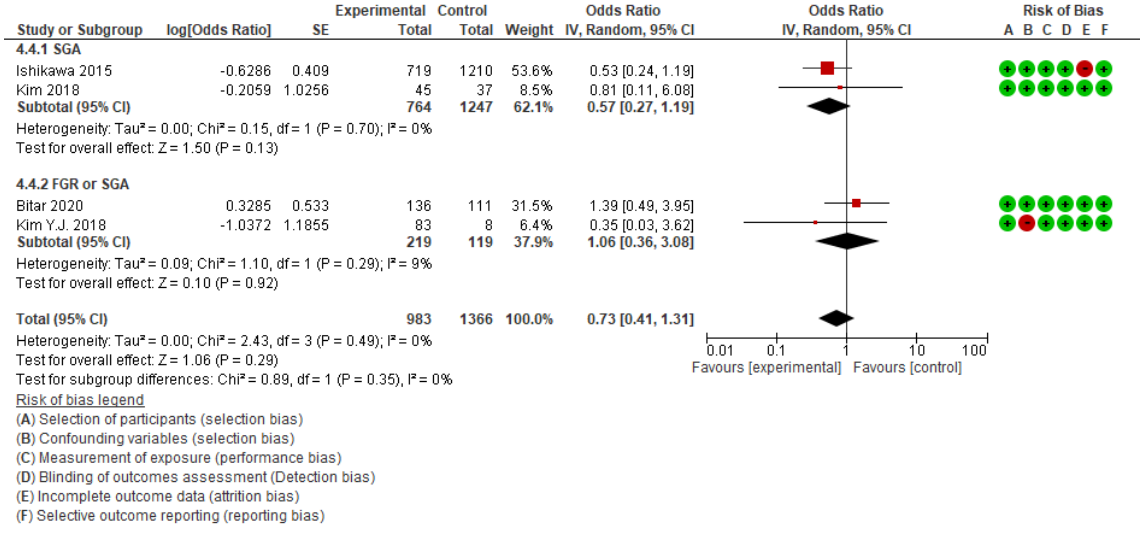
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Preeclampsia.



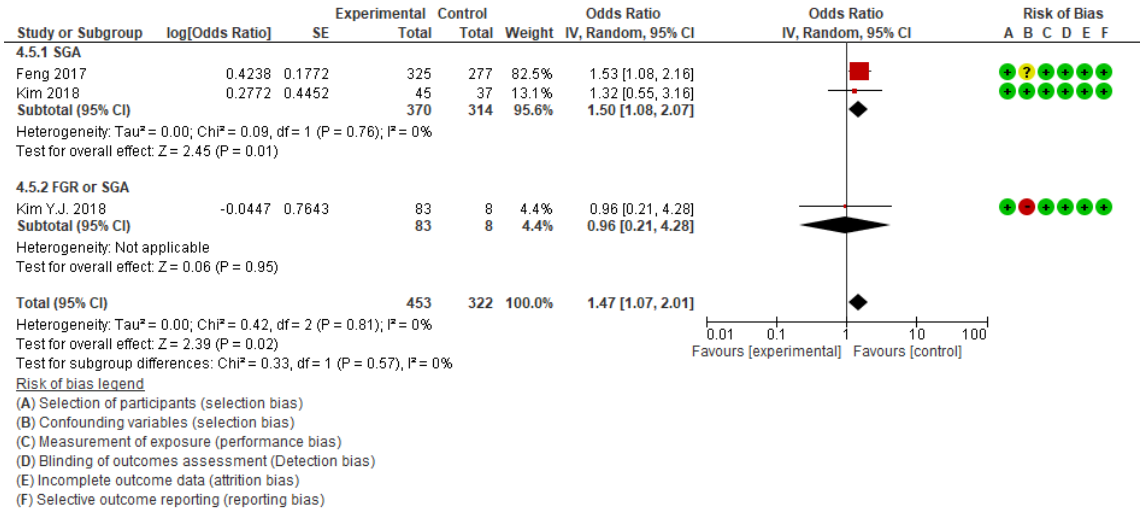
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Gestational diabetes mellitus.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

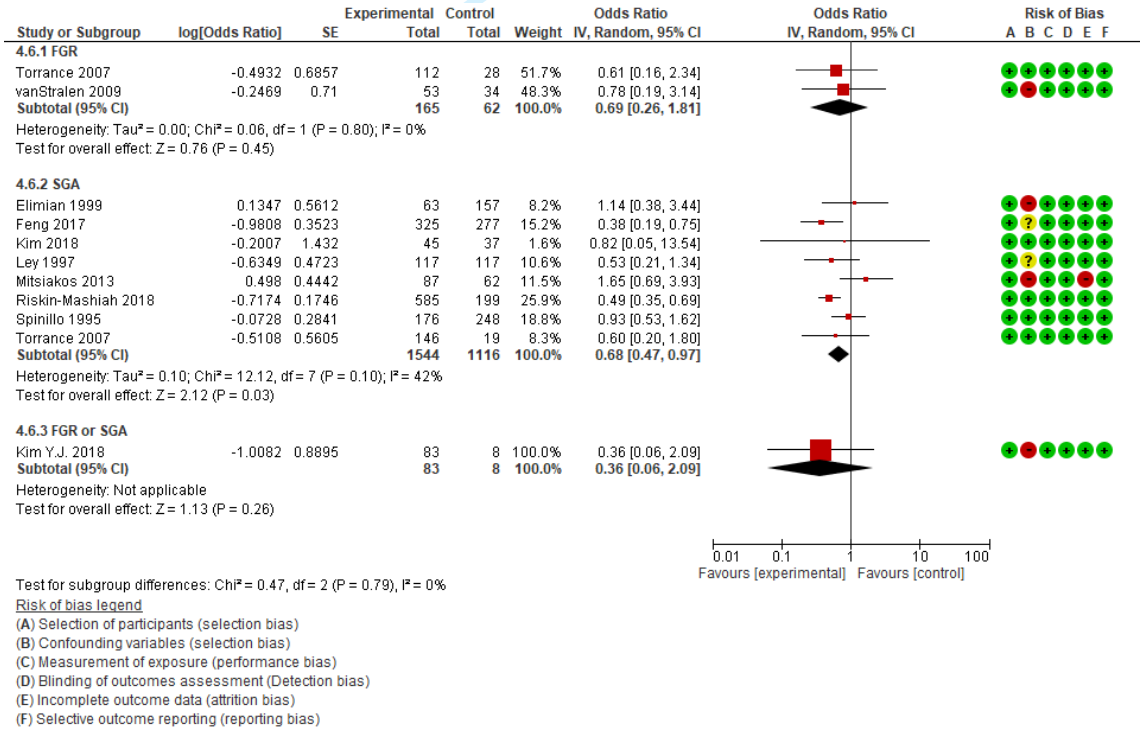
5) Pregnancy induced hypertension.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

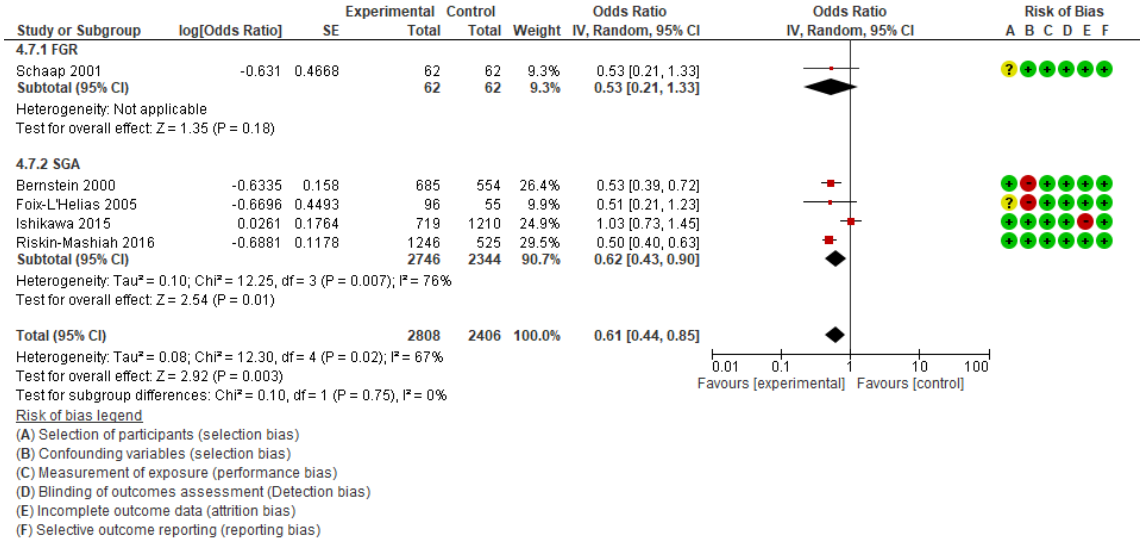
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



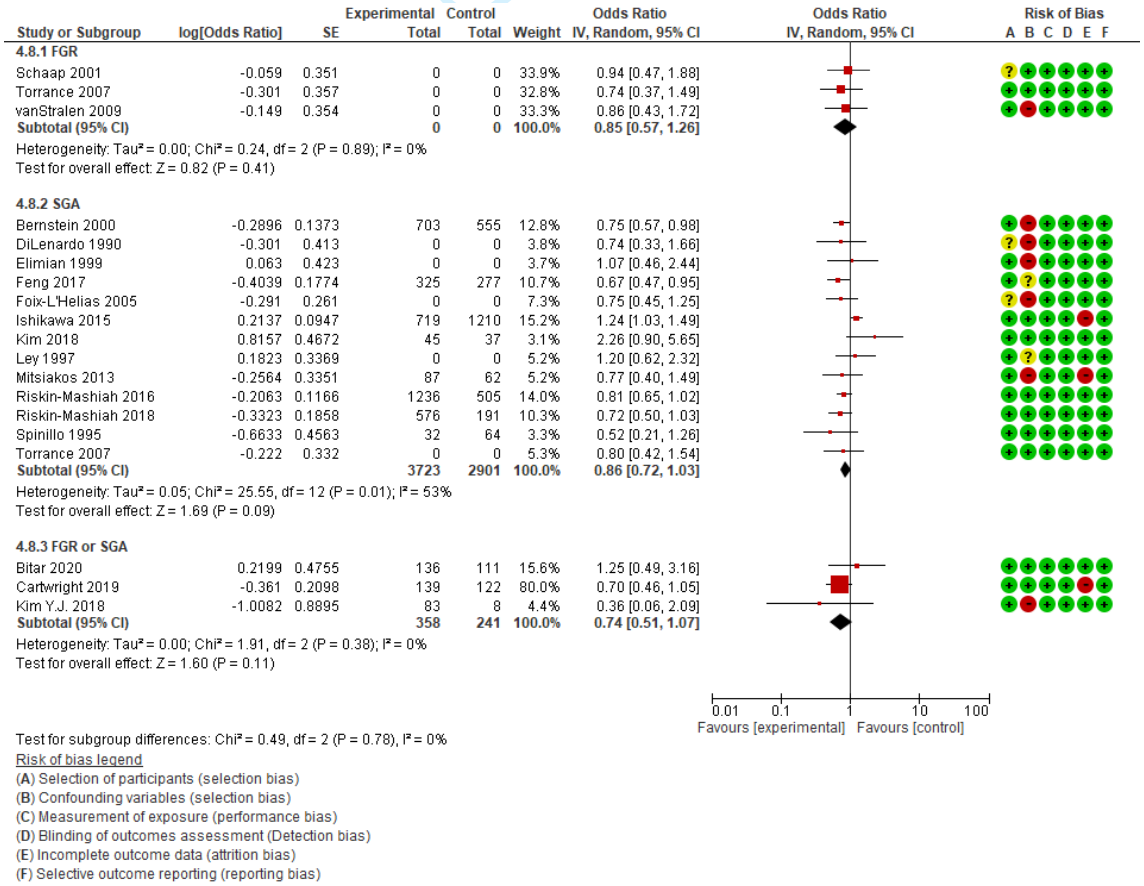
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Death before discharge home



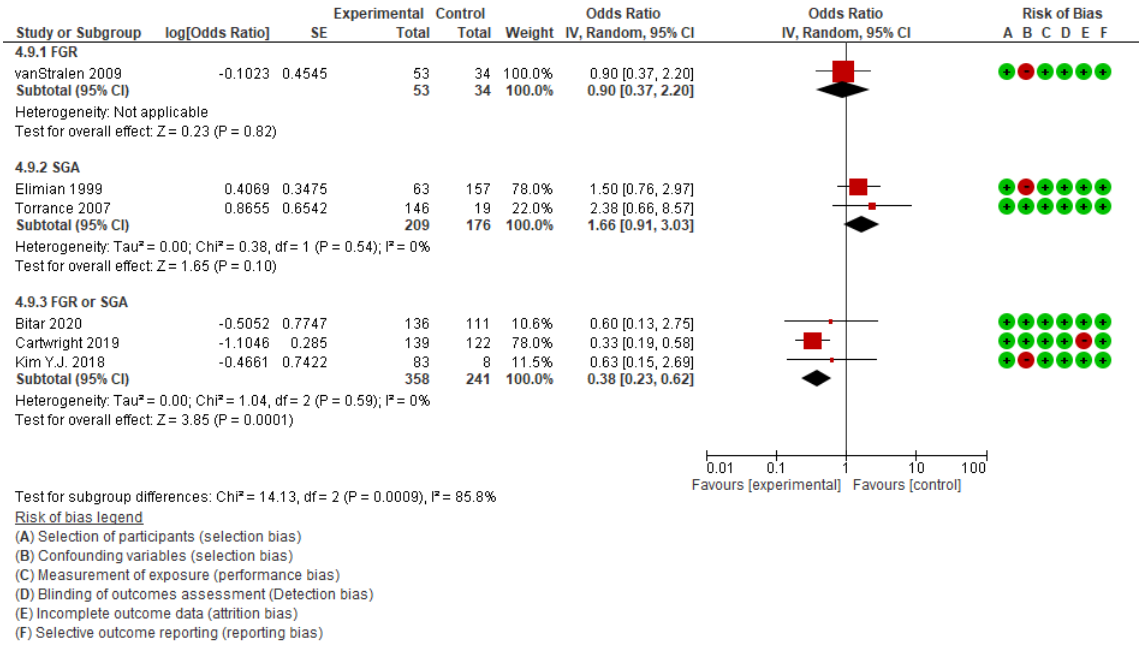
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Respiratory distress syndrome (RDS) and moderate / severe RDS



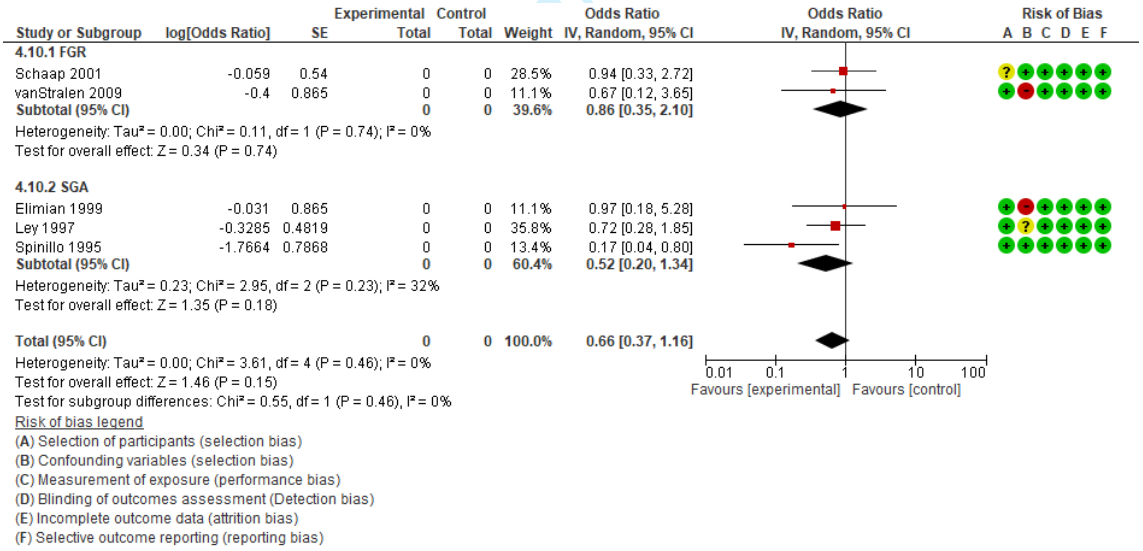
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Surfactant use



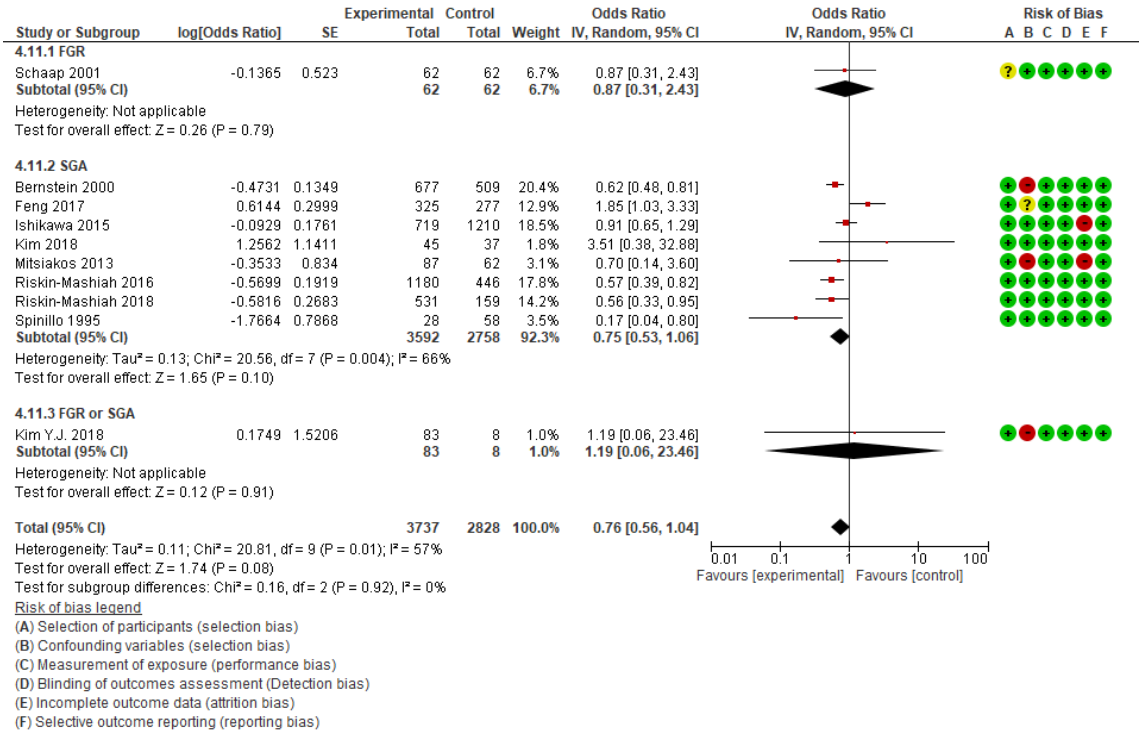
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

5) Major brain lesion (IVH, ICH, PVH, PVL)



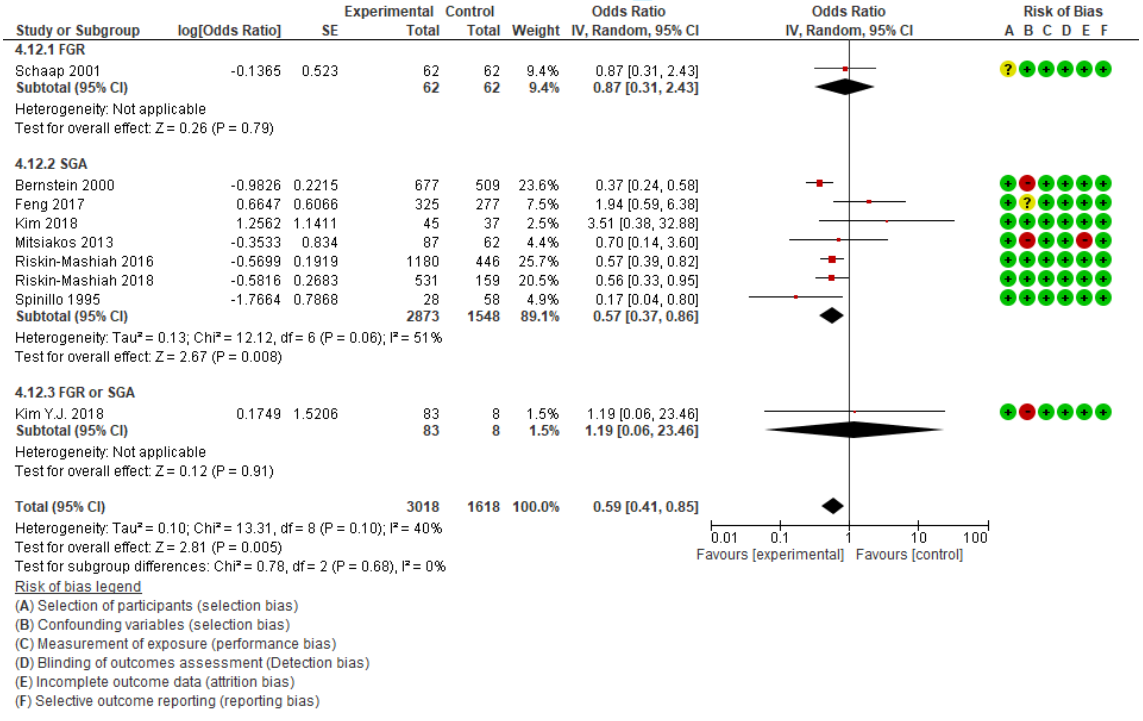
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

6) Interventricular haemorrhage



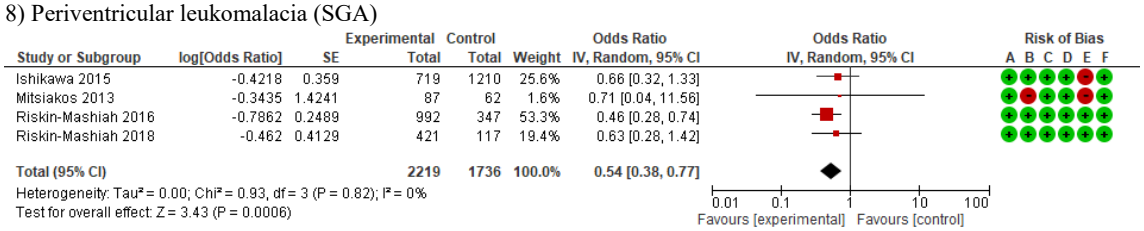
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

7) Severe interventricular haemorrhage (grade3-4)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

8) Periventricular leukomalacia (SGA)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
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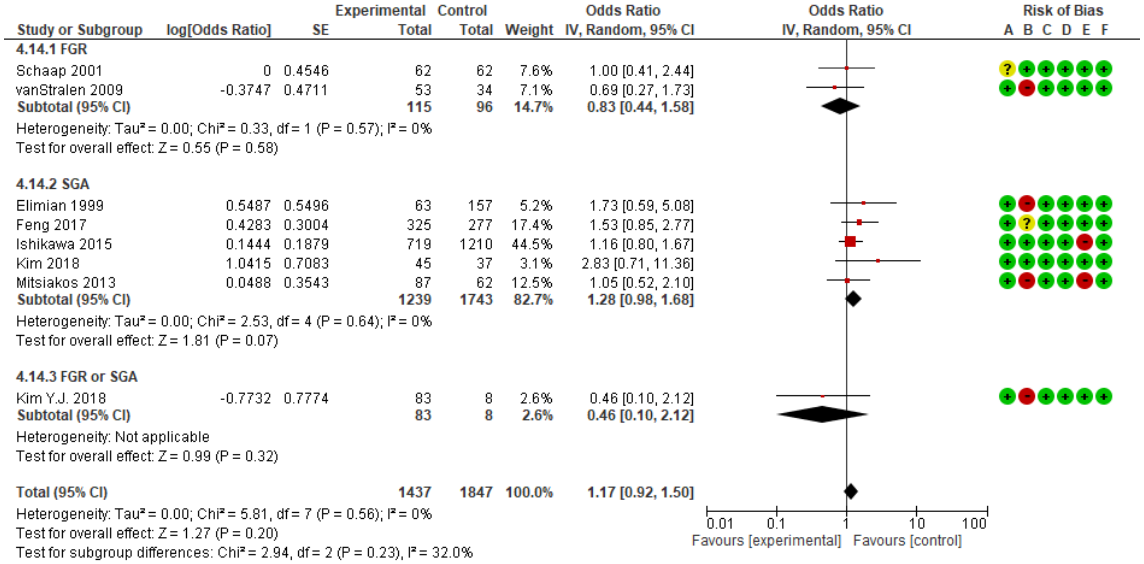
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

9) Neonatal sepsis



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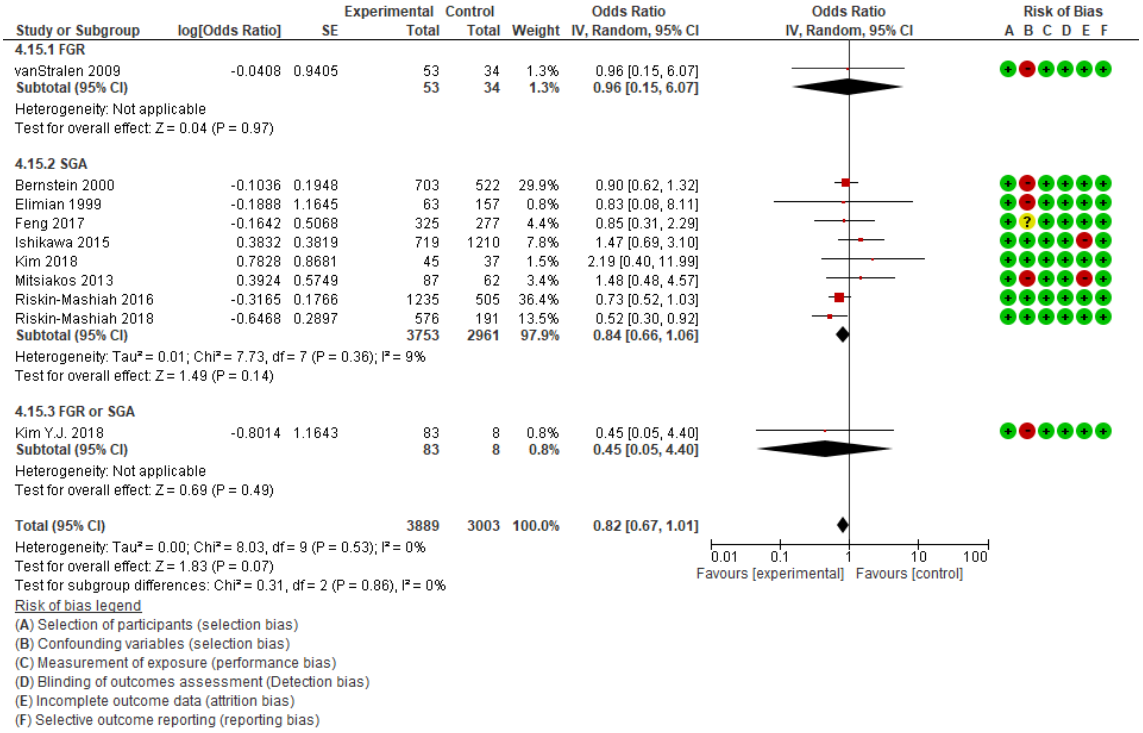
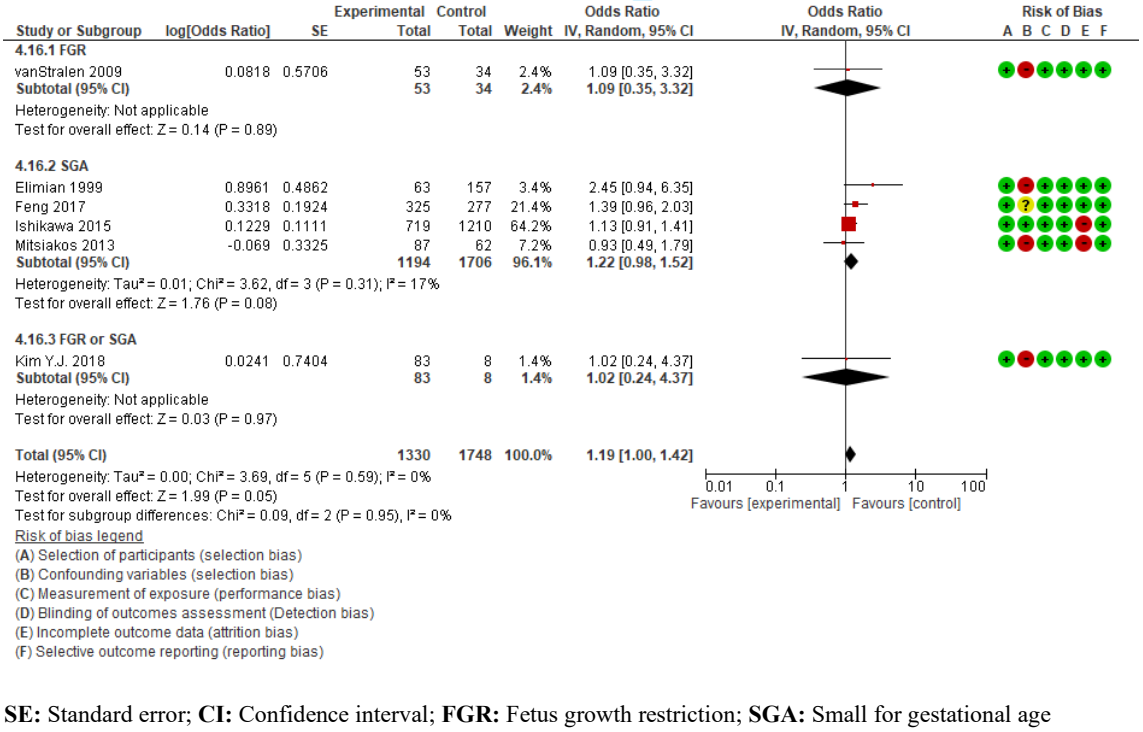
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

10) Necrotizing enterocolitis



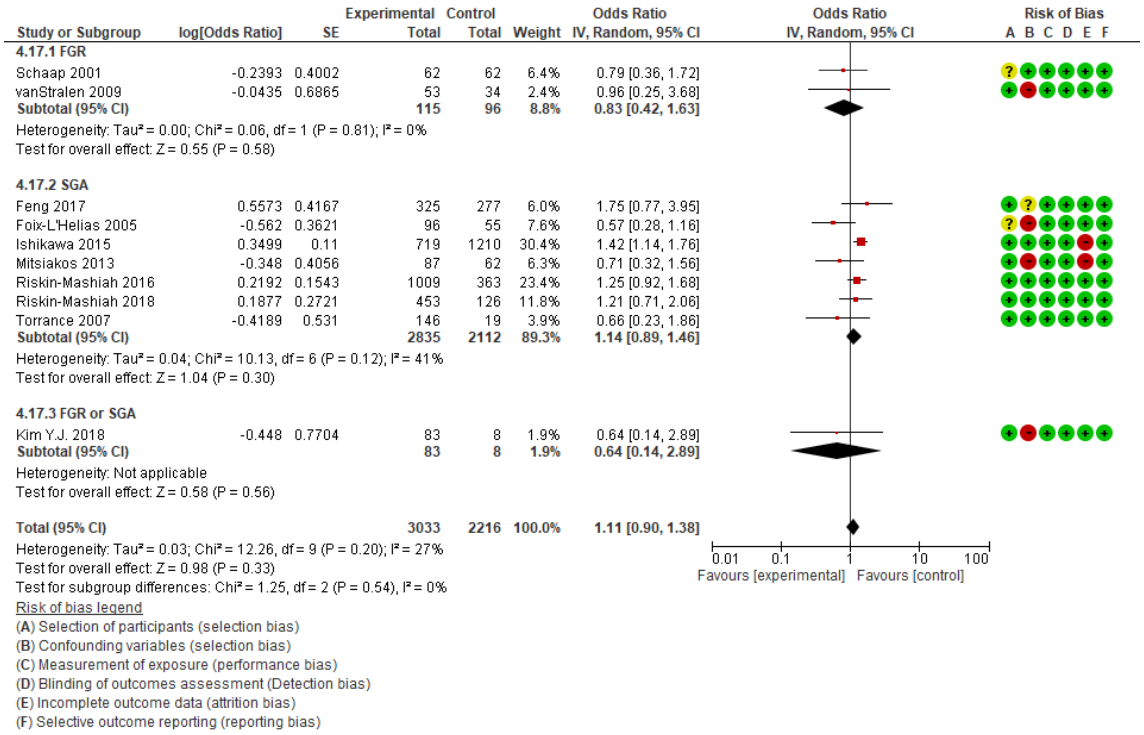
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

11) Patent ductus arteriosus



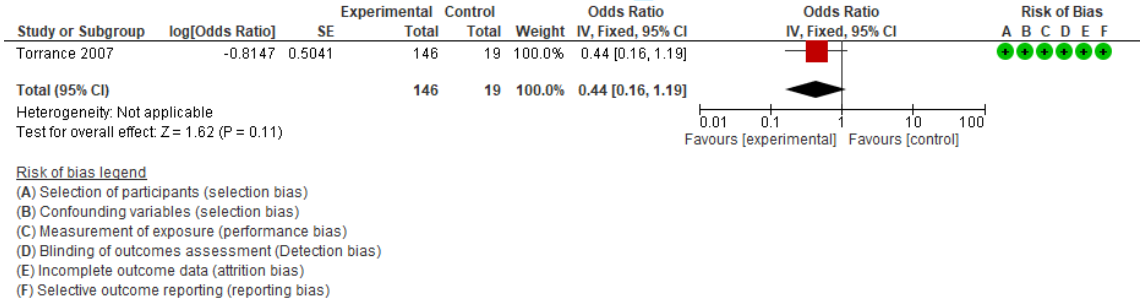
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



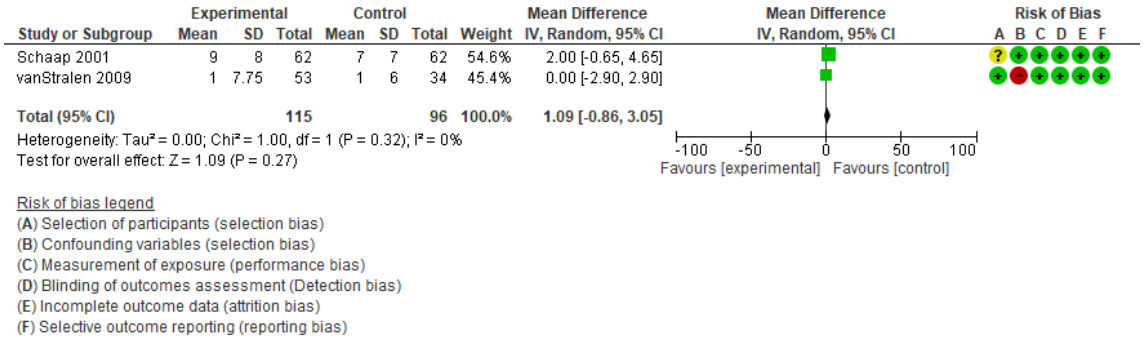
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

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



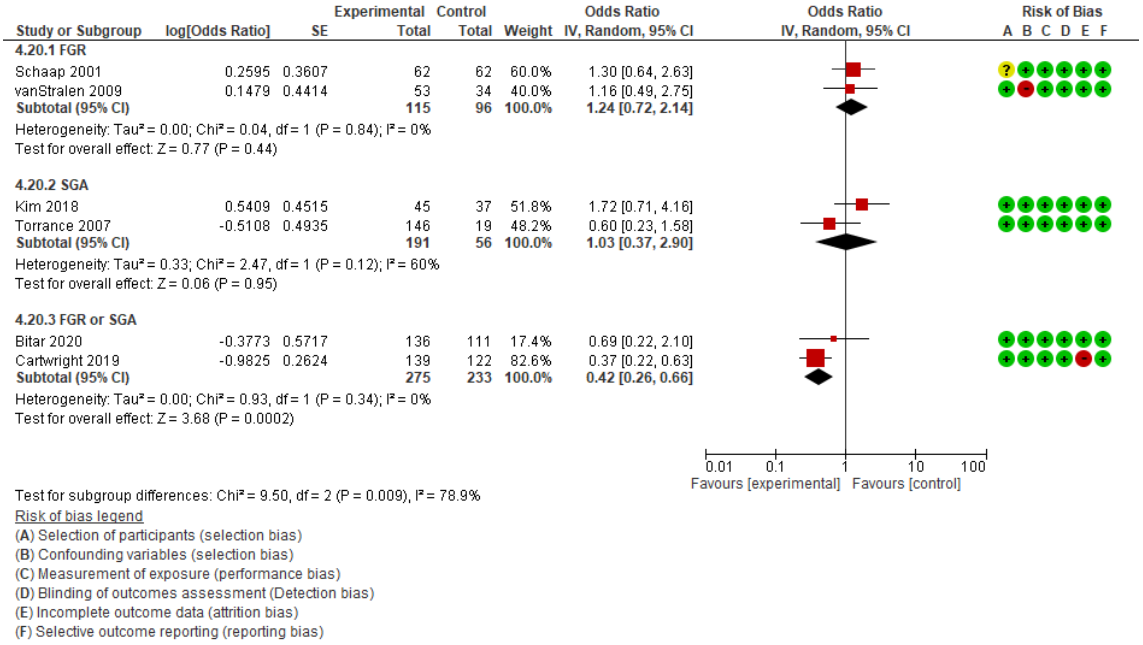
SE: Standard error; **CI:** Confidence interval

14) Duration of mechanical ventilation (FGR)



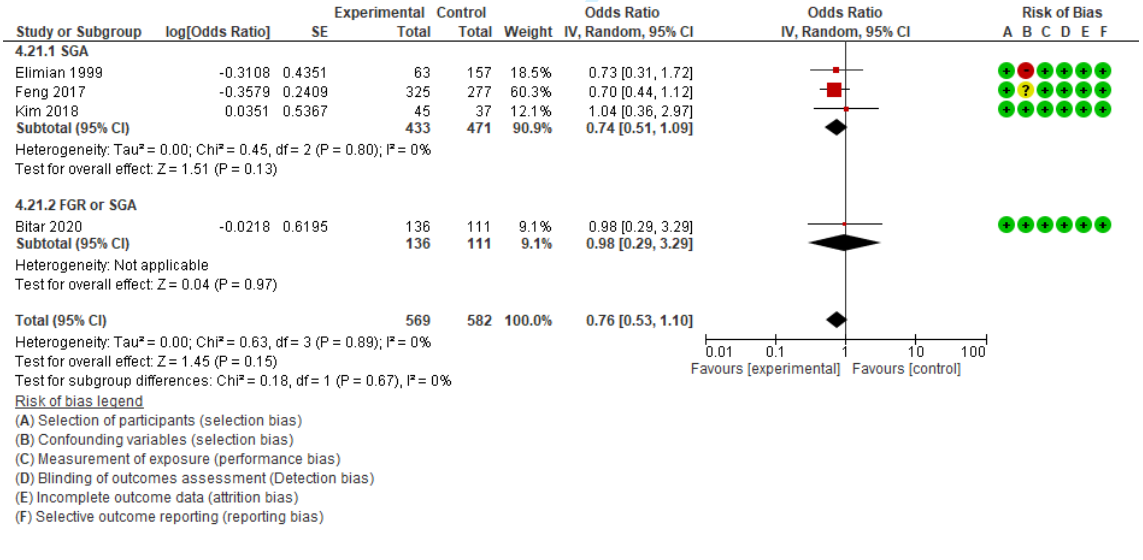
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

15) Use of mechanical ventilation



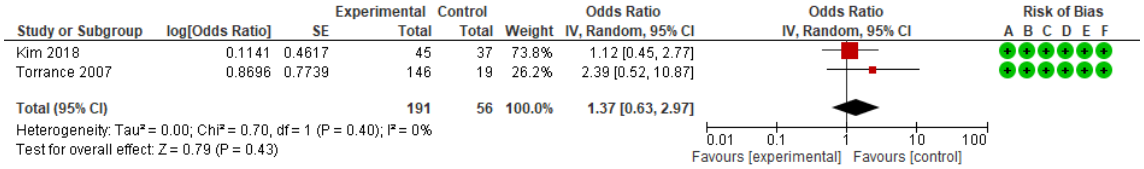
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

16) Apgar score < 7 at 5 minutes



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

17) Apgar score < 5 at 1 minute (SGA)



Risk of bias legend
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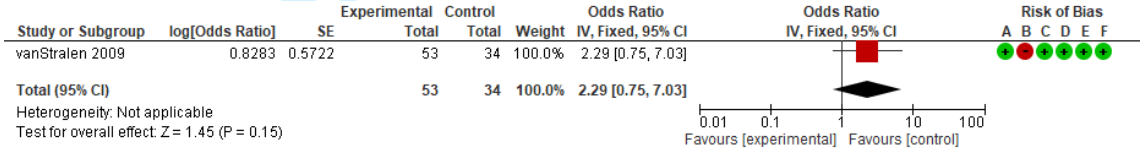
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

18) Hypotension (FGR)



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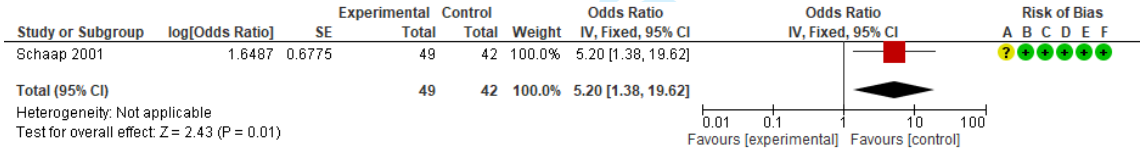
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

19) Growth < 10th percentile in early childhood (FGR)



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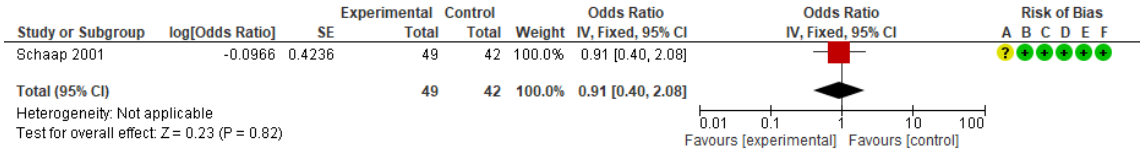
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

20) Abnormal behavior at long-term follow-up at school age (FGR)



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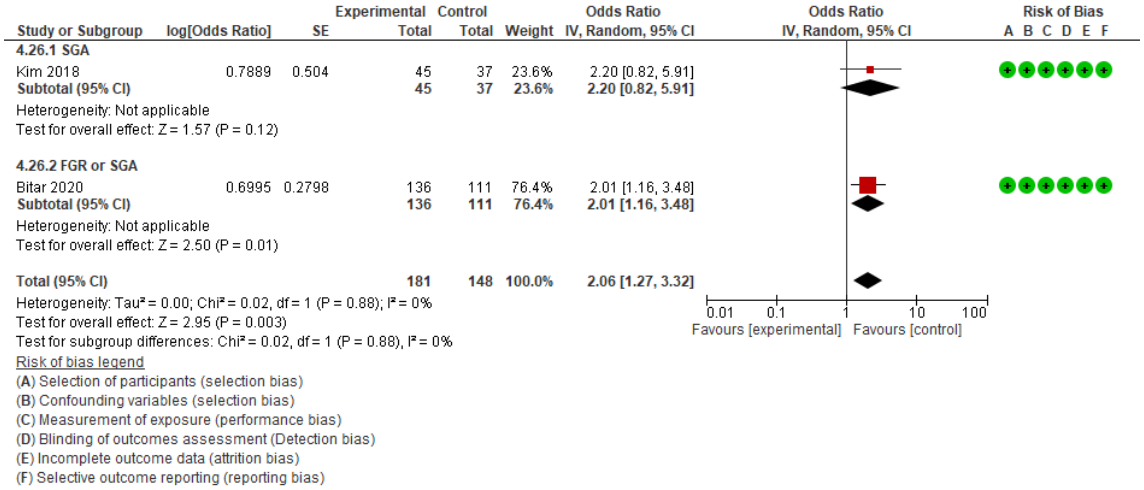
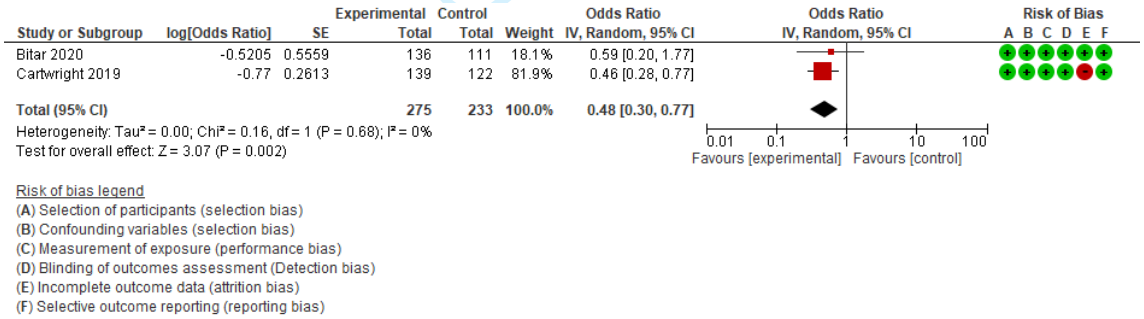
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

21) Neonatal hypoglycemia



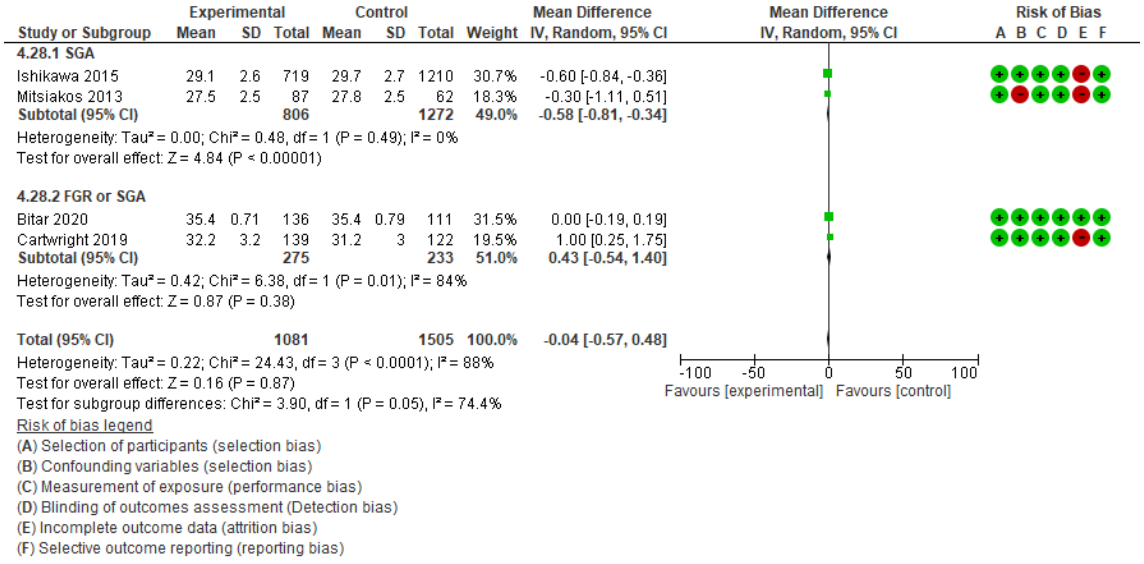
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

22) Oxygen therapy (FGR or SGA)



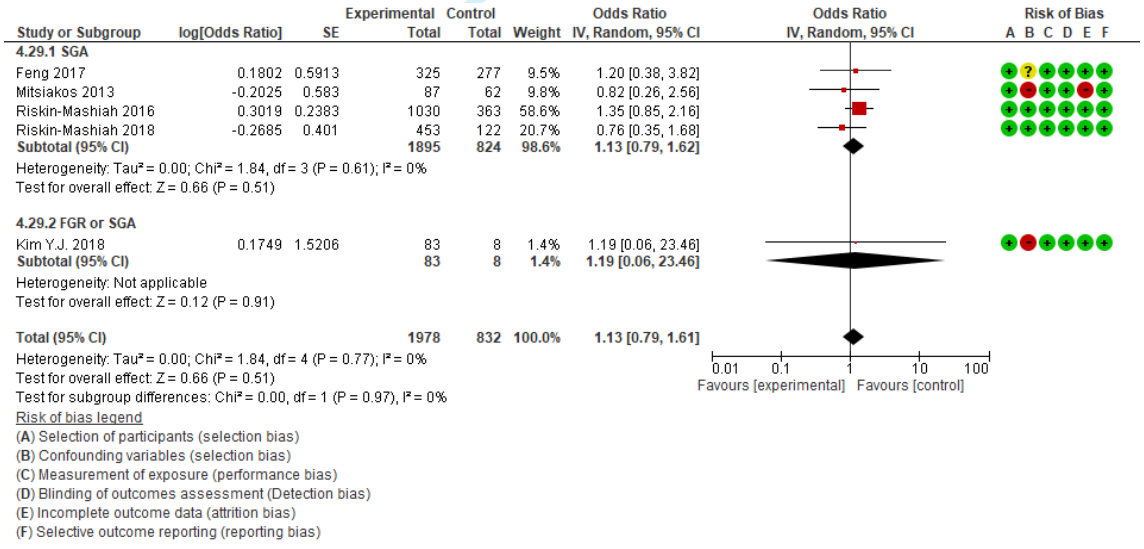
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

23) Gestational age at birth



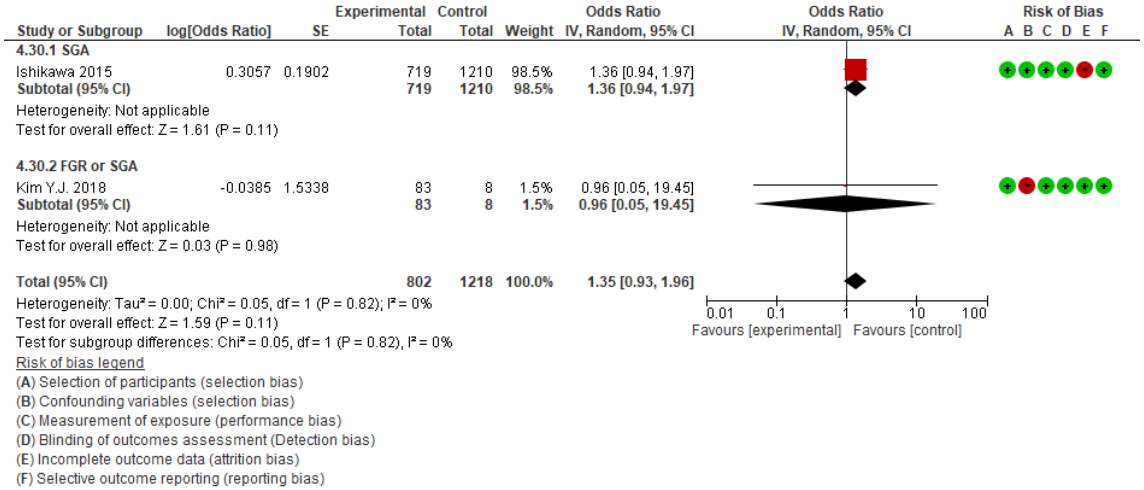
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

24) Retinopathy of prematurity



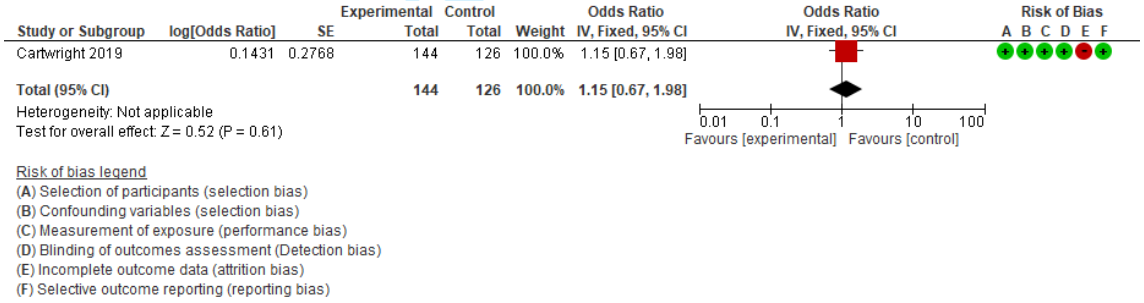
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

25) Neonatal adrenal insufficiency



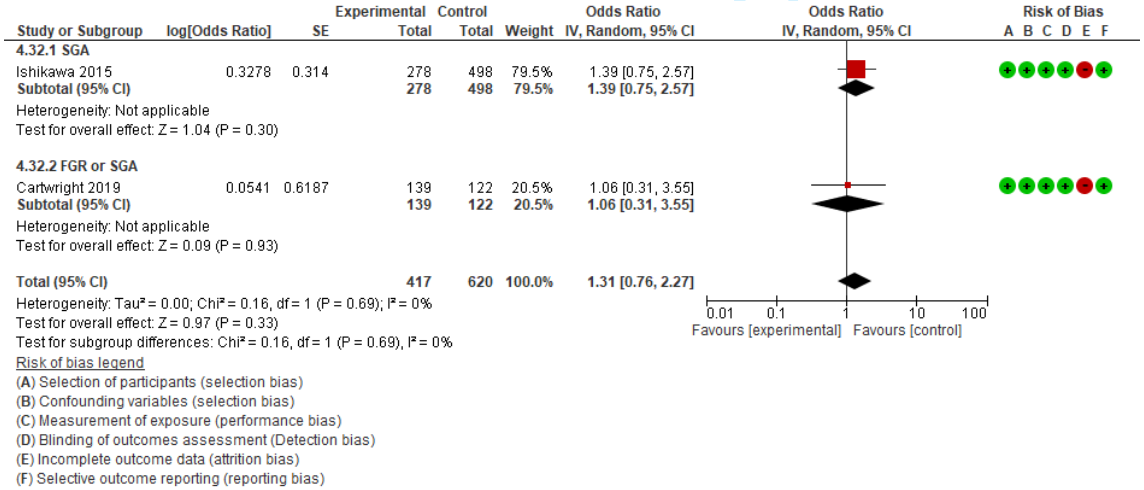
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

26) Survival free of disability (FGR or SGA)



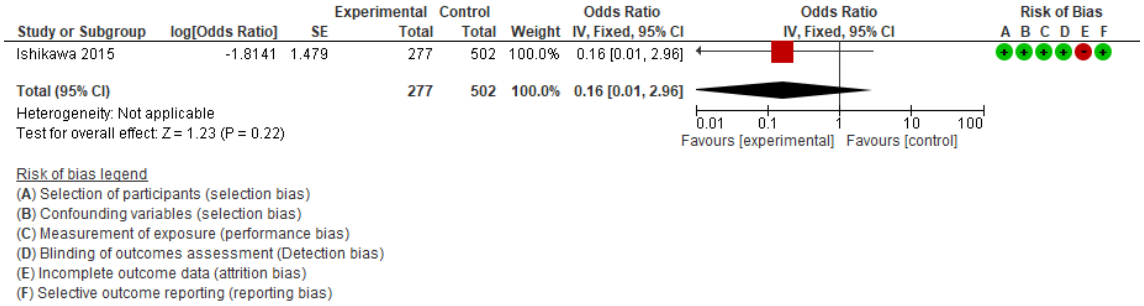
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

27) Cerebral palsy



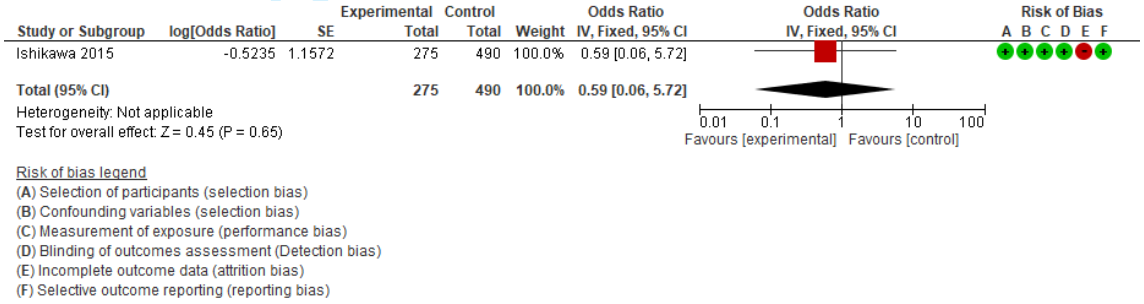
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

28) Severe hearing impairment (SGA)



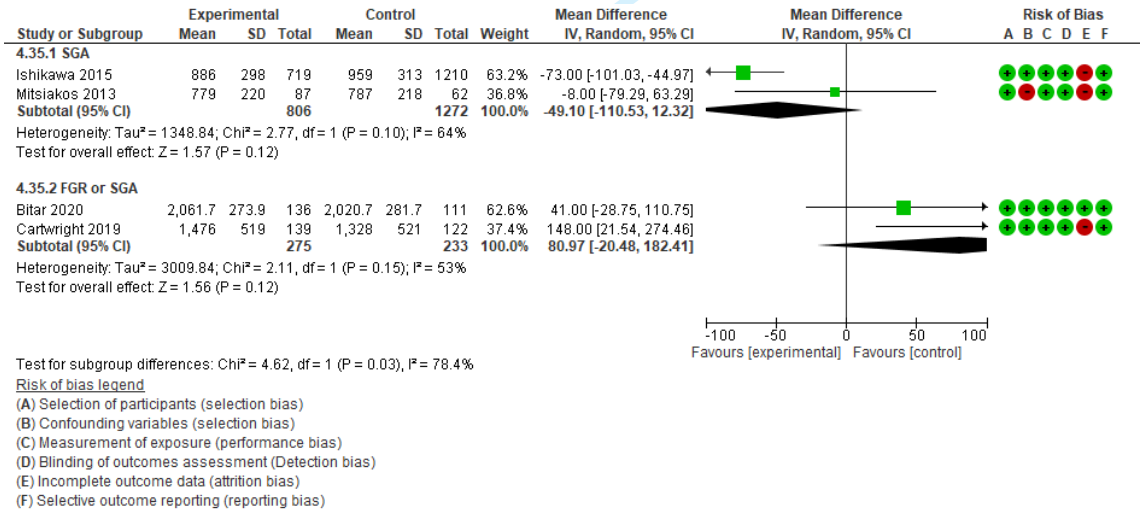
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

29) Visual impairment (SGA)



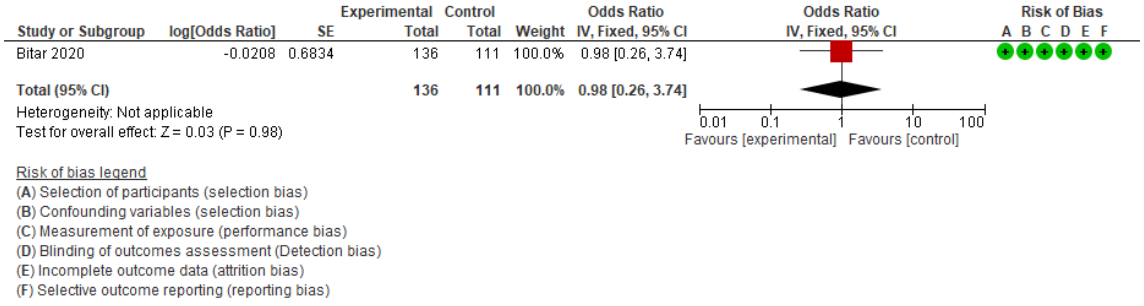
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

30) Birth weight



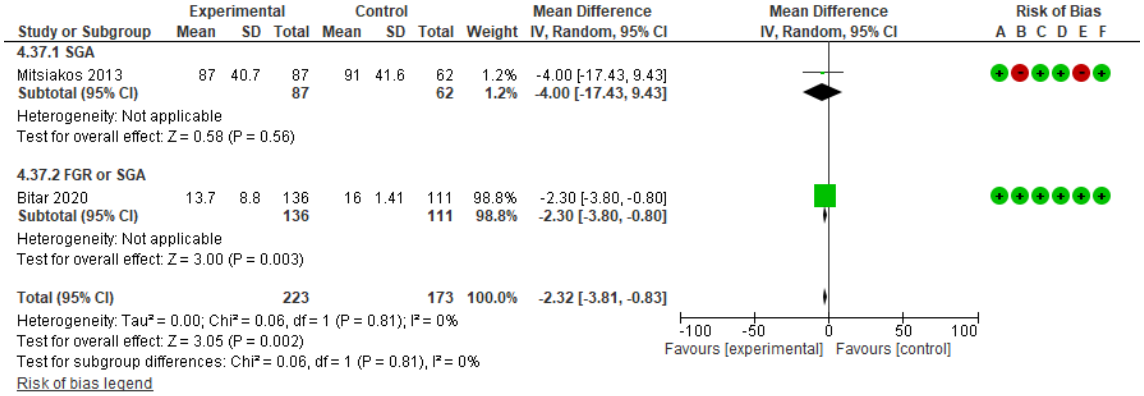
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

31) Admission to neonatal intensive care unit (FGR or SGA)



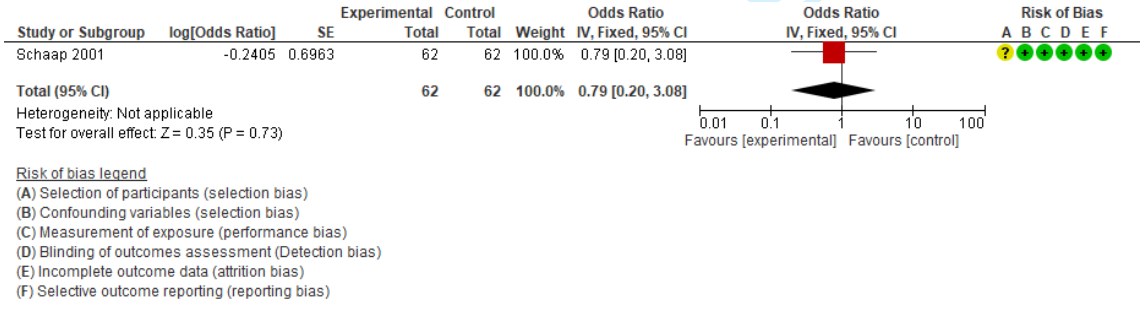
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

32) Duration of hospital stay



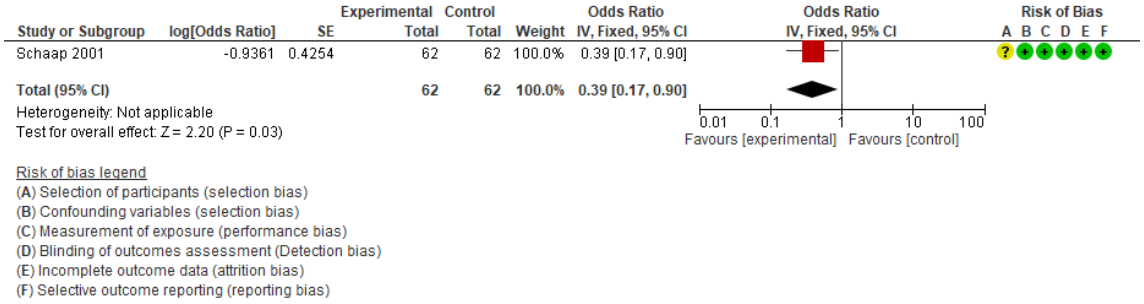
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

33) Death at long-term follow-up (school age) (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

34) Death or disability/handicap at 2yrs' corrected age (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

Supplementary table 1: Chracteristic tables

Table 1: Characteristics of included studies for women with pregestational and/or gestational diabetes mellitus

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	PGDM or GDM	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Battarbee et al., 2020	Retrospective cohort	Pregnant women 510 (439, 71) Infants 615 (536, 79)	2008–2011	USA	Women giving birth at GA 23–33weeks	Stillborn, nonresuscitated cases	PGDM or GDM	NS	NS	NS	Yes
Cassimatis et al., 2020	Retrospective cohort	Pregnant women=infants 54 (18, 36)	2014–2017	USA	Women giving birth in late preterm	Congenital anomalies, multiple pregnancy	PGDM	Beta	12	24	No
Krispin et al., 2018	Retrospective cohort	Pregnant women=infants 161 (47, 114) [1)]	2012–2016	Israel	Women giving birth in late preterm period	Preterm PROM, multiple gestations, PGDM, fetal anomaly, fetal chromosomal abnormalities	GDM	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, Dex: Dexamethasone, GA: Gestational age, GDM: Gestational diabetes mellitus, NS: Not stated, PGDM: Pregestational diabetes mellitus, PROM: Premature rupture of the membranes

[1)] This study included 2262 women who gave birth in the late preterm and term period. Data were extracted and reported for women in the late-preterm delivery group (n = 161) only.

Table 2: Characteristics of included studies for women undergoing elective cesarean section in the late preterm period

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	Antenatal corticosteroid course			
							Drug	Dose (mg)	Interval (h)	Repeat ACS

de la Huerga et al., 2019	Retrospective cohort	Pregnant women=infants 40 (30, 10)	2013–2017	Spain	Women undergoing elective CS between 35 weeks 0 days and 36 weeks 6 days	Congenital anomalies, transferred to other hospitals	Beta	NS	NS	NS
Kirshenbaum et al., 2018	Case-control	Pregnant women=infants 165 (58, 107)	2011–2013	Israel	Women undergoing elective CS between GA 34 weeks 0 days and 37 weeks 0 days	Multiple pregnancy, congenital anomalies, chromosomal abnormalities, chorioamnionitis	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, GA: Gestational age, NS: Not stated

Table 3-a: Characteristics of included studies for women with chorioamnionitis (histological or clinical)

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	HC CC	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Ryu et al., 2019	Retrospective cohort	Pregnant women=infants 109 (97, 12)	2007–2014	Republic of Korea	Women giving birth between GA 23weeks 0 days and 33 weeks 6 days	Multiple gestations, congenital anomalies, SGA or LGA, transferred to other hospitals, incomplete information	HC	Beta /Dex	NS	NS	No
Ahn et al., 2012	Prospective cohort	Pregnant women no data Infants 88 (52, 36)	2005–2010	Republic of Korea	Women giving birth at GA < 34 weeks	Congenital anomalies, transferred from other hospitals	HC	Dex	5	12	No
Been et al., 2009	Prospective cohort	Pregnant women=infants HC121 (89, 32) CC93 (64,29)	2001–2003	Netherlands	Women giving birth at GA < 32 weeks	Congenital anomalies	HC CC	Beta	12	24	No

Goldernberg et al., 2006	Retrospective cohort	Pregnant women=infants HC218 (182, 36) CC93 (64, 29)	1996–2001	USA	Women giving birth between GA 23 weeks 0 days and 32 weeks 6 days	Multiple gestations	HC CC	Beta	12	24	Yes
Dempsey et al., 2005	Retrospective cohort	Pregnant women=infants 130 (88, 42)	1989–1999	USA	Women giving birth at GA < 30 weeks	Multiple gestations	HC	Beta	12	24	NS
Foix-L'Helias et al., 2005	Retrospective cohort	Pregnant women=infants 97 (45, 52)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations	CC	Beta /Dex	12 6	24 12	Yes
Baud et al., 2000	Retrospective cohort	Pregnant women=infants 170 (60, 110)	1993–1997	France	Women giving birth at GA < 33 weeks	Multiple gestations, severe DM	CC	Beta /Dex	12 6	24 12	Yes
Elimian et al., 2000	Retrospective cohort	Pregnant women=infants 527 (169, 358)	1990–1997	USA	Birth weight: 500–1750 g	CC	HC	Beta	12	24	Yes

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CC: Clinical chorioamnionitis, Dex: Dexamethasone, DM: Diabetes mellitus, GA: Gestational age, HC: Histological chorioamnionitis, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

Table 3-b: Diagnostic criteria on histological and clinical chorioamnionitis from individual studies

Author, year	HC, CC	Diagnostic criteria
Ryu et al., 2019	HC	Salafia et al.*2
Ahn et al., 2012	HC	No written diagnostic criteria

Been et al., 2009	HC/ CC	HC: Redline et al. *3 CC: maternal temperature greater than 38.0°C in the absence of another focus for infection, with two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leucocytosis (WBC>15000cells/µL), raised serum C-reactive protein, maternal tachycardia (>100 beats/min), and fetal tachycardia (>160 beats/min)
Goldernberg et al., 2006	HC/ CC	HC: Redline et al.*3, Faye-Petersen et al.*4, Bendon et al.*5 CC: diagnosed by an obstetrician, usually for a combination of fever, abdominal pain, and elevated white count
Dempsey et al., 2005	HC	HC: the presence of abundant polymorphonuclear leukocytes in the chorion and amnion
Foix-L'Helias et al., 2005	CC	CC: defined by the association of preterm labor and at least two of the following criteria: a) maternal temperature greater than 38°C, b) maternal serum C reactive protein concentration >20mg/l, c) positive bacterial culture of amniotic fluid (amniocentesis), d) documented early onset neonatal sepsis
Baud et al., 2000	CC	CC: defined by the association of preterm labor and at least two pre and/ or intrapartum criteria of maternal fever (temperature > 38°C on at least two occasions); blood inflammatory response (C-reactive protein plasma concentration > 40 ml/L or white blood count > 18000/mm3; or bacteriological evidence of infection in amnionic fluid obtained by amniocentesis
Elimian et al., 2000	HC	HC: Salafia et al. *2

*1 HC: Histological chorioamnionitis ,CC: Clinical chorioamnionitis

*2 Salafia CM, Weigl C, Silberman L. The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. *Obstet Gynecol*. 1989;73(3 Pt 1):383-389.
*3 Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003;6(5):435-448. doi:10.1007/s10024-003-7070-y.
*4 Faye-Petersen O, Heller DS, Joshi VV. Handbook of Placental Pathology. Oxford: Taylor and Francis Medical Publishers; 2005. 142-52.
*5 Bendon RW, Faye-Petersen O, Pavlova Z, et al. Histologic features of chorioamnion membrane rupture: development of methodology. Pediatr Pathol Lab Med. 1997;17(1):27-42.

Table 4-a: Characteristics of included studies for women with growth-restricted fetuses and/or small for gestational age infants

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	FGR SGA	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Bitar et al., 2020	Retrospective cohort	Pregnant women=infants 247 (136, 111)	2015–2019	USA	Women giving birth between GA 34 weeks 0 days and 36 weeks 6 days	Multiple gestations, mother age ≥ 18 years	SGA or FGR	Beta	NS	NS	NS

Cartwright et al., 2019	Retrospective cohort	Pregnant women 216 (118, 98) Infants 261 (139, 122)	1998–2004	Australia New Zealand	Women giving birth at GA < 32 weeks, single, twin, and triplet pregnancy	Chorioamnionitis requiring urgent delivery, labor at the second stage, mature fetal lung development, and further steroid therapy	SGA or FGR	Beta	13.8	NS	Yes
Kim WJ et al., 2018	Retrospective cohort	Pregnant women=infants 82 (45, 37)	2009–2016	Republic of Korea	Women giving birth between GA 29 weeks 0 days and 34 weeks 6 days	Multiple gestations, still birth, major congenital abnormality, ACS administration within 24 h before births, ACS administration >7 days before birth	SGA	Dex	5	12	NS
Kim YJ et al., 2018	Retrospective cohort	Pregnant women=infants 91 (83, 8)	2007–2014	Republic of Korea	Women giving birth between GA 23 weeks 0 days and 33 weeks 6 days	Multiple gestations, major congenital abnormality, fetal hydrops, incomplete information, LGA, repeated ACS, transfer to other hospitals, SGA without fetal umbilical artery Doppler abnormalities	FGR or SGA	Beta/ Dex	NS	24 12	No
Riskin-Mashiah et al., 2018	Retrospective cohort	Pregnant women=infants 784 (585,199)	1995–2012	Israel	Women giving birth to twins between GA 24 weeks 0 days and 31 weeks 6 days	Congenital anomalies	SGA	NS	NS	NS	NS
Feng et al., 2017	Retrospective cohort	Pregnant women No data Infants 602 (325, 277)	2013–2014	China	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days	Major congenital abnormality, inherited metabolic disease	SGA	Beta/ Dex	12 5–6	24 12	No
Riskin-Mashiah et al., 2016	Retrospective cohort	Pregnant women=infants 1771 (1246, 525)	1995–2012	Israel	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital malformation, incomplete data	SGA	NS	NS	NS	NS
Ishikawa et al., 2015	Retrospective cohort	Pregnant women=infants 1929 (719, 1210)	2003–2007	Japan	Birth weight < 1500 g	Multiple gestations, Women giving birth ≥34 weeks, major congenital malformation, incomplete information, out-of-hospital birth	SGA	NS	NS	NS	NS

Mitsiakos et al., 2013	Retrospective cohort	Pregnant women=infants 149 (87, 62)	NS	Canada	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital anomalies	SGA	Beta	12	24	No
van Stralen et al, 2009	Retrospective cohort	Pregnant women=infants 88 (54,34)	2001–2005	Netherlands	Birth weight < 1500 g	Multiple gestations, major congenital malformation or infection, incomplete information	FGR	Beta	11.4	24	NS
Torrance et al., 2007	Retrospective cohort	Pregnant women 165 (146, 19) FGR140 (112,28), SGA165 (146, 19)	1999–2003	Netherlands	Women giving birth at GA < 34 weeks	Congenital, chromosomal or syndromic abnormalities	SGA	Beta	12	24	NS
Foix-L'Helias et al, 2005	Retrospective cohort	Pregnant women No data Infants 151 (96,55)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	NS	SGA	NS	NS	NS	NS
Schaap et al, 2001	Case-control	Pregnant women=infants 124 (62,62)	1984–1991	Netherlands	Women giving birth between GA 26 weeks 0 days and 31 weeks 6 days	ACS < 24 h before delivery, fetal death or fetal distress at admission to the hospital, abruptio placentae, lethal congenital abnormalities or infections, multiple gestations	FGR	Beta	12.5	24	NS
Bernstein et al, 2000 *1	Retrospective cohort	Pregnant women=infants 1258 (703,555)	1991–1996	USA, Canada	Women giving birth between GA 25 weeks 0 days and 30 weeks 6 days, white and African-American infants	Multiple gestations, major anomalies	SGA	NS	NS	NS	NS
Elimian et al, 1999	Retrospective cohort	Pregnant women No data Infants 220 (63,157)	1990–1997	USA	Birth weight ≤ 1750 g	NS	SGA	Beta	12	24	Yes

Ley et al, 1997	Retrospective cohort	Pregnant women No data Infants 234 (117, 117)	1984–1985	Sweden	Women giving birth at GA < 33 weeks	NS	SGA	NS	NS	NS	NS
Spinillo et al, 1995	Prospective cohort	Pregnant women No data Infants 96 (32,64)	1988–1993	Italy	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days, indetermined or immature lecithin/sphingomyelin ratio, planned delivery with medication complications, liveborn	Congenital anomalies	SGA	Beta/Dex	12 12	NS	NS
Lenardo et al, 1990	Retrospective cohort	Pregnant women=infants 72 (15,57)	NS	Italy	Women giving birth at GA ≤ 35 weeks	Twin gestations	SGA	Beta	12	24	NS

*ACS: Antenatal corticosteroid, Beta: Betamethasone, Dex: Dexamethasone, FGR: Fetal growth restriction, GA: Gestational age, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated
*1: The data was obtained through personal communication.

Table 4-b: Diagnostic criteria on fetal growth restriction (FGR) from individual studies

Author, year	Diagnostic criteria on FGR
Bitar et al., 2020	Identified by International Classification of Diseases, Tenth Revision (ICD-10) codes..
Cartwright et al., 2019	Defined a priori as one or more of the following: obstetric diagnosis of FGR at trial entry; cesarean delivery for FGR; or customized birth weight of no greater than the third centile (GROW, version 6.7.8.3; Perinatal Institute).

Kim YJ et al., 2018	Defined as any fetal growth restriction (estimated fetal weight <10th percentile) documented from serial maternal medical records or a birth weight of less than the 10th percebtile based on the growth curve of Olsen et al. [*1]with absent or reverse umbilical artery end-diastolic flow in the fetal Doppler studies.
van Stralen et al, 2009	Defined id at least one measurement of the U/C ratio was higher than 0.725.[*2] U:umbilical artery, C:middle cerebaral artery
Schaap et al, 2001	Diagnosed by fundal height measurement and by sonographic fetal biometry. The FGR was due to placental dysfunction, as confirmed by pathological examination of placenta.

*1 Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010;125(2):e214-e224. doi:10.1542/peds.2009-0913
*2 Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol. 1993;169(1):169-175. doi:10.1016/0002-9378(93)90156-d

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplementary file S2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6,7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7,8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6,7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6,7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8,9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8,9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8,9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8,9
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7,8

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8,9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9-15
Study characteristics	17	Cite each included study and present its characteristics.	Page 9-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9-15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 9-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16-22
	23b	Discuss any limitations of the evidence included in the review.	Page 21-22
	23c	Discuss any limitations of the review processes used.	Page 21-22
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 24
Competing interests	26	Declare any competing interests of review authors.	Page 25
Availability of	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from	Page 24

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
data, code and other materials		included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Supplementary table 2: PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary table 3: Review outcomes

Table 1-a. Review outcomes

Maternal outcomes	Neonatal outcomes
Preeclampsia or eclampsia	Neonatal death
Preeclampsia	Neonatal death within 48 h after birth
Hypertensive disorders	Death before discharge home
Pregnancy induced hypertension (PIH)	Apgar score ≤ 7 at 5 min after birth
Chorioamnionitis	Apgar score < 7 at 5 min after birth
Gestational diabetes mellitus	Apgar score < 5 at 1 min after birth
	Respiratory distress syndrome (RDS)
	Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)
	Pneumonia
	Use of mechanical ventilation
	Surfactant use
	Oxygen therapy
	Oxygen requirement for at least 4 h
	Mean duration of mechanical ventilations
	Duration of oxygen use
	Patent ductus arteriosus (PDA)
	Hypotension within 7 postnatal days
	Hypotension
	Intraventricular hemorrhage (IVH)
	Severe IVH

Periventricular leukomalacia (PVL)
Major brain lesion damage
Necrotizing enterocolitis (NEC)
Sepsis
Early onset sepsis
Systemic inflammatory response syndrome
Meningitis
Neonatal hypoglycemia
Neonatal adrenal insufficiency
Intrahepatic cholestasis
Retinopathy of prematurity (ROP)
Gestational age at birth
Birth weight
Neonatal intensive care unit (NICU) admission
Duration of hospital stay
Survival free from disability
Death at long-term follow up
Death or disability/handicap at 2 years
Cerebral palsy
Severe hearing impairment
Visual impairment

	Discharge with respiratory support
	Growth < 10%ile in early childhood
	Abnormal behavior at long-term follow up at school-age

Table 1-b. Outcome definition

Maternal outcomes	Definition
Preeclampsia or eclampsia	**P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].
Preeclampsia	**P4** Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Cartwright et al. (2019): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a systolic Blood pressure(BP) >160mmHg and a diastolic BP ≧ 90mmHg measured at least twice and proteinuria ≧0.3g/24g.
Hypertensive disorders	**P2** Kirshembaum et al. (2018): No data.
Pregnancy induced hypertension (PIH)	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as any maternal diagnoses of preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Feng et al. (2017): No data.
Chorioamnionitis	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): No data. Elimian et al. (1999): No data.
Gestational diabetes mellitus	**P2** de la Hueruga et al. (2019): No data. **P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].

	P4 Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Kim et al. (2018): No data. Kim YJ et al. (2018):No data. Ishikawa et al. (2015): No data.
Neonatal outcomes	**Definition**
Neonatal death	Deaths during the first 28 completed days of life.*[2]
Neonatal death within 48h after birth	**P1** Battarbee et al. (2020): Death within 48h after birth.
Death before discharge home	**P3** Foix-L'Helias et al. (2005): Death before discharge home. **P4** Riskin-Mashiah et al. (2016): Death before discharge home. Ishikawa et al. (2015): Death before discharge home. Foix-L'Helias et al. (2005): Death before discharge home. Schaap et al. (2001): Death before discharge home. Bernstein et al. (2000): Death before discharge home.
Apgar score ≤7 at 5 min after birth	**P2** Kishenbaum et al. (2018): Apgar score ≤7 at 5 min after birth.
Apgar score <7 at 5min after birth	**P1** Krispin et al. (2018): Apgar score <7 at 5 min after birth. **P3** Elimian et al. (2000): Apgar score <7 at 5 min after birth. **P4** Bitar et al. (2020): Apgar score <7 at 5 min after birth. Kim et al. (2018): Apgar score <7 at 5min after birth. Feng et al. (2017): Apgar score <7 at 5min after birth. Elimian et al. (1999): Apgar score <7 at 5min after birth.
Apgar score <5 at 1min after birth	**P4** Kim et al. (2018): Apgar score <5 at 1min after birth. Torrance et al. (2007): Apgar score <5 at 1min after birth.
Respiratory distress syndrome (RDS)	**P1** Battarbee et al. (2020): Defined as a clinical diagnosis of respiratory distress syndrome, hyaline

membrane disease, or respiratory insufficiency requiring oxygen therapy with FiO2 ≧0.40 started within the first 24 hours after birth and continued for ≧24 hours or until neonatal demise.

Krispin et al. (2018): No data.

P2

de la Huerga Lopez et al. (2019): Defined ad the presence of clinical signs of respiratory distress with oxygen requirement and chest X-ray with reticulonodular infiltrate.

Kishenbaum et al. (2018): Defined as early respiratory distress that comprised cyanosis, grunting, retraction and tachypnea combined with ground glass appearance and air bronchogram on chest X-ray.

P3

Ryu et al. (2019): Defined if the chest radiographic findings were consistent with RDS together with an oxygen requirement of >0.4 for the fraction of inspired oxygen.

Ahn et al. (2012): Diagnosed in infants with respiratory distress, an increased oxygen requirement and a radiological finding consistent with RDS.

Been et al. (2009): Diagnosed in a clinical presentation (expiratory grunting, sub- or intercostal or sternal retractions, nasal flaring, tachypnea, cyanosis in room air with or without apnea) and characteristic radiographic appearance according to Giedion et al. [*3]

Goldenberg et al. (2006): Defined as the documentation of any of three criteria: (1) oxygen requirement at 6 through 24 hours of life; (2) an abnormal chest radiograph consistent with RDS within the first 24 hours of life; and (3) need for surfactant.

Dempsey et al. (2005): Defined from a combination of three of the following: clinical signs, oxygen need greater than 30% from 12 to 72 hours, need for assisted ventilation (continuous positive airway pressure or mechanical ventilation), and typical chest X-ray appearance.

Foix-L'Helias et al. (2005): No data.

Baud et al. (2000): Diagnosed if any two criteria were present in the first 24 hours of life: clinical symptoms (respiratory failure requiring assisted ventilation and administration of exogenous surfactant), typical radiological feature, and biological evidence of lung immaturity (fetal lung maturity test on tracheal aspirates).

Elimian et al. (2018): Diagnosed clinically by need for mechanical ventilation and oxygen for at least 48 hours, and radiologic chest findings.

P4

Kim et al. (2018): No data.

Riskin-Mashiah et al. (2018): No data.

Riskin-Mashiah et al. (2016): Diagnosed by a chest radiography consistent with RDS together with supplementary oxygen or mechanical ventilation therapy.

Feng et al. (2017): No data.

Ishikawa et al. (2015): Diagnosed based on the clinical and radiographic finings.

Mitsiakos et al. (2013): Diagnosed based on clinical and radiological criteria and oxygen requirements

	≧30%. van Stralen et al. (2009): Based on radiological criteria (poor lung expansion) and clinical criterial (need for supplemental oxygen, sternal retraction, intercostal and subcostal recession, grunting and tachypnea). Torrance et al. (2007): Defined as clinical signs of RDS with oxygen requirement and typical findings on a chest X-ray. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as tachypnea, chest wall retractions, and oxygen requirement in the presence of a chest X-ray classified as RDS. Bernstein et al. (2000): Required both a PaO2 <50mmHg in room air plus central cyanosis in room air or a requirement for supplemental oxygen to maintain a PaO2 >50mmHg. Elimian et al. (1999): Diagnosed clinically and by the need for mechanical ventilation and oxygen for a least 48 hors and the presence of radiologic chest findings. Ley et al. (1997): No data. Spinillo et al. (1995): Diagnosed with physical signs of respiratory distress (grunting, chest retraction, tachypnea) and required ventilatory support for >48hr and radiologic chest findings. Di Lenardo et al. (1990): Based on the basis of radiological indications and worsening of the symptoms from a clinical point of view.
Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Based on National Institute of Child and Human Development criteria.[*4] Been et al. (2009): Diagnosed with a dependency on oxygen supplementation at a postmenstrual age of 36 weeks. Goldenberg et al. (2006): Defined as infant oxygen requirement at 28 days or oxygen requirement at 36 weeks of life. Foix-L'Helias et al. (2005): No data. **P4** Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): No data. Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed according to the criteria of Bancalari et al.[*5] including clinical and radiologic features. Together with the requirement for oxygen supplementation at 36 weeks post menstrual age. Ishikawa et al. (2015): Defined when an infant continued to receive supplemental oxygen on the 28th day after birth and at the 36th week based on postmenstrual age. Mitsiakos et al. (2013): Based on oxygen supplementation at 36 weeks postmenstrual age. van Stralen et al. (2009): No data.

	Torrance et al. (2007): Defined as the need for extra oxygen on day 28 of life with chronic abnormalities on a chest X-ray and symptoms of respiratory distress. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as the presence of chronic respiratory distress and oxygen requirement beyond 28 days of life accompanied by a chest radiograph that showed persistent streaks of increased density in both lungs interspersed with normal hyperlucent areas.
Pneumonia	**P3** Dempsey et al. (2005): Defined by a combination of X-ray changes, endotracheal tube aspirates, and positive inflammatory markers.
Use of mechanical ventilation	**P3** Been et al. (2009): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim et al. (2018): Mechanical ventilation within 48 hours after birth. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Schaap et al. (2001): No data.
Surfactant use	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Been et al. (2009): No data. Elimian et al. (2000): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim YJ et al. (2018):Defined as the administration of any prophylactic or rescue surfactant. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Elimian et al. (1999): No data.
Oxygen therapy	**P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data.
Oxygen requirement for at least 4 h	**P2** Kishenbaum et al. (2018): Oxygen requirement for at least 4 hours.

Mean duration of mechanical ventilations	**P2** de la Huerga Lopez et al. (2019): No data. **P3** Ahn et al. (2012): No data.
Duration of oxygen use	**P3** Ahn et al. (2012): No data.
Patent ductus arteriosus (PDA)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Diagnosed by echocardiography and medical treatment or surgical ligation were performed when necessary. Been et al. (20009): Persistence of the open ductus arteriosus postnatally, as demonstrated by ultrasonographic examination. Elimian et al. (2000): Required medical or surgical intervention. **P4** Kim YJ et al. (2018): No data. Feng et al. (2019): No data. Ishikawa et al. (2015): Diagnosed based on both echocardiographic findings and clinical evidence of a volume overload due toa left-to-right shunt. Mitsiakos et al. (2013): No data. van Stralen et al. (2009): No data. Elimian et al. (1999): No data.
Hypotension within 7 postnatal days	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1]
Hypotension	**P4** van Stralen et al. (2009): Defined as a mean arterial pressure ≤30mmHg requiring treatment with volume expanders and/or inotropic support.
Intraventricular hemorrhage (IVH)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): Defined as grade ≧3 and listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined according to the IVH grading by Papile et al.[*6] Been et al. (2009): Defined according to Volpe. [*7] Goldenberg et al. (2006): Defined as grade 3 or 4 by ultrasound criteria.[*7] Dempsey (2005): Graded according to the Papile classification [*6] Baud et al. (2000): Defined as grade 3 or 4 of Papile classification. [*6]

	P4 Kim et al. (2018): Defined as grade 3 or 4. Kim YJ et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Ishikawa et al. (2015): Defined as Papile grade 1 or more. Schaap et al. (2001): Defined as grade 3 or 4. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Severe IVH	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined as grade 3 or 4 of Papile classification. *6 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): No data. Baud et al. (2000): No data. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Mitsiakos et al. (2013): Defined as grade 3 or 4. Schaap et al. (2001): No data. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Periventricular leukomalacia (PVL)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined according to Volpe. *7 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): Defined according to Volpe. *7 Baud et al. (2000): Diagnosed on cerebral ultrasound scan.

	P4 Riskin-Mashiah et al. (2018): No data. Riskin-Mashiah et al. (2016): Diagnosed by the presence of multiple periventricular cysts identified by cranial ultrasound examination after 28 days of life. Ishikawa et al. (2015): Based on either head ultrasound or cranial MRI scan performed at 2 weeks of age or later. Mitsiakos et al. (2013): No data.
Major brain lesion damage	**P4** van Stralen et al. (2009): Defined as the presence of a least one of the following findings: IVH ≧grade3 or ventricular dilatation or cystic PVL. Schaap et al. (2001): No data. Elimian et al. (1999): Defined as IVH grade 3 and 4, IVH with PVL, and PVL. Ley et al. (1997): Defined ad IVH grade 3, IVH grade 4, or PVL. Spinillo et al. (1995): No data.
Necrotizing enterocolitis (NEC)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): NEC stage ≧2b. [*8] Been et al. (2009): Defined as stage 2 or higher according to Bell et al.[*8] Goldenberg et al. (2006): Defined as stage 2 or higher. Dempsey et al. (2005): Classified as the presence of intramural gas on X-ray, perforation or evidence of intestinal necrosis at surgery or autopsy. Elimian et al. (2000): Diagnosed clinically and radiologically, and confirmed by surgery or autopsy. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as stage 2b or higher according to Bell et al.[*8] Riskin-Mashiah et al. (2018): Defined as stage 2 or higher according to Bell et al.[*8] Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Presence of clinical and radiologic features according to the criteria of Bell et al. [*8] Ishikawa et al. (2015): Defined as stage 2 or higher according to Bell et al.[*8] Mitsiakos et al. (2013): No data. Bernstein et al. (2010): No data. van Stralen et al. (2009): Defined as stage 2 or higher. Elimian et al. (1999): Diagnosed clinically and radiologically and confirmed at surgery or autopsy.

Sepsis	**P3** Ryu et al. (2019): Defined as culture proven sepsis. The presence of clinical symptoms, and signs with proven causative organisms documented from blood cultures. Ahn et al. (2012): Defined as a positive blood culture. Been et al. (2009): Clinical sepsis or culture-proven sepsis. Clinical sepsis was clinical presentation of sepsis with raised CRP. Culture-proven sepsis was any systemic bacterial infection documented by a positive blood or cerebrospinal fluid culture. Goldenberg et al. (2006): No data. Dempsey et al. (2005): Defined as a positive blood culture. Elimian et al. (2000): Defined as positive blood or cerebrospinal fluid cultures. **P4** Kim et al. (2018): Included both suspected infections (with clinical findings suggesting infection) and proven infections. Kim YJ et al. (2018): Defined as the presence of clinical symptoms and signs with proven causative organisms documented from blood cultures. Feng et al. (2017): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a positive blood culture and the need for intravenous antibiotics for minimum of 7 days. van Stralen (2009): Based on the need for intravenous antibiotics administration for more than 7 days. Schaap et al. (2001): Defined as neonatal septicemia or meningitis confirmed by positive cultures. Elimian et al. (1999): Defined as positive blood or cerebrospinal fluid cultures.
Early onset sepsis	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined as a positive blood culture occurring within the first 72 hours. Been et al. (2009): Neonatal sepsis occurring during the first 72 hours of life. Dempsey et al. (2005): Defined as a positive blood culture in the first 72 hours.
Systemic inflammatory response syndrome	**P3** Goldenberg et al. (2006): Defined as clinically suspected sepsis with negative cerebrospinal fluid and blood cultures or a band: band + polymorphonuclear cell ratio of 0.15 or greater.
Meningitis	**P3** Dempsey et al. (2005): Defined as a positive cerebrospinal fluid culture.
Neonatal hypoglycemia	**P1** Cassimatis et al. (2020): Defined as Blood sugar <40mg/dL within 4 hours of birth. Krispin et al. (2018): No data.

	P2 De la Huerga Lopez et al. (2019): No data. Kishenbaum et al. (2018): Defined as glucose level ≤45 mg/dl. **P4** Bitar et al. (2020): Defined as glucose level <40 mg/dl. Kim et al. (2018): Defined as glucose level <40 mg/dl.
Neonatal adrenal insufficiency	**P4** Kim YJ et al. (2018): Defined as the requirement of hydrocortisone treatment. Ishikawa et al. (2015): No data.
Intrahepatic cholestasis	**P3** Ahn et al. (2012): Defined when conjugated bilirubin exceed 2.0mg/dl.
Retinopathy of prematurity (ROP)	**P3** Ryu et al. (2019): Defined as requiring treatment. **P4** Kim YJ et al. (2018): Defined as requiring treatment. Riskin-Mashiah et al. (2018): No data. Feng et al (2017): No data. Riskin-Mashiah et al. (2016): Defined as grade 3-4 in international standard classification.[*9] Mitsiakos et al. (2013): No data.
Gestational age at birth	**P4** Bitar et al. (2020): Defined as gestational age birth. Cartwright et al. (2019): Defined as gestational age at birth. Ishikawa et al. (2015): Defined as gestational age at birth. Mitsiakos et al. (2013): Defined as gestational age birth.
Birth weight	**P4** Bitar et al. (2020): Defined as birth weight. Cartwright et al. (2019): Defined as birth weight. Ishikawa et al. (2015): Defined as birth weight. Mitsiakos et al. (2013): Defined as birth weight.
Neonatal intensive care unit (NICU) admission	**P1** Krispin et al. (2018): Defined as NICU admission. **P2** de la Huerga Lopez et al. (2019): Defined as NICU admission. Kishenbaum et al. (2018): Defined as NICU admission.

	P4 Bitar et al. (2020): Defined as NICU admission.
Duration of hospital stay	**P4** Bitar et al. (2020): No data. Mitsiakos et al. (2013): No data.
Survival free from disability	**P4** Cartwright et al. (2019): No data
Death at long-term follow up	**P4** Schaap et al. (2001): No data.
Death or disability/handicap at 2 years	**P4** Schaap et al. (2001): No data.
Cerebral palsy	**P4** Ishikawa et al. (2015): Defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Cartwright et al. (2019): Defined as a nonprogressive loss of motor function with disordered muscle tone or tendon reflexes.
Severe hearing impairment	**P4** Ishikawa et al. (2015): Defined as the need for hearing aids.
Visual impairment	**P4** Ishikawa et al. (2015): Defined as unilateral or bilateral blindness diagnosed by an ophthalmologist.
Discharge with respiratory support	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1
Growth<10%ile in early childhood	**P4** Schaap et al. (2001): Defined by using standard deviation to adjust for discrepancies in age and sex at school age.*10
Abnormal behavior at long-term follow up at school-age	**P4** Schaap et al. (2001): Defined by the DuPaul-score. *11

*1. www.karger.com/doi/10.1159/000502650.
*2. Neonatal mortality rate (0 to 27 days) per 1000 live births) (SDG 3.2.2) (who.int).
*3. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol*. 1973;1(3):145-152. doi:10.1007/BF00974058.
*4. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-1729. doi:10.1164/ajrccm.163.7.2011060.
*5. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95(5 Pt 2):819-823. doi:10.1016/s0022-3476(79)80442-4.
*6. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-534. doi:10.1016/s0022-3476(78)80282-0.

*7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
*8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7. doi:10.1097/00000658-197801000-00001.
*9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol. 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
*10. Frederiks AM, Nederlandes groeidoagrammen 1997 in historisch persepectief. In: Wit JM, ed. De Vierde Landelijke Groeistidie 1997. Presentatie nieuwe groepidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
*11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.

Supplementary table 4: Database-specific search terms and strategies

MEDLINE (via Ovid) 2021/6/6

#	Searches	Annotations
1	exp *Adrenal Cortex Hormones/ad, tu	
2	exp *Adrenal Cortex Hormones/ and (ci or de or dt).fs.	
3	exp Adrenal Cortex Hormones/ae, po, to	
4	or/1-3	
5	exp Pregnancy/	
6	exp Pregnancy Outcome/	
7	Fetal Death/	
8	Maternal Death/	
9	Obstetric Labor Complications/	
10	exp Obstetric Labor, Premature/	
11	Pregnancy, Prolonged/	
12	Fetus/	
13	exp Infant, Newborn/	
14	Prenatal Care/	
15	exp Fetal Development/	
16	exp Birth Weight/	
17	Prenatal Exposure Delayed Effects/	
18	or/5-17	
19	4 and 18	
20	limit 19 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactivetutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
21	limit 20 to meta analysis	
22	20 not 21	
23	19 not 22	
24	limit 23 to humans	
25	("*corticosteroid" or "*corticoid").mp.	
26	(pregnan* or labor or labour or gestation* or delivery* or preterm* or fetus or fetal or baby or babies or newborn* or neonat* or antenat* or prenat* or birth*).mp.	
27	25 and 26	
28	MEDLINE.st.	
29	27 not 28	
30	(biograph* or case report* or comment or congress* or conference* or editor* or tutorial* or interview* or lecture* or news* or handout* or guideline* or (review* not (meta analys* or metaanalys*))).mp.	

31	29 not 30	
32	exp Diabetes Mellitus/	
33	exp Hyperglycemia/	
34	or/32-33	
35	34 and 18	
36	exp Diabetes, Gestational/	
37	Pregnancy in Diabetics/	
38	or/36-37	
39	or/5-17	
40	38 and 39	
41	or/35,40	
42	4 and 41	
43	limit 42 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
44	limit 43 to meta analysis	
45	43 not 44	
46	42 not 45	
47	limit 46 to humans	
48	diabet*.mp.	
49	31 and 48	
50	or/47,49	
51	remove duplicates from 50	
52	exp epidemiologic study/	
53	(trial* or comparative or meta analysis or metaanalysis or multicenter or observational or randomized or randomised or rct or cct or cohort or cross sectional or longitudinal or evaluation or prospective or retrospective or control*).mp.	
54	or/52-53	
55	51 and 54	P1-1
56	51 not 55	P1-2
57	exp Cesarean Section/	
58	(cesarean or cesarian or caesarean or caesarian).mp.	
59	or/57-58	
60	or/24,31	
61	60 and 59	
62	remove duplicates from 61	
63	62 and 54	P2-1
64	62 not 63	P2-2
65	exp "Bacterial Infections and Mycoses"/	
66	Pregnancy Complications, Infectious/	

67	or/65-66	
68	24 and 67	
69	(infect* or chorioamnionitis).mp.	
70	31 and 69	
71	or/68,70	
72	remove duplicates from 71	
73	72 and 54	P3-1
74	72 not 73	P3-2
75	exp *Fetal Development/	
76	(growth adj3 restrict*).mp.	
77	or/75-76	
78	24 and 77	
79	((fetal or fetus or baby or babies or restricted) adj3 (development or growth or maturity or weight)).mp.	
80	31 and 79	
81	or/78,80	
82	remove duplicates from 81	
83	82 and 54	P4-1
84	82 not 83	P4-2

Embase (via embase.com) 2021/6/6

set	query	Annotations
#1	'corticosteroid'/exp/mj/dd_do,dd_cm,dd_dt,dd_ad,dd_to,dd_ct,dd_it	
#2	'corticosteroid'/exp/dd_ae	
#3	#1 OR #2	
#4	#3 AND 'human'/de	
#5	#4 AND [embase]/lim NOT [medline]/lim	
#6	'parameters concerning the fetus, newborn and pregnancy'/exp	
#7	'fetus death'/exp	
#8	'labor complication'/exp	
#9	'prolonged pregnancy'/de	
#10	'fetus'/de	
#11	'newborn'/de	
#12	'prenatal care'/exp	
#13	'prenatal development'/exp	
#14	'prenatal exposure'/de	
#15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
#16	#5 AND #15	
#17	'editorial'/de OR 'erratum'/exp OR 'note'/de OR 'review'/de	
#18	'meta analysis'/exp	
#19	#17 NOT #18	
#20	#16 NOT #19	
#21	'case report'/exp	
#22	#20 NOT #21	

#23	'diabetes mellitus'/exp	
#24	'hyperglycemia'/de	
#25	#23 OR #24	
#26	#22 AND #25	P1
#27	'cesarean section'/de	
#28	#22 AND #27	P2
#29	'infection'/exp	
#30	'chorioamnionitis'/de	
#31	#29 OR #30	
#32	#22 AND #31	P3
#33	'prenatal development'/exp/mj	
#34	#22 AND #33	P4

Cochrane Library (via Wiley) 2021/6/8

ID	Search	Annotations
#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	
#2	*corticosteroid* or *corticoid*	
#3	#1 or #2	
#4	MeSH descriptor: [Pregnancy] explode all trees	
#5	pregnan* or labor or labour	
#6	MeSH descriptor: [Pregnancy Outcome] explode all trees	
#7	stillbirth or livebirth	
#8	MeSH descriptor: [Fetal Death] explode all trees	
#9	MeSH descriptor: [Maternal Death] explode all trees	
#10	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	
#11	MeSH descriptor: [Pregnancy, Prolonged] explode all trees	
#12	MeSH descriptor: [Obstetric Labor Complications] this term only	
#13	MeSH descriptor: [Fetus] this term only	
#14	fetus or fetal	
#15	MeSH descriptor: [Infant, Newborn] explode all trees	
#16	infant* or newborn* or neonate* or baby or babies	
#17	MeSH descriptor: [Prenatal Care] explode all trees	
#18	prenatal or antenatal or perinatal	
#19	MeSH descriptor: [Fetal Development] explode all trees	
#20	matur* or immatur* or prematur*	
#21	MeSH descriptor: [Birth Weight] explode all trees	
#22	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees	
#23	gestation* or birth* or offspring	
#24	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	
#25	#3 and #24	
#26	MeSH descriptor: [Diabetes Mellitus] explode all trees	P1
#27	diabet* or dm	

#28	MeSH descriptor: [Hyperglycemia] explode all trees	
#29	hyperglycem*	
#30	MeSH descriptor: [Diabetes, Gestational] explode all trees	
#31	MeSH descriptor: [Pregnancy in Diabetics] explode all trees	
#32	#26 or #27 or #28 or #29 or #30 or #31	
#33	#25 and #32	
#34	handsrch	
#35	#33 and #34	P1
#36	MeSH descriptor: [Cesarean Section] explode all trees	
#37	cesarean or cesarian or caesarean or caesarian	
#38	#36 or #37	
#39	#25 and #38	
#40	#39 and #34	P2
#41	MeSH descriptor: [Bacterial Infections and Mycoses] explode all trees	
#42	infect*	
#43	MeSH descriptor: [Pregnancy Complications, Infectious] explode all trees	
#44	chorioamnionitis	
#45	#41 or #42 or #43 or #44	
#46	#25 and #45	
#47	#46 and #34	P3
#48	growth near restrict*	
#49	#25 and #48	
#50	#49 and #34	P4

CINAHL (via EBSCOhost) 2021/6/6

ID#	Search Terms	Search Options	Annotations
S1	(MM "Adrenal Cortex Hormones+/AD/DE/TU")		
S2	(MH "Adrenal Cortex Hormones+/AE")		
S3	S1 or S2		
S4	(MH "Pregnancy+")		
S5	(MH "Expectant Mothers")		
S6	(MH "Pregnancy Outcomes")		
S7	(MH "Perinatal Death")		
S8	(MH "Maternal Mortality")		
S9	(MH "Labor Complications+")		
S10	(MH "Labor, Premature")		
S11	(MH "Pregnancy, Prolonged")		
S12	(MH "Fetus+")		
S13	(MH "Infant, Newborn+")		
S14	(MH "Prenatal Care")		
S15	(MH "Fetal Development+")		
S16	(MH "Birth Weight")		

S17	(MH "Prenatal Exposure Delayed Effects")		
S18	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17		
S19	S3 and S18		
S20	S19	Limiters - Human	
S21	S20	Limiters - Research Article; Exclude MEDLINE records	
S22	(MH "Metabolic Diseases") OR (MH "Diabetes Mellitus+")		
S23	(MH "Hyperglycemia")		
S24	(MH "Pregnancy in Diabetes+")		
S25	S22 or S23 or S24		
S26	S21 and S25		P1
S27	(MH "Cesarean Section+")		
S28	S21 and S27		P2
S29	(MH "Bacterial and Fungal Diseases+")		
S30	S21 and S29		P3
S31	(MM "Fetal Development+")		
S32	restrict* N3 (growth or development or matur*)		
S33	S31 or S32		
S34	S21 and S33		P4

WHO Global Index Medicus (via WHO-GIM site) 2021/6/8

	Search Terms	Annotations
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (diaebet* OR DM OR hyperglycem*)	P1
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (elective caesarean)	P2
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (infect*)	P3
	cortico AND restrict* AND growth	P4

Web of Science Core Collection (via Web of Science) 2021/6/8

Set	Searches	Annotations
# 1	CITED AUTHOR: (amiya r*) AND CITED YEAR: (2016)	Cited Reference Search

Supplementary table 5: Risk of bias

Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cassimatis 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants from three institutions had PGDM (type 1 or type 2) with singleton pregnancies and delivered in late preterm between April 2014 and May 2017.	**Unclear** No information about confounding variables	**Low** Data obtained from an obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Krispin 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single, university-affiliated, tertiary medical center had GDM and delivered after 34 weeks of gestation between 2012 and 2016.	**Low** No differences in maternal age, gravidity, body mass index, and hypertensive disorders were confirmed between the exposed and unexposed groups. Women treated with corticosteroids had higher rates of nulliparity than women who were not treated (55% vs. 34%, respectively, p = 0.001). Multivariate analysis adjusting for gravity, parity, primiparity, hypertensive disorders, BMI, birth weight and gestational age at delivery was conducted in adverse composite neonatal outcome.	**Low** Data obtained from a comprehensive computerized perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Battarbee 2020 (Retrospective cohort study)	N/A	N/A	**Low** A cohort study included 115,502 participants from 25 hospitals in the United States between March 2008 and February 2011. To avoid overrepresentation of participants from larger hospitals, up to one-third of participants had spent days at hospitals with annual delivery volumes from 2,000 to 7,000 and up to one-sixth had spent days in hospitals with annual deliveries > 7,000.	**Low** The following potential confounders were adjusted: maternal age, body mass index, race and ethnicity, nulliparity, labor prior to delivery, gestational age, neonatal sex, multiple gestation, congenital malformation, GDM or PGDM, and study site.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Eleven sets of missing data (11 women and 12 neonates) were excluded from the data for steroids, but the proportion of missing data was very small (less than 1%).	**Low** All predefined outcomes reported	-

N/A: Not Applicable; **PGDM:** Pregestational diabetes mellitus; **GDM:** gestational diabetes mellitus; **ACS:** Antenatal corticosteroid

Risk of bias assessments for studies of antenatal corticosteroids in women undergoing elective cesarean section in the late preterm period

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kirshenbaum 2018 (Case-control study)	N/A	N/A	**Low** All participants, from a single tertiary medical center, delivered by elective cesarean section at 34 + 0–37 + 0 weeks of gestation between January 2011 and December 2013.	**High** Multiple logistic regression was not performed.	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
de la Huerga López 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017).	**High** No confirmation or consideration on confounding variables in the analysis phase	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	-

N/A: Not Applicable

Risk of bias assessments for studies of antenatal corticosteroids in women with chorioamnionitis (histological or clinical)

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Ahn 2012 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at Ewha Women's University between 2005 and 2010.	**High** Multiple logistic regression models were used for several outcomes (RDS, mechanical ventilation, use of oxygen, BPD, Sepsis, IHC, IVH, PVL), controlling only by gestational age. Confounding was not considered in the analysis phase for NEC, PDA, and neonatal death.	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All expected outcomes reported	-
Been 2009 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at the Erasmus University Medical Center-Sophia Children's Hospital between May 2001 and February 2003.	**High** Multiple logistic regression models used, controlled for ethnicity, preeclampsia, and gestational age, and birth weight on outcomes. However, adjusted analysis was not available for separating HC/CC results.	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome. measurements.	**Low** No missing data	**Low** All expected outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Goldenberg 2006 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution during the same period (December 5, 1996–June 13, 2001).	**High** In the analysis phase, differences in preeclampsia and type of preterm birth were confirmed between the exposed and unexposed groups. However, confounding was not considered in the analysis phase.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All expected outcomes were reported	-
Dempsey 2005 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1989 and January 1999.	**High** Multiple logistic regression models with and without corticosteroid administration were not performed, and results adjusted for confounding factors were not available.	**Low** Data obtained from medical records (obstetrical and neonatal database and pathology database, cross-referenced with data from pathology database and from maternal and neonatal chart review).	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All expected outcomes were reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Unclear** Participants drawn from different institutions between 1993 and 1996. However, other participant information was scarce.	**High** Adjusted analyses for results stratified by IUGR not available	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential the underestimation.
Baud 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted to Antoine Beclere University Hospital between 1993 and 1997.	**Low** Multiple logistic regression models used, controlling for antenatal antibiotic administration, mode of delivery, gestational age, and origin (inborn or out born).	**Low** Data obtained from computerized database	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1990 and December 1997.	**High** Multiple logistic regression models with and without corticosteroid administration were not performed, and results adjusted for confounding factors were not available.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low.** All expected outcomes were reported.	-
Ryu 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single university hospital, admitted to the same institution (Seoul National University Hospital) between 2007 and 2014.	**Low** Multiple logistic regression performed, and inclusion of confounding factors specified (e.g., GA, genders, and CS).	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** At the beginning of the study incomplete information was excluded.	**Low** All predefined outcomes reported.	-

N/A: Not applicable**; RDS:** Respiratory distress syndrome; **BPD:** Bronchopulmonary dysplasia; **IHC:** Intrahepatic cholestasis; **IVH:** Intraventricular hemorrhage; **PVL:** Periventricular leukomalacia; **NEC:** Necrotizing enterocolitis; **PDA:** Patent ductus arteriosus; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis; **IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **GA:** Gestational age; **CS:** Cesarean section

Risk of bias assessments for of studies of antenatal corticosteroids in women with growth-restricted fetuses and/or small-for-gestational-age infants

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
van Stralen 2009 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (Leiden University Medical Center) over the same period (January 2001–December 2005).	**High** No confirmation or consideration in either design or analysis phase	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Although equally divided, the difference in origin, i.e., referral pattern, may also have influenced the results.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Torrance 2007 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single tertiary referral center admitted to the same institution (neonatal intensive care unit at the University Medical Centre Utrecht, the Netherlands) over the same period (from January 1, 1999, to December 31, 2003). Cases and controls were selected from same pool (e.g., same gestational age, same birth weight).	**Low** Partial correlation performed for scale data to correct for potential confounding factors: for nominal data, binary logistic regression was used for this purpose. Variables were considered potential confounders when the Chi-square test or independent t-test identified a significant difference.	**Low** Data was obtained from an electronic database.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No loss to follow-up	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Unclear** Participants drawn from different institutions during the same period (1993–1996), although the distribution of treatment and control groups was unclear.	**High** Adjusted analyses for results stratified by IUGR not available.	**Low** Data obtained from medical records.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential underestimation.
Schaap 2001 (Case-control study)	N/A	N/A	**Unclear** Participants drawn from different institutions during the same period (1984–1991) although the distribution of treatment and control groups was unclear. Possibility of selection bias cannot be excluded due to retrospective design.	**Low** Treated group matched with control group by random electronic selection based on birth weight (difference < 175 g), sex, and year of birth (difference < 2 years).	**Low** Data obtained from medical records. Because all mothers had been admitted at least 24 h before delivery, a difference in fetal condition on admission was unlikely.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Nine losses at school age follow-up (4 in steroid group, 5 in control group) but no significant difference in sociodemographic details between those lost and retained at follow-up.	**Low** All predefined outcomes reported.	Hypertensive mothers less often treated with corticosteroids. Further, matching notwithstanding, birth weight and gestational age were significantly lower in the AGA group, although magnitude of the difference is small.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 1999 (Retrospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (January 1990–July 1997)	**High** Consideration in design, but there is no adjusted stratified analysis for sub-sample of interest	**Low** Data obtained from medical records	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Ley 1997 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (University Hospital of Lund) during the same period (1985–1994).	**Unclear** Multiple logistic regressions performed, but inclusion of confounding factors not specified.	**Low** Data obtained from hospital records	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Spinillo 1995 (Prospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (1988–1993)	**Low** Multivariate models used to account for potential confounders (age, birth weight, and sex of the infant).	**Low** Data obtained from hospital records	**Low.** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Missing data was less than 10%.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Di Lenardo 1990 (Retrospective cohort study)	N/A	N/A	**Unclear** All participants admitted/delivered and treated at the same institution (Prenatal Care Ward of Univ. of Padua's Gynecology & Obstetrics Institution) but unclear if over the same period.	**High** No confirmation or consideration in either design or analysis phase	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Bitar 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants, from a single hospital, who delivered at 34.0–36.6 weeks of gestation, with small-for-gestational-age or fetal-growth-restriction infants between January 2015 and December 2019.	**Low** Multiple logistic regression performed, and the inclusion of confounding factors specified: birth weight, gestational diabetes mellitus, indication for cesarean section, gestational age at delivery, and neonatal gender.	**Low** Data obtained from electronic medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes were reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cartwright 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from 23 collaborating hospitals, 16 in Australia and 7 in New Zealand, with a single, twin, or triplet pregnancy at less than 32 weeks of gestational age from April 1998 to July 2004.	**Low** Major confounding variables: gestational age at trial entry, antepartum hemorrhage, preterm pre-labor rupture of membranes, and country of birth were adjusted.	**Low** Data obtained from case notes	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High** For long-term outcomes, the missing data could affect the study outcome.	**Low** The predefined outcomes were described as planned.	-
Riskin-Mashiah 2018 (Retrospective cohort study)	NA	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**Low** Major confounding variables: maternal age, ethnicity, infertility treatment, maternal hypertensive disorder, preterm labor, premature rupture of membranes and/or amnionitis, gestational age, delivery mode, birth weight z-score, gender, birth order, delivery room resuscitation and year of birth were adjusted.	**Low** Data obtained from the national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single hospital between 2009 and 2016	**Low** Major confounding variables: gestational age, parity, mode of delivery, maternal diabetes, gestational hypertensive disorder, and preterm premature rupture of membrane were adjusted.	**Low** Data obtained from medical records and perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
Ishikawa 2015 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Research Network Database in Japan between 2003 and 2007	**Low.** Major confounding variables: maternal age, parity, preeclampsia, preterm rupture of membranes, non-reassuring fetal status, mode of delivery, gestational age at delivery, birth weight, gender of the infant, and histological chorioamnionitis (≥ stage 2) were adjusted.	**Low.** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High** For long-term outcomes, the missing data could affect the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Riskin-Mashiah 2016 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**Low** Major confounding variables: maternal age, ethnicity, infertility treatment, maternal diabetes, maternal hypertensive disorder, preterm labor, premature rupture of membranes, amnionitis, antepartum hemorrhage, gestational age, delivery mode, birthweight z-score, gender, delivery room resuscitation and year of birth were adjusted.	**Low** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Mitsiakos 2013 (Retrospective cohort study)	N/A	N/A	**Low** All participants between 24 and 31 6/7 weeks of gestational age from a single hospital. The study period was not specifically mentioned, but intervention and control groups seem to be selected from the same population groups.	**High** No consideration in either design or analysis phase	**Low** Data obtained from obstetric and neonatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**High** For long-term outcomes, the missing data could affect the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim YJ 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants born at 23 + 0 to 33 + 6 weeks of gestation between January 2007 and December 2014 in a single university hospital in South Korea.	**High** Major confounding variables, birthweight, Apgar score at 5 minutes, were adjusted. However, multiple logistic regression was separated and complete and incomplete courses on antenatal corticosteroid use were included, and, therefore, results adjusted for confounding factors were not available for this meta-analysis.	**Low** Data obtained from medical records and perinatal databases	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
The collaborative study group for respiratory distress syndrome in preterm infants 2017 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from 14 hospitals during the same period (2013–2014).	**Unclear** Multiple logistic regression performed, but inclusion of confounding factors not specified.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Bernstein 2000 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from North American hospitals during the same period (1991–1996).	**High** No consideration in either design or analysis phase of confounding variables.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

N/A: Not Applicable**; IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **AGA:** Appropriate for gestational age

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							№ of patients		Effect		Certainty	Importance
№ 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[b]	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[b]	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[b]	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[b]	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[b]	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[c]	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

a. Heterogeneity is high (I-square=>60%).
b. Estimate based on wide confidence interval crossing the line of no effect.
c. 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							№ of patients		Effect		Certainty	Importance
№ 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	serious[b]	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 =<7 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												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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)		
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.

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							№ of patients		Effect		Certainty	Importance
№ 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	serious[c]	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)	⨁◯◯◯ Very low	
Neonatal death (CC)												
2	observational studies	serious[c]	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	serious[c]	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	serious[c]	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)	⨁◯◯◯ Very low	
Respiratory distress syndrome (RDS) and moderate/severe RDS (CC)												
4	observational studies	serious[c]	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	serious[c]	serious[d]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with chorioamnionitis	placebo	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	serious[c]	not serious	not serious	not serious	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)	⨁⨁◯◯ Low	
Severe interventricular haemorrhage (grade3-4) (CC)												
3	observational studies	serious[c]	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	serious[c]	not serious	not serious	not serious	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with chorioamnionitis	placebo	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	not serious	not serious	not serious	none	-/169	-/358	**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	serious[c]	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	serious[c]	not serious	not serious	serious[b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with chorioamnionitis	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[c]	not serious	not serious	serious[b]	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[b]	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	serious[c]	not serious	not serious	serious[b]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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	serious[c]	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. Confounding factors are high risk of bias.
d. 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: 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							№ of patients		Effect		Certainty	Importance
№ 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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	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	serious[a]	not serious	not serious	serious[b]	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	serious[e]	serious[d]	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	serious[a]	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[b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
3	observational studies	not serious	not serious	not serious	very serious[b,c]	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[d]	not serious	serious[b]	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	serious[a]	serious[d]	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	serious[a]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	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[d]	not serious	very serious[b,c]	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[b]	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	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Apgar score < 5 at 1 minute (SGA)												
2	observational studies	not serious	not serious	not serious	very serious[b,c]	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[b,c]	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	serious[a]	not serious	not serious	not serious	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[b,c]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	serious[d]	not serious	serious[b]	none	806	1272	-	MD **49.1 lower** (110.53 lower to 12.32 higher)	⨁◯◯◯ Very low	
Duration of hospital stay (SGA)												
1	observational studies	serious[a]	not serious	not serious	very serious[b,c]	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. Evidence based on high missing data,
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
d. Heterogeneity is high (I-square=>60%).
e. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
f. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

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							№ of patients		Effect		Certainty	Importance
№ 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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	very serious[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[c]	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[b,c]	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[b,c]	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[c]	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. Evidence based on high missing data,
b. Estimate based on wide confidence interval crossing the line of no effect.

c. Estimate based on small sample size.
d. Heterogeneity is high (I-square=>60%).
e. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
f. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

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							№ of patients		Effect		Certainty	Importance
№ 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[b]	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[b,c]	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	serious[a]	serious[d]	not serious	serious[b]	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[b]	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[b,c]	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[b,c]	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[b]	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[b,c]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	very serious[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[b,c]	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[c]	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	serious[a]	serious[d]	not serious	serious[b]	none	275	233	-	MD **0.43 higher** (0.54 lower to 1.4 higher)	⨁◯◯◯ Very low	
Retinopathy of prematurity (FGR or SGA)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	very serious[b,c]	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[b,c]	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[b,c]	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	serious[a]	not serious	not serious	very serious[b,c]	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	serious[a]	not serious	not serious	serious[b]	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[b,c]	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[c]	none	136	111	-	MD **2.3 lower** (3.8 lower to 0.8 lower)	⨁◯◯◯ Very low	

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Explanations

a. Evidence based on high missing data,
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
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Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	serious[d]	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	serious[d]	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[b,c]	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	serious[a]	not serious	not serious	serious[b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
8	observational studies	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	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	serious[a]	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[b]	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	serious[a]	serious[d]	not serious	serious[b]	none	1081	1505	-	MD **0.04 lower** (0.57 lower to 0.48 higher)	⨁◯◯◯ Very low	
Retinopathy of prematurity (total)												
5	observational studies	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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	serious[a]	not serious	not serious	serious[b]	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)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	not serious	not serious	not serious	not serious	none	223	173	-	MD **2.32 lower** (3.81 lower to 0.83 lower)	⨁⨁◯◯ Low	

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

Explanations

a. Evidence based on high missing data,
b. Estimate based on wide confidence interval crossing the line of no effect.
c. Estimate based on small sample size.
d. Heterogeneity is high (I-square=>60%).
e. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
f. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).

ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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Short title: Systematic review: antenatal steroids in specific women

ABSTRACT

Objective: ~~Synthesize~~ **This study aimed to synthesize** available evidence on **the efficacy of antenatal corticosteroid** (ACS ~~effectiveness~~) **therapy** among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period.

Methods: A **systematic** search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, **and** Global Index Medicus was conducted for all comparative randomized or non-randomized interventional studies in the four subpopulations. ~~Data~~ **The authors** extracted ~~independently by authors~~ **data individually.** Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was used to assess **the risk of bias** in non-randomized studies. Grading of Recommendations, Assessment, Development**,** and Evaluations (GRADE) tool was used to assess the certainty of evidence.

Results: ~~Twenty-three~~ **Thirty-one studies involving 5018 pregnant women and 10819 neonates**~~18003 pregnant women/neonates~~ were included. All **the** included articles were observational studies **in high-income countries**. Data on women with diabetes were limited, and evidence on women undergoing planned CS was inconclusive. ACS **use** was associated with possibly reduced odds of ~~neonatal mortality (pooled OR: 0.49; 95%CI: 0.33–0.74, low certainty),~~ severe intraventricular hemorrhage (IVH) (pooled OR: 0.41; 95%CI: **0.19**~~0.23–~~**0.87**~~0.72~~, low **certainty**), and IVH (pooled OR: 0.41; 95%CI: **0.23**~~0.19–~~**0.72**~~0.87~~, low **certainty**) in women with histological chorioamnionitis. Among women with FGR, **the rates of** surfactant use (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate **certainty**), mechanical ventilation (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate **certainty**), and oxygen therapy (pooled OR: 0.48; 95%CI: 0.30–0.77, moderate **certainty**) were probably reduced~~, but~~**; however, the rate of** hypoglycemia probably increased (pooled OR: 2.06; 95%CI: 1.27–3.32, moderate **certainty**). Definitional differences ~~for~~ **in** populations and outcomes complicated meta-analyses. ~~Most studies were conducted in high-income countries.~~

Conclusions: ~~Evidence~~ **There** is ~~lacking~~ **a paucity of evidence** for women ~~with~~ **who have** diabetes or **are** undergoing planned CS. ACS ~~might~~ **therapy may** have benefits in

women with chorioamnionitis~~. ACS~~ **and** is probably beneficial in FGR **~~but; ; however,~~ it** can increase neonatal hypoglycemia. Well-designed studies with adequate follow-up are required.

Protocol registration:

PROSPERO (CRD42021267816~~; Supplementary File S1~~)

Strengths and limitations of this study:

-This review included a broad search strategy.

-This review applied rigorous quality assessment and GRADE methodology.

-All included studies were observational studies.

-Definitional differences ~~for population~~ **between populations** and outcomes complicated **the** meta-analysis.

-Most studies were conducted in high-income countries.

INTRODUCTION

~~Antenatal~~ **Previous studies demonstrated that antenatal** corticosteroids (ACS), such as intramuscular dexamethasone or betamethasone, ~~have been shown to~~ cross the placenta and can induce fetal lung maturation (1). When ~~ACS is~~ administered to women at risk of imminent preterm birth ~~prior to~~ **before** 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly reduced (2). ACS **therapy** also probably decreases the risk of intraventricular hemorrhage (IVH) and reduces **the rate of** developmental delay in childhood (2).

Therefore, ~~As a result,~~ the World Health Organization (WHO) and several **international** obstetric and gynecological societies ~~internationally~~ recommend ACS

therapy in women **before or** up to 34 weeks' gestation for improving preterm **newborns'** outcomes (3-6). Some national organizations have recommended ~~the~~ **ACS** use ~~of ACS~~ in women at risk of preterm birth up to 36 weeks' gestation **based** on ~~the basis of the~~ evidence ~~that there may be some~~ **of the existence of possible** respiratory-related benefits for the newborn (3,5).

However, ~~the~~ **current** evidence regarding **the** benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis**,** or ~~babies~~ fetal growth restriction (FGR), is ~~more~~ controversial. Women with diabetes, chorioamnionitis, or ~~babies with~~ FGR are at **a** higher risk of adverse perinatal outcomes~~, but~~**; however,** they are generally excluded from ACS efficacy trials (2). Consequently, any subgroup **analysis** to explore the effects of ACS ~~in~~ **on** women with these complications is unlikely to ~~provide direct~~ **yield** **concrete** evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycemic effects**, and** respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor maternal **glycemic** control (7) (8) . Chorioamnionitis **is** ~~(acute inflammation of the membranes and chorion of the placenta)~~ is estimated to affect 3.9% of women giving

birth, ~~and~~ **causing 22.6–36.9% of total stillbirths (9-11)**. Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS **therapy** is avoided due to concerns that its immunosuppressive effects may worsen outcomes for ~~the woman~~ **women** and ~~her baby~~ **their babies.** However, the relative benefits and harms of using ACS in ~~this~~ clinical **settings** are unclear. **FGR is associated with an increased risk of morbidity and mortality (12-15). Small for gestational age (SGA) status does not accurately represent FGR as SGA neonates include constitutionally small ones (16). In most cases, FGR fetuses are delivered as SGA neonates (17). In this study, we targeted pregnant women with both FGR fetuses and SGA neonates.** ~~In many high-income countries, small for gestational age (SGA) neonates account for approximately 10% of all babies; this proportion is generally higher in low-to-middle-income countries.[11-13] SGA is associated with an increased risk of neonatal morbidity and mortality than those babies born appropriate for gestational age (AGA).[14,15] The term SGA is often used as a proxy measure for FGR because most cases of SGA are caused by FGR.[16] Clarifying ACS effects in women at risk of imminent preterm birth with growth-restricted fetuses is necessary.~~

One ~~additional~~ clinical scenario **with** ~~where there is~~ uncertainty regarding ACS efficacy is ~~in~~ women undergoing elective Caesarean section (CS) in the late preterm period (i.e.,

34 to <37 weeks' gestation). Babies born in **the** late preterm **period** have lower risks of mortality and morbidity ~~compared with~~ **than** those born ~~prior to~~ **before** 34 weeks' gestation; however, they have higher risks of adverse outcomes than ~~babies~~ **those** born at term (18-21). In many countries, the **rising** rate of provider-initiated late preterm birth ~~is rising, which~~ has been linked to the ~~more generalised~~ **generalized** increase in **the** CS ~~use~~ **rate (22)**. Regardless of **the** gestational age, babies born via elective CS do not have the usual physical and hormonal stimuli of passage through the birth canal; thus, they tend to have higher rates of respiratory morbidity (23-25). Some studies have suggested that the risk of neonatal **hypoglycemia** is greater following CS ~~although.~~;; **however,** this may be confounded by the underlying indication for CS (26).

In 2016, members of our team published a systematic review ~~to~~ **assessing** the effectiveness of ACS **therapy** in these four clinical situations (27). **No** ~~The review did not find any~~ direct evidence ~~on~~ **of** the effects of ACS ~~in~~ **therapy on** pregnant women with diabetes **who were** at risk of preterm birth or for those undergoing elective CS in the late preterm period **was found**. The review could not draw firm conclusions regarding the effects of ACS ~~in~~ **on** women with growth-restricted fetuses, although low-quality evidence suggested that ACS reduces neonatal IVH in women with chorioamnionitis (27). **The review's findings** ~~of the previous review~~ informed WHO~~'s~~

2015 ACS recommendations (28). **ACS recommendation are currently being updated as** part of **the** WHO's living guidelines in maternal and perinatal health **programs**~~, the ACS recommendations are currently being updated~~ (29). ~~Hence,~~ **Our** aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians, and maternal and newborn health stakeholders on safe**,** ~~and~~ effective clinical management in preterm birth.

METHODS

The specific review objectives are ~~described~~ **presented** in Box 1, comprising four related questions on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA infants. **Diagnostic criteria used to define clinical and histological chorioamnionitis are explained in Supplementary table 1. SGA infants are all neonates with birth weights below the 10th percentile. In this survey, FGR fetuses were defined with each study inclusion criterion (Supplementary table 1).** The review protocol was registered on PROSPERO (CRD42021267816) and reported ~~according to~~ **per** the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) checklist (**Supplementary file 1, Supplementary table 2**) (30).

Box 1. Four Participant, Intervention, Comparison, **and** Outcome ~~(PICO)~~questions for ~~the~~ **a** systematic review

P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes
P: Women at risk of imminent preterm birth **less than 37 weeks** with pregestational diabetes mellitus and/or gestational diabetes mellitus
I: ACS administration
C: Placebo or no treatment
O: World Health Organization (WHO) priority outcomes for preterm birth

P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period
P: Women undergoing elective CS in the late preterm period **between 34 weeks and 0 days and 36 weeks and 6 days**
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P3: Effects of ACS therapy on women with chorioamnionitis
P: Women at risk of imminent preterm birth **less than 37 weeks** with chorioamnionitis
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants
P: Women at risk of imminent preterm birth **less than 37 weeks** with growth-restricted fetuses and/or small-for-gestational-age infants
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

Study eligibility criteria

Eligible studies were randomized or **non-~~non~~randomized** primary ~~research~~ studies that reported on the effects of ACS **therapy** in the four subpopulations. This included published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-after studies, interrupted-time-series studies, historically controlled

studies, cohort studies, and cross-sectional studies comparing any ACS ~~administration~~ (betamethasone, dexamethasone, or hydrocortisone) ~~given~~ **administered** either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis, and women with ~~a~~ FGR **fetuses** or SGA **infants**.

Articles in any language and from any country were eligible for inclusion if they reported on one or more of ~~the review outcomes of interest that reflected~~ WHO's priority outcomes for preterm birth guideline development (28). Maternal outcomes were death, maternal morbidity, and ~~side effects of~~ therapy **side effects**. Newborn and child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric status, and ~~side effects of~~ therapy **side effects (Supplementary table 3)**.

Data sources and search strategy

An information specialist was consulted for ~~developing~~ **the development of** the search

strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions **on June 6, 2021**. Controlled vocabularies supplemented with free keywords were used to search for the relevant concept areas, with duplicates removed in the process to yield a total number of abstracts for each database _. Reference lists of the included articles, including any recent systematic reviews, were also hand-searched for further potentially relevant studies. All citations were imported into a Rayyan (http://rayyan.qcri.org) library for eligibility assessment.

Study selection, data extraction, and quality assessment

Two reviewers (KS, EN) independently assessed **the** titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies were obtained and assessed in duplicate by two reviewers **working** independently, with disagreements resolved through **discussions** or **by** consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through **discussions** or **by** consulting a third reviewer. Extracted data were entered into **the** Review Manager

version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) (31). If we identified any randomized trials, we planned to use the Cochrane Risk of Bias tool (32). ~~We planned to assess for~~ **P**otential publication bias **was** ~~through visual inspection~~ **inspected visually using** ~~of~~ funnel plots for asymmetry in situations where data for a single outcome were available from ~~10 or more~~ **at least ten** studies.

Data synthesis and analysis

Aggregate odds ratios (ORs) and relative risks ~~(RRs)~~ with 95% confidence intervals (CIs) were determined for dichotomous data using **the** Mantel–Haenszel analysis (fixed-effects model). Where between-study clinical or methodological heterogeneity undermined the compatibility of the quantitative results, or if substantial statistical heterogeneity was detected, **the** random-effects meta-analysis was used. Data were pooled using ORs when the numbers of events were available and using logarithms of the ORs weighted by the inverse variance when events were not available. For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics.

Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for heterogeneity. For the analysis ~~on~~ **of** women with FGR fetuses and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only, **and** SGA **or** FGR). Data from the three populations were combined, and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%.

All statistical analyses were performed using RevMan5. ~~Statistical~~ **The threshold for statistical** significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development, and Evaluation (GRADE~~) is~~), an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines ~~and~~, was used in this review.

Patients and public involvement

~~As~~ **Since** this ~~paper~~ is a systematic review of previously published data, there was no direct involvement ~~from~~ **of** patients or the public.

RESULTS

Effects of ACS ~~in~~ therapy on women with pregestational and/or gestational

diabetes mellitus

The search identified 179 citations**;** ~~, from which~~ 11 potentially eligible studies were evaluated, and **three** ~~five~~ studies met the eligibility criteria, providing data ~~for~~ **on** **725** ~~8,067~~ pregnant women **and 830** neonates (**Supplementary file 2** ~~Figure 1~~) (33) (34) (35). All studies were conducted in high-income countries and ~~collected~~ data **collection was performed** between 200~~6~~**8** and 2017**(Supplementary table 1)**. One study involved women with pregestational diabetes only, ~~two~~ **one study** involved women with gestational diabetes only, and ~~two~~ **one study** involved women with either pregestational or gestational diabetes. ~~Three~~ **Two** ~~studies used betamethasone only, one study used dexamethasone or betamethasone, and in one study, the corticosteroid used was not specified.~~ All included studies were judged as **having a** low risk of bias across all domains~~, except for the two studies that were judged as having a high risk of selection bias~~ (**Supplementary file 3, Supplementary table 5**~~Figure 2; Supplementary File S6~~). Data were available for ~~5~~**six** outcomes (Table 1~~; Supplementary File S7~~). One retrospective cohort study found that in women with gestational diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (~~1~~**one** study, **161**~~2262~~ infants; OR**:** 7.41**;** 95%CI**:** 5.04**–**10.89, *low-certainty evidence*) ~~(33)~~; however, the effect of ACS **therapy** on neonatal hypoglycemia was uncertain (~~3~~**two** studies,

215~~2376~~ infants; pooled OR**:** **1.44**~~1.74~~**;** 95%CI**:** **0.70–2.97**, *very-low-certainty evidence*) **(33)**. **The certainty** of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn ~~(Supplementary File S8)~~.

Table 1: Maternal and neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

Neonatal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Caesarean section	**2**	**31/65 (47.7%)**	**58/150 (38.7%)**	**1.75 (0.63-4.82)**	**138 more per 1000 (from 102 fewer to 366 more)**	**Very Low**
Neonatal death within 48 h of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09–2.20)	14 fewer per 1000 (from 23 fewer to 29 more)	Very Low
RDS	**2**	**179/583 (30.7%)**	**39/193 (19.2%)**	**2.79 (0.85–9.08)**	**207more per 1000 (from 24 fewer to 491 more)**	Very Low
Neonatal hypoglycemia	**2**	**14/65 (21.5%)**	**66/150 (44.0%)**	**1.44 (0.70–2.97)**	**91 more per 1000 (from 85 fewer to 260 more)**	Very Low
Apgar score < 7 at 5 min	1	**1/47 (2.1%)**	**21/114 (18.4%)**	0.79 (0.10–5.89)	**33 fewer per 1000 (from 162 fewer to 387 more)**	Very Low
Admission to NICU	1	**19/47 (40.4%)**	**36/114 (36.1%)**	7.41 (5.04–10.89)	**458 more per 1000 (from 384 more to 518 more)**	Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome. ~~*There was no maternal outcome.~~

Effects of ACS ~~in~~ **therapy on** women undergoing elective CS in the late preterm period

The search identified 211 citations**;** ~~, from which~~ 17 potentially eligible studies were evaluated, and two studies were included (**Supplementary file 2**~~Figure 2~~**3**) (36,37). **The two studies** were observational studies ~~(one case-control, one retrospective cohort)~~ conducted in high-income countries between 2011 and 2017, providing data ~~for~~ **on** 205 pregnant women/neonates **(Supplementary table 1)**. ~~In both studies, betamethasone was used. The case-control study was judged as having a low risk of bias for all~~

domains (Figure 4; Supplementary File S6). The two studies were retrospective cohort study was judged as **having a** high risk of bias for the selection of participants and confounding variables **(Supplementary file 3, Supplementary table 5)**. Data for 10 **on eleven** outcomes were available; however, **but** all had very low certainty**;** so**,** no meaningful conclusions could be drawn (Table 2; Supplementary Files S7 **and** S8).

Table 2: Maternal and neonatal outcomes for women undergoing elective cesarean section in the late preterm period

Maternal outcomes	**No of studies**	**No of the patients**			**Effect**	**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09–1.21)	89 fewer per 1000 (from 126 fewer to 25 more)	Very Low
Gestational diabetes mellitus	**1**	**3/30 (10.0%)**	**4/10 (40.0%)**	**0.17 (0.03-0.95)**	**298 fewer per 1000 (from 380 to 12 fewer)**	**Very Low**
Neonatal outcomes	**No of studies**	**No of the patients**			**Effect**	**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29–2.24)	17 fewer per 1000 (from 65 fewer to 95 more)	Very Low
IVH	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Necrotizing enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Neonatal hypoglycemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81–2.78)	93 more per 1000 (from 44 fewer to 246 more)	Very Low
Use of mechanical ventilation	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.30–2.12)	17 fewer per 1000 (from 64 fewer to 86 more)	Very Low
Admission to NICU	2	10/88 (11.4%)	14/117 (12.0%)	**0.78 (0.23–2.72)**	**24 fewer per 1000 (from 89 fewer to 150 more)**	Very Low
Apgar score ≤ 7 at 5 min	1	2/58 (3.4%)	0/107 (0.0%)	9.51 (0.45–201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very Low
Mean duration of mechanical ventilation	**1**	**30**	**10**	**-**	**MD 0.2 lower (1.35 lower to 0.95 higher)**	**Very Low**
Oxygen requirement for at least 4 hours	**1**	**13/58 (22.4%)**	**25/107 (23.4%)**	**0.95 (0.44-2.03)**	**9 fewer per 1000 (from 115 fewer to 149 more)**	**Very Low**

*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS in therapy on women with chorioamnionitis (histological or clinical)

The search identified 418 citations**;** , from which 12 potentially eligible studies were evaluated, and eight studies met the eligibility criteria **were found to be eligible** (**Supplementary file 2** Figure **3**5) (38) (39) (40) (41) (42) (43) (44) (45). Two were

prospective cohort studies and six were retrospective ~~cohorts~~, providing data on ~~1460~~ **1372** pregnant women~~/~~ **and 1460** neonates **(Supplementary table 1)** ~~(Supplementary table 1File S5)~~. **Four studies included pregnant women with clinical chorioamnionitis, and ~~variation~~ there were variations in the diagnostic criteria (Supplementary table 1).** All studies were conducted in high-income countries**~~, and women were~~** ~~enrolled~~ ~~women~~ between 1989 and 2014. ~~One study evaluated dexamethasone, four studies evaluated betamethasone, and three studies evaluated either betamethasone or dexamethasone.~~ Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process (38) (41) (42) (43) (46). All included studies were judged as **having a** low risk of bias overall**,** although six studies were judged as **having a** high risk of bias ~~for the domain~~ regarding confounding variables ~~as adjusted analyses were not reported~~ (**Supplementary file 3, Supplementary table 5**~~Figure 6; Supplementary File S6~~). Data for ~~25~~ **27** outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3; Supplementary **file 4**~~File S7~~). Amongst women with histological chorioamnionitis, ACS administration was associated with a possible reduction in the odds of **severe intraventricular hemorrhage** ~~neonatal mortality~~ (~~six~~ **four** studies, **528**~~1193~~ infants;

pooled OR**:** **0.41**~~0.49~~**;** 95%CI**:** **0.19**~~0.33~~ **–0.87**~~0.74~~, *low-certainty evidence*)**, IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*)**~~, IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*), and severe IVH (four studies, 528 infants; pooled OR: 0.41; 95%CI: 0.19–0.87, *low-certainty evidence*)~~. ACS might result in no difference in neonatal sepsis; however, **the** evidence was uncertain (**six** studies, 1193 infants: pooled OR**:** 1.03**;** 95%CI**:** 0.73–1.47, *very-low-certainty evidence*). The certainty of evidence was very low for other outcomes ~~ (Supplementary **table S9**File S8)~~. In women with clinical chorioamnionitis, ~~ACS administration was associated with a possible reduction in the odds of IVH (three studies, 318 infants, pooled OR: 0.39; 95%CI: 0.15–0.99, *low-certainty evidence*), and periventricular leukomalacia (three studies, 318 infants, pooled OR: 0.30; 95%CI: 0.11–0.86, *low-certainty evidence*).~~ ~~neonatal sepsis,~~ only very-low-certainty evidence was available **for neonatal sepsis** (**two** studies, 150 infants, pooled OR**: 0.71**~~0.96~~**;** 95%CI: **0.13** ~~0.40–2.29~~**3.89**). The certainty of evidence was very low for all other outcomes **(Supplementary table 6)** ~~(Supplementary **table 6**File S8)~~.

Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						

Caesarean section	**1**	**42/97 (43.3%)**	**2/12 (16.7%)**	**3.82 (0.79–18.36)**	**266 fewer per 1000 (from 30 fewer to 619 more)**	**Very Low**
Gestational diabetes mellitus	**1**	**6/97 (6.2%)**	**2/12 (16.7%)**	**0.33 (0.06-1.86)**	**105 fewer per 1000 (from 155 fewer to 104 more)**	**Very Low**
Preeclampsia or eclampsia	**1**	**5/97 (5.2%)**	**1/12 (8.3%)**	**0.60 (0.06–5.59)**	**32 fewer per 1000 (from 78 fewer to 254 more)**	**Very Low**
Neonatal outcomes (histological chorioamnionitis)						
		ACS	**Non-ACS**	**OR (95% CI)**	**Absolute (95% CI)**	
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	**0.51 (0.31–0.85)**	**75 fewer per 1000 (from 109 fewer to 22 fewer)**	**Very Low**
Severe IVH	4	25/414 (6.0%)	13/114 (11.4%)	0.41 (0.19–0.87)	64 fewer per 1000 (from 90 fewer to 13 fewer)	Low
IVH	5	42/502 (8.4%)	26/156 (16.7%)	0.41 (0.23–0.72)	91 fewer per 1000 (from 123 fewer to 41 fewer)	Low
RDS	**6**	**305/677 (45.1%)**	**289/516 (56.0%)**	**0.59 (0.45-0.77)**	**131fewer per 1000 (from 196 fewer to 65 fewer)**	**Very Low**
Sepsis	6	112/677 (16.5%)	83/516 (16.1%)	1.03 (0.73–1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very Low
Neonatal outcomes (clinical chorioamnionitis)						
		ACS	**Non-ACS**	**OR (95% CI)**	**Absolute (95% CI)**	
Neonatal death	**2**	**14/109 (12.8%)**	**14/81 (17.3%)**	**0.71 (0.32-1.60)**	**44 fewer per 1000 (from 110 fewer to 78 more)**	**Very Low**
Severe IVH	**3**	**5/163 (3.1%)**	**14/155 (9/0%)**	**0.32 (0.03–3.19)**	**60 fewer per 1000 (from 87 fewer to 150 more)**	**Very Low**
IVH	**3**	**13/163 (8.0%)**	**20/155 (12.9%)**	**0.43 (0.07–2.44)**	**69 fewer per 1000 (from 119 fewer to 136 more)**	**Very Low**
RDS	**4**	**99/209 (47.45)**	**99/208 (47.6%)**	**0.74 (0.48-1.12)**	**74 fewer per 1000 (from 172 fewer to 28 more)**	**Very Low**
Sepsis	2	26/104 (25.0%)	12/46 (26.1%)	**0.71 (0.13–3.89)**	**60 fewer per 1000 (from 271 fewer to 318 more)**	Very Low

*There **was** no maternal outcome in clinical chorioamnionitis.

*ACS: Antenatal corticosteroid, ~~BPD/CLD: Bronchopulmonary dysplasia/chronic lung disease, CC: Clinical chorioamnionitis,~~ CI: Confidence interval, ~~HC: Histological chorioamnionitis,~~ IVH: Intraventricular hemorrhage, OR: Odds ratio, ~~PDA: Patent ductus arteriosus, PVL: Periventricular leukomalacia,~~ RDS: Respiratory distress syndrome

Effects of ACS ~~in~~ **therapy on** women with growth-restricted fetuses and/or small-for-gestational-age infants

The search identified 261 citations**:** ~~, from which~~ 36 potentially eligible studies were assessed, and 18 studies were included (**Supplementary file 2** ~~Figure 4~~**7**) (41,47-63). Of these, ~~12~~**twelve** studies included women with SGA infants only, 4**four** studies included women with FGR or SGA infants, and ~~2~~**two** studies included women with

FGR infants only **(Supplementary table 1)** ~~(Supplementary **table 1**File S5)~~. ~~The five~~ **Among the studies that included FGR fetuses, ~~and~~ the definitions of FGR ~~showed a wide variety~~ varied widely. Since SGA status is insufficient to determine FGR, we separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three populations were combined, and the pooled OR in total ~~were~~ was calculated. Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 (50,53,58). These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event.** All were observational studies conducted in high-income countries. ~~Data were available from 8271 pregnant women/neonates enrolled between 1984 and 2019.~~ Additional unpublished data from the study by Torrance et al. (2007) were extracted from a review paper published in 2009~~, which was~~ identified through the search strategy (53,64). Most ~~of the~~ included studies ~~(17 of 18 studies)~~ were judged as **having a** low risk of bias across all domains. **Seven** ~~Five~~ studies **had** ~~were judged as **having a**~~ high risk of bias for the domain regarding confounding variables. **Three** ~~Four~~ studies were judged as **having a** high risk of bias regarding incomplete outcome data (**Supplementary file 3,**

Supplementary table 5~~Figure 8; Supplementary File S6~~). For SGA infants only, 12 studies provided data on **30**~~27~~ outcomes (**Supplementary file 4, Supplementary table 6**~~Files S7 and S8~~). **The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH)**~~chorioamnionitis~~ **(2 studies, 684 women; pooled OR 1.50, 95%CI:1.08–2.07, *low-certainty evidence*)**~~The administration of ACS for women with SGA was associated with the increasing odds of pregnancy-induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI: 1.08 to 2.07, *low certainty evidence*)~~ although the odds of neonatal mortality (~~8~~**eight** studies, **2660**~~2710~~ infants; pooled OR: **0.68**~~0.61~~**;** 95%CI: **0.47**~~0.49~~ **–0.97**~~0.78~~, *low-certainty evidence*) ~~and severe IVH (six studies, 3235 infants; pooled OR: 0.60; 95%CI: 0.45–0.80, *low-certainty evidence)*~~ were possibly reduced (Table 4~~; Supplementary Files S7 and S8~~). Two studies involving FGR infants only provided data for **18**~~19~~ review outcomes; **the odds of death or disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17-0.98, low–certainty evidence) were possibly reduced (Table 4).** ~~however, all outcomes were assessed as very-low-certainty evidence (Supplementary Files S7 and S8).~~ Four studies involved SGA or FGR infants, providing data for **25**~~24~~ outcomes (**Supplementary file 4, Supplementary table 6**). The administration of ACS for women with SGA or FGR was

associated with a possible reduction in the odds of surfactant use (~~3~~**three** studies, 599 infants; pooled OR**:** 0.38**;** 95%CI**:** 0.23**–**0.62, *moderate**-**certainty evidence*), ~~use of~~ mechanical ventilation **use** (~~2~~**two** studies, 508 infants; pooled OR**:** 0.42**;** 95%CI**:** 0.26**–**0.66, *moderate**-**certainty evidence*), **and** oxygen use (~~2~~**two** studies, 508 infants; pooled OR**:** 0.48**;** 95%CI**:** 0.30**–**0.77, *moderate-certainty evidence*) **although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01; 95%CI: 1.16–3.48, *low-certainty* evidence)**~~, and duration of hospital stay (one study, 247 infants; MD −2.3 days, 95%CI: −3.8 −0.8, *low-certainty evidence*)~~ (Table 4~~; Supplementary **Files S7 and** S8~~). Pooled ORs involving women and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be determined for **20**~~18~~ outcomes (**Supplementary file 4, Supplementary table 6**). ~~The administration of~~ ACS **administration** for women with SGA and/or FGR was associated with a possible reduction in severe IVH (~~8~~nine studies, **4636**~~3450~~ infants; pooled OR**:** **0.59**~~0.62~~, 95%CI**:** **0.41**~~0.47~~ **–0.85**~~0.82~~, *low**-**certainty evidence*) and ~~in~~ duration of hospital stay (~~2~~**two** studies, 396 infants; MD −2.23 days**;** 95%CI**:** −3.81**–**−0.83, *low**-**certainty evidence*). **However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32,**

***moderate-certainty evidence*) were possibly increased (Table 4, ~~Supplementary Files S7 and S8).~~** ~~However, the odds of PIH (3 studies, 775 women; pooled OR 1.47; 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06; 95%CI: 1.27–3.32, *moderate-certainty evidence*) were possibly increased (Table 4; Supplementary Files S7 and S8).~~

Table 4: Maternal and neonatal outcomes for women with growth-restricted fetuses and/or small-for-gestational-age infants

Maternal outcomes	**No of study**	**No of the patients**			**Effect**	**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Pregnancy induced hypertension						
Total	**3**	**195/453 (43.0%)**	**99/322 (30.7%)**	**1.47 (1.07–2.01)**	**87 more per 1000 (from 15 more to 164 more)**	**Low**
SGA	**2**	**144/370 (38.9%)**	**94/314 (29.9%)**	**1.50 (1.08–2.07)**	**91 more per 1000 (from 16 more to 170 more)**	**Low**
Neonatal outcomes	**No of study**	**No of the patients**			**Effect**	**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death						
SGA	8	**242/1544 (15.7%)**	**196/1116 (17.6%)**	**0.68~~0.61~~ (0.47-0.97~~0.49-0.78~~)**	**49~~0~~ fewer per 1000 (from 85~~0~~ fewer to 40 fewer)**	Low
Severe IVH						
Total	**9~~8~~**	**190/3018 (6.3%)** ~~156/2341 (6.7%)~~	**171/1618 (10.6%)** ~~108/1109 (9.7%)~~	**0.59 (0.41-0.85)** ~~0.62 (0.47–0.82)~~	**41~~35~~** fewer per 1000 (from **59~~49~~** fewer to **14~~16~~** fewer)	Low
~~SGA~~	~~6~~	~~143/2196 (6.5%)~~	~~99/1039 (9.5%)~~	~~0.60 (0.45–0.80)~~	~~36 fewer per 1000 (from 50 fewer to 18 fewer)~~	~~Low~~
Neonatal hypoglycemia						
Total	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27–3.32)	155 more per 1000 (from 47 more to 273 more)	Moderate

FGR or SGA	**1**	**55/136 (40.4%)**	**28/111 (25.2%)**	**2.01 (1.16-3.48)**	**152 more per 1000 (from 29 more to 288 more)**	**Low**
Surfactants use						
FGR or SGA	3	61/358 (17.0%)	58/241 (24.1%)	0.38 (0.23–0.62)	133 fewer per 1000 (from 173 fewer to 76 fewer)	Moderate
Use of mechanical ventilation						
FGR or SGA	2	73/275 (26.5%)	94/233 (40.3%)	0.42 (0.26–0.66)	182 fewer per 1000 (from 254 fewer to 95 fewer)	Moderate
Oxygen therapy						
FGR or SGA	2	79/275 (28.7%)	94/233 (40.3%)	0.48 (0.30–0.77)	158 fewer per 1000 (from 235 fewer to 61 fewer)	Moderate
Duration of hospital stay (days)						
Total	2	223	173		MD 2.32 lower (3.81 lower to 0.83 lower)	Low
~~FGR or SGA~~	~~1~~	~~136~~	~~111~~	—	~~MD 2.3 lower (3.8 lower to 0.8 lower)~~	~~Low~~
Death or disability/handicap at 2years' corrected age						
FGE	**1**	**11/62 (17.7%)**	**22/62 (35.5%)**	**0.39 (0.17-0.90)**	**178 fewer per 1000 (from 269 fewer to 24 fewer)**	**Low**

*The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in total **and** calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH: Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, SGA: Small for gestational age. **[a] We calculated the numerators using the crude OR in the study by Ley et al. (1997).**

DISCUSSION

This systematic review identified 31 observational studies on the benefits and drawbacks of using ACS in subgroups of women with specific pregnancy complications. ~~This systematic review identified 33 observational studies pertaining to the benefits and possible harms of using ACS in subgroups of women with specific complications of pregnancy~~ In women with diabetes and those undergoing elective late preterm CS, the available evidence on **the** effects of ACS **therapy** was largely **very-low-certainty; thus,** conclusions could not be drawn. In women with histological and clinical chorioamnionitis, ACS **therapy** was associated with **the** benefits of **IVH reduction**. In women with FGR and/or SGA babies, ACS **therapy** possibly has benefits **regarding** neonatal morbidity and mortality, as well as **the** reduced use of respiratory support interventions for the newborn; **however,** neonatal hypoglycemia might be increased.

Effects of ACS therapy on women with pregestational and/or gestational diabetes

A clinical concern regarding ~~the~~ ACS use ~~of ACS~~ in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycemia ~~causing~~**,** **which causes** avoidable harm to the neonate. For example, in women with insulin-

dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid administration (65). A 2002 Danish study **conducted** on 24 pregnant women with diabetes who received steroids suggested that insulin dose adjustment may be required for up to ~~5~~**five** days after ACS administration (66). However, in the current review, there was insufficient evidence to ~~assess~~ **determine** whether ACS increased neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU **admission;** however, the authors noted that **the** ~~neonatal~~ birthweight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding (33). ~~Further~~ **Well**-designed studies are needed **that** ~~on this clinical question and would ideally~~ describe ~~any~~ adjustments to maternal diabetic regimens at the time of ACS therapy and **from** the time **of** ~~from~~ ACS administration to birth and report on important newborn health outcomes.

Effects of ACS ~~in~~ therapy on women undergoing elective CS in the late preterm period

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from seven

trials recruiting women in the late preterm period (2). This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period (2). Deshmukh M et al. reported that ACS reduced the need for respiratory support and increased the risk of hypoglycemia with moderate certainty in late preterm (67). However, no subgroup analyses were conducted on CS (67). Hence, these findings cannot be generalized to all women undergoing CS in the late preterm period. The RCT by Gyamfi-Bannerman CEA et al. reported that ACS in the late preterm period reduced the risk of transient tachypnea of the newborn, surfactant use, and BPD (68). Their subgroup analysis of planned CS showed ACS resulted in no significant difference in their primary outcome and severe respiratory complication (68). Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, mechanical ventilation, stillbirth, neonatal death, or the need for extracorporeal membrane oxygenation (ECMO) (68). Their severe respiratory complications were defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a

fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death, or the need for ECMO (68). Their outcomes did not adequately fit our outcomes, and the study was not included in this review. ~~The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported on findings from seven trials (4142 women) recruiting women at ≥34 weeks 0 days gestation.[2] This subgroup analysis suggested that ACS reduces RDS and increases neonatal hypoglycemia when used in the late preterm period. Two systematic reviews (2018 and 2021) on trials of ACS in the late preterm period drew similar conclusions.[68,69] However, the CS rate (only reported in five trials) was less than 30% in four of these trials[70–73]; hence, these findings cannot be generalized to all women undergoing CS in the late preterm period.~~ Our review demonstrates **that** there is currently insufficient evidence to draw conclusions on the benefits and possible harms of ACS when used in this subpopulation**,** although an ongoing randomized trial in New Zealand is assessing the effects of ACS ~~in~~ t**herapy on** women with CS planned between 35 weeks 0 days and 39 weeks 6 days (69).

Effects of ACS ~~in~~ on women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to

concerns that **the** prolongation of pregnancy and/or immunosuppression may worsen outcomes for **these** women and **their** newborns. ~~While~~ **Although** ACS appears to be associated with reduced ~~neonatal mortality,~~ IVH, and severe IVH **rates** in women with histological chorioamnionitis, there was insufficient evidence ~~for~~ **of** other important infection-related maternal and ~~newborn~~ **neonatal** outcomes **in this review**. While these conclusions are ~~broadly~~ similar to **those of** a 2011 review by Been et al., we do not consider that the available evidence supports the routine use of ACS **therapy** in women with chorioamnionitis**,** as clinical trials comparing ACS therapy ~~with~~ **to** no ACS **therapy** in this population and reliable evidence ~~for~~ **regarding** infection-related outcomes are still lacking (46). **Significant overlap exists between clinical and histological chorioamnionitis (70). Histological chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis (71). However, since physicians must decide the indications for ACS therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant women with clinical chorioamnionitis should be encouraged.** ~~It is unlikely that such trials will be performed, although well-conducted observational studies could provide useful additional evidence.~~

Effects of ACS ~~in~~ therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The totality of **the** evidence identified in this review suggests that ACS **therapy** should be used in the ~~setting of~~ fetal growth restriction **setting**. **Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes, and no harm was reported.** ~~While the evidence was largely low or very low certainty, benefits were observed for several outcomes (including neonatal death, severe IVH, and use of respiratory support interventions) and an absence of harms.~~ The current review identified more **substantial** evidence ~~(18 studies)~~ than that identified in our 2016 systematic review**,** ~~(8eight studies) that~~ **which** was unable to draw **solid** conclusions ~~of~~ **about** the effects of ACS **therapy** in this subpopulation (27). It is also noteworthy that the largest trial ~~of~~ **on** ACS **therapy** in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected fetal growth restriction (72). The current review did not identify **the** benefits ~~for~~ **regarding** the outcome RDS, which might be attributable to a single retrospective cohort study in Japan in which neonates in the ACS group were delivered significantly earlier than those in the control group (56). A sensitivity analysis in which we excluded this study **suggested** that RDS is

significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases **the rate of** neonatal hypoglycemia in this subpopulation, which warrants further exploration in future research. **In this meta-analysis, only two studies targeted pregnant women with FGR. Since the SGA status does not accurately represent FGR, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.**

Strengths and limitations

~~Strengths~~ **The strengths** of this review **were its** ~~included a~~ broad search strategy, which included studies published in languages other than English, rigorous quality **assessments**, and **the** use of **the** GRADE methodology to assess the reliability of the **review's** findings. ~~We thus~~ **Thus, we** consider the risk of missing potentially eligible studies to be low, although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified, or diagnosed the subgroup conditions and outcomes ~~and~~ **of** interest. These differences might have created **a** bias in the review conclusions. However, we explored and reported heterogeneity for meta-analyses~~, as well as downgrading for imprecision~~. Another limitation is that most **of the** included studies were conducted in high-income

countries, although over 60% of all preterm births globally occur in African and South Asian countries (73). **This review did not lead to any evidence of high certainty, and one reason for this observation is that all 31 studies were observational. In 1990, Crowley P et al. reported a structured review of ACS for preterm birth (74). The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity (74). In 1995, the National Institutes of Health developed a consensus on recommending ACS treatment for preterm birth (75). In our review, only one study targeting women with chorioamnionitis and two studies targeting women with FGR started before 1990 (49) (52) (40). It would be challenging to conduct the RCTs on ACS efficacy even in these special populations after the review by Crowley P et al. (74). The latest Cochrane review on ACS treatment for preterm birth involved a subgroup analysis in the seven special conditions (2). However, the review did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis, and FGR (2). Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery (67). Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective**

cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes.

CONCLUSION

ACS **has** possible benefits in the setting of FGR and/or SGA; however, direct evidence ~~on~~ **of** its ~~effectiveness~~ **efficacy** and safety for pregnant women with pregestational and/or gestational diabetes mellitus and those undergoing elective CS in **the** late preterm **period** is **still** lacking. ~~While~~ **Although** ACS might **may** have some benefits in the context of histological chorioamnionitis, more evidence is required. Well-designed studies **(ideally trials)** with adequate follow-up for long-term child outcomes are needed to confirm the ~~effects~~ **upsides** and ~~harms~~ **downsides** of ACS use in these subpopulations.

AUTHOR CONTRIBUTIONS

Dr. Saito participated in the conceptualization and design of the study**,** conducted title, abstract, and full-text screening**,** performed data extraction, analysis, and interpretation,

assessed the risk of bias, drafted the initial manuscript, and critically reviewed the manuscript. Ms. Nishimura conducted the title abstract and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, and critically reviewed the manuscript. Dr. Swa conceptualized and designed the search strategy, conducted a systematic search, and critically reviewed the manuscript for important intellectual content. Dr. Ramson assisted in the interpretation of data and the assessment of the risk of bias and critically reviewed the manuscript for important intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel designed and planned the study, assisted with developing the literature search strategy and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the execution of the study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DATA SHARING STATEMENT

Data were obtained from the published journal article, and extracts are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

None declared.

SUPPLEMENTARY FILES

Supplementary table 1: Characteristic tables

Supplementary table 2: PRISMA 2020 Checklist

Supplementary table 3: Review outcomes

Supplementary table 4: Database-specific search terms and strategies

Supplementary table 5: Risk of bias tables

Supplementary table 6: GRADE tables

Supplementary file 1: PROSPERO

Supplementary file 2: PRISMA flow diagrams

Supplementary file 3: Risk of bias figures

Supplementary file 4: Forest plots

ETHICS APPROVAL

As this study is a systematic review of published studies**; thus**, ethical approval was not required.

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~~FIGURE LEGENDS~~

~~**Figure 1.** Flow diagram of search results and **the** study selection **process** for women with **pregestational and/or gestational** diabetes~~

~~**Figure 2.** Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes. Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias.~~

~~**Figure 3.** Flow diagram of search results and the study selection process for women undergoing elective Cesarean section in **the** late preterm period~~

~~**Figure 4.** Summary of risk of bias for each trial for women undergoing elective Cesarean section in **the** late preterm period. Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias.~~

~~**Figure 5.** Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)~~

~~**Figure 6. A summary** of **the** risk of bias for each trial for women with chorioamnionitis (histological or clinical). Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias.~~

~~**Figure 7.** Flow diagram of search results and **the** study selection **process** for women with growth-restricted fetuses and/or small-for-gestational-age infants~~

~~**Figure 8.** Summary of **the** risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants. Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias.~~

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ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This study aimed to synthesize available evidence on the efficacy of antenatal corticosteroid (ACS) therapy among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period.

Methods: A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted for all comparative randomized or non-randomized interventional studies in the four subpopulations on June 6, 2021. Risk of Bias Assessment tool for Non-randomized Studies and the Cochrane Risk of Bias tool were used to assess the risk of bias. Grading of Recommendations, Assessment, Development, and Evaluations tool assessed the certainty of evidence.

Results: Thirty-two studies involving 5018 pregnant women and 10819 neonates were included. Data on women with diabetes were limited, and evidence on women undergoing planned CS was inconclusive. ACS use was associated with possibly reduced odds of neonatal death (pooled OR: 0.51; 95%CI: 0.31–0.85, low certainty), IVH (pooled OR: 0.41; 95%CI: 0.23–0.72, low certainty), and respiratory distress syndrome (pooled OR: 0.59; 95%CI: 0.45–0.77, low certainty) in women with chorioamnionitis. Among women with FGR, the rates of surfactant use (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate certainty), mechanical ventilation (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate certainty), and oxygen therapy (pooled OR: 0.48; 95%CI: 0.30–0.77, moderate certainty) were probably reduced; however, the rate of hypoglycemia probably increased (pooled OR: 2.06; 95%CI: 1.27–3.32, moderate certainty).

Conclusions: There is a paucity of evidence on ACS for women who have diabetes. ACS therapy may have benefits in women with chorioamnionitis and is probably beneficial in FGR. There is limited direct trial evidence on ACS efficacy in women undergoing planned CS in the late preterm period, though the totality of evidence suggests it is probably beneficial.

Protocol registration:
PROSPERO (CRD42021267816)

Strengths and limitations of this study:
-This review included a broad search strategy.
-This review applied rigorous quality assessment and GRADE methodology.
-Most included studies were observational studies.
-Definitional differences between populations and outcomes complicated the meta-analysis.
-Most studies were conducted in high-income countries.

INTRODUCTION

Previous studies have demonstrated that antenatal corticosteroids (ACS), such as intramuscular dexamethasone or betamethasone, cross the placenta and can induce fetal lung maturation [1]. When administered to women at risk of imminent preterm birth before 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly reduced [2]. ACS therapy also probably decreases the risk of intraventricular hemorrhage (IVH) and reduces the rate of developmental delay in childhood [2]. Therefore, the World Health Organization (WHO) and several obstetric and gynecological societies internationally recommend ACS therapy in women before or up to 34 weeks' gestation for improving preterm newborns' outcomes [3-6]. Some national organizations have recommended ACS use in women at risk of preterm birth up to 36 weeks' gestation based on evidence of the existence of possible respiratory-related benefits for the newborn [3,5].

However, current evidence regarding the benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis, or fetal growth restriction (FGR), is controversial. Women with diabetes, chorioamnionitis, or FGR are at a higher risk of adverse perinatal outcomes; however, they are generally excluded from ACS efficacy trials [2]. Consequently, any subgroup analysis to explore the effects of ACS on women with these complications is unlikely to yield concrete evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycemic effects, and respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor

maternal glycemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women giving birth, causing 22.6–36.9% of stillbirths [9-11]. Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided due to concerns that its immunosuppressive effects may worsen outcomes for women and their babies. However, the relative benefits and harms of using ACS in clinical settings are unclear. FGR is associated with an increased risk of morbidity and mortality [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as SGA neonates are constitutionally, rather than pathologically, small [16]. In most cases, FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant women with both FGR fetuses and SGA neonates.

Another clinical scenario where there is uncertainty is around ACS efficacy is women undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37 weeks' gestation). Babies born in the late preterm period have lower risks of mortality and morbidity than those born before 34 weeks' gestation; however, they have higher risks of adverse outcomes than those born at term [18-21]. In many countries, the rising rate of provider-initiated late preterm birth has been linked to the generalized increase in the CS rate [22]. Regardless of gestational age, babies born via elective CS do not have the usual physical and hormonal stimuli of passage through the birth canal; thus, they tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested that the risk of neonatal hypoglycemia is greater following CS; however, this may be confounded by the underlying indication for CS [26].

In 2016, members of our team published a systematic review assessing the effectiveness of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for

those undergoing elective CS in the late preterm period was found. The review could not draw firm conclusions regarding the effects of ACS on women with growth-restricted fetuses, although low-quality evidence suggested that ACS reduced neonatal IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015 ACS recommendations [28]. Now, WHO's ACS recommendations are being updated as part of the WHO's living guidelines in maternal and perinatal health [29]. Our aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians, and maternal and newborn health stakeholders on safe, effective clinical management in preterm birth.

METHODS

The specific review objectives are presented in Box 1, comprising four related questions on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are explained in Supplementary table 1. SGA infants are all neonates with birth weights below the 10th percentile. In this study, FGR fetuses were defined using the operational definition used in eligible studies (Supplementary table 1). The review protocol was registered on PROSPERO (CRD42021267816) and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary file 1, Supplementary table 2) [30].

Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a systematic review

P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes
P: Women at risk of imminent preterm birth less than 37 weeks with pregestational diabetes mellitus and/or gestational diabetes mellitus
I: ACS administration
C: Placebo or no treatment
O: World Health Organization (WHO) priority outcomes for preterm birth

P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period
P: Women undergoing elective CS in the late preterm period between 34 weeks and 0 days and 36 weeks and 6 days
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P3: Effects of ACS therapy on women with chorioamnionitis
P: Women at risk of imminent preterm birth less than 37 weeks with chorioamnionitis
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants
P: Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or small-for-gestational-age infants
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

Study eligibility criteria

Eligible studies were randomized or non-randomized primary studies that reported on the effects of ACS therapy in the four subpopulations. This included published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-after studies, interrupted-time-series studies, historically controlled studies, cohort studies, and cross-sectional studies comparing any ACS (betamethasone, dexamethasone, or hydrocortisone) administered either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational

diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis, and women with FGR fetuses or SGA infants.

Articles in any language and from any country were eligible for inclusion if they reported on one or more of WHO's priority outcomes for preterm birth guideline development [28]. Maternal outcomes were death, maternal morbidity, and therapy side effects. Newborn and child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric status, and therapy side effects (Supplementary table 3).

Data sources and search strategy

An information specialist was consulted for the development of the search strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions on June 6, 2021. Controlled vocabularies supplemented with free keywords were used to search for the relevant concept areas, with duplicates removed in the process to yield a total number of abstracts for each database (Supplementary table 4). Reference lists of the included articles, including any recent systematic reviews, were also hand-searched for further potentially relevant studies. All citations were imported into a Rayyan (http://rayyan.qcri.org) library for eligibility assessment.

Study selection, data extraction, and quality assessment

Two reviewers (KS, EN) independently assessed the titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies

were obtained and assessed in duplicate by two reviewers working independently, with disagreements resolved through discussions or by consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through discussions or by consulting a third reviewer. Extracted data were entered into the Review Manager version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [31]. We used the Cochrane Risk of Bias tool for randomized trials [32]. Potential publication bias was inspected visually using funnel plots for asymmetry in situations where data for a single outcome were available from at least ten studies.

Data synthesis and analysis

Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs) were determined for dichotomous data using the random-effects model. Crude data were used when the numbers of events were available and crude OR were employed when events were not available. For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for heterogeneity. For the analysis of women with FGR fetuses and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only, and SGA or FGR). Data from the three populations were combined, and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%. Based on the evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at

high risk of bias. All statistical analyses were performed using RevMan5. The threshold for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development, and Evaluation (GRADE), an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines, was used in this review.

Patients and public involvement

Since this is a systematic review of previously published data, there was no direct involvement of patients or the public.

RESULTS

Effects of ACS therapy on women with pregestational and/or gestational diabetes mellitus

The search identified 179 citations: 11 potentially eligible studies were evaluated, and three studies met the eligibility criteria, providing data on 725 pregnant women and 830 neonates (Supplementary file 2) [33-35]. All studies were conducted in high-income countries and data collection was performed between 2008 and 2017 (Supplementary table 1). One study involved women with pregestational diabetes only, one study involved women with gestational diabetes only, and one study involved women with either pregestational or gestational diabetes. All included studies were judged as having a low risk of bias across all domains except high risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). Data were available for six outcomes (Table 1). One retrospective cohort study found that in women with gestational

diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (one study, 162 infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty evidence*); however, the effect of ACS therapy on neonatal hypoglycemia was uncertain (two studies, 215 infants; pooled OR: 1.44; 95%CI: 0.702.97, *very-low-certainty evidence*) [33]. The certainty of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn.

Table 1: Maternal and neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

Neonatal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Caesarean section	2	31/65 (47.7%)	58/150 (38.7%)	1.75 (0.63–4.82)	138 more per 1,000 (from 102 fewer to 366 more)	Very Low
Neonatal death within 48 h of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09–2.20)	14 fewer per 1000 (from 23 fewer to 29 more)	Very Low
RDS	2	179/583 (30.7%)	37/193 (19.2%)	2.79 (0.85–9.08)	207 more per 1000 (from 24 fewer to4 91 more)	Very Low
Neonatal hypoglycemia	2	14/65 (21.5%)	66/150 (44.0%)	1.44 (0.70–2.97)	91 more per 1000 (from 85 fewer to 260 more)	Very Low
Apgar score < 7 at 5 min	1	1/47 (2.1%)	21/114 (18.4%)	0.79 (0.10–5.89)	33 fewer per 1000 (from 162 fewer to 387 more)	Very Low
Admission to NICU	1	19/47 (40.4%)	36/114 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome.

Effects of ACS therapy on women undergoing elective CS in the late preterm period

The search identified 211 citations:17 potentially eligible studies were evaluated, and three studies were included (Supplementary file 2) [36,37,38]. These were two observational studies and a randomized controlled trial (RCT). All studies were conducted in high-income countries between 2010 and 2017, providing data on 205 pregnant women/neonates (Supplementary table 1). The two observational studies were judged as having a high risk of bias for confounding variables (Supplementary file 3, Supplementary table 5). Data on eleven outcomes were available but all had very low certainty; so, no meaningful conclusions could be drawn (Table 2).

Table 2: Maternal and neonatal outcomes for women undergoing elective cesarean section in the late preterm period

Maternal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09–1.21)	89 fewer per 1000 (from 126 fewer to 25 more)	Very Low
Gestational diabetes mellitus	1	3/30 (10.0%)	4/10 (40.0%)	0.17 (0.03-0.95)	298 fewer per 1000 (from 380 to 12 fewer)	Very Low
Neonatal outcomes	**No of studies**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29–2.24)	17 fewer per 1000 (from 65 fewer to 95 more)	Very Low
IVH	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Necrotizing enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Neonatal hypoglycemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81–2.78)	93 more per 1000 (from 44 fewer to 246 more)	Very Low
Use of mechanical ventilation	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.30–2.12)	17 fewer per 1000 (from 64 fewer to 86 more)	Very Low
Admission to NICU	2	10/88 (11.4%)	14/117 (12.0%)	0.78 (0.23–2.72)	24 fewer per 1000 (from 89 fewer to 150 more)	Very Low
Apgar score ≤ 7 at 5 min	1	2/58 (3.4%)	0/107 (0.0%)	9.51 (0.45–201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very Low
Mean duration of mechanical ventilation	1	30	10	-	MD 0.2 lower (1.35 lower to 0.95 higher)	Very Low
Oxygen requirement for at least 4 hours	1	13/58 (22.4%)	25/107 (23.4%)	0.95 (0.44-2.03)	9 fewer per 1000 (from 115 fewer to 149 more)	Very Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS therapy on women with chorioamnionitis (histological or clinical)

The search identified 418 citations: 12 potentially eligible studies were evaluated, and eight were found to be eligible (Supplementary file 2) [39-46]. Two were prospective cohort studies and six were retrospective, providing data on 1372 pregnant women and 1460 neonates (Supplementary table 1). Four studies included pregnant women with clinical chorioamnionitis, and there were variations in the diagnostic criteria (Supplementary table 1). All studies were conducted in high-income countries between 1989 and 2014. Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process [39,42-44,47]. All included studies were judged as having a low risk of bias overall except high risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). Data for 27 outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3; Supplementary file 4). Among women with histological chorioamnionitis, ACS

administration was associated with a possible reduction in the odds of neonatal death (six studies, 1193 infants; pooled OR: 0.51; 95%CI: 0.31–0.85, *low-certainty evidence*), severe intraventricular hemorrhage (IVH) (four studies, 528 infants; pooled OR: 0.41; 95%CI: 0.19–0.87, *low-certainty evidence*), IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*), RDS (six studies, 1193 infants; pooled OR: 0.59; 95%CI: 0.45–0.77, *low-certainty*). ACS might result in no difference in neonatal sepsis; however, the evidence was uncertain (six studies, 1193 infants: pooled OR: 1.03; 95%CI: 0.73–1.47, *very-low-certainty evidence*). The certainty of evidence was very low for other outcomes (Supplementary table 6). In women with clinical chorioamnionitis, only very-low-certainty evidence was available for neonatal sepsis (two studies, 150 infants, pooled OR: 0.71; 95%CI: 0.13–3.89). The certainty of evidence was very low for all other outcomes (Supplementary table 6).

Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						
Caesarean section	1	42/97 (43.3%)	2/12 (16.7%)	3.82 (0.79–18.36)	266 fewer per 1000 (from 30 fewer to 619 more)	Very Low
Gestational diabetes mellitus	1	6/97 (6.2%)	2/12 (16.7%)	0.33 (0.06-1.86)	105 fewer per 1000 (from 155 fewer to 104 more)	Very Low
Preeclampsia or eclampsia	1	5/97 (5.2%)	1/12 (8.3%)	0.60 (0.06–5.59)	32 fewer per 1000 (from 78 fewer to 254 more)	Very Low
Neonatal outcomes (histological chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	0.51 (0.31–0.85)	75 fewer per 1000 (from 109 fewer to 22 fewer)	Low
Severe IVH	4	25/414 (6.0%)	13/114 (11.4%)	0.41 (0.19–0.87)	64 fewer per 1000 (from 90 fewer to 13 fewer)	Low
IVH	5	42/502 (8.4%)	26/156 (16.7%)	0.41 (0.23–0.72)	91 fewer per 1000 (from 123 fewer to 41 fewer)	Low
RDS	6	305/677 (45.1%)	289/516 (56.0%)	0.59 (0.45-0.77)	131fewer per 1000 (from 196 fewer to 65 fewer)	Low
Sepsis	6	112/677 (16.5%)	83/516 (16.1%)	1.03 (0.73–1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very Low
Neonatal outcomes (clinical chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	2	14/109 (12.8%)	14/81 (17.3%)	0.71 (0.32-1.60)	44 fewer per 1000 (from 110 fewer to 78 more)	Very Low
Severe IVH	3	5/163 (3.1%)	14/155 (9/0%)	0.32 (0.03–3.19)	60 fewer per 1000 (from 87 fewer to 150 more)	Very Low
IVH	3	13/163 (8.0%)	20/155 (12.9%)	0.43 (0.07–2.44)	69 fewer per 1000 (from 119 fewer to 136 more)	Very Low
RDS	4	99/209 (47.45)	99/208 (47.6%)	0.74 (0.48-1.12)	74 fewer per 1000 (from 172 fewer to 28 more)	Very Low
Sepsis	2	26/104 (25.0%)	12/46 (26.1%)	0.71 (0.13–3.89)	60 fewer per 1000 (from 271 fewer to 318 more)	Very Low

*There was no maternal outcome in clinical chorioamnionitis.
*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, OR: Odds ratio, RDS: Respiratory distress syndrome

Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The search identified 261 citations: 36 potentially eligible studies were assessed, and 18 studies were included (Supplementary file 2) [42,48-64]. Of these, twelve studies included women with SGA infants only, four studies included women with FGR or SGA infants, and two studies included women with FGR infants only (Supplementary table 1). Among the studies that included FGR fetuses, the definitions of FGR varied widely (Supplementary table 1). Since SGA status is insufficient to determine FGR, we separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three populations were combined, and the pooled OR in total was calculated. Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 [51,54,59]. These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event. All were observational studies conducted in high-income countries. Additional unpublished data from the study by Torrance et al. (2007) were extracted from a review paper published in 2009 identified through the search strategy [54,65]. We extracted crude data from the included studies except Ley et al. (1997) [50]. The study by Ley et al. only provided the adjusted ORs, controlled by birthweight deviation, gestational age, pre-eclampsia, premature rupture of membranes, and mode of delivery [50]. Most of these studies were judged as having a low risk of bias across all domains except high risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). For SGA infants

only, 12 studies provided data on 30 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the odds of pre-eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95%CI: 0.66–0.94, *low-certainty evidence*), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–0.97, *low-certainty evidence*), periventricular leukomalacia (PVL) (four studies, 3955 infants; pooled OR: 0.54; 95%CI: 0.38–0.77, *low-certainty evidence*) were possibly reduced (Table 4). Two studies involving FGR infants only provided data for 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17–0.90, *low-certainty evidence*) were possibly reduced (Table 4). Four studies involved SGA or FGR infants, providing data for 25 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA or FGR was associated with a possible reduction in the odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62, *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants; pooled OR: 0.42; 95%CI: 0.26–0.66, *moderate-certainty evidence*), oxygen use (two studies, 508 infants; pooled OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*) although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01; 95%CI: 1.16–3.48, *low-certainty evidence*) (Table 4). Pooled ORs involving women and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be determined for 20 outcomes (Supplementary file 4, Supplementary table 6). ACS administration for women with SGA and/or FGR was associated with a possible reduction in severe IVH (nine studies, 4636 infants;

pooled OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital stay (two studies, 396 infants; MD −2.23 days; 95%CI: −3.81–−0.83, *low-certainty evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were possibly increased (Table 4).

Table 4: Maternal and neonatal outcomes for women with growth-restricted fetuses and/or small-for-gestational-age infants

Maternal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Pregnancy induced hypertension						
Total	3	195/453 (43.0%)	99/322 (30.7%)	1.47 (1.07–2.01)	87 more per 1000 (from 15 more to 164 more)	Low
SGA	2	144/370 (38.9%)	94/314 (29.9%)	1.50 (1.08–2.07)	91 more per 1000 (from 16 more to 170 more)	Low
Pre-eclampsia						
SGA	2	359/806 (44.5%)	640/1271 (50.4%)	0.78 (0.66-0.94)	62 fewer per 1000 (from 103 fewer to 15 fewer)	Low
Neonatal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death [a)]						
SGA	8	242/1544 (15.7%)	196/1116 (17.6%)	0.68 (0.47-0.97)	49 fewer per 1000 (from 85 fewer to 4 fewer)	Low
Severe IVH						
Total	9	190/3018 (6.3%)	171/1618 (10.6%)	0.59 (0.41-0.85)	41 fewer per 1000 (from 59 fewer to 14 fewer)	Low
Neonatal hypoglycemia						
Total	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27–3.32)	155 more per 1000 (from 47 more to 273 more)	Moderate
FGR or SGA	1	55/136 (40.4%)	28/111 (25.2%)	2.01 (1.16-3.48)	152 more per 1000 (from 29 more to 288 more)	Low
Surfactants use						
FGR or SGA	3	61/358 (17.0%)	58/241 (24.1%)	0.38 (0.23–0.62)	133 fewer per 1000 (from 173 fewer to 76 fewer)	Moderate
PVL						
SGA	4	74/2219 (3.3%)	68/1736 (3.9%)	0.54 (0.38–0.77)	18 fewer per 1000 (from 24 fewer to 9 fewer)	Low
Use of mechanical ventilation						
FGR or SGA	2	73/275 (26.5%)	94/233 (40.3%)	0.42 (0.26–0.66)	182 fewer per 1000 (from 254 fewer to 95 fewer)	Moderate
Oxygen therapy						
FGR or SGA	2	79/275 (28.7%)	94/233 (40.3%)	0.48 (0.30–0.77)	158 fewer per 1000 (from 235 fewer to 61 fewer)	Moderate
Duration of hospital stay (days)						
Total	2	223	173		MD 2.32 lower (3.81 lower to 0.83 lower)	Low
Death or disability/handicap at 2years' corrected age						
FGR	1	11/62 (17.7%)	22/62 (35.5%)	0.39 (0.17-0.90)	178 fewer per 1000 (from 269 fewer to 24 fewer)	Low

*The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in total and calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH: Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, PVL: Periventricular leukomalacia, SGA: Small for gestational age. [a)] We calculated the numerators using the adjusted OR in the study by Ley et al. (1997).

DISCUSSION

This systematic review identified 31 observational studies and a RCT on the benefits and harms of using ACS in subgroups of women with specific pregnancy complications. In women with diabetes and those undergoing elective late preterm CS, the available evidence on the effects of ACS therapy was largely very-low-certainty; thus, conclusions could not be drawn. In women with histological and clinical chorioamnionitis, ACS therapy was associated with the benefit of neonatal death, IVH and RDS reduction. In women with FGR and/or SGA babies, ACS therapy possibly has benefits regarding neonatal morbidity and mortality, as well as the reduced use of respiratory support interventions for the newborn; however, neonatal hypoglycemia might be increased.

Effects of ACS therapy on women with pregestational and/or gestational diabetes

A clinical concern regarding ACS use in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycemia, which causes avoidable harm to the neonate. For example, in women with insulin-dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid administration [66]. A 2002 Danish study conducted on 24 pregnant women with

diabetes who received steroids suggested that insulin dose adjustment may be required for up to five days after ACS administration [67]. However, in the current review, there was insufficient evidence to determine whether ACS increased neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU admission; however, the authors noted that average birthweight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding [33]. Well-designed studies are needed that describe adjustments to maternal diabetic regimens at the time of ACS therapy and from the time of ACS administration to birth and report on important newborn health outcomes.

Effects of ACS therapy on women undergoing elective CS in the late preterm period

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from seven trials recruiting women in the late preterm period [2]. This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh et al. reported that ACS reduced the need for respiratory support and increased the risk of

hypoglycemia with moderate certainty in late preterm [68]. However, no subgroup analyses were conducted on CS [68]. Hence, these findings cannot be generalized to all women undergoing CS in the late preterm period. The trial by Gyamfi-Bannerman et al. reported that ACS in the late preterm period reduced their primary outcome and severe newborn respiratory complications [38]. Their subgroup analysis showed that these beneficial effects persisted among women admitted for planned CS only [38]. Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, mechanical ventilation, or the need for extracorporeal membrane oxygenation (ECMO) [38]. Severe respiratory complications were defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death within 72 hours after delivery, or the need for ECMO [38]. Their outcomes did not adequately fit our outcomes, and the study did not provide their outcome data. Our review suggests there is insufficient evidence to draw firm conclusions on the benefits and possible harms of ACS when used in this subpopulation. At the same time, the

multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective effects from ACS for neonatal respiratory morbidity amongst women with late preterm CS [38]. An ongoing randomized trial in New Zealand will provide further information on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and 39 weeks 6 days [69].

Effects of ACS on women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to concerns that the prolongation of pregnancy and/or immunosuppression may worsen outcomes for these women and their newborns. Although ACS appears to be associated with reduced neonatal death, IVH and RDS rates in women with histological chorioamnionitis, there was insufficient evidence of other important infection-related maternal and neonatal outcomes in this review. While these conclusions are similar to those of a 2011 review by Been et al., we do not consider that the available evidence supports the routine use of ACS therapy in women with chorioamnionitis, as clinical trials comparing ACS therapy to no ACS therapy in this population and reliable evidence regarding infection-related outcomes are still lacking [47]. Significant overlap exists between clinical and histological chorioamnionitis [70]. Histological

chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis [71]. However, since physicians must decide the indications for ACS therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant women with clinical chorioamnionitis should be encouraged.

Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The totality of the evidence identified in this review suggests that ACS therapy should be used in the fetal growth restriction setting. Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes, and no harm was reported. The current review identified more substantial evidence than that identified in our 2016 systematic review, which was unable to draw solid conclusions about the effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected fetal growth restriction [72]. The current review did not identify the benefits regarding the outcome RDS, which might be attributable to a single retrospective cohort study in Japan in which neonates in the ACS group were

delivered significantly earlier than those in the control group [57]. A sensitivity analysis in which we excluded this study suggested that RDS is significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal hypoglycemia in this subpopulation, which warrants further exploration in future research. In this meta-analysis, two studies targeted pregnant women with FGR while the other 16 included pregnant women with SGA. SGA status does not perfectly represent FGR [16]. Since physicians must decide the indication for ACS therapy when FGR is detected, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.

Strengths and limitations

The strengths of this review were its broad search strategy, which included studies published in languages other than English, rigorous quality assessments, and the use of the GRADE methodology to assess the reliability of the review's findings. Thus, we consider the risk of missing potentially eligible studies to be low, although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified, or diagnosed the subgroup conditions and outcomes of interest. These differences might have created a bias in the

review conclusions. However, we explored and reported heterogeneity for meta-analyses. This analysis extracted all data from observational studies. Since adjusted confounding variables showed a wide variety in each included study, crude data were employed in our review. No included studies adequately considered their study design to adjust the confounding bias. Therefore, confounding bias should be cautiously considered in our results' interpretation. Another limitation is that most of the included studies were conducted in high-income countries, although over 60% of all preterm births globally occur in African and South Asian countries [73]. This review did not lead to any evidence of high certainty, and one reason for this observation is that all studies were observational. In 1990, Crowley P et al. reported a structured review of ACS for preterm birth [74]. The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity [74]. In 1995, the National Institutes of Health developed a consensus on recommending ACS treatment for preterm birth [75]. In our review, only one study targeting women with chorioamnionitis and two studies targeting women with FGR started before 1990 [41,50,53]. It would be challenging to conduct the RCTs on ACS efficacy even in these special populations after the review by Crowley P et al. [74]. The latest Cochrane review on ACS treatment for preterm birth involved a subgroup analysis in the seven special conditions [2]. However, the review

did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis, and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery [68]. Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes. Our search was last conducted in June 2021 and required time for publication. Despite scrutinizing additional sources between June 2021 and February 2023, we did not find any further relevant studies.

CONCLUSION

ACS has possible benefits in the setting of FGR and/or SGA; however, direct trial evidence of its efficacy and safety for pregnant women with pregestational and/or gestational diabetes mellitus and those undergoing elective CS in the late preterm period is still lacking. Although ACS may have some benefits in the context of histological

chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with adequate follow-up for long-term child outcomes are needed to confirm the upsides and downsides of ACS use in these subpopulations.

AUTHOR CONTRIBUTIONS

Dr. Saito participated in the conceptualization and design of the study, conducted title, abstract, and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, drafted the initial manuscript, and critically reviewed the manuscript. Ms. Nishimura conducted the title abstract and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, and critically reviewed the manuscript. Dr. Swa conceptualized and designed the search strategy, conducted a systematic search, and critically reviewed the manuscript for important intellectual content. Dr. Ramson assisted in the interpretation of data and the assessment of the risk of bias and critically reviewed the manuscript for important intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel designed and planned the study, assisted with developing the literature search strategy and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the

execution of the study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DATA SHARING STATEMENT

Data were obtained from the published journal article, and extracts are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

None declared.

SUPPLEMENTARY FILES

Supplementary table 1: Characteristic tables

Supplementary table 2: PRISMA 2020 Checklist

Supplementary table 3: Review outcomes

Supplementary table 4: Database-specific search terms and strategies

Supplementary table 5: Risk of bias tables

Supplementary table 6: GRADE tables

Supplementary file 1: PROSPERO

Supplementary file 2: PRISMA flow diagrams

Supplementary file 3: Risk of bias figures

Supplementary file 4: Forest plots

ETHICS APPROVAL

This study is a systematic review of published studies; thus, ethical approval was not required.

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Supplementary table 1: Chracteristic tables

Table 1: Characteristics of included studies for women with pregestational and/or gestational diabetes mellitus

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	PGDM or GDM	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Battarbee et al., 2020	Retrospective cohort	Pregnant women 510 (439, 71) Infants 615 (536, 79)	2008–2011	USA	Women giving birth at GA 23–33weeks	Stillborn, nonresuscitated cases	PGDM or GDM	NS	NS	NS	Yes
Cassimatis et al., 2020	Retrospective cohort	Pregnant women=infants 54 (18, 36)	2014–2017	USA	Women giving birth in late preterm	Congenital anomalies, multiple pregnancy	PGDM	Beta	12	24	No
Krispin et al., 2018	Retrospective cohort	Pregnant women=infants 161 (47, 114) [1)]	2012–2016	Israel	Women giving birth in late preterm period	Preterm PROM, multiple gestations, PGDM, fetal anomaly, fetal chromosomal abnormalities	GDM	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, Dex: Dexamethasone, GA: Gestational age, GDM: Gestational diabetes mellitus, NS: Not stated, PGDM: Pregestational diabetes mellitus, PROM: Premature rupture of the membranes

[1)] This study included 2262 women who gave birth in the late preterm and term period. Data were extracted and reported for women in the late-preterm delivery group (n = 161) only.

Table 2: Characteristics of included studies for women undergoing elective cesarean section in the late preterm period

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	Antenatal corticosteroid course			
							Drug	Dose (mg)	Interval (h)	Repeat ACS
de la Huerga et al., 2019	Retrospective cohort	Pregnant women=infants 40 (30, 10)	2013–2017	Spain	Women undergoing elective CS between 35 weeks 0 days and 36 weeks 6 days	Congenital anomalies, transferred to other hospitals	Beta	NS	NS	NS
Kirshenbaum et al., 2018	Case-control	Pregnant women=infants 165 (58, 107)	2011–2013	Israel	Women undergoing elective CS between GA 34 weeks 0 days and 37 weeks 0 days	Multiple pregnancy, congenital anomalies, chromosomal abnormalities, chorioamnionitis	Beta	12	24	No

Gyamfi-Bannerman et al., 2016[a)]	RCT	Pregnant women=infants 2827 (1427, 1400)	2010-2015	USA	Women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation, who were high probability of delivery in the late preterm period	Received ACS previously during the pregnancy, Expected to deliver in less than 12 hours for any reasons, Lack of gestational dating based on ultrasonography before GA 32 weeks, Lack of gestational dating based on last menstrual period before GA 24 weeks	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, GA: Gestational age, NS: Not stated, RCT: Randomized controlled trial
[a)]Gyamfi-Bannerman (2016) did not provide the data on our review outcomes.

Table 3-a: Characteristics of included studies for women with chorioamnionitis (histological or clinical)

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	HC CC	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Ryu et al., 2019	Retrospective cohort	Pregnant women=infants 109 (97, 12)	2007–2014	Republic of Korea	Women giving birth between GA 23weeks 0 days and 33 weeks 6 days	Multiple gestations, congenital anomalies, SGA or LGA, transferred to other hospitals, incomplete information	HC	Beta /Dex	NS	NS	No
Ahn et al., 2012	Prospective cohort	Pregnant women no data Infants 88 (52, 36)	2005–2010	Republic of Korea	Women giving birth at GA < 34 weeks	Congenital anomalies, transferred from other hospitals	HC	Dex	5	12	No
Been et al., 2009	Prospective cohort	Pregnant women=infants HC121 (89, 32) CC93 (64,29)	2001–2003	Netherlands	Women giving birth at GA < 32 weeks	Congenital anomalies	HC CC	Beta	12	24	No
Goldernberg et al., 2006	Retrospective cohort	Pregnant women=infants HC218 (182, 36) CC93 (64, 29)	1996–2001	USA	Women giving birth between GA 23 weeks 0 days and 32 weeks 6 days	Multiple gestations	HC CC	Beta	12	24	Yes
Dempsey et al., 2005	Retrospective cohort	Pregnant women=infants 130 (88, 42)	1989–1999	USA	Women giving birth at GA < 30 weeks	Multiple gestations	HC	Beta	12	24	NS
Foix-L'Helias et al., 2005	Retrospective cohort	Pregnant women=infants 97 (45, 52)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations	CC	Beta /Dex	NS	NS	Yes
Baud et al., 2000	Retrospective cohort	Pregnant women=infants 170 (60, 110)	1993–1997	France	Women giving birth at GA < 33 weeks	Multiple gestations, severe DM	CC	Beta /Dex	NS	NS	Yes
Elimian et al., 2000	Retrospective cohort	Pregnant women=infants 527 (169, 358)	1990–1997	USA	Birth weight: 500–1750 g	CC	HC	Beta	12	24	Yes

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CC: Clinical chorioamnionitis, Dex: Dexamethasone, DM: Diabetes mellitus, GA: Gestational age, HC: Histological chorioamnionitis, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

Table 3-b: Diagnostic criteria on histological and clinical chorioamnionitis from individual studies

Author, year	HC, CC	Diagnostic criteria
Ryu et al., 2019	HC	Salafia et al.*2
Ahn et al., 2012	HC	No written diagnostic criteria
Been et al., 2009	HC/ CC	HC: Redline et al. *3 CC: maternal temperature greater than 38.0℃ in the absence of another focus for infection, with two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leucocytosis (WBC>15000cells/μL), raised serum C-reactive protein, maternal tachycardia (>100 beats/min), and fetal tachycardia (>160 beats/min)
Goldernberg et al., 2006	HC/ CC	HC: Redline et al.*3, Faye-Petersen et al.*4, Bendon et al.*5 CC: diagnosed by an obstetrician, usually for a combination of fever, abdominal pain, and elevated white count
Dempsey et al., 2005	HC	HC: the presence of abundant polymorphonuclear leukocytes in the chorion and amnion
Foix-L'Helias et al., 2005	CC	CC: defined by the association of preterm labor and at least two of the following criteria: a) maternal temperature greater than 38℃, b) maternal serum C reactive protein concentration >20mg/l, c) positive bacterial culture of amniotic fluid (amniocentesis), d) documented early onset neonatal sepsis
Baud et al., 2000	CC	CC: defined by the association of preterm labor and at least two pre and/ or intrapartum criteria of maternal fever (temperature > 38℃ on at least two occasions); blood inflammatory response (C-reactive protein plasma concentration > 40 ml/L or white blood count > 18000/mm3; or bacteriological evidence of infection in amnionic fluid obtained by amniocentesis
Elimian et al., 2000	HC	HC: Salafia et al. *2

*1 HC: Histological chorioamnionitis ,CC: Clinical chorioamnionitis

*2 Salafia CM, Weigl C, Silberman L. The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. *Obstet Gynecol*. 1989;73(3 Pt 1):383-389.
*3 Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003;6(5):435-448. doi:10.1007/s10024-003-7070-y.
*4 Faye-Petersen O, Heller DS, Joshi VV. Handbook of Placental Pathology. Oxford: Taylor and Francis Medical Publishers; 2005. 142-52.
*5 Bendon RW, Faye-Petersen O, Pavlova Z, et al. Histologic features of chorioamnion membrane rupture: development of methodology. Pediatr Pathol Lab Med. 1997;17(1):27-42.

Table 4-a: Characteristics of included studies for women with growth-restricted fetuses and/or small for gestational age infants

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	FGR SGA	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Bitar et al., 2020	Retrospective cohort	Pregnant women=infants 247 (136, 111)	2015–2019	USA	Women giving birth between GA 34 weeks 0 days and 36 weeks 6 days	Multiple gestations, mother age ≥ 18 years	SGA or FGR	Beta	NS	NS	NS
Cartwright et al., 2019	Retrospective cohort	Pregnant women 216 (118, 98) Infants 261 (139, 122)	1998–2004	Australia New Zealand	Women giving birth at GA < 32 weeks, single, twin, and triplet pregnancy	Chorioamnionitis requiring urgent delivery, labor at the second stage, mature fetal lung development, and further steroid therapy	SGA or FGR	Beta	13.8	NS	Yes
Kim WJ et al., 2018	Retrospective cohort	Pregnant women=infants 82 (45, 37)	2009–2016	Republic of Korea	Women giving birth between GA 29 weeks 0 days and 34 weeks 6 days	Multiple gestations, still birth, major congenital abnormality, ACS administration within 24 h before births, ACS administration >7 days before birth	SGA	Dex	5	12	NS
Kim YJ et al., 2018	Retrospective cohort	Pregnant women=infants 91 (83, 8)	2007–2014	Republic of Korea	Women giving birth between GA 23 weeks 0 days and 33 weeks 6 days	Multiple gestations, major congenital abnormality, fetal hydrops, incomplete information, LGA, repeated ACS, transfer to other hospitals, SGA without fetal umbilical artery Doppler abnormalities	FGR or SGA	Beta/ Dex	NS	24/ 12	No
Riskin-Mashiah et al., 2018	Retrospective cohort	Pregnant women=infants 784 (585,199)	1995–2012	Israel	Women giving birth to twins between GA 24 weeks 0 days and 31 weeks 6 days	Congenital anomalies	SGA	NS	NS	NS	NS
Feng et al., 2017	Retrospective cohort	Pregnant women No data Infants 602 (325, 277)	2013–2014	China	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days	Major congenital abnormality, inherited metabolic disease	SGA	Beta/ Dex	12/ 5–6	24/ 12	No
Riskin-Mashiah et al., 2016	Retrospective cohort	Pregnant women=infants 1771 (1246, 525)	1995–2012	Israel	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital malformation, incomplete data	SGA	NS	NS	NS	NS
Ishikawa et al., 2015	Retrospective cohort	Pregnant women=infants 1929 (719, 1210)	2003–2007	Japan	Birth weight < 1500 g	Multiple gestations, Women giving birth ≥34 weeks, major congenital malformation, incomplete information, out-of-hospital birth	SGA	NS	NS	NS	NS
Mitsiakos et al., 2013	Retrospective cohort	Pregnant women=infants 149 (87, 62)	NS	Canada	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital anomalies	SGA	Beta	12	24	No

van Stralen et al, 2009	Retrospective cohort	Pregnant women=infants 88 (54,34)	2001–2005	Netherlands	Birth weight < 1500 g	Multiple gestations, major congenital malformation or infection, incomplete information	FGR	Beta	11.4	24	NS
Torrance et al., 2007	Retrospective cohort	Pregnant women 165 (146, 19) FGR140 (112,28), SGA165 (146, 19)	1999–2003	Netherlands	Women giving birth at GA < 34 weeks	Congenital, chromosomal or syndromic abnormalities	SGA	Beta	12	24	NS
Foix-L'Helias et al, 2005	Retrospective cohort	Pregnant women No data Infants 151 (96,55)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	NS	SGA	NS	NS	NS	NS
Schaap et al, 2001	Case-control	Pregnant women=infants 124 (62,62)	1984–1991	Netherlands	Women giving birth between GA 26 weeks 0 days and 31 weeks 6 days	ACS < 24 h before delivery, fetal death or fetal distress at admission to the hospital, abruptio placentae, lethal congenital abnormalities or infections, multiple gestations	FGR	Beta	12.5	24	NS
Bernstein et al, 2000 *1	Retrospective cohort	Pregnant women=infants 1258 (703,555)	1991–1996	USA, Canada	Women giving birth between GA 25 weeks 0 days and 30 weeks 6 days, white and African-American infants	Multiple gestations, major anomalies	SGA	NS	NS	NS	NS
Elimian et al, 1999	Retrospective cohort	Pregnant women No data Infants 220 (63,157)	1990–1997	USA	Birth weight ≤ 1750 g	NS	SGA	Beta	12	24	Yes
Ley et al, 1997	Retrospective cohort	Pregnant women No data Infants 234 (117, 117)	1984–1985	Sweden	Women giving birth at GA < 33 weeks	NS	SGA	NS	NS	NS	NS
Spinillo et al, 1995	Prospective cohort	Pregnant women No data Infants 96 (32,64)	1988–1993	Italy	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days, indetermined or immature lecithin/sphingomyelin ratio, planned delivery with medication complications, liveborn	Congenital anomalies	SGA	Beta/Dex	12/ 12	NS	NS
Lenardo et al, 1990	Retrospective cohort	Pregnant women=infants 72 (15,57)	NS	Italy	Women giving birth at GA ≤ 35 weeks	Twin gestations	SGA	Beta	12	24	NS

*ACS: Antenatal corticosteroid, Beta: Betamethasone, Dex: Dexamethasone, FGR: Fetal growth restriction, GA: Gestational age, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

*1: The data was obtained through personal communication.

Table 4-b: Diagnostic criteria on fetal growth restriction (FGR) from individual studies

Author, year	Diagnostic criteria on FGR
Bitar et al., 2020	Identified by International Classification of Diseases, Tenth Revision (ICD-10) codes..
Cartwright et al., 2019	Defined a priori as one or more of the following: obstetric diagnosis of FGR at trial entry; cesarean delivery for FGR; or customized birth weight of no greater than the third centile (GROW, version 6.7.8.3; Perinatal Institute).
Kim YJ et al., 2018	Defined as any fetal growth restriction (estimated fetal weight <10th percentile) documented from serial maternal medical records or a birth weight of less than the 10th percebtile based on the growth curve of Olsen et al. [*1]with absent or reverse umbilical artery end-diastolic flow in the fetal Doppler studies.
van Stralen et al, 2009	Defined id at least one measurement of the U/C ratio was higher than 0.725.[*2] U:umbilical artery, C:middle cerebaral artery
Schaap et al, 2001	Diagnosed by fundal height measurement and by sonographic fetal biometry. The FGR was due to placental dysfunction, as confirmed by pathological examination of placenta.

*1 Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010;125(2):e214-e224. doi:10.1542/peds.2009-0913

*2 Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol. 1993;169(1):169-175. doi:10.1016/0002-9378(93)90156-d

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplementary table 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4, 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7,8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6,7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6,7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8,9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8,9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8,9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8,9
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7,8

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8,9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9-15
Study characteristics	17	Cite each included study and present its characteristics.	Page 9-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9-15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 9-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16-21
	23b	Discuss any limitations of the evidence included in the review.	Page 21-23
	23c	Discuss any limitations of the review processes used.	Page 21-23
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23, 24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 25
Competing interests	26	Declare any competing interests of review authors.	Page 25
Availability of	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from	Page 25

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
data, code and other materials		included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Supplementary table 2: PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary table 3: Review outcomes

Table 1-a. Review outcomes

Maternal outcomes	Neonatal outcomes
Preeclampsia or eclampsia	Neonatal death
Preeclampsia	Neonatal death within 48 h after birth
Hypertensive disorders	Death before discharge home
Pregnancy induced hypertension (PIH)	Apgar score ≤ 7 at 5 min after birth
Chorioamnionitis	Apgar score < 7 at 5 min after birth
Gestational diabetes mellitus	Apgar score < 5 at 1 min after birth
	Respiratory distress syndrome (RDS)
	Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)
	Pneumonia
	Use of mechanical ventilation
	Surfactant use
	Oxygen therapy
	Oxygen requirement for at least 4 h
	Mean duration of mechanical ventilations
	Duration of oxygen use
	Patent ductus arteriosus (PDA)
	Hypotension within 7 postnatal days
	Hypotension
	Intraventricular hemorrhage (IVH)
	Severe IVH

Periventricular leukomalacia (PVL)
Major brain lesion damage
Necrotizing enterocolitis (NEC)
Sepsis
Early onset sepsis
Systemic inflammatory response syndrome
Meningitis
Neonatal hypoglycemia
Neonatal adrenal insufficiency
Intrahepatic cholestasis
Retinopathy of prematurity (ROP)
Gestational age at birth
Birth weight
Neonatal intensive care unit (NICU) admission
Duration of hospital stay
Survival free from disability
Death at long-term follow up
Death or disability/handicap at 2 years
Cerebral palsy
Severe hearing impairment
Visual impairment

	Discharge with respiratory support
	Growth < 10%ile in early childhood
	Abnormal behavior at long-term follow up at school-age

Table 1-b. Outcome definition

Maternal outcomes	Definition
Preeclampsia or eclampsia	**P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].
Preeclampsia	**P4** Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Cartwright et al. (2019): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a systolic Blood pressure(BP) >160mmHg and a diastolic BP ≧ 90mmHg measured at least twice and proteinuria ≧0.3g/24g.
Hypertensive disorders	**P2** Kirshembaum et al. (2018): No data.
Pregnancy induced hypertension (PIH)	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as any maternal diagnoses of preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Feng et al. (2017): No data.
Chorioamnionitis	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): No data. Elimian et al. (1999): No data.
Gestational diabetes mellitus	**P2** de la Hueruga et al. (2019): No data. **P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].

	P4 Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Kim et al. (2018): No data. Kim YJ et al. (2018):No data. Ishikawa et al. (2015): No data.
Neonatal outcomes	**Definition**
Neonatal death	Deaths during the first 28 completed days of life.*[2]
Neonatal death within 48h after birth	**P1** Battarbee et al. (2020): Death within 48h after birth.
Death before discharge home	**P3** Foix-L'Helias et al. (2005): Death before discharge home. **P4** Riskin-Mashiah et al. (2016): Death before discharge home. Ishikawa et al. (2015): Death before discharge home. Foix-L'Helias et al. (2005): Death before discharge home. Schaap et al. (2001): Death before discharge home. Bernstein et al. (2000): Death before discharge home.
Apgar score ≤7 at 5 min after birth	**P2** Kishenbaum et al. (2018): Apgar score ≤7 at 5 min after birth.
Apgar score <7 at 5min after birth	**P1** Krispin et al. (2018): Apgar score <7 at 5 min after birth. **P3** Elimian et al. (2000): Apgar score <7 at 5 min after birth. **P4** Bitar et al. (2020): Apgar score <7 at 5 min after birth. Kim et al. (2018): Apgar score <7 at 5min after birth. Feng et al. (2017): Apgar score <7 at 5min after birth. Elimian et al. (1999): Apgar score <7 at 5min after birth.
Apgar score <5 at 1min after birth	**P4** Kim et al. (2018): Apgar score <5 at 1min after birth. Torrance et al. (2007): Apgar score <5 at 1min after birth.
Respiratory distress syndrome (RDS)	**P1** Battarbee et al. (2020): Defined as a clinical diagnosis of respiratory distress syndrome, hyaline

membrane disease, or respiratory insufficiency requiring oxygen therapy with FiO2 ≧0.40 started within the first 24 hours after birth and continued for ≧24 hours or until neonatal demise.

Krispin et al. (2018): No data.

P2

de la Huerga Lopez et al. (2019): Defined ad the presence of clinical signs of respiratory distress with oxygen requirement and chest X-ray with reticulonodular infiltrate.

Kishenbaum et al. (2018): Defined as early respiratory distress that comprised cyanosis, grunting, retraction and tachypnea combined with ground glass appearance and air bronchogram on chest X-ray.

P3

Ryu et al. (2019): Defined if the chest radiographic findings were consistent with RDS together with an oxygen requirement of >0.4 for the fraction of inspired oxygen.

Ahn et al. (2012): Diagnosed in infants with respiratory distress, an increased oxygen requirement and a radiological finding consistent with RDS.

Been et al. (2009): Diagnosed in a clinical presentation (expiratory grunting, sub- or intercostal or sternal retractions, nasal flaring, tachypnea, cyanosis in room air with or without apnea) and characteristic radiographic appearance according to Giedion et al. [*3]

Goldenberg et al. (2006): Defined as the documentation of any of three criteria: (1) oxygen requirement at 6 through 24 hours of life; (2) an abnormal chest radiograph consistent with RDS within the first 24 hours of life; and (3) need for surfactant.

Dempsey et al. (2005): Defined from a combination of three of the following: clinical signs, oxygen need greater than 30% from 12 to 72 hours, need for assisted ventilation (continuous positive airway pressure or mechanical ventilation), and typical chest X-ray appearance.

Foix-L'Helias et al. (2005): No data.

Baud et al. (2000): Diagnosed if any two criteria were present in the first 24 hours of life: clinical symptoms (respiratory failure requiring assisted ventilation and administration of exogenous surfactant), typical radiological feature, and biological evidence of lung immaturity (fetal lung maturity test on tracheal aspirates).

Elimian et al. (2018): Diagnosed clinically by need for mechanical ventilation and oxygen for at least 48 hours, and radiologic chest findings.

P4

Kim et al. (2018): No data.

Riskin-Mashiah et al. (2018): No data.

Riskin-Mashiah et al. (2016): Diagnosed by a chest radiography consistent with RDS together with supplementary oxygen or mechanical ventilation therapy.

Feng et al. (2017): No data.

Ishikawa et al. (2015): Diagnosed based on the clinical and radiographic finings.

Mitsiakos et al. (2013): Diagnosed based on clinical and radiological criteria and oxygen requirements

	≧30%. van Stralen et al. (2009): Based on radiological criteria (poor lung expansion) and clinical criterial (need for supplemental oxygen, sternal retraction, intercostal and subcostal recession, grunting and tachypnea). Torrance et al. (2007): Defined as clinical signs of RDS with oxygen requirement and typical findings on a chest X-ray. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as tachypnea, chest wall retractions, and oxygen requirement in the presence of a chest X-ray classified as RDS. Bernstein et al. (2000): Required both a PaO2 <50mmHg in room air plus central cyanosis in room air or a requirement for supplemental oxygen to maintain a PaO2 >50mmHg. Elimian et al. (1999): Diagnosed clinically and by the need for mechanical ventilation and oxygen for a least 48 hors and the presence of radiologic chest findings. Ley et al. (1997): No data. Spinillo et al. (1995): Diagnosed with physical signs of respiratory distress (grunting, chest retraction, tachypnea) and required ventilatory support for >48hr and radiologic chest findings. Di Lenardo et al. (1990): Based on the basis of radiological indications and worsening of the symptoms from a clinical point of view.
Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Based on National Institute of Child and Human Development criteria.[*4] Been et al. (2009): Diagnosed with a dependency on oxygen supplementation at a postmenstrual age of 36 weeks. Goldenberg et al. (2006): Defined as infant oxygen requirement at 28 days or oxygen requirement at 36 weeks of life. Foix-L'Helias et al. (2005): No data. **P4** Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): No data. Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed according to the criteria of Bancalari et al.[*5] including clinical and radiologic features. Together with the requirement for oxygen supplementation at 36 weeks post menstrual age. Ishikawa et al. (2015): Defined when an infant continued to receive supplemental oxygen on the 28th day after birth and at the 36th week based on postmenstrual age. Mitsiakos et al. (2013): Based on oxygen supplementation at 36 weeks postmenstrual age. van Stralen et al. (2009): No data.

	Torrance et al. (2007): Defined as the need for extra oxygen on day 28 of life with chronic abnormalities on a chest X-ray and symptoms of respiratory distress. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as the presence of chronic respiratory distress and oxygen requirement beyond 28 days of life accompanied by a chest radiograph that showed persistent streaks of increased density in both lungs interspersed with normal hyperlucent areas.
Pneumonia	**P3** Dempsey et al. (2005): Defined by a combination of X-ray changes, endotracheal tube aspirates, and positive inflammatory markers.
Use of mechanical ventilation	**P3** Been et al. (2009): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim et al. (2018): Mechanical ventilation within 48 hours after birth. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Schaap et al. (2001): No data.
Surfactant use	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Been et al. (2009): No data. Elimian et al. (2000): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim YJ et al. (2018):Defined as the administration of any prophylactic or rescue surfactant. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Elimian et al. (1999): No data.
Oxygen therapy	**P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data.
Oxygen requirement for at least 4 h	**P2** Kishenbaum et al. (2018): Oxygen requirement for at least 4 hours.

Mean duration of mechanical ventilations	**P2** de la Huerga Lopez et al. (2019): No data. **P3** Ahn et al. (2012): No data.
Duration of oxygen use	**P3** Ahn et al. (2012): No data.
Patent ductus arteriosus (PDA)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Diagnosed by echocardiography and medical treatment or surgical ligation were performed when necessary. Been et al. (20009): Persistence of the open ductus arteriosus postnatally, as demonstrated by ultrasonographic examination. Elimian et al. (2000): Required medical or surgical intervention. **P4** Kim YJ et al. (2018): No data. Feng et al. (2019): No data. Ishikawa et al. (2015): Diagnosed based on both echocardiographic findings and clinical evidence of a volume overload due toa left-to-right shunt. Mitsiakos et al. (2013): No data. van Stralen et al. (2009): No data. Elimian et al. (1999): No data.
Hypotension within 7 postnatal days	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1]
Hypotension	**P4** van Stralen et al. (2009): Defined as a mean arterial pressure ≤30mmHg requiring treatment with volume expanders and/or inotropic support.
Intraventricular hemorrhage (IVH)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): Defined as grade ≧3 and listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined according to the IVH grading by Papile et al.[*6] Been et al. (2009): Defined according to Volpe. [*7] Goldenberg et al. (2006): Defined as grade 3 or 4 by ultrasound criteria.[*7] Dempsey (2005): Graded according to the Papile classification [*6] Baud et al. (2000): Defined as grade 3 or 4 of Papile classification. [*6]

	P4 Kim et al. (2018): Defined as grade 3 or 4. Kim YJ et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Ishikawa et al. (2015): Defined as Papile grade 1 or more. Schaap et al. (2001): Defined as grade 3 or 4. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Severe IVH	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined as grade 3 or 4 of Papile classification. *6 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): No data. Baud et al. (2000): No data. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Mitsiakos et al. (2013): Defined as grade 3 or 4. Schaap et al. (2001): No data. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Periventricular leukomalacia (PVL)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined according to Volpe. *7 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): Defined according to Volpe. *7 Baud et al. (2000): Diagnosed on cerebral ultrasound scan.

	P4 Riskin-Mashiah et al. (2018): No data. Riskin-Mashiah et al. (2016): Diagnosed by the presence of multiple periventricular cysts identified by cranial ultrasound examination after 28 days of life. Ishikawa et al. (2015): Based on either head ultrasound or cranial MRI scan performed at 2 weeks of age or later. Mitsiakos et al. (2013): No data.
Major brain lesion damage	**P4** van Stralen et al. (2009): Defined as the presence of a least one of the following findings: IVH ≧grade3 or ventricular dilatation or cystic PVL. Schaap et al. (2001): No data. Elimian et al. (1999): Defined as IVH grade 3 and 4, IVH with PVL, and PVL. Ley et al. (1997): Defined ad IVH grade 3, IVH grade 4, or PVL. Spinillo et al. (1995): No data.
Necrotizing enterocolitis (NEC)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): NEC stage ≧2b. [*8] Been et al. (2009): Defined as stage 2 or higher according to Bell et al.[*8] Goldenberg et al. (2006): Defined as stage 2 or higher. Dempsey et al. (2005): Classified as the presence of intramural gas on X-ray, perforation or evidence of intestinal necrosis at surgery or autopsy. Elimian et al. (2000): Diagnosed clinically and radiologically, and confirmed by surgery or autopsy. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as stage 2b or higher according to Bell et al.[*8] Riskin-Mashiah et al. (2018): Defined as stage 2 or higher according to Bell et al.[*8] Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Presence of clinical and radiologic features according to the criteria of Bell et al. [*8] Ishikawa et al. (2015): Defined as stage 2 or higher according to Bell et al.[*8] Mitsiakos et al. (2013): No data. Bernstein et al. (2010): No data. van Stralen et al. (2009): Defined as stage 2 or higher. Elimian et al. (1999): Diagnosed clinically and radiologically and confirmed at surgery or autopsy.

Sepsis	**P3** Ryu et al. (2019): Defined as culture proven sepsis. The presence of clinical symptoms, and signs with proven causative organisms documented from blood cultures. Ahn et al. (2012): Defined as a positive blood culture. Been et al. (2009): Clinical sepsis or culture-proven sepsis. Clinical sepsis was clinical presentation of sepsis with raised CRP. Culture-proven sepsis was any systemic bacterial infection documented by a positive blood or cerebrospinal fluid culture. Goldenberg et al. (2006): No data. Dempsey et al. (2005): Defined as a positive blood culture. Elimian et al. (2000): Defined as positive blood or cerebrospinal fluid cultures. **P4** Kim et al. (2018): Included both suspected infections (with clinical findings suggesting infection) and proven infections. Kim YJ et al. (2018): Defined as the presence of clinical symptoms and signs with proven causative organisms documented from blood cultures. Feng et al. (2017): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a positive blood culture and the need for intravenous antibiotics for minimum of 7 days. van Stralen (2009): Based on the need for intravenous antibiotics administration for more than 7 days. Schaap et al. (2001): Defined as neonatal septicemia or meningitis confirmed by positive cultures. Elimian et al. (1999): Defined as positive blood or cerebrospinal fluid cultures.
Early onset sepsis	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined as a positive blood culture occurring within the first 72 hours. Been et al. (2009): Neonatal sepsis occurring during the first 72 hours of life. Dempsey et al. (2005): Defined as a positive blood culture in the first 72 hours.
Systemic inflammatory response syndrome	**P3** Goldenberg et al. (2006): Defined as clinically suspected sepsis with negative cerebrospinal fluid and blood cultures or a band: band + polymorphonuclear cell ratio of 0.15 or greater.
Meningitis	**P3** Dempsey et al. (2005): Defined as a positive cerebrospinal fluid culture.
Neonatal hypoglycemia	**P1** Cassimatis et al. (2020): Defined as Blood sugar <40mg/dL within 4 hours of birth. Krispin et al. (2018): No data.

	P2 De la Huerga Lopez et al. (2019): No data. Kishenbaum et al. (2018): Defined as glucose level ≤45 mg/dl. **P4** Bitar et al. (2020): Defined as glucose level <40 mg/dl. Kim et al. (2018): Defined as glucose level <40 mg/dl.
Neonatal adrenal insufficiency	**P4** Kim YJ et al. (2018): Defined as the requirement of hydrocortisone treatment. Ishikawa et al. (2015): No data.
Intrahepatic cholestasis	**P3** Ahn et al. (2012): Defined when conjugated bilirubin exceed 2.0mg/dl.
Retinopathy of prematurity (ROP)	**P3** Ryu et al. (2019): Defined as requiring treatment. **P4** Kim YJ et al. (2018): Defined as requiring treatment. Riskin-Mashiah et al. (2018): No data. Feng et al (2017): No data. Riskin-Mashiah et al. (2016): Defined as grade 3-4 in international standard classification.[*9] Mitsiakos et al. (2013): No data.
Gestational age at birth	**P4** Bitar et al. (2020): Defined as gestational age birth. Cartwright et al. (2019): Defined as gestational age at birth. Ishikawa et al. (2015): Defined as gestational age at birth. Mitsiakos et al. (2013): Defined as gestational age birth.
Birth weight	**P4** Bitar et al. (2020): Defined as birth weight. Cartwright et al. (2019): Defined as birth weight. Ishikawa et al. (2015): Defined as birth weight. Mitsiakos et al. (2013): Defined as birth weight.
Neonatal intensive care unit (NICU) admission	**P1** Krispin et al. (2018): Defined as NICU admission. **P2** de la Huerga Lopez et al. (2019): Defined as NICU admission. Kishenbaum et al. (2018): Defined as NICU admission.

	P4 Bitar et al. (2020): Defined as NICU admission.
Duration of hospital stay	**P4** Bitar et al. (2020): No data. Mitsiakos et al. (2013): No data.
Survival free from disability	**P4** Cartwright et al. (2019): No data
Death at long-term follow up	**P4** Schaap et al. (2001): No data.
Death or disability/handicap at 2 years	**P4** Schaap et al. (2001): No data.
Cerebral palsy	**P4** Ishikawa et al. (2015): Defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Cartwright et al. (2019): Defined as a nonprogressive loss of motor function with disordered muscle tone or tendon reflexes.
Severe hearing impairment	**P4** Ishikawa et al. (2015): Defined as the need for hearing aids.
Visual impairment	**P4** Ishikawa et al. (2015): Defined as unilateral or bilateral blindness diagnosed by an ophthalmologist.
Discharge with respiratory support	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1
Growth<10%ile in early childhood	**P4** Schaap et al. (2001): Defined by using standard deviation to adjust for discrepancies in age and sex at school age.*10
Abnormal behavior at long-term follow up at school-age	**P4** Schaap et al. (2001): Defined by the DuPaul-score. *11

*1. www.karger.com/doi/10.1159/000502650.
*2. Neonatal mortality rate (0 to 27 days) per 1000 live births) (SDG 3.2.2) (who.int).
*3. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol*. 1973;1(3):145-152. doi:10.1007/BF00974058.
*4. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-1729. doi:10.1164/ajrccm.163.7.2011060.
*5. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95(5 Pt 2):819-823. doi:10.1016/s0022-3476(79)80442-4.
*6. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-534. doi:10.1016/s0022-3476(78)80282-0.

*7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
*8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7. doi:10.1097/00000658-197801000-00001.
*9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol. 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
*10. Frederiks AM, Nederlandes groeidoagrammen 1997 in historisch persepectief. In: Wit JM, ed. De Vierde Landelijke Groeistidie 1997. Presentatie nieuwe groepidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
*11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.

Supplementary table 4: Database-specific search terms and strategies

MEDLINE (via Ovid) 2021/6/6

#	Searches	Annotations
1	exp *Adrenal Cortex Hormones/ad, tu	
2	exp *Adrenal Cortex Hormones/ and (ci or de or dt).fs.	
3	exp Adrenal Cortex Hormones/ae, po, to	
4	or/1-3	
5	exp Pregnancy/	
6	exp Pregnancy Outcome/	
7	Fetal Death/	
8	Maternal Death/	
9	Obstetric Labor Complications/	
10	exp Obstetric Labor, Premature/	
11	Pregnancy, Prolonged/	
12	Fetus/	
13	exp Infant, Newborn/	
14	Prenatal Care/	
15	exp Fetal Development/	
16	exp Birth Weight/	
17	Prenatal Exposure Delayed Effects/	
18	or/5-17	
19	4 and 18	
20	limit 19 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactivetutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
21	limit 20 to meta analysis	
22	20 not 21	
23	19 not 22	
24	limit 23 to humans	
25	("*corticosteroid" or "*corticoid").mp.	
26	(pregnan* or labor or labour or gestation* or delivery* or preterm* or fetus or fetal or baby or babies or newborn* or neonat* or antenat* or prenat* or birth*).mp.	
27	25 and 26	
28	MEDLINE.st.	
29	27 not 28	
30	(biograph* or case report* or comment or congress* or conference* or editor* or tutorial* or interview* or lecture* or news* or handout* or guideline* or (review* not (meta analys* or metaanalys*))).mp.	

31	29 not 30	
32	exp Diabetes Mellitus/	
33	exp Hyperglycemia/	
34	or/32-33	
35	34 and 18	
36	exp Diabetes, Gestational/	
37	Pregnancy in Diabetics/	
38	or/36-37	
39	or/5-17	
40	38 and 39	
41	or/35,40	
42	4 and 41	
43	limit 42 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
44	limit 43 to meta analysis	
45	43 not 44	
46	42 not 45	
47	limit 46 to humans	
48	diabet*.mp.	
49	31 and 48	
50	or/47,49	
51	remove duplicates from 50	
52	exp epidemiologic study/	
53	(trial* or comparative or meta analysis or metaanalysis or multicenter or observational or randomized or randomised or rct or cct or cohort or cross sectional or longitudinal or evaluation or prospective or retrospective or control*).mp.	
54	or/52-53	
55	51 and 54	P1-1
56	51 not 55	P1-2
57	exp Cesarean Section/	
58	(cesarean or cesarian or caesarean or caesarian).mp.	
59	or/57-58	
60	or/24,31	
61	60 and 59	
62	remove duplicates from 61	
63	62 and 54	P2-1
64	62 not 63	P2-2
65	exp "Bacterial Infections and Mycoses"/	
66	Pregnancy Complications, Infectious/	

67	or/65-66	
68	24 and 67	
69	(infect* or chorioamnionitis).mp.	
70	31 and 69	
71	or/68,70	
72	remove duplicates from 71	
73	72 and 54	P3-1
74	72 not 73	P3-2
75	exp *Fetal Development/	
76	(growth adj3 restrict*).mp.	
77	or/75-76	
78	24 and 77	
79	((fetal or fetus or baby or babies or restricted) adj3 (development or growth or maturity or weight)).mp.	
80	31 and 79	
81	or/78,80	
82	remove duplicates from 81	
83	82 and 54	P4-1
84	82 not 83	P4-2

Embase (via embase.com) 2021/6/6

set	query	Annotations
#1	'corticosteroid'/exp/mj/dd_do,dd_cm,dd_dt,dd_ad,dd_to,dd_ct,dd_it	
#2	'corticosteroid'/exp/dd_ae	
#3	#1 OR #2	
#4	#3 AND 'human'/de	
#5	#4 AND [embase]/lim NOT [medline]/lim	
#6	'parameters concerning the fetus, newborn and pregnancy'/exp	
#7	'fetus death'/exp	
#8	'labor complication'/exp	
#9	'prolonged pregnancy'/de	
#10	'fetus'/de	
#11	'newborn'/de	
#12	'prenatal care'/exp	
#13	'prenatal development'/exp	
#14	'prenatal exposure'/de	
#15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
#16	#5 AND #15	
#17	'editorial'/de OR 'erratum'/exp OR 'note'/de OR 'review'/de	
#18	'meta analysis'/exp	
#19	#17 NOT #18	
#20	#16 NOT #19	
#21	'case report'/exp	
#22	#20 NOT #21	

#23	'diabetes mellitus'/exp	
#24	'hyperglycemia'/de	
#25	#23 OR #24	
#26	#22 AND #25	P1
#27	'cesarean section'/de	
#28	#22 AND #27	P2
#29	'infection'/exp	
#30	'chorioamnionitis'/de	
#31	#29 OR #30	
#32	#22 AND #31	P3
#33	'prenatal development'/exp/mj	
#34	#22 AND #33	P4

Cochrane Library (via Wiley) 2021/6/8

ID	Search	Annotations
#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	
#2	*corticosteroid* or *corticoid*	
#3	#1 or #2	
#4	MeSH descriptor: [Pregnancy] explode all trees	
#5	pregnan* or labor or labour	
#6	MeSH descriptor: [Pregnancy Outcome] explode all trees	
#7	stillbirth or livebirth	
#8	MeSH descriptor: [Fetal Death] explode all trees	
#9	MeSH descriptor: [Maternal Death] explode all trees	
#10	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	
#11	MeSH descriptor: [Pregnancy, Prolonged] explode all trees	
#12	MeSH descriptor: [Obstetric Labor Complications] this term only	
#13	MeSH descriptor: [Fetus] this term only	
#14	fetus or fetal	
#15	MeSH descriptor: [Infant, Newborn] explode all trees	
#16	infant* or newborn* or neonate* or baby or babies	
#17	MeSH descriptor: [Prenatal Care] explode all trees	
#18	prenatal or antenatal or perinatal	
#19	MeSH descriptor: [Fetal Development] explode all trees	
#20	matur* or immatur* or prematur*	
#21	MeSH descriptor: [Birth Weight] explode all trees	
#22	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees	
#23	gestation* or birth* or offspring	
#24	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	
#25	#3 and #24	
#26	MeSH descriptor: [Diabetes Mellitus] explode all trees	P1
#27	diabet* or dm	

#28	MeSH descriptor: [Hyperglycemia] explode all trees	
#29	hyperglycem*	
#30	MeSH descriptor: [Diabetes, Gestational] explode all trees	
#31	MeSH descriptor: [Pregnancy in Diabetics] explode all trees	
#32	#26 or #27 or #28 or #29 or #30 or #31	
#33	#25 and #32	
#34	handsrch	
#35	#33 and #34	P1
#36	MeSH descriptor: [Cesarean Section] explode all trees	
#37	cesarean or cesarian or caesarean or caesarian	
#38	#36 or #37	
#39	#25 and #38	
#40	#39 and #34	P2
#41	MeSH descriptor: [Bacterial Infections and Mycoses] explode all trees	
#42	infect*	
#43	MeSH descriptor: [Pregnancy Complications, Infectious] explode all trees	
#44	chorioamnionitis	
#45	#41 or #42 or #43 or #44	
#46	#25 and #45	
#47	#46 and #34	P3
#48	growth near restrict*	
#49	#25 and #48	
#50	#49 and #34	P4

CINAHL (via EBSCOhost) 2021/6/6

ID#	Search Terms	Search Options	Annotations
S1	(MM "Adrenal Cortex Hormones+/AD/DE/TU")		
S2	(MH "Adrenal Cortex Hormones+/AE")		
S3	S1 or S2		
S4	(MH "Pregnancy+")		
S5	(MH "Expectant Mothers")		
S6	(MH "Pregnancy Outcomes")		
S7	(MH "Perinatal Death")		
S8	(MH "Maternal Mortality")		
S9	(MH "Labor Complications+")		
S10	(MH "Labor, Premature")		
S11	(MH "Pregnancy, Prolonged")		
S12	(MH "Fetus+")		
S13	(MH "Infant, Newborn+")		
S14	(MH "Prenatal Care")		
S15	(MH "Fetal Development+")		
S16	(MH "Birth Weight")		

S17	(MH "Prenatal Exposure Delayed Effects")		
S18	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17		
S19	S3 and S18		
S20	S19	Limiters - Human	
S21	S20	Limiters - Research Article; Exclude MEDLINE records	
S22	(MH "Metabolic Diseases") OR (MH "Diabetes Mellitus+")		
S23	(MH "Hyperglycemia")		
S24	(MH "Pregnancy in Diabetes+")		
S25	S22 or S23 or S24		
S26	S21 and S25		P1
S27	(MH "Cesarean Section+")		
S28	S21 and S27		P2
S29	(MH "Bacterial and Fungal Diseases+")		
S30	S21 and S29		P3
S31	(MM "Fetal Development+")		
S32	restrict* N3 (growth or development or matur*)		
S33	S31 or S32		
S34	S21 and S33		P4

WHO Global Index Medicus (via WHO-GIM site) 2021/6/8

	Search Terms	Annotations
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (diaebet* OR DM OR hyperglycem*)	P1
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (elective caesarean)	P2
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (infect*)	P3
	cortico AND restrict* AND growth	P4

Web of Science Core Collection (via Web of Science) 2021/6/8

Set	Searches	Annotations
# 1	CITED AUTHOR: (amiya r*) AND CITED YEAR: (2016)	Cited Reference Search

Supplementary table 5: Risk of bias

Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cassimatis 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants from three institutions had PGDM (type 1 or type 2) with singleton pregnancies and delivered in late preterm between April 2014 and May 2017.	**High** -Study design No consideration -Analysis No consideration	**Low** Data obtained from an obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low** No missing data	**Low** All predefined outcomes reported	-
Krispin 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single, university-affiliated, tertiary medical center had GDM and delivered after 34 weeks of gestation between 2012 and 2016.	**High** -Study design No consideration -Analysis The following potential confounders were adjusted: primiparity, birth weight, gestational age at delivery, gravidity, parity, hypertensive disorders, and body mass index.	**Low** Data obtained from a comprehensive computerized perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Battarbee 2020 (Retrospective cohort study)	N/A	N/A	**Low** A cohort study included 115,502 participants from 25 hospitals in the United States between March 2008 and February 2011. To avoid overrepresentation of participants from larger hospitals, up to one-third of participants had spent days at hospitals with annual delivery volumes from 2,000 to 7,000 and up to one-sixth had spent days in hospitals with annual deliveries > 7,000.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** Eleven sets of missing data (11 women and 12 neonates) were excluded from the data for steroids, but the proportion of missing data was very small (less than 1%).	**Low** All predefined outcomes reported	-

N/A: Not Applicable; **PGDM:** Pregestational diabetes mellitus; **GDM:** gestational diabetes mellitus; **ACS:** Antenatal corticosteroid

*Krispin (2018) and Battarbee (2020) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

Risk of bias assessments for studies of antenatal corticosteroids in women undergoing elective cesarean section in the late preterm period

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kirshenbaum 2018 (Case-control study)	N/A	N/A	**Low** All participants, from a single tertiary medical center, delivered by elective cesarean section at 34 + 0–37 + 0 weeks of gestation between January 2011 and December 2013.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
de la Huerga López 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	-

N/A: Not Applicable

Cochrane Risk of Bias tool

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Gyamfi-Bannerman 2016 (Randomized controlled trial)	**Low** The randomization sequence was developed using the simple urn method.	**Low** The randomization sequences were generated by an independent data coordinating center using the simple urn method.	**Low** Neither the participants nor the investigators were informed of the study group assignments.	**Low** All outcome reviewers were unaware of study-group assignments.	**Low** Only two participants in each of the two groups were lost to follow-up.	**Low** The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes have been reported.	**Low** No other bias is found.

Risk of bias assessments for studies of antenatal corticosteroids in women with chorioamnionitis (histological or clinical)

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Ahn 2012 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at Ewha Women's University between 2005 and 2010.	**High** -Study design No consideration -Analysis Multiple logistic regression model was used but controlled only by gestational age.	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All expected outcomes reported	-
Been 2009 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at the Erasmus University Medical Center-Sophia Children's Hospital between May 2001 and February 2003.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome. Measurements . .	**Low** No missing data	**Low** All expected outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Goldenberg 2006 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution during the same period (December 5, 1996–June 13, 2001).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements .	**Low** No missing data	**Low** All expected outcomes were reported	-
Dempsey 2005 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1989 and January 1999.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records (obstetrical and neonatal database and pathology database, cross-referenced with data from pathology database and from maternal and neonatal chart review).	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All expected outcomes were reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from different institutions between 1993 and 1996.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential the underestimation.
Baud 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted to Antoine Beclere University Hospital between 1993 and 1997.	**High** -Study design No consideration -Analysis Multiple logistic regression model was used, controlled for causes of delivery, antenatal antibiotics administration, mode of delivery, gestational age, origin (inborn or out born), and hemodynamic failure.	**Low** Data obtained from computerized database	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1990 and December 1997.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low.** All expected outcomes were reported.	-
Ryu 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single university hospital, admitted to the same institution (Seoul National University Hospital) between 2007 and 2014.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, sex, and cesarean section.	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** At the beginning of the study incomplete information was excluded.	**Low** All predefined outcomes reported.	-

N/A: Not applicable**; RDS:** Respiratory distress syndrome; **BPD:** Bronchopulmonary dysplasia; **IHC:** Intrahepatic cholestasis; **IVH:** Intraventricular hemorrhage; **PVL:** Periventricular leukomalacia; **NEC:** Necrotizing enterocolitis; **PDA:** Patent ductus arteriosus; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis; **IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **GA:** Gestational age; **CS:** Cesarean section

*Baud (2000), Ahn (2012) and Ryu (2019) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

Risk of bias assessments for of studies of antenatal corticosteroids in women with growth-restricted fetuses and/or small-for-gestational-age infants

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
van Stralen 2009 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (Leiden University Medical Center) over the same period (January 2001–December 2005).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Although equally divided, the difference in origin, i.e., referral pattern, may also have influenced the results.
Torrance 2007 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single tertiary referral center admitted to the same institution (neonatal intensive care unit at the University Medical Centre Utrecht, the Netherlands) over the same period (from January 1, 1999, to December 31, 2003). Cases and controls were selected from same pool (e.g., same gestational age, same birth weight).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data was obtained from an electronic database.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No loss to follow-up	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from different institutions during the same period (1993–1996).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential underestimation.
Schaap 2001 (Case-control study)	N/A	N/A	**Low** Participants drawn from different two institutions during the same period (1984–1991).	**High** -Study design Matched by birth weight, sex and year of birth. -Analysis No consideration on confounding variables	**Low** Data obtained from medical records. Because all mothers had been admitted at least 24 h before delivery, a difference in fetal condition on admission was unlikely.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Nine losses at school age follow-up (4 in steroid group, 5 in control group) but no significant difference in sociodemographic details between those lost and retained at follow-up.	**Low** All predefined outcomes reported.	Hypertensive mothers less often treated with corticosteroids. Further, matching notwithstanding, birth weight and gestational age were significantly lower in the AGA group, although magnitude of the difference is small.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 1999 (Retrospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (January 1990–July 1997)	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Ley 1997 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (University Hospital of Lund) during the same period (1985–1994).	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for birthweight deviation, gestational age, pre-eclampsia, premature rupture of membranes and mode of delivery.	**Low** Data obtained from hospital records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Spinillo 1995 (Prospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (1988–1993)	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, birth weight and sex.	**Low** Data obtained from hospital records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Missing data was less than 10%.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Di Lenardo 1990 (Retrospective cohort study)	N/A	N/A	**Unclear** All participants admitted/delivered and treated at the same institution (Prenatal Care Ward of Univ. of Padua's Gynecology & Obstetrics Institution) but unclear if over the same period.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Bitar 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants, from a single hospital, who delivered at 34.0–36.6 weeks of gestation, with small-for-gestational-age or fetal-growth-restriction infants between January 2015 and December 2019.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for parity and preeclampsia.	**Low** Data obtained from electronic medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes were reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cartwright 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from 23 collaborating hospitals, 16 in Australia and 7 in New Zealand, with a single, twin, or triplet pregnancy at less than 32 weeks of gestational age from April 1998 to July 2004.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age at trial entry, antepartum hemorrhage, preterm pre-labor rupture of membranes, and country of birth.	**Low** Data obtained from case notes	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** The predefined outcomes were described as planned.	-
Riskin-Mashiah 2018 (Retrospective cohort study)	NA	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, ethnicity, infertility treatment, maternal hypertensive disorder, preterm labor, premature rupture of membranes and/or amnionitis, gestational age, delivery mode, birth weight z-score, gender, birth order, delivery room resuscitation and year of birth.	**Low** Data obtained from the national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single hospital between 2009 and 2016	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, parity, mode of delivery, maternal diabetes, gestational hypertensive disorder, and preterm premature rupture of membrane.	**Low** Data obtained from medical records and perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
Ishikawa 2015 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Research Network Database in Japan between 2003 and 2007	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, parity, preeclampsia, preterm rupture of membranes, non-reassuring fetal status, mode of delivery, gestational age at delivery, birth weight, gender of the infant, and histological chorioamnionitis (≥ stage 2).	**Low.** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Riskin-Mashiah 2016 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, ethnicity, infertility treatment, maternal diabetes, maternal hypertensive disorder, preterm labor, premature rupture of membranes, amnionitis, antepartum hemorrhage, gestational age, delivery mode, birthweight z-score, gender, delivery room resuscitation and year of birth.	**Low** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Mitsiakos 2013 (Retrospective cohort study)	N/A	N/A	**Low** All participants between 24 and 31 6/7 weeks of gestational age from a single hospital. The study period was not specifically mentioned, but intervention and control groups seem to be selected from the same population groups.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric and neonatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim YJ 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants born at 23 + 0 to 33 + 6 weeks of gestation between January 2007 and December 2014 in a single university hospital in South Korea.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for birth weight and Apgar score at 5 minutes.	**Low** Data obtained from medical records and perinatal databases	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
The collaborative study group for respiratory distress syndrome in preterm infants 2017 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from 14 hospitals during the same period (2013–2014).	**High** -Study design No consideration -Analysis Multiple logistic regression was used, but their confounding factors were not specified.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Bernstein 2000 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from North American hospitals during the same period (1991–1996).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

N/A: Not Applicable**; IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **AGA:** Appropriate for gestational age

*****Spinillo (1995), Ishikawa (2015), Riskin-Mashiah (2016), Feng (2017), Riskin-Mashiah (2018), Kim (2018), Kim YJ (2018), Cartwright (2019), and Bitar (2020) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

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							№ of patients		Effect		Certainty	Importance
№ 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[b]	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[b]	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[b]	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[b]	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[b]	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[c]	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

a. Heterogeneity is high (I-square=>60%).
b. Estimate based on wide confidence interval crossing the line of no effect.
c. 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							№ of patients		Effect		Certainty	Importance
№ 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 =<7 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							№ of patients		Effect		Certainty	Importance
№ 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[c]	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[b]	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[b]	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[b]	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[b]	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 ≥ 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							№ of patients		Effect		Certainty	Importance
№ 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[a]	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[a]	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[a]	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[c]	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[a]	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[c]	not serious	serious[a]	non e	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[c]	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[c]	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[a,b]	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[a,b]	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[a,b]	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[c]	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[a,b]	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							№ of patients		Effect		Certainty	Importance
№ 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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[b]	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							№ of patients		Effect		Certainty	Importance
№ 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	**not serious**	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[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	
Neonatal sepsis (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[c]	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[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	
Neonatal adrenal insufficiency (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious[a,b]	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[a,b]	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[a,b]	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[a,b]	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

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%).

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							№ of patients		Effect		Certainty	Importance
№ 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[c]	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[c]	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[a]	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[a]	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[a]	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[c]	not serious	serious[a]	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[a]	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[a]	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[a]	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%).

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Systematic review

1. * Review title.

Give the title of the review in English

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

06/06/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2021

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

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Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Kana Saito

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Kana Saito

7. * Named contact email.

Give the electronic email address of the named contact.

kana988@saitama-med.ac.jp

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1981, Kamoda, Kawagoe-city, Saitama, Japan

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

81-49-228-3400

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Saitama Medical University

Organisation web address:

http://www.saitama-med.ac.jp/

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr KANA SAITO. Saitama Medical University, Neonatology Department
Ms Etsuko Nishimura. St. Luke's International University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Non funded research

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Toshiyuki Swa. Osaka University Graduate School of Medicine
Dr Fumihiko Namba. Saitama Medical University
Dr Erika Ota. St. Luke's International University
Dr Joshua P. Vogel. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Ramson. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Cao. Child and Adolescent Health Program, Burnet Institute, Melbourne

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

This study aims to synthesize available evidence on antenatal corticosteroid (ACS) use among specific subgroups of women at risk of imminent preterm birth.

The primary objective is to determine the effects of ACS administration for four subgroups of pregnant women at risk of imminent preterm birth on maternal and child outcomes. These subgroups are as follows.

1) women with pregestational or gestational diabetes mellitus

2) women undergoing elective CS in the late preterm period (from 34 weeks 0 days to 36 weeks 6 days)

3) women with an intrapartum inflammation, infection, or both (eg: chorioamnionitis)

4) women with growth-restricted fetuses

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search electronic databases (e.g. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP).

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

We will search electronic databases (i.e. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP). Search terms include “adrenal cortex hormones”, “pregnancy”, “pregnancy outcome”, “fetal death”, “maternal death”, “obstetric labor complications”, “obstetric labor, premature”, “pregnancy, prolonged”, “fetus”, “infant, newborn”, “prenatal care”, “fetal development”, “birth weight”, “prenatal exposure delayed effects”, “diabetes mellitus”, “hyperglycemia”, “diabetes, gestational”, “pregnancy in diabetics”, “cesarean section”, “bacterial infections and mycoses”, “chorioamnionitis“, “pregnancy complications, infectious”, “fetal development”.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Pregnancy

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: We will not restrict the population to pregnant women less than 20 completed weeks gestation and their babies.
Exclusion: Pregnancy beyond 20 completed weeks gestation and their babies.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

We will include women who received at least one dose of antenatal corticosteroid, either betamethasone, dexamethasone, or hydrocortisone after 20 weeks of gestation.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Women and babies who did not receive antenatal corticosteroids.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-and-after studies, interrupted-time-series studies, historical controlled studies, cohort studies, and cross-sectional studies comparing ACS administration (betamethasone, dexamethasone, or hydrocortisone), given parenterally or enterally, compared with placebo or no treatment in women at risk of imminent preterm birth as a result of either spontaneous preterm labor, preterm rupture of the membranes, or elective preterm delivery, and where all (or at least a well-defined sub-sample) of the women under study also have a singleton pregnancy at the following gestational ages:

1. having fetal growth restriction or gestational diabetes mellitus;

2. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);

3. having intrauterine inflammation, infection, or both; or

4. having a growth-restricted infant (or, more broadly, one that was at least small for gestational age).

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

We aim to establish the existing evidence that examines the implications of using or not using ACS in cases of imminent preterm birth in these subgroups of women. This evidence-based effort will be the source for the World Health Organization's (WHO) updated recommendations on interventions to improve preterm birth outcomes.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a) maternal outcomes

-severe morbidity (e.g. organ dysfunction, intensive care unit admission, chorioamnionitis)

-maternal morbidity(e.g. puerperal sepsis, pregnancy-induced hypertension, gestational diabetes mellitus, placental abruption, postpartum haemorrhage, or as defined by the author)

-route of delivery

-side effects of therapy

b) neonatal outcomes

-perinatal mortality

-fetal mortality

-neonatal mortality

-respiratory distress syndrome (RDS) and moderate/severe RDS

-surfactant use

-interventricular haemorrhage (IVH)

-periventricular leukomalacia (PVL)

-sepsis; early onset sepsis

-necrotizing enterocolitis (NEC)

-mechanical ventilation use and mean duration

-patent ductus arteriosus (PDA)

-chronic lung disease (CLD)/ bronchopulmonary dysplasia (BPD)

-Apgar scores seven at 5 minutes

-neurodevelopment

-anthropometric status; birth weight, height, and head circumference

-NICU admission and mean duration

-side effects of therapy

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

We will conduct the sub-group analysis; extremely preterm (less than GA 28weeks), very preterm (GA28 to 32weeks) and moderate to late preterm (GA 32 to 37weeks) on each predetermined outcome.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

At least two researchers will work independently to assess each title and abstract for eligibility. Disagreement will yield automatic inclusion into the next level of screening. After the initial screening of titles and abstracts, full-text publications of studies with the potential for inclusion will be obtained and assessed. The same reviewers will independently evaluate studies under consideration for inclusion without consideration of their results. Any disagreement will be resolved through discussion to reach a consensus. Finally, the reviewers independently will extract baseline and outcome data and assess the quality of the included studies. Any discrepancies will be resolved through discussion to reach a consensus.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Study quality will be assessed independently by the aforementioned reviewers at the outcome level using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS). Randomized control trials will be assessed with Risk of Bias 2 (RoB2). Potential publication bias will be assessed by visual inspection of funnel plots for asymmetry, subject to a sufficient number of included studies. Any disagreement will be resolved by discussion to reach a consensus.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the

number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference with 95% CIs will be used.

The heterogeneity of studies will be assessed using both qualitative and quantitative measures. Statistical heterogeneity will be determined for each meta-analysis using T2, I², and ?² statistics.

Heterogeneity will be deemed substantial if T2 will be greater than zero and either I² will be greater than 50% or p0.10 in the ?² test for heterogeneity. To further assess potential heterogeneity, both fixed- and random-effects models will be compared for each outcome, where possible.

All statistical analyses will be performed using RevMan 5. Existing meta-analyses will be reviewed for relevance and completeness, and new meta-analyses will be performed where deemed necessary.

Statistical significance will be set at an alpha level of 0.05 for all analyses, except when testing study heterogeneity, where p0.10 will be regarded as significant.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat

No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
Yes

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Japan

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We will disseminate the finding with a relevant medical journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Antenatal corticosteroid

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. PLoS ONE. 2016; 11(2): e0147604.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Supplementary file 2: PRISMA flow diagrams

Figure 1: Flow diagram of search results and study selection for women with pregestational and/or gestational diabetes

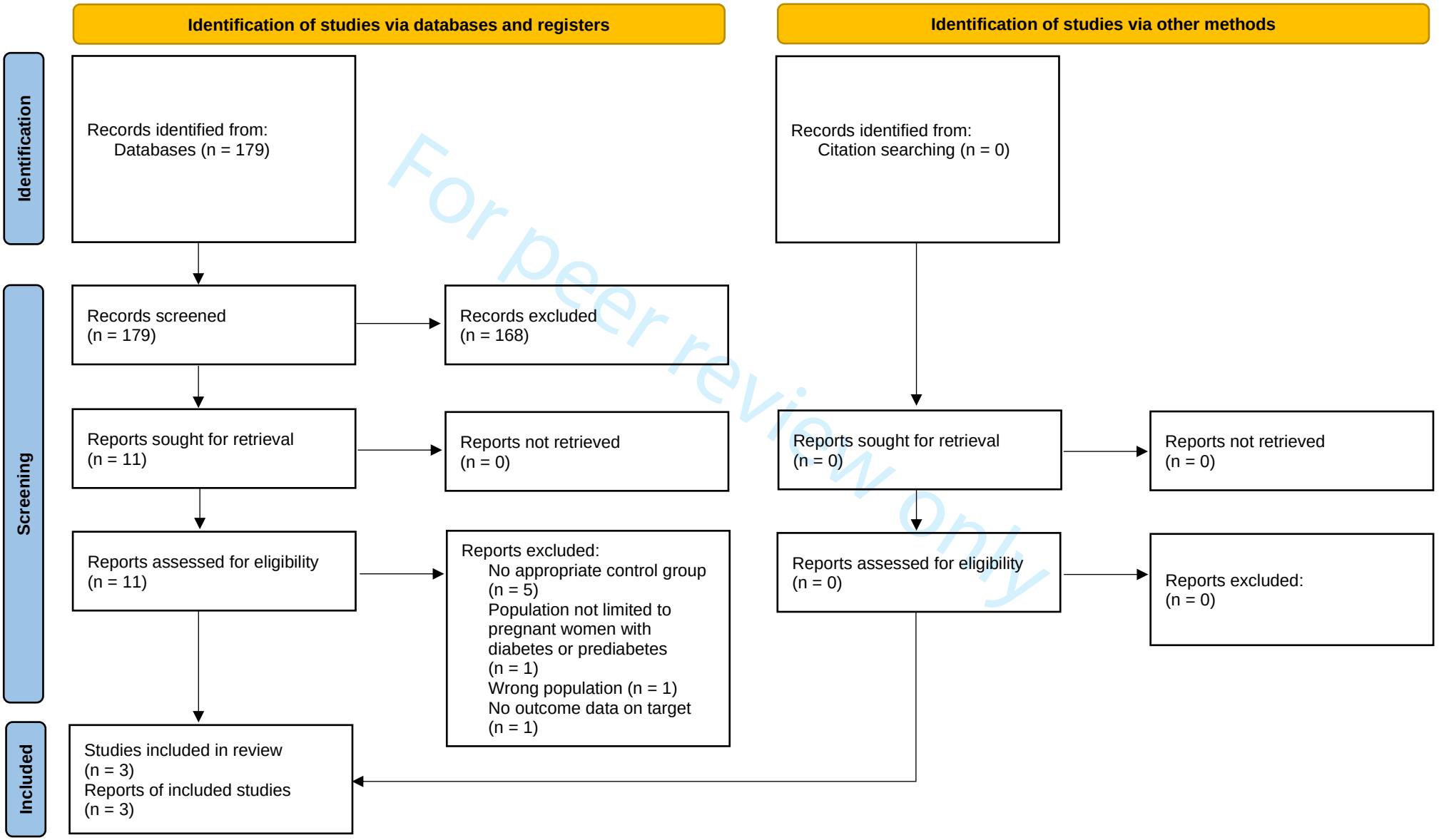


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

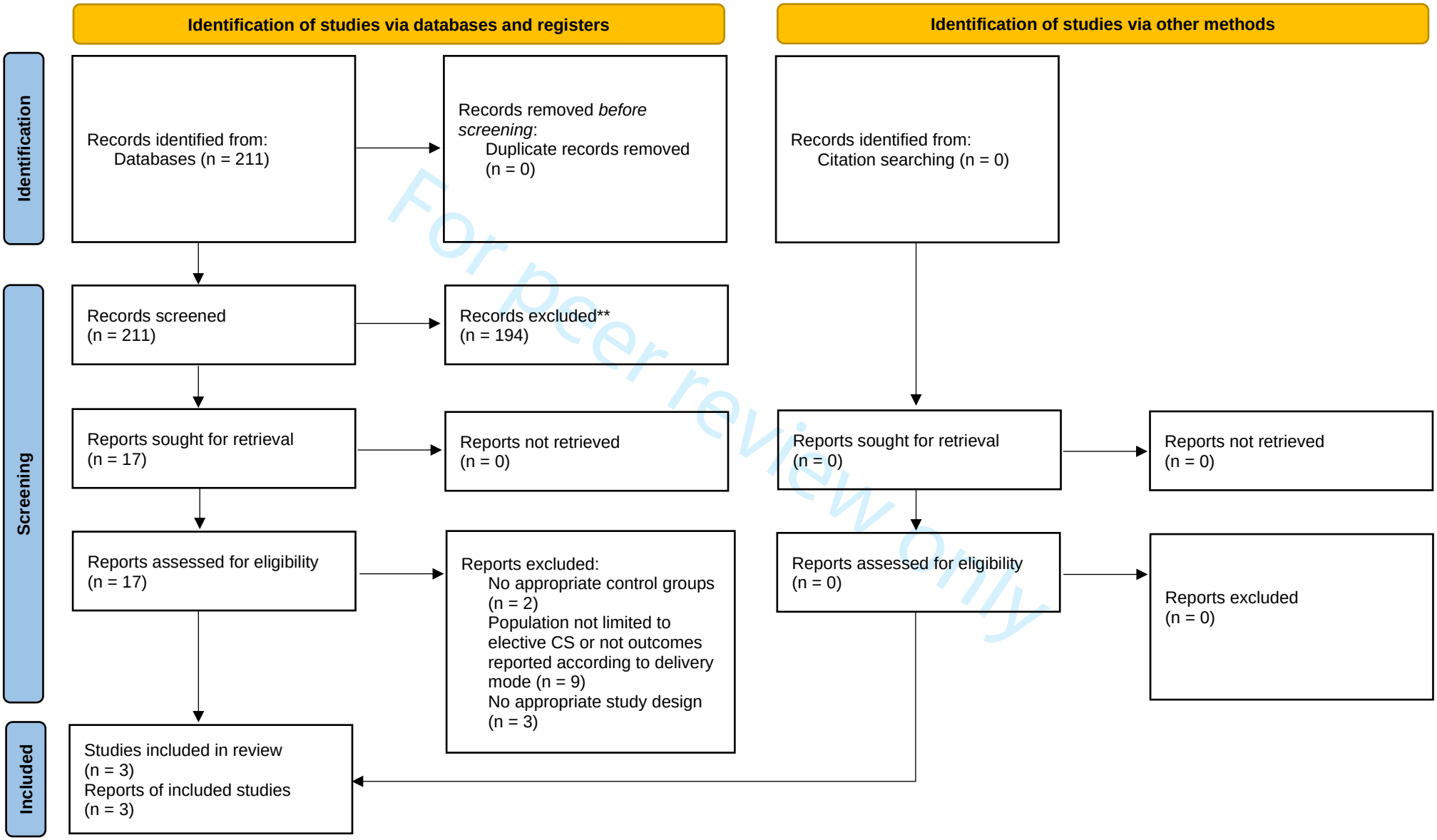


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

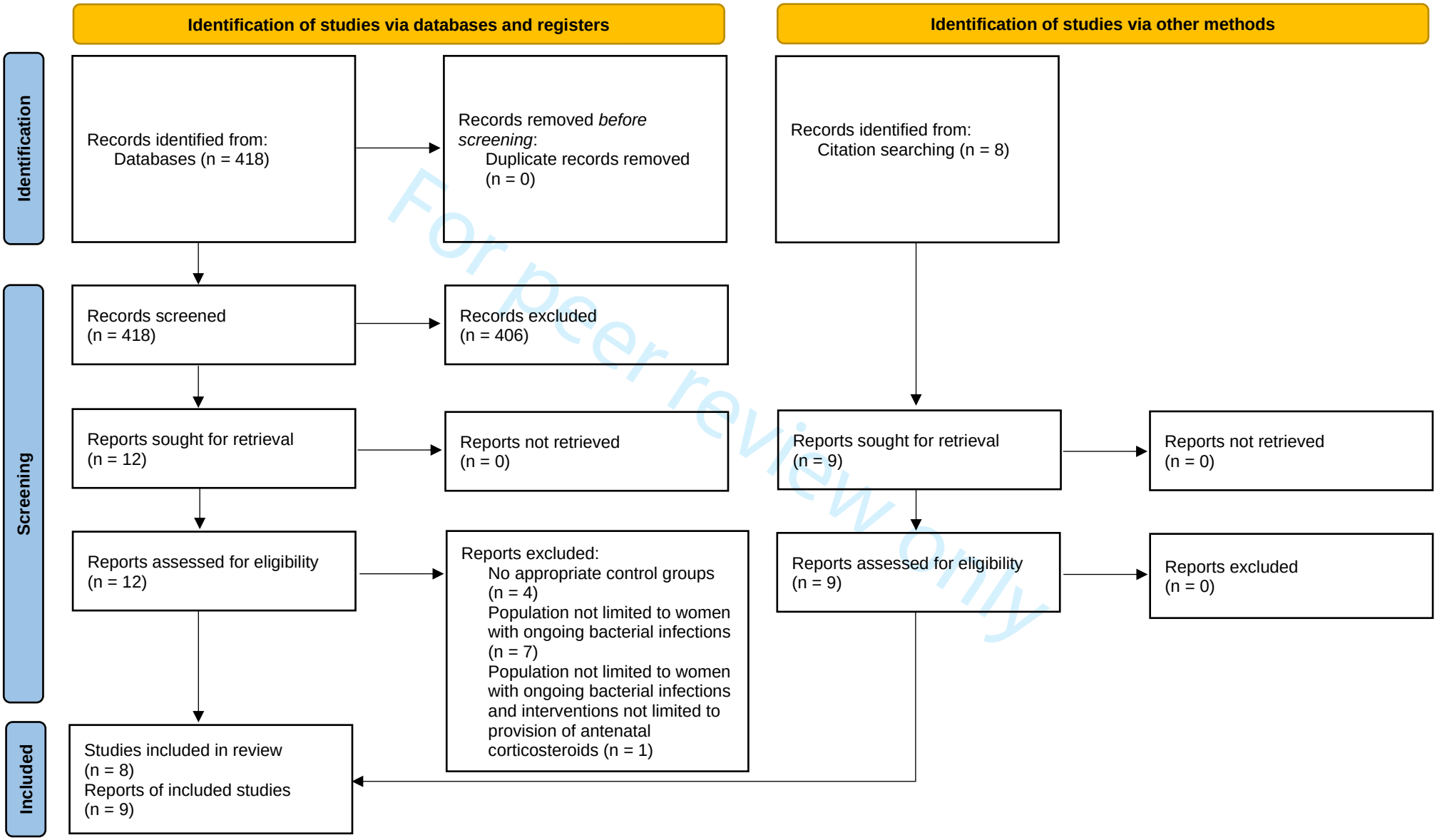
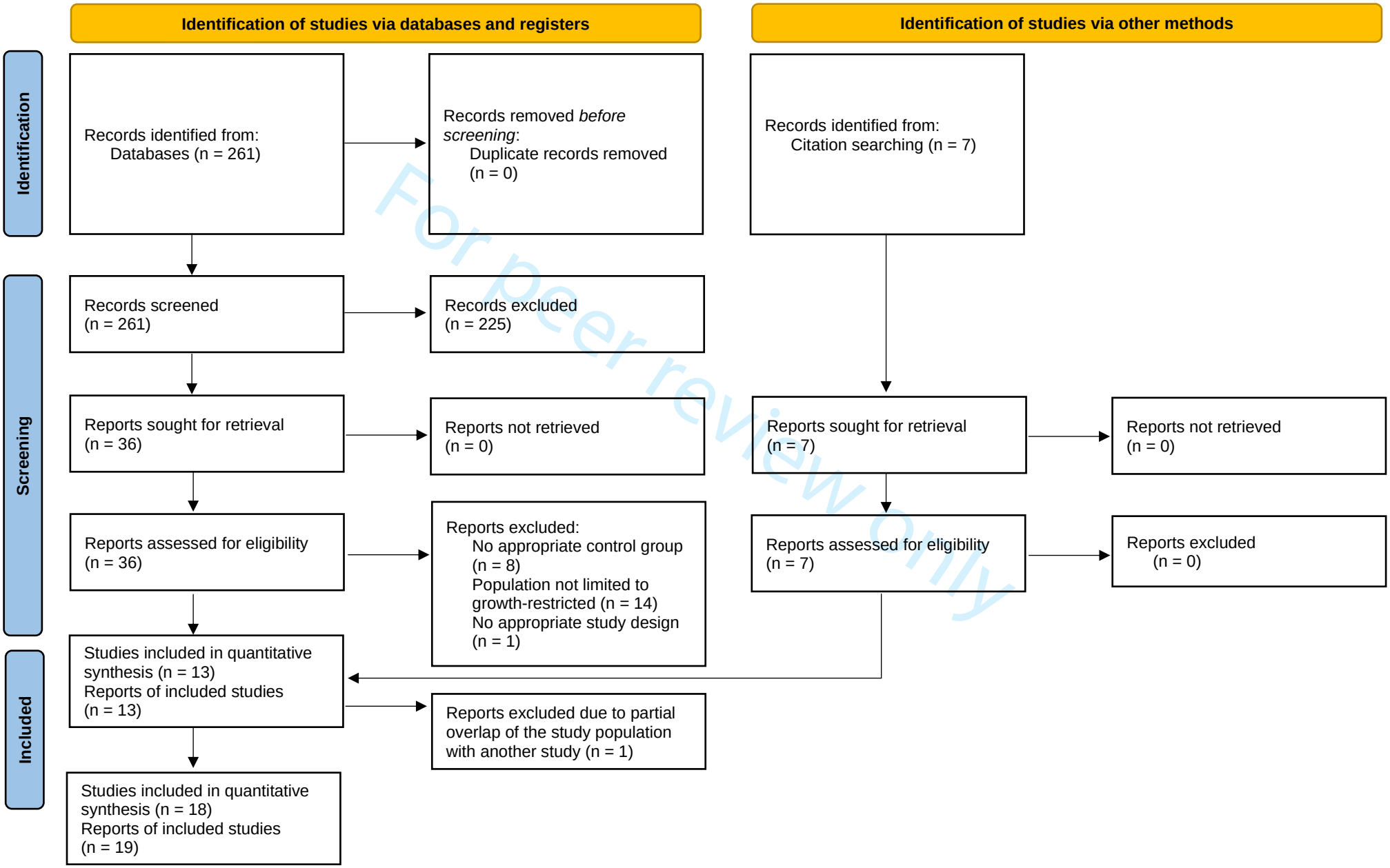


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure1: Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

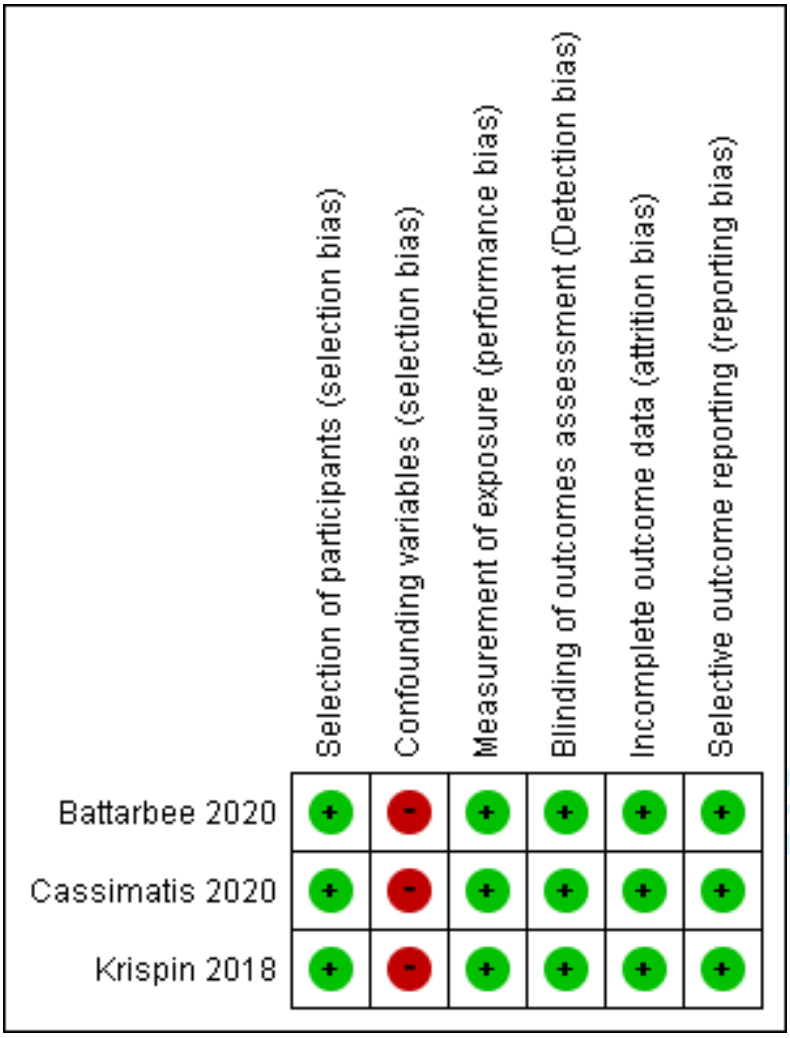
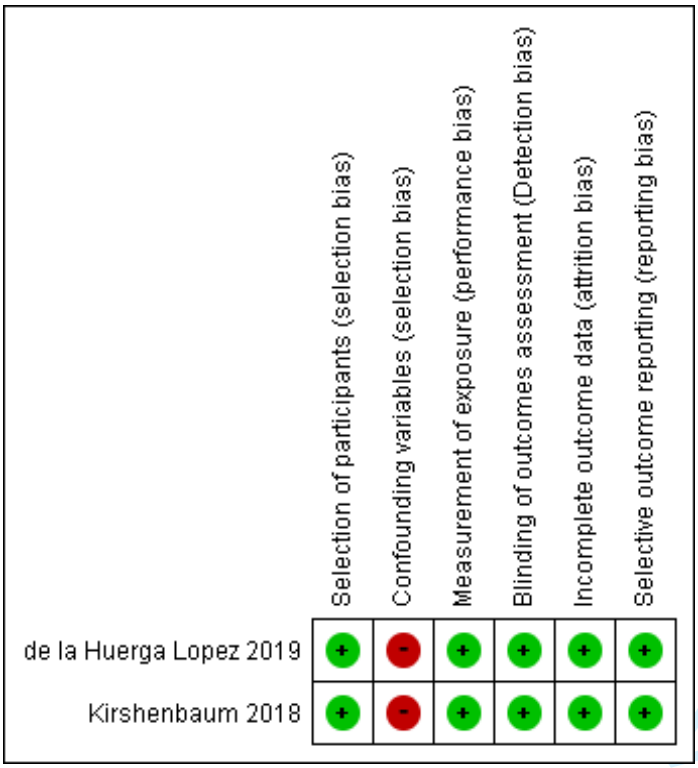


Figure 2: Summary of risk of bias for each trial for women undergoing elective Cesarean section in late preterm period
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



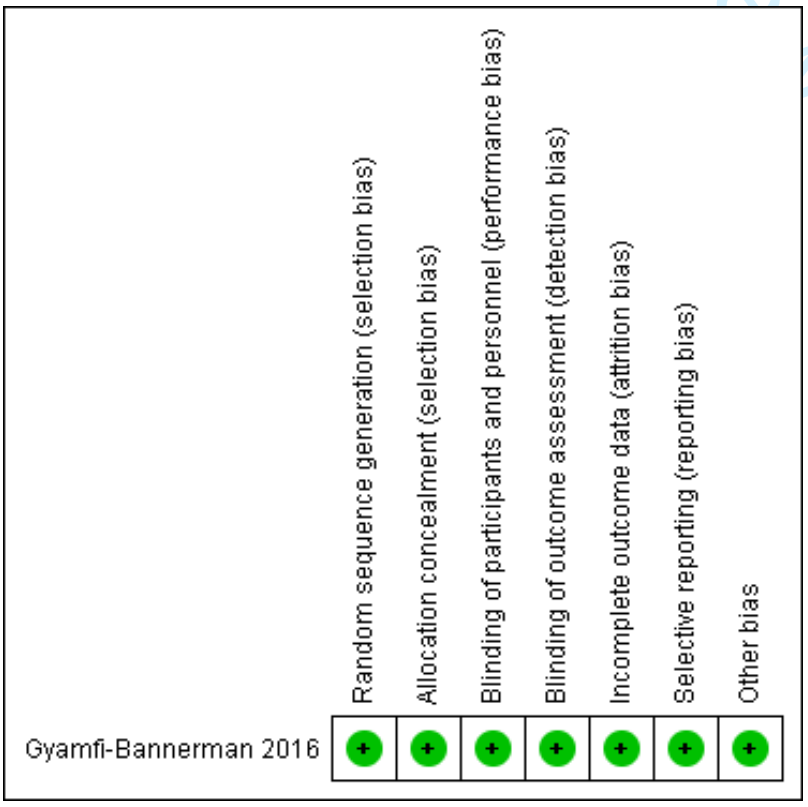


Figure 3: Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical)
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

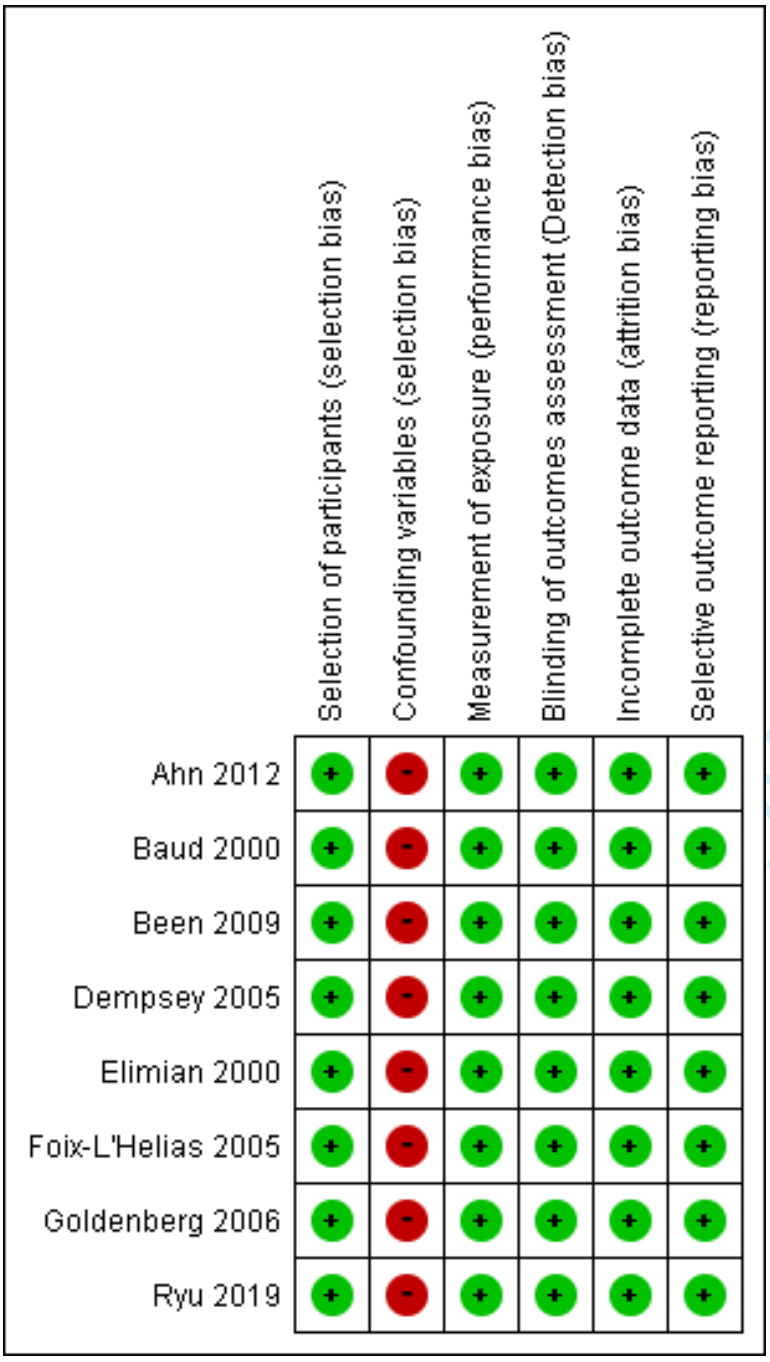
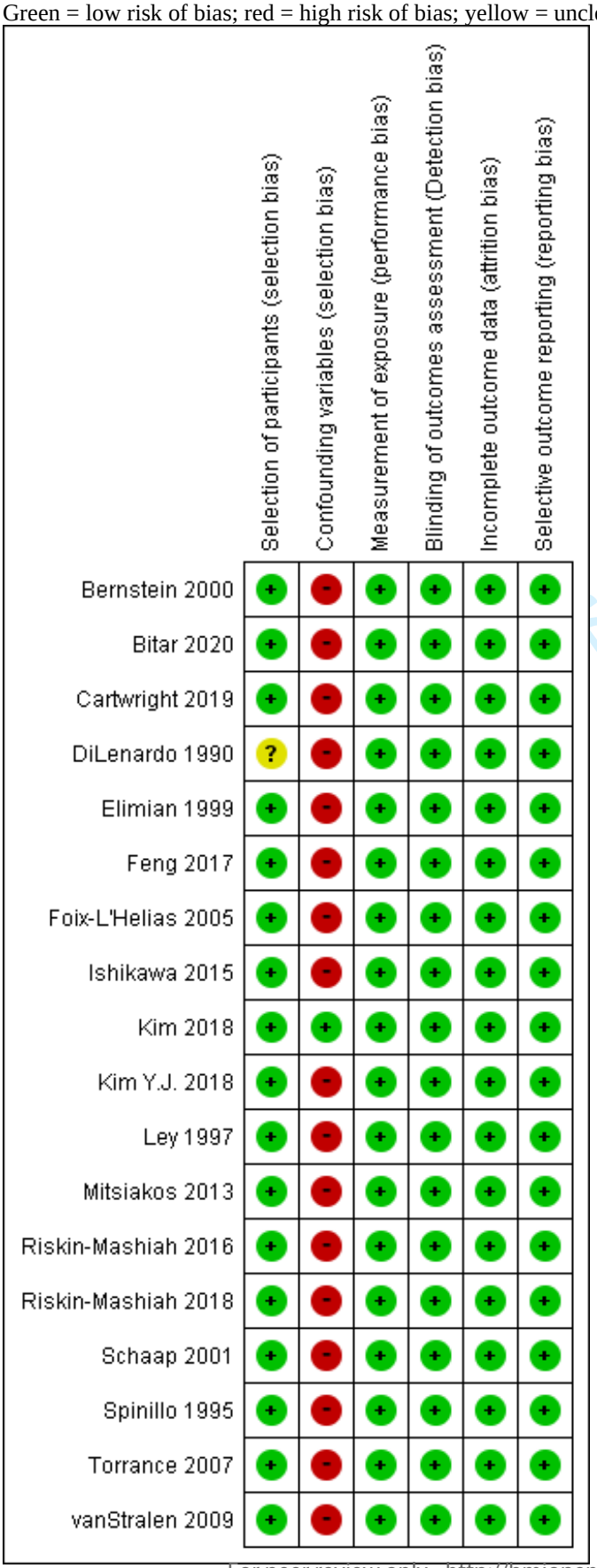


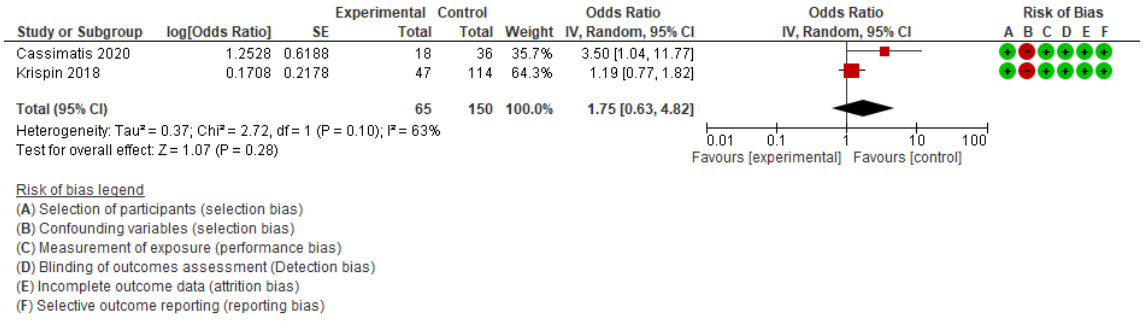
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



Supplementary file 4: Forest plots

Maternal outcomes for women with pregestational and/or gestational diabetes mellitus

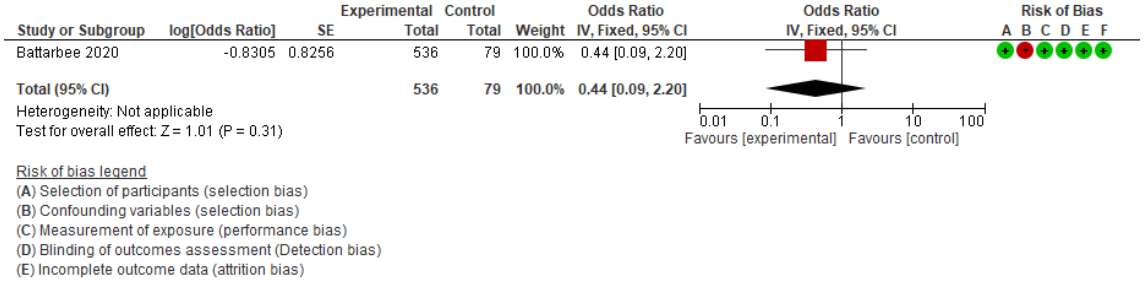
1) Caesarean section



SE: Standard error; **CI:** Confidence interval

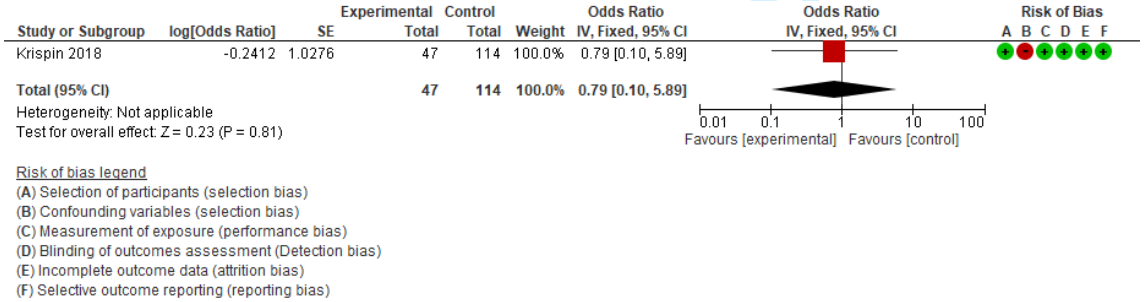
Neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

1) Neonatal death within 48 h of birth



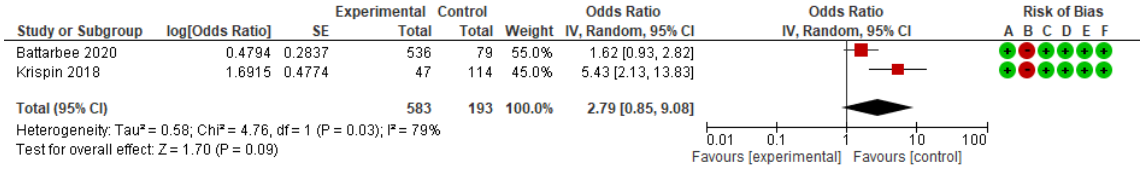
SE: Standard error; **CI:** Confidence interval

2) Apgar score < 7 at 5 min



SE: Standard error; **CI:** Confidence interval

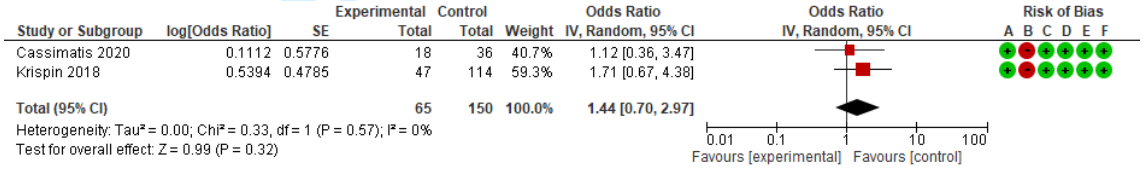
3) Respiratory distress syndrome (RDS)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia



Risk of bias legend
(A) Selection of participants (selection bias)
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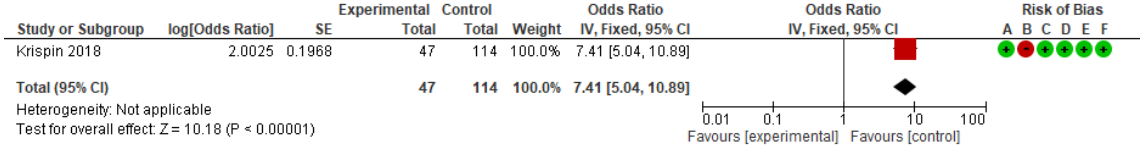
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

5) Admission to neonatal intensive care unit (NICU)



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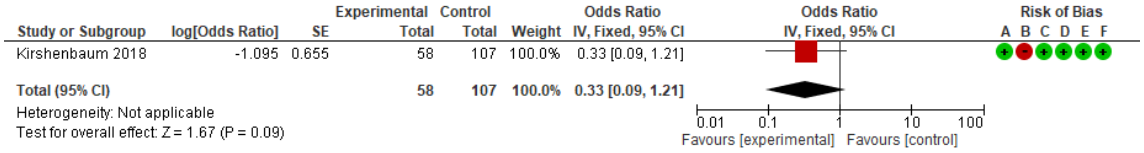
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders



Risk of bias legend
(A) Selection of participants (selection bias)
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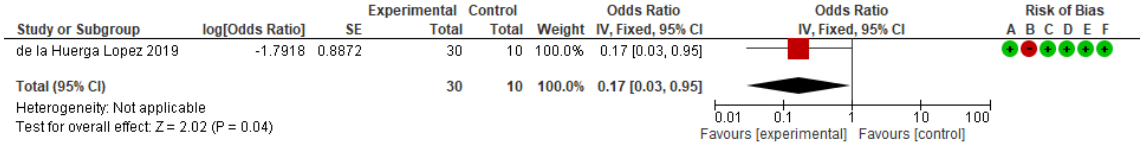
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

2) Gestational diabetes mellitus



Risk of bias legend
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(B) Confounding variables (selection bias)
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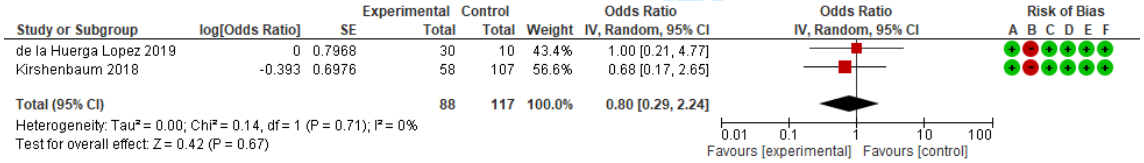
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women undergoing elective cesarean section in late preterm period

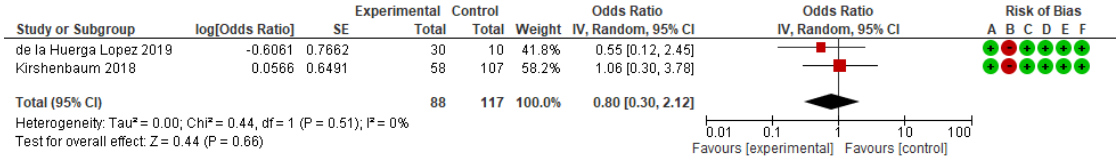
1) Respiratory distress syndrome (RDS)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

2) Use of mechanical ventilation



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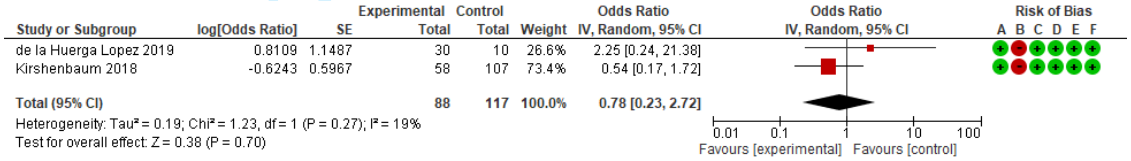
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

3) Admission to neonatal intensive care unit (NICU)



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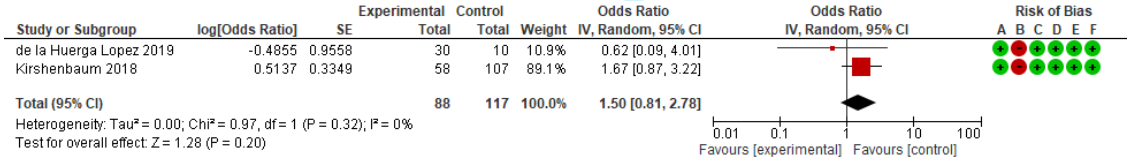
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

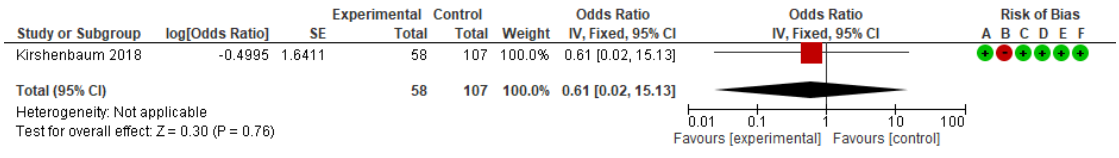
4) Neonatal hypoglycemia



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

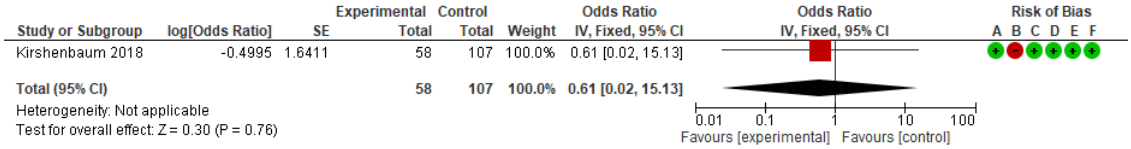
5) Intraventricular hemorrhage (IVH)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

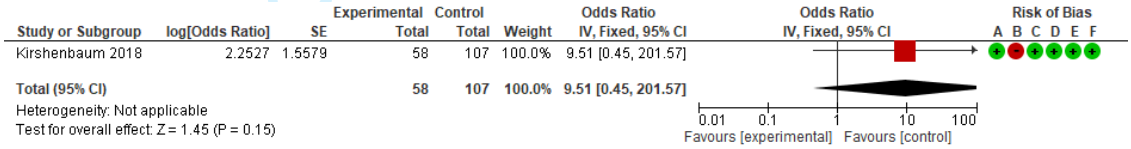
6) Necrotizing enterocolitis (NEC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

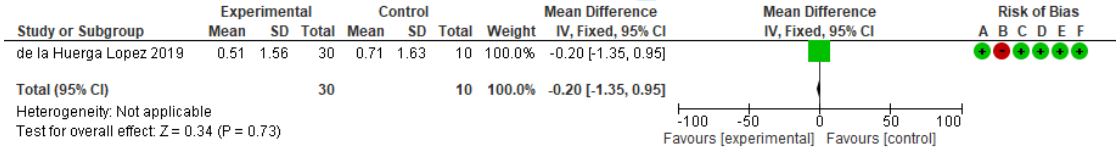
7) Apgar score ≤ 7 at 5min



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

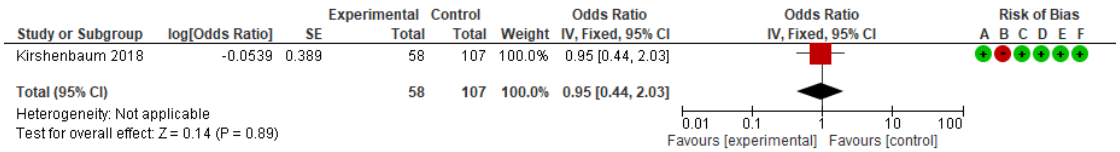
8) Mean duration of mechanical ventilation, days



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

9) Oxygen requirement for at least 4 hours



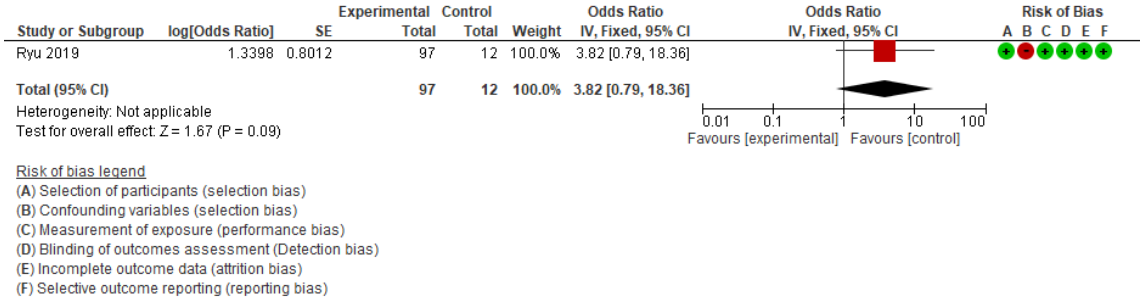
Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women with histological chorioamnionitis

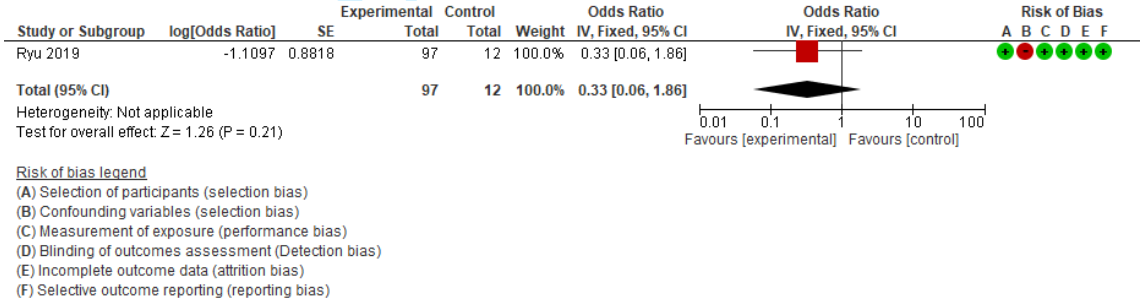
*There is no maternal outcome in clinical chorioamnionitis.

1) Caesarean section (HC)



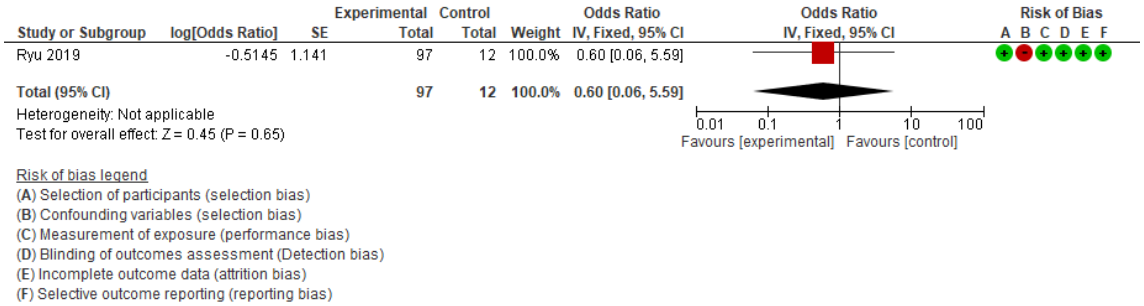
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

2) Gestational diabetes mellitus (HC)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

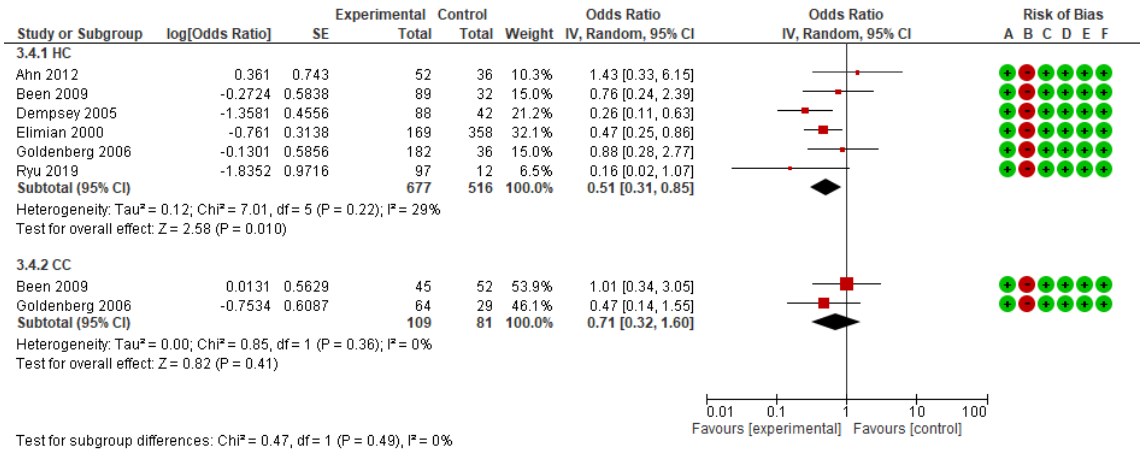
3) Preeclampsia or eclampsia (HC)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

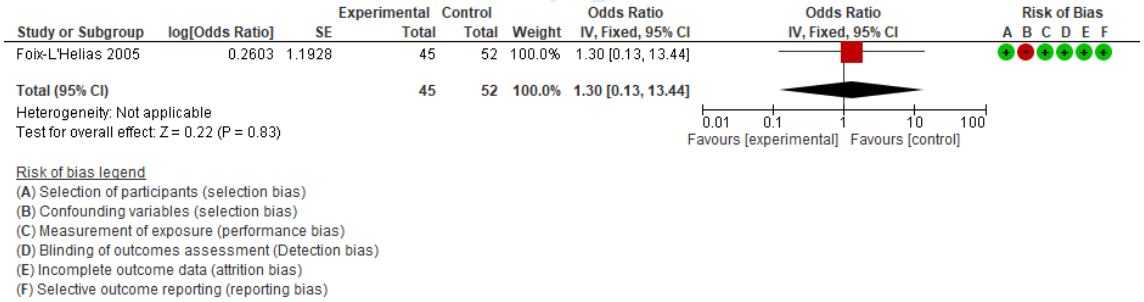
Neonatal outcomes for women with histological chorioamnionitis (HC) and clinical chorioamnionitis (CC)

1) Neonatal death



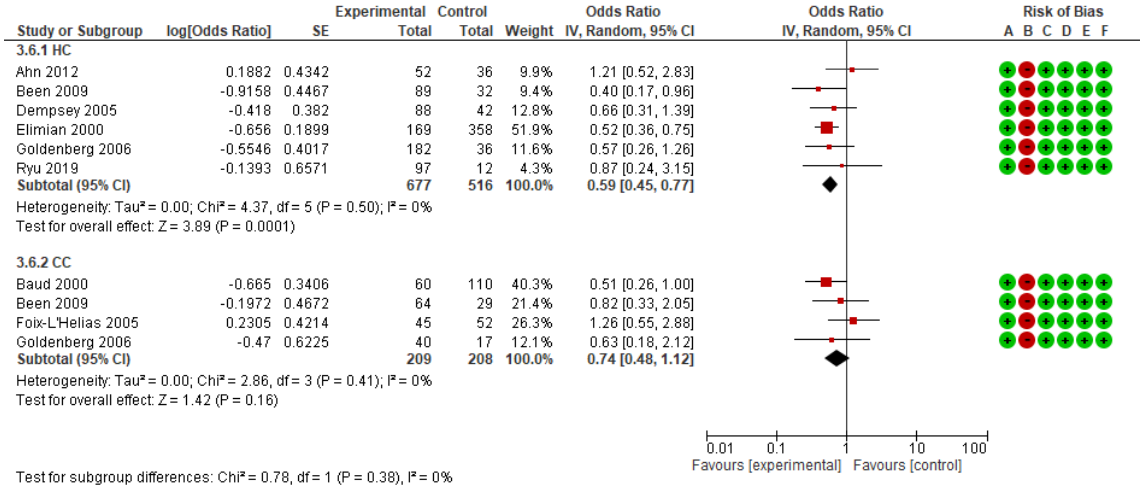
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

2) Death before discharge home (CC)



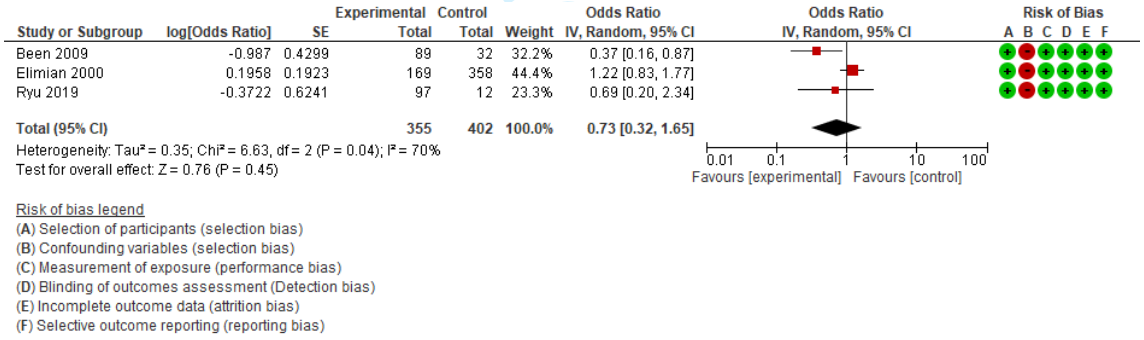
SE: Standard error; **CI:** Confidence interval; **CC:** Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



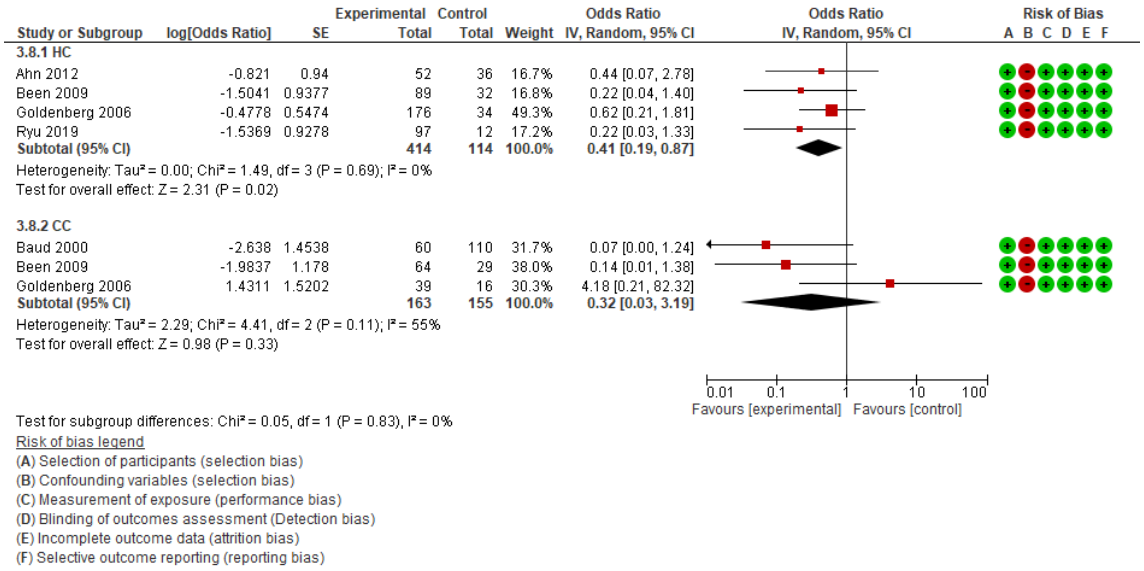
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

4) Surfactant use (HC)



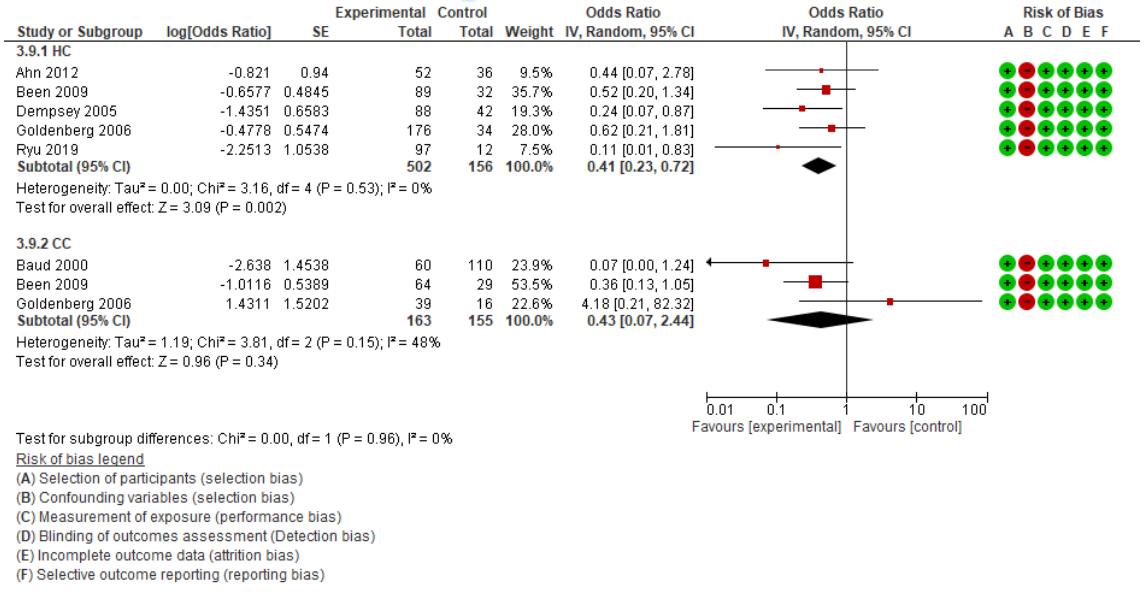
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

5) Severe intraventricular hemorrhage (IVH)



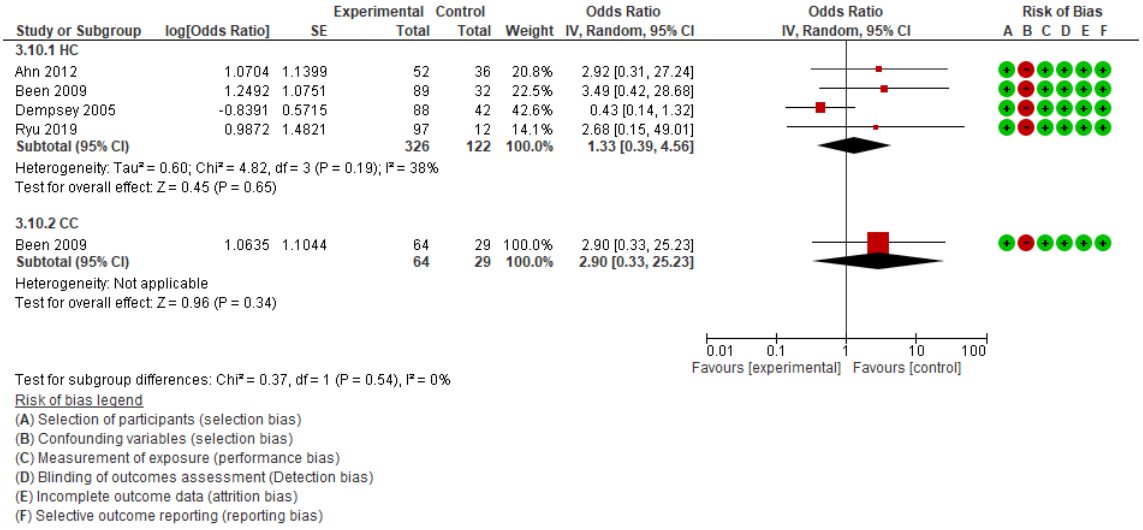
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



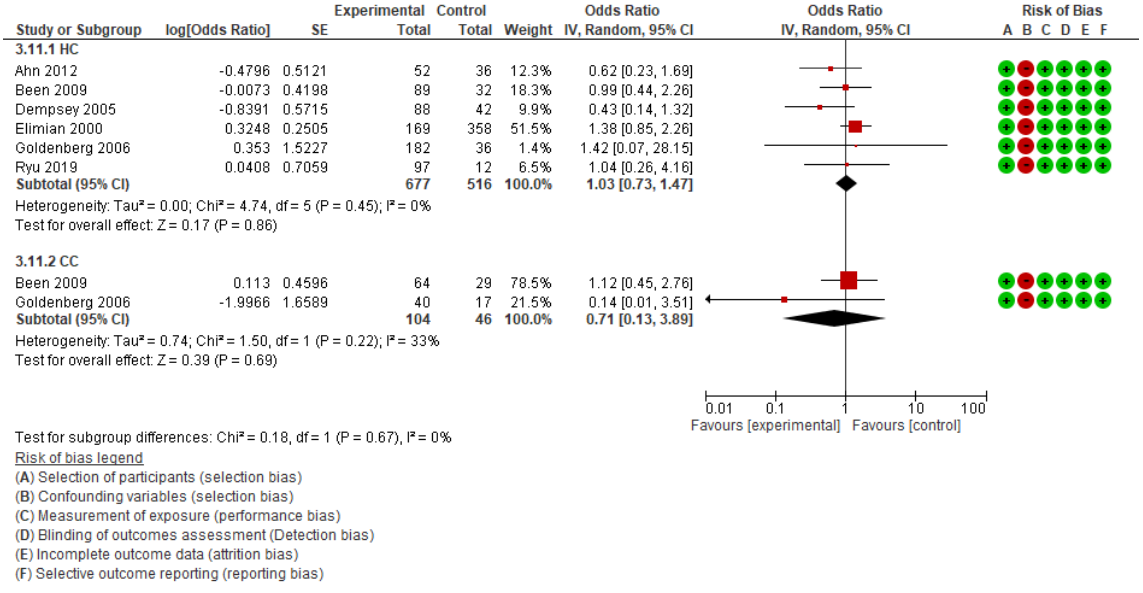
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

7) Early-onset sepsis



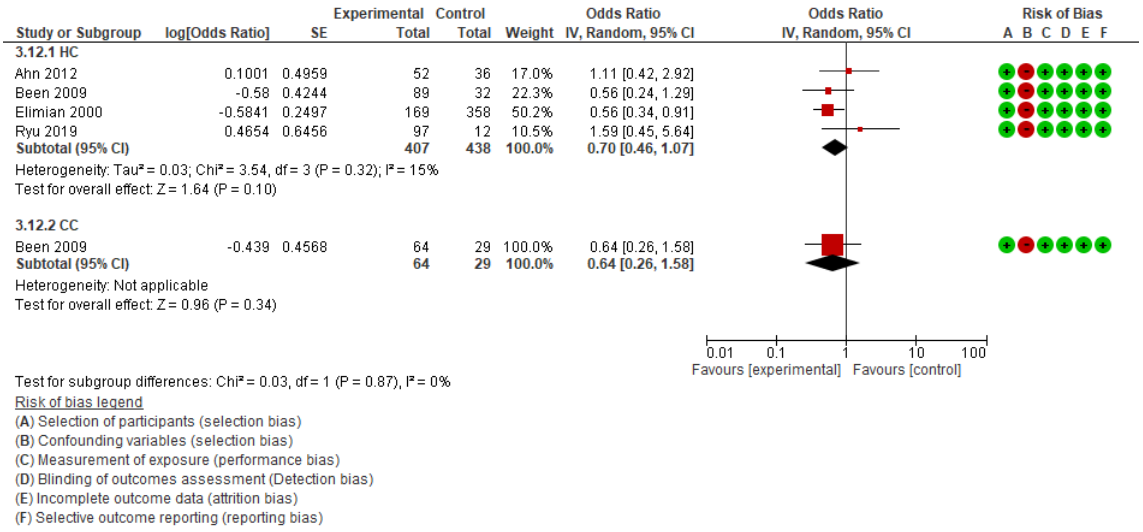
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

8) Sepsis



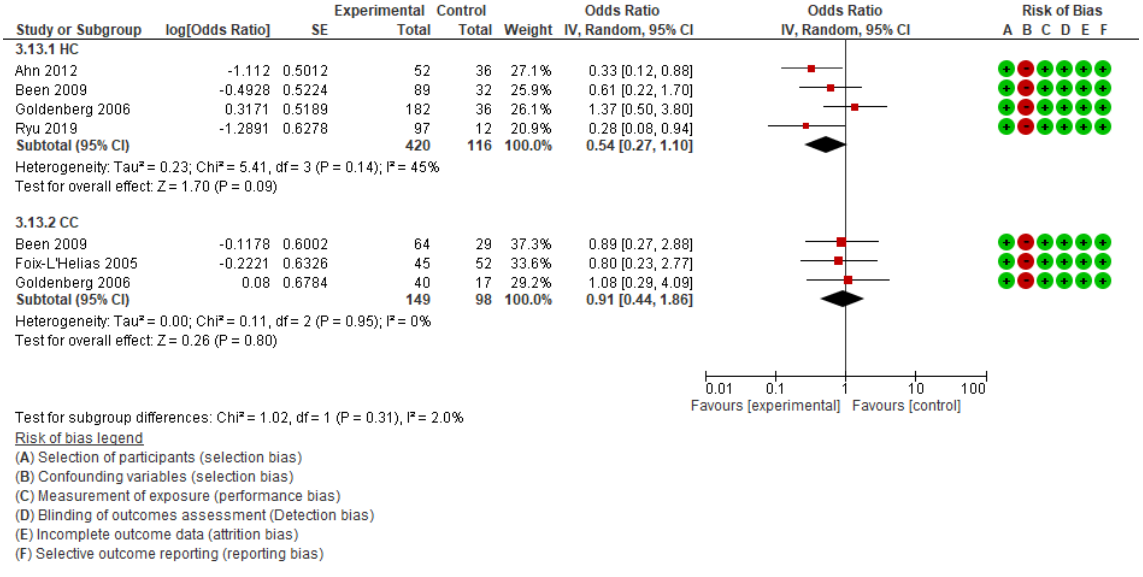
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



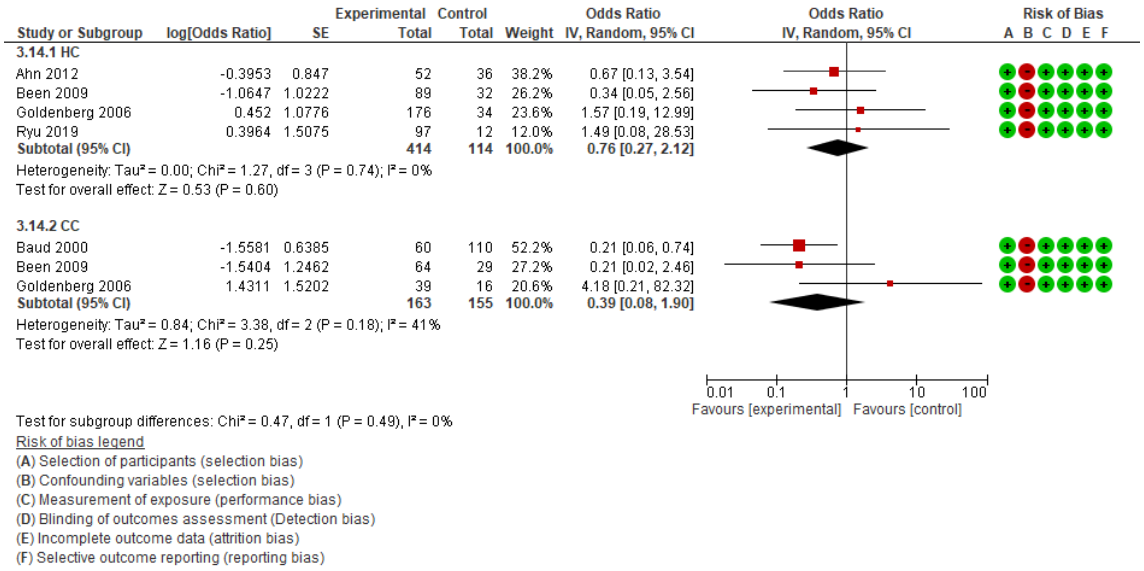
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

10) Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)



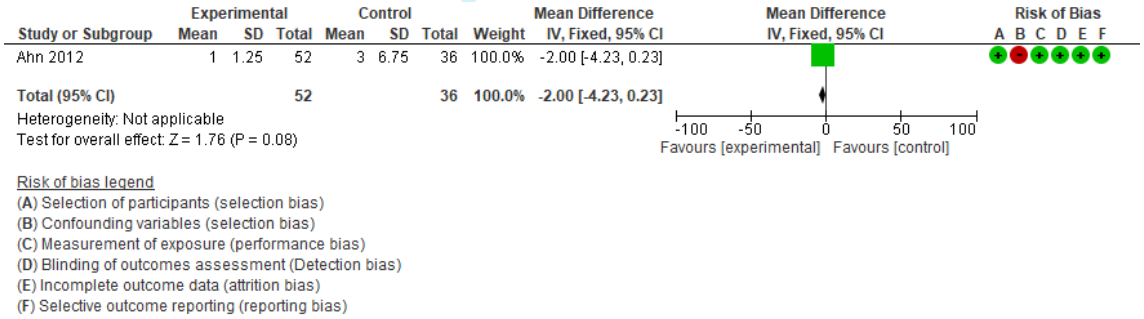
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

11) Periventricular leukomalacia (PVL)



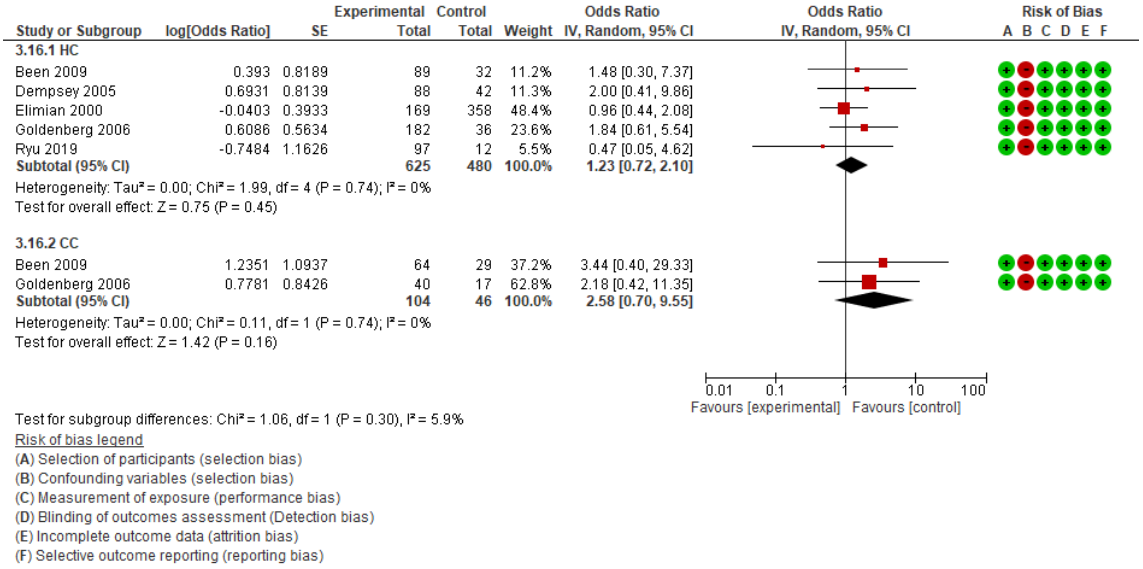
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

12) Mean duration of mechanical ventilation, days (HC)



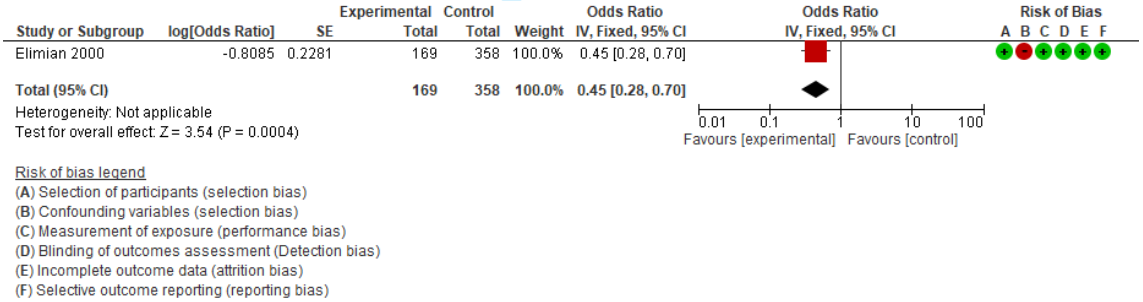
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

13) Necrotizing enterocolitis (NEC)



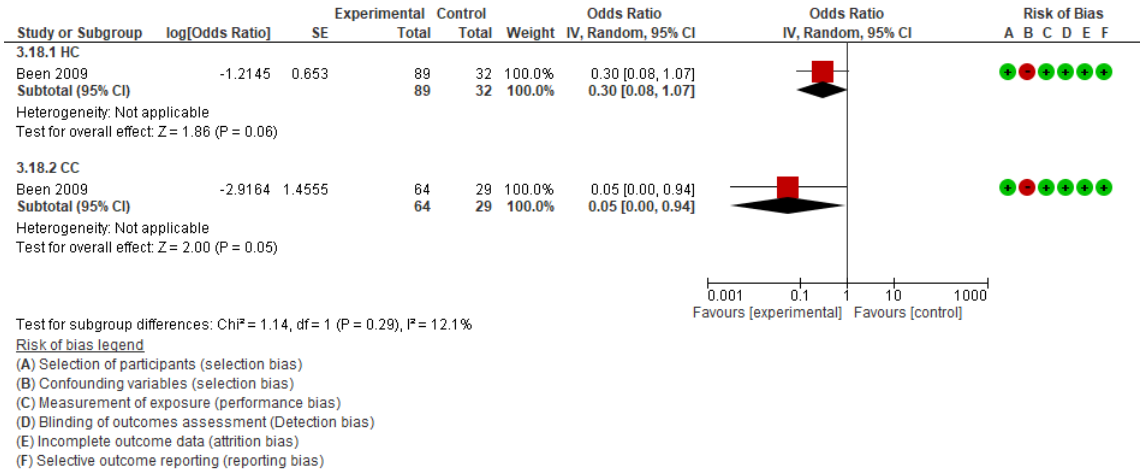
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

14) Apgar score < 7 at 5 minutes (HC)



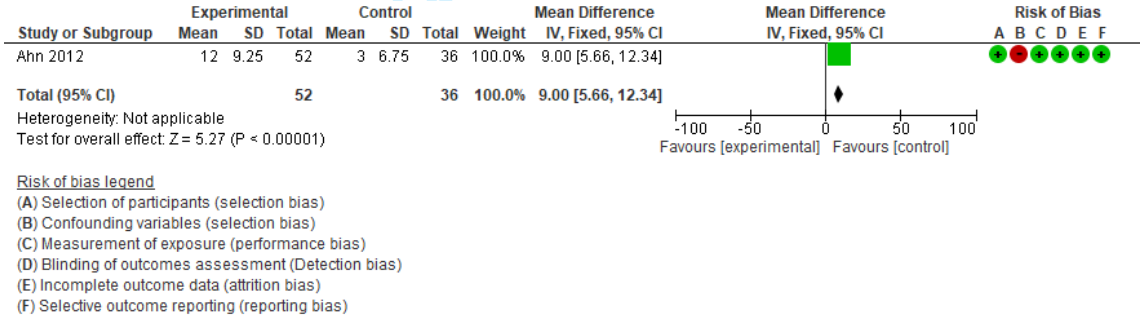
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

15) Use of mechanical ventilation



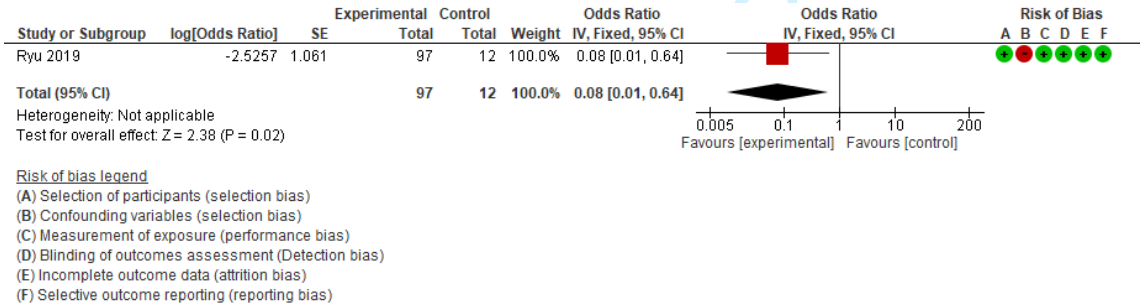
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)



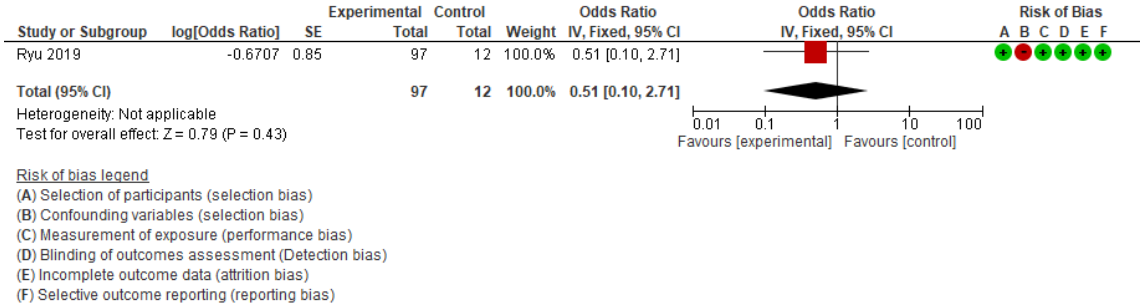
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

17) Hypotension within 7 postnatal days (HC)



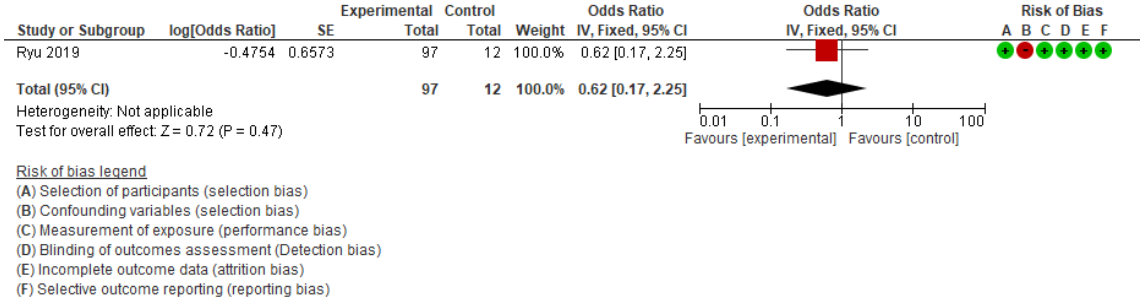
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Retinopathy of prematurity requiring treatment (HC)



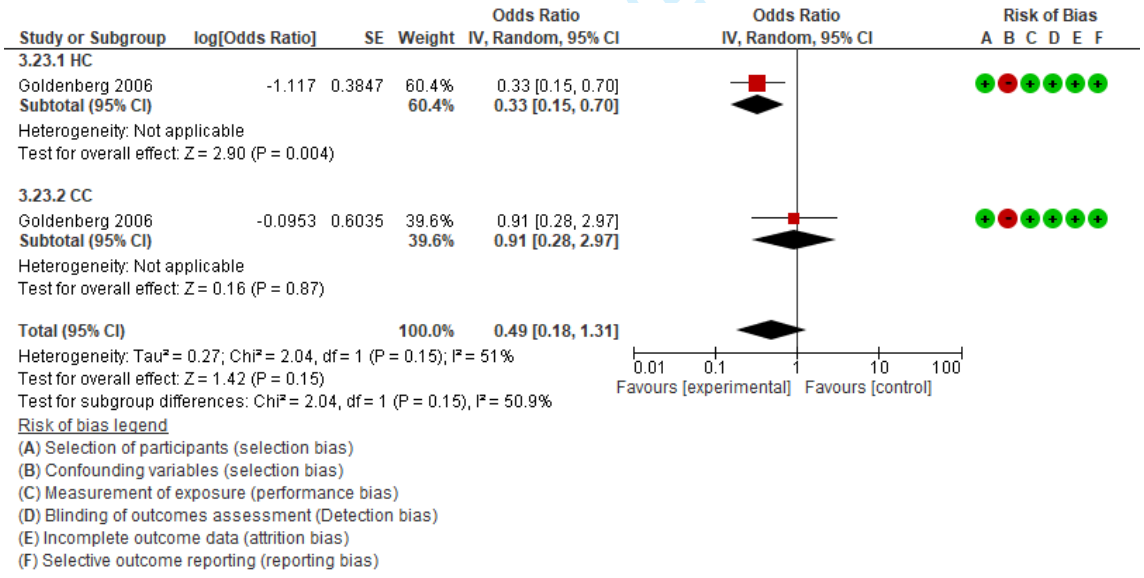
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

19) Discharge with respiratory support (HC)



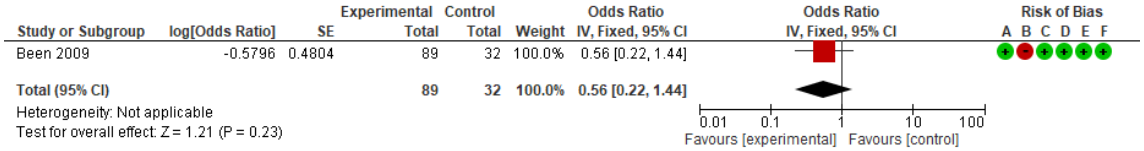
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

20) Systemic inflammatory response syndrome



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

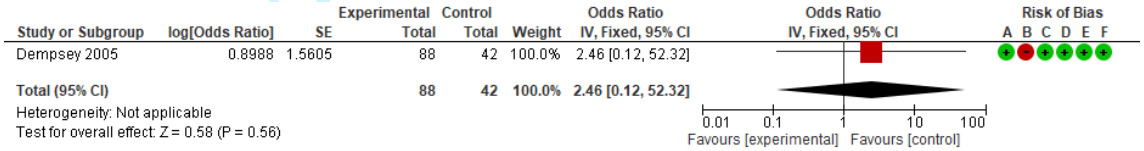
21) Severe respiratory distress syndrome (RDS) (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

22) Meningitis (HC)



Risk of bias legend
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(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
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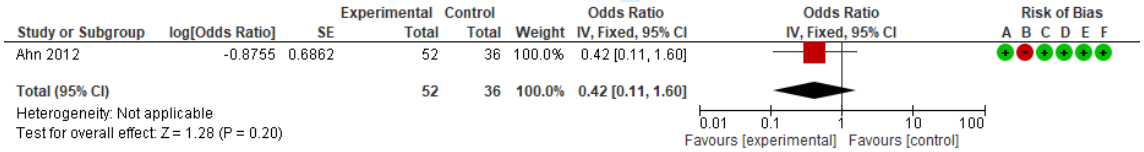
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

23) Intrahepatic cholestasis (HC)



Risk of bias legend
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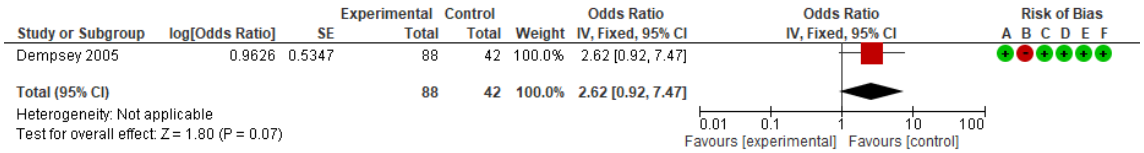
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

24) Pneumonia (HC)



Risk of bias legend
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(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
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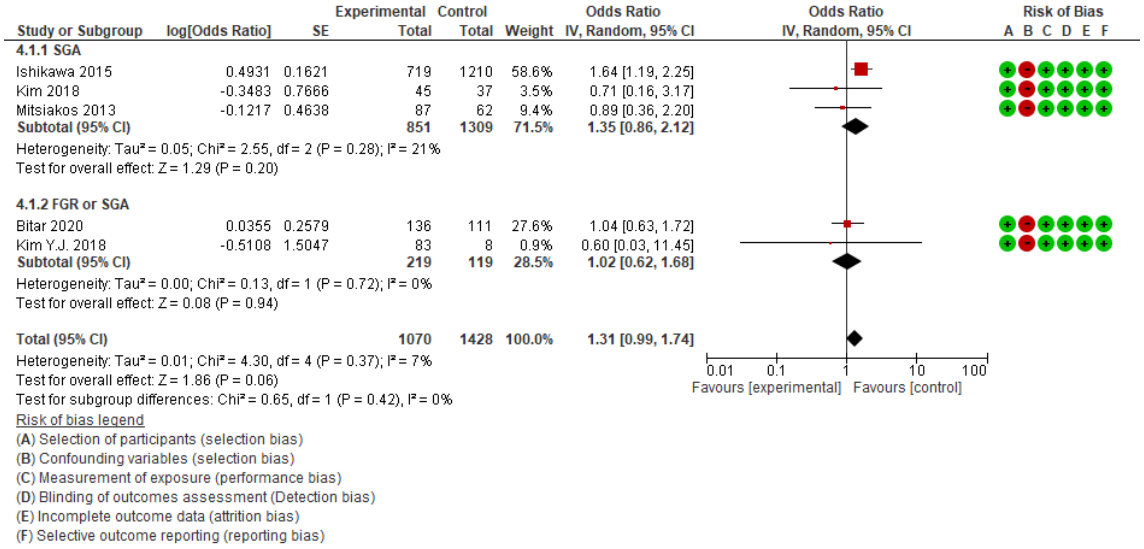
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

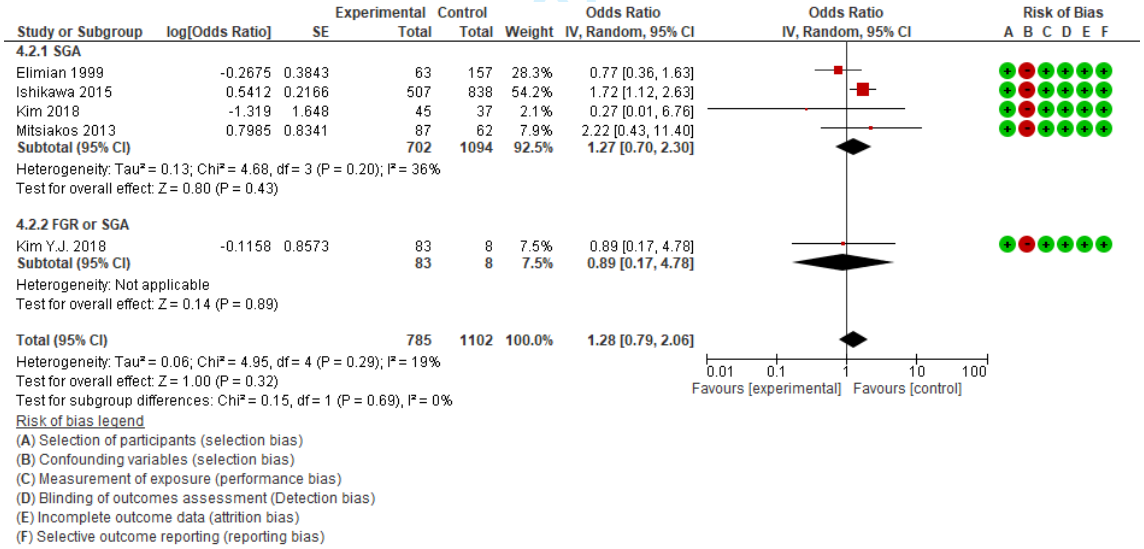
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



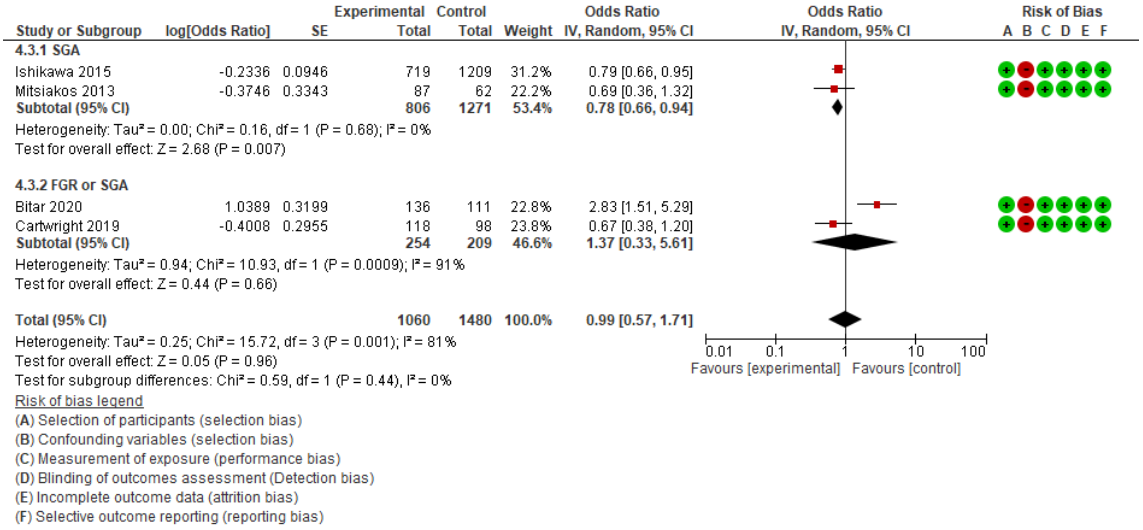
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Chorioamnionitis (histologic and /or clinical)



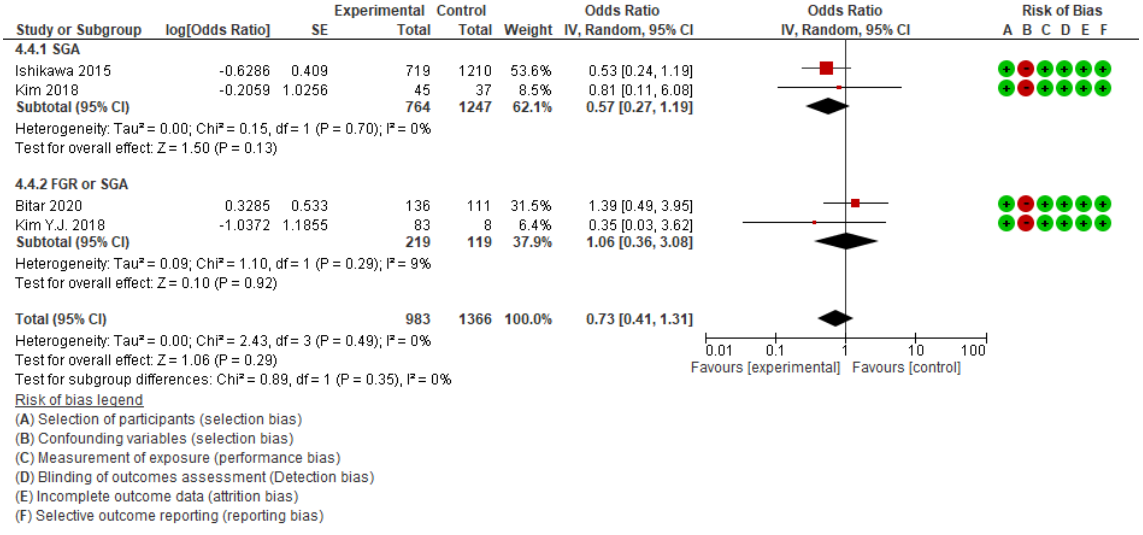
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Preeclampsia.



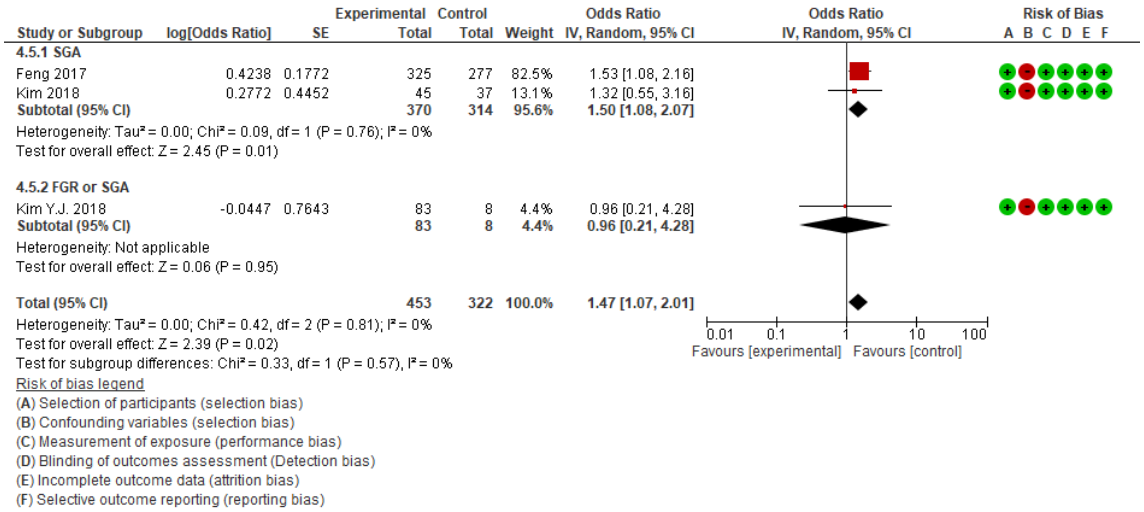
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Gestational diabetes mellitus.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

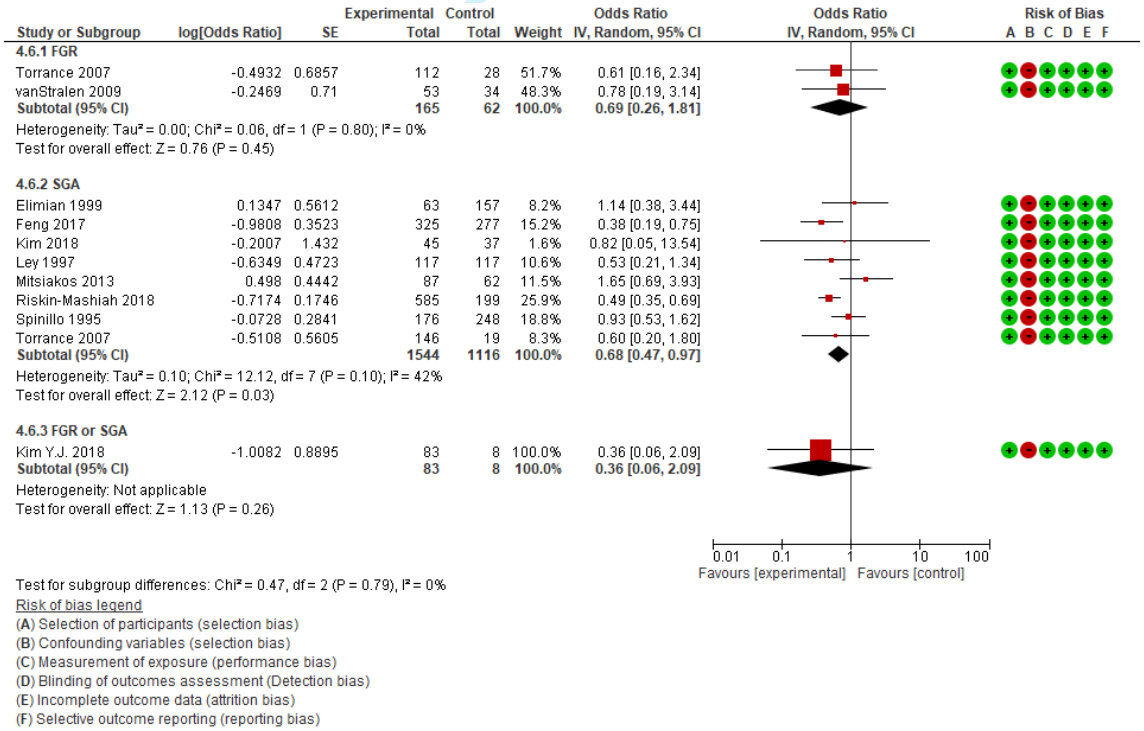
5) Pregnancy induced hypertension.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

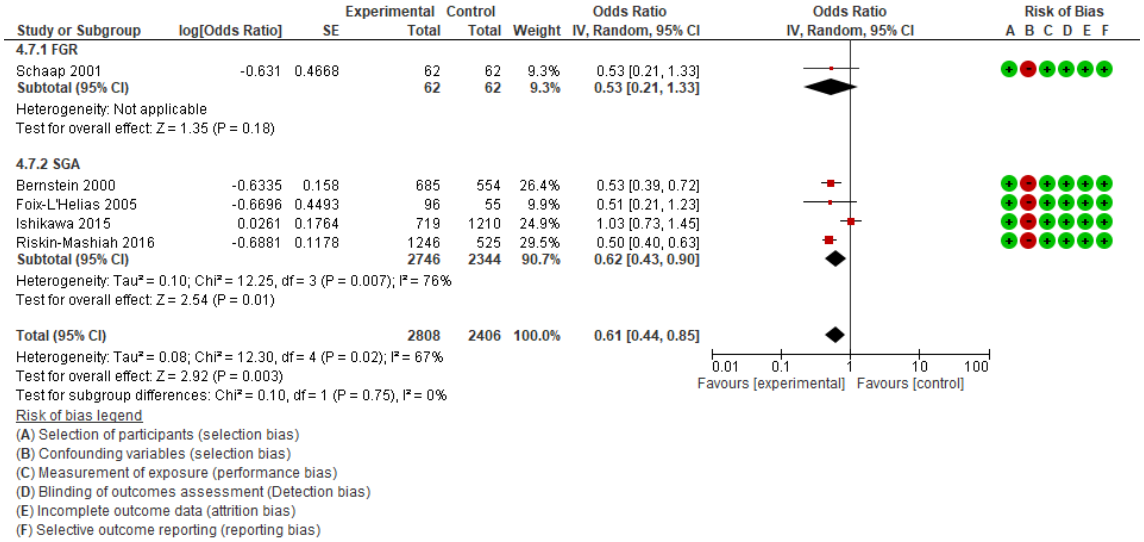
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



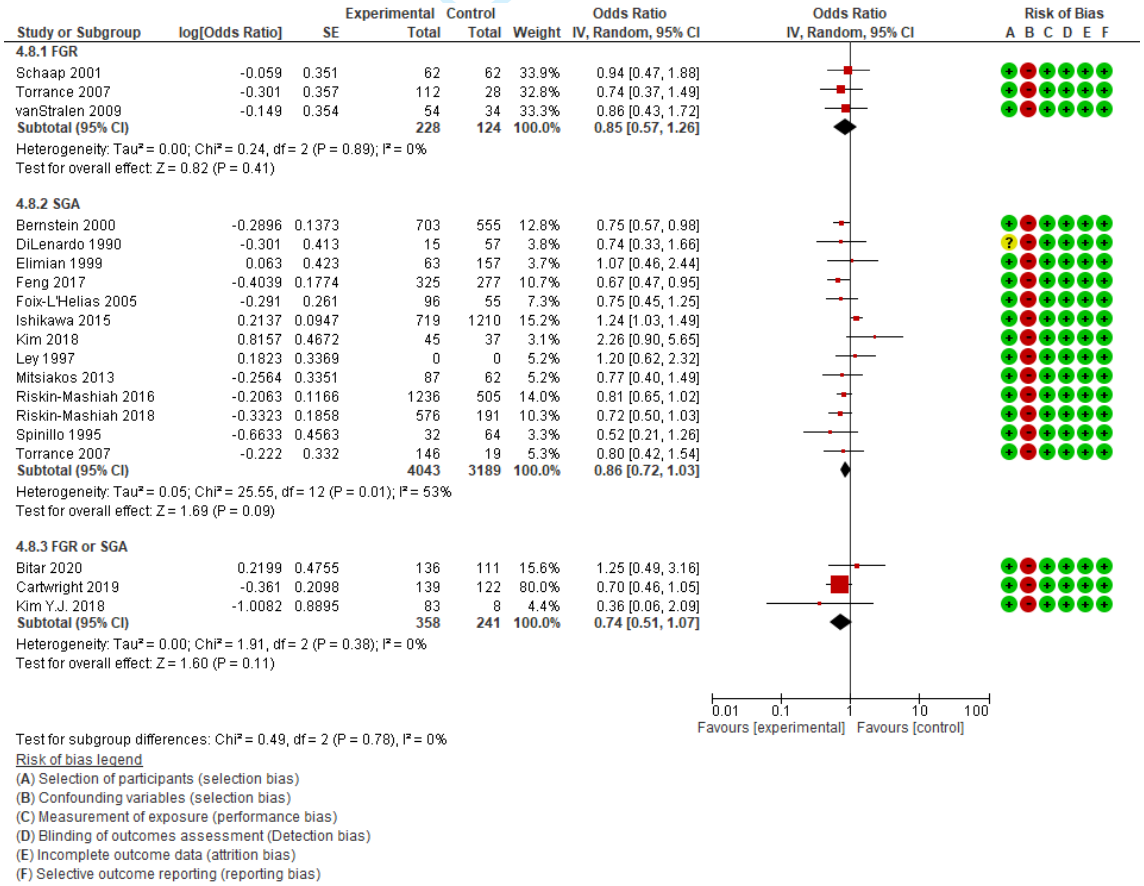
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Death before discharge home



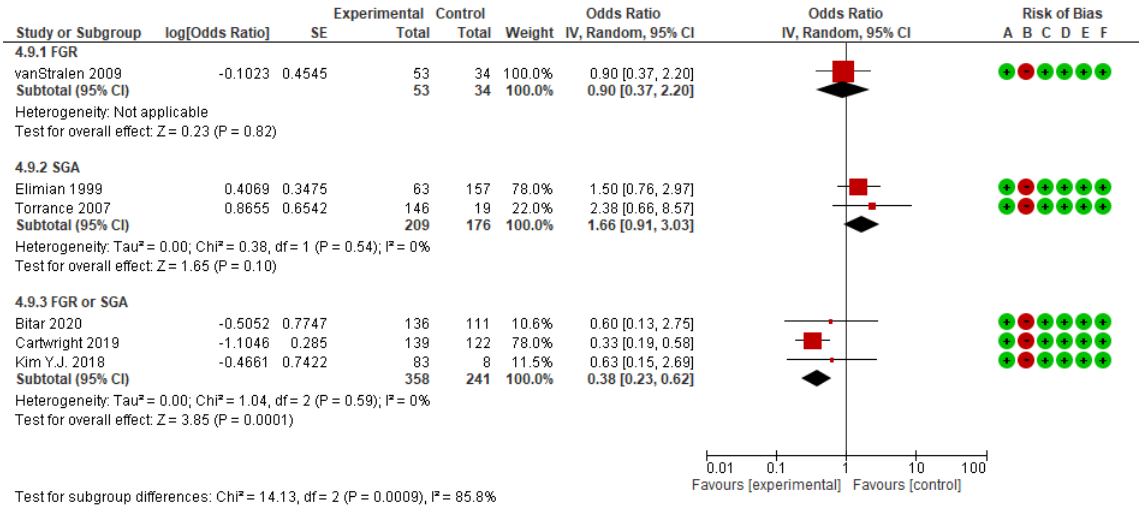
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Respiratory distress syndrome (RDS) and moderate / severe RDS



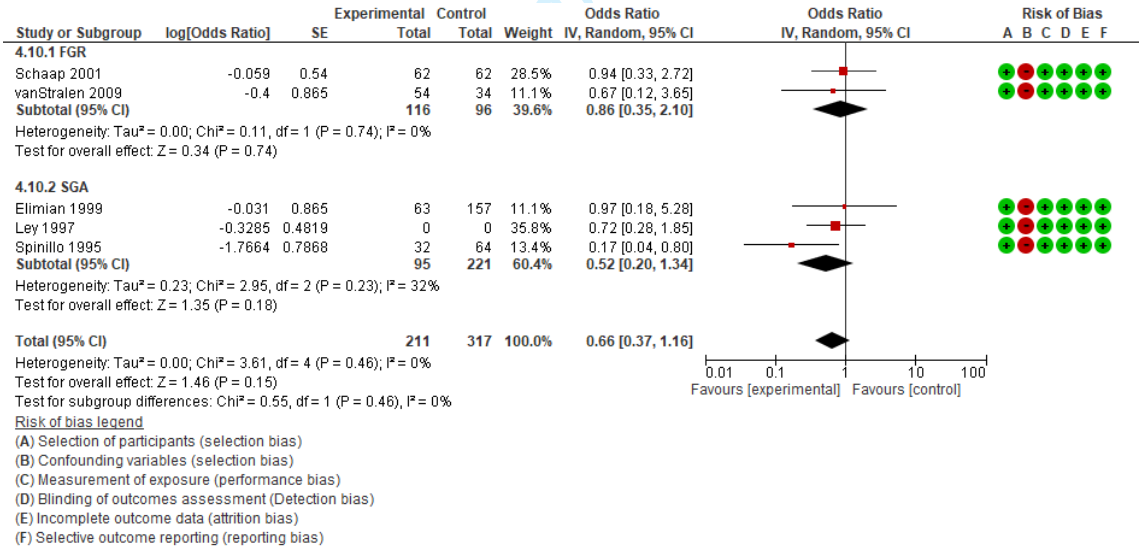
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Surfactant use



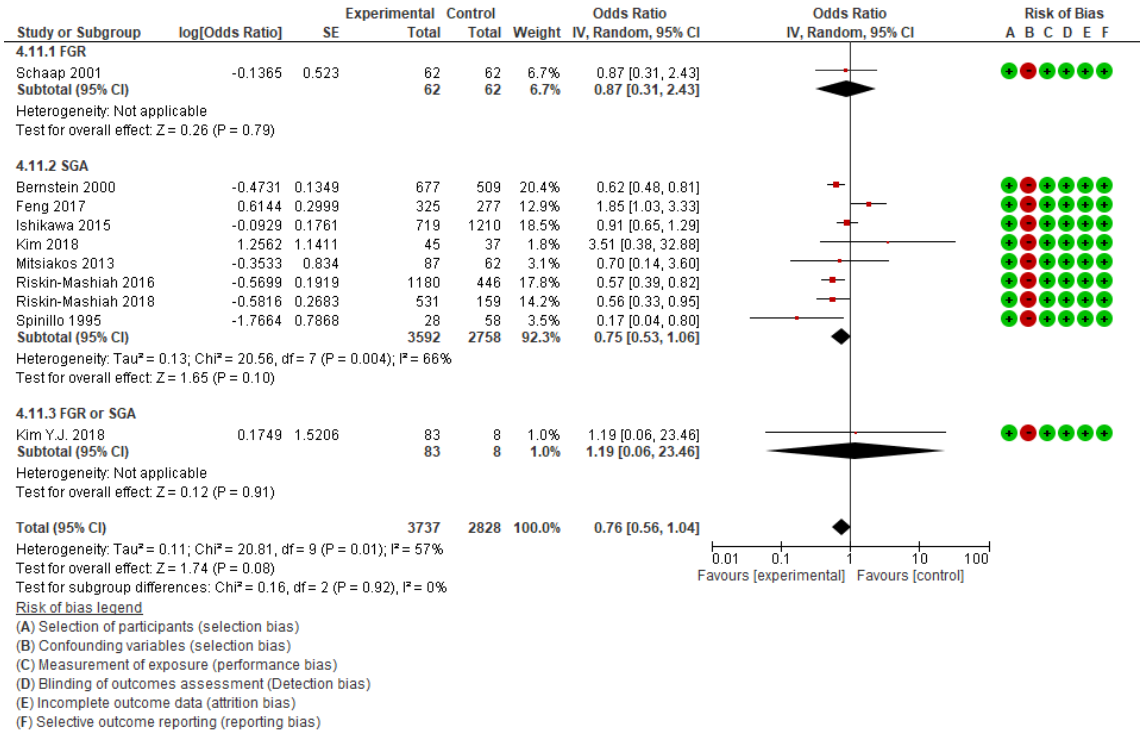
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

5) Major brain lesion (IVH, ICH, PVH, PVL)



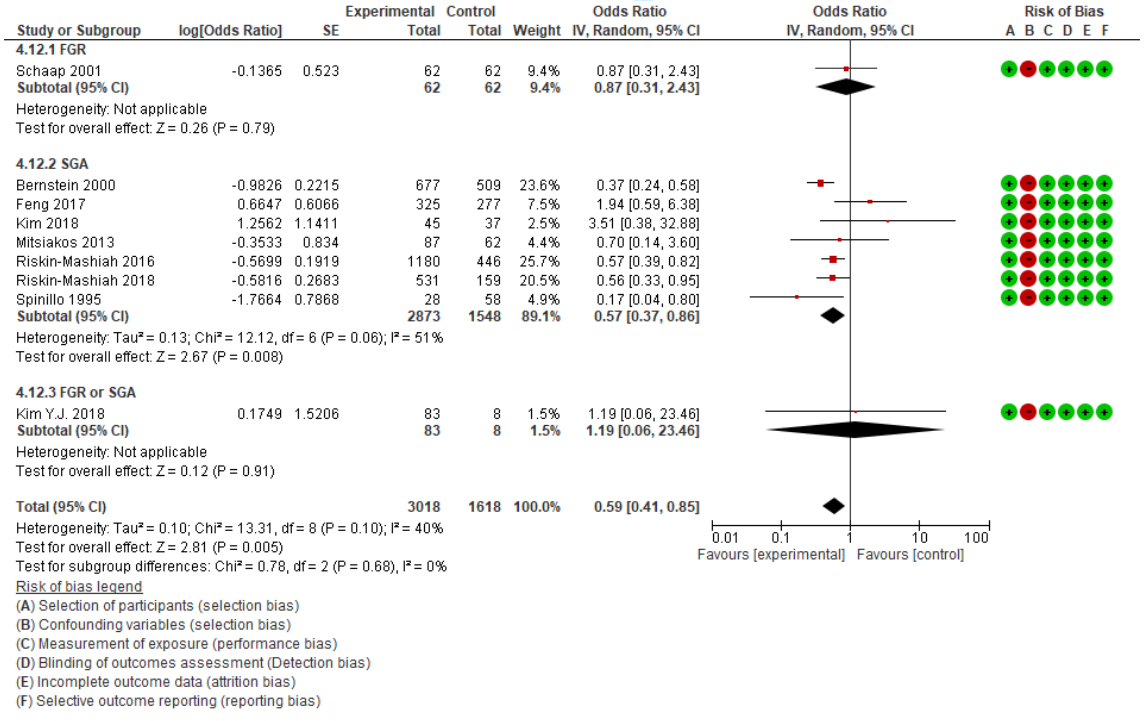
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

6) Interventricular haemorrhage



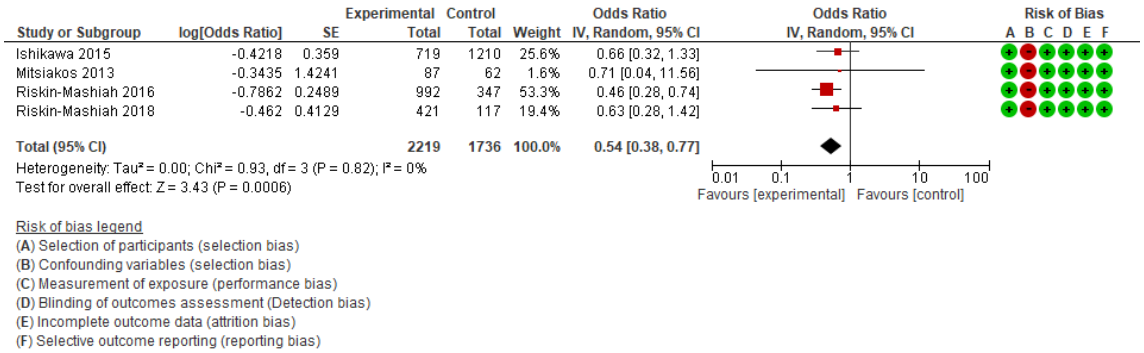
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

7) Severe interventricular haemorrhage (grade3-4)



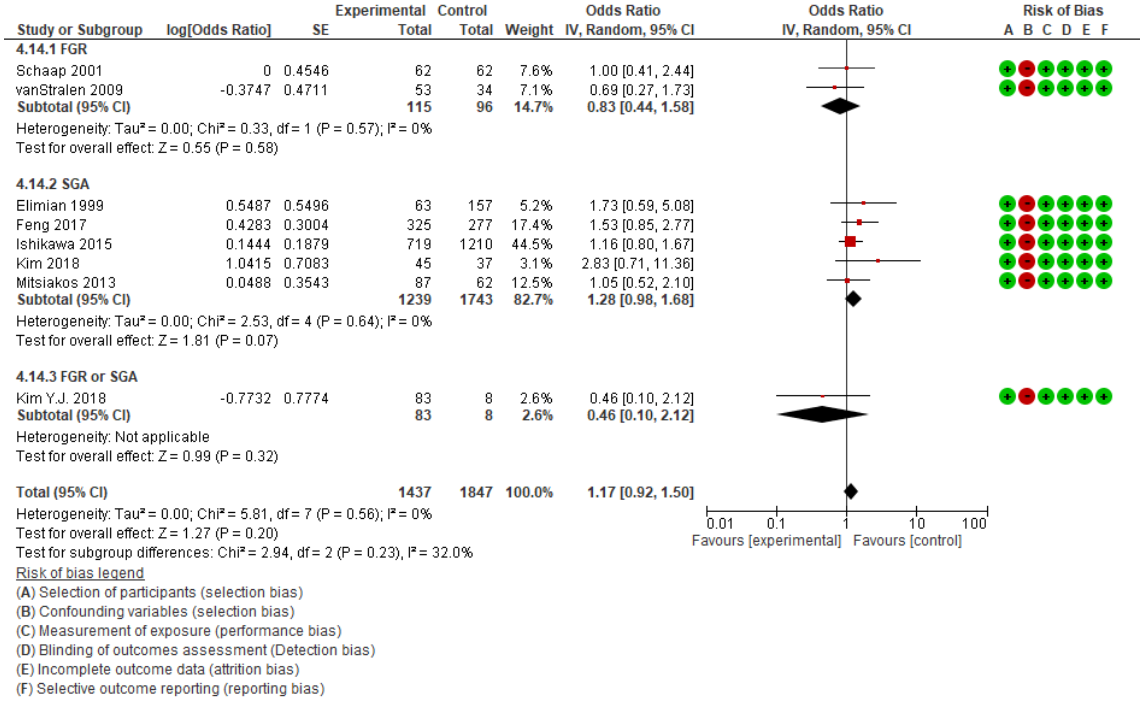
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

8) Periventricular leukomalacia (SGA)



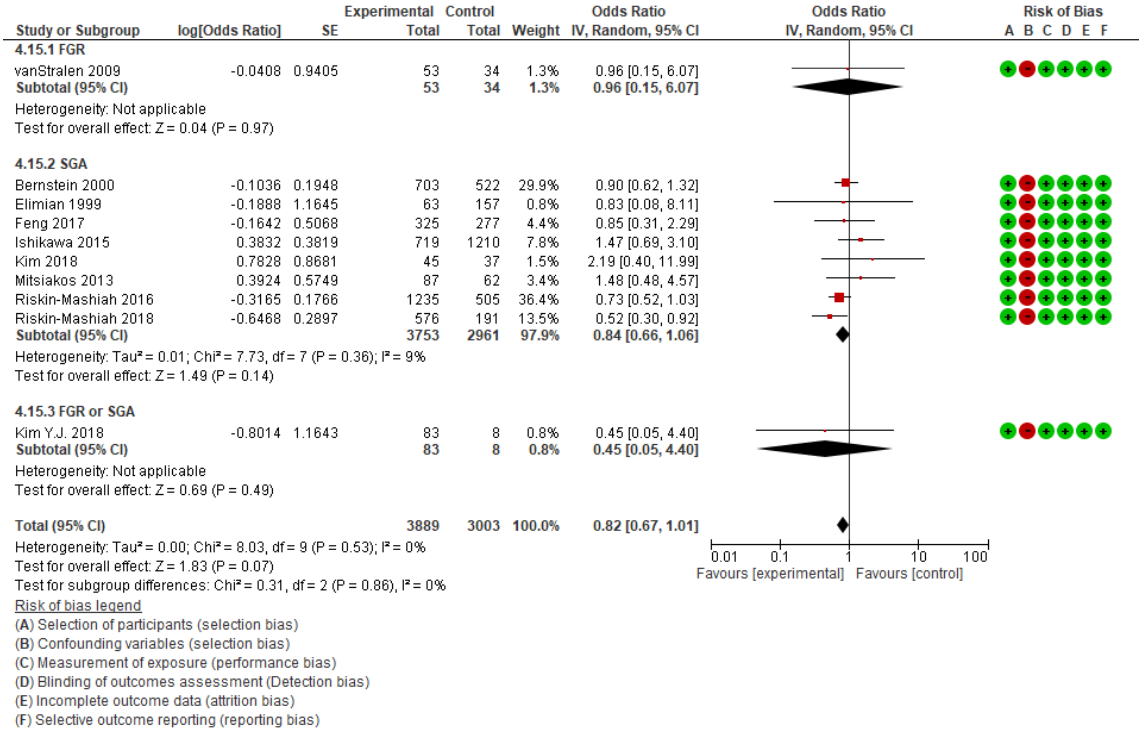
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

9) Neonatal sepsis



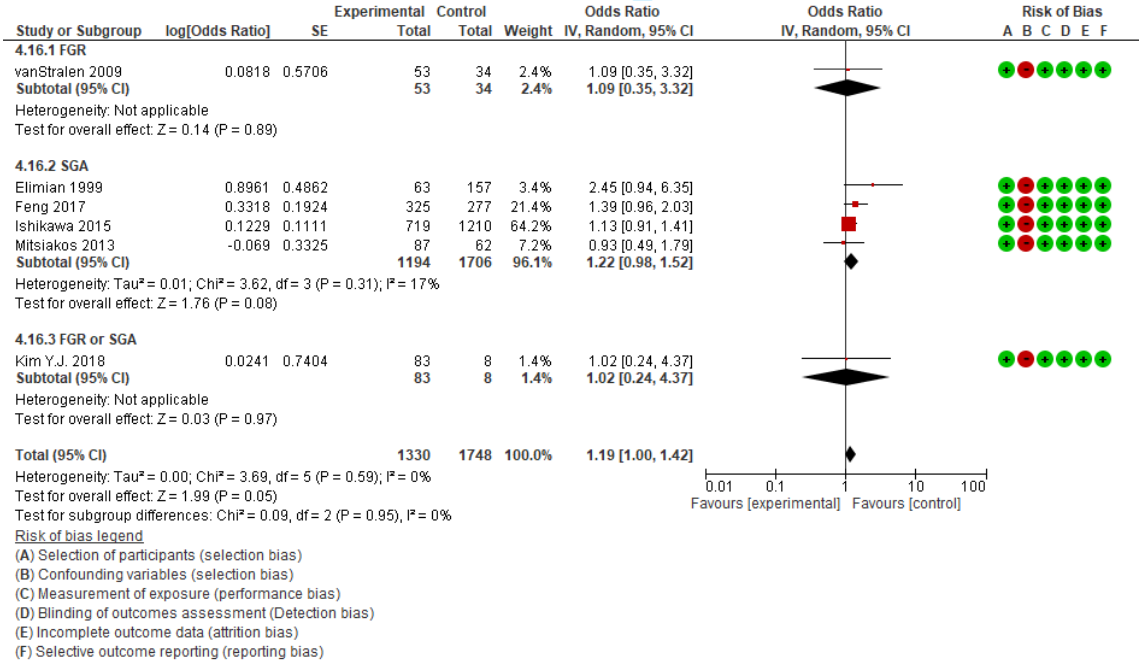
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

10) Necrotizing enterocolitis



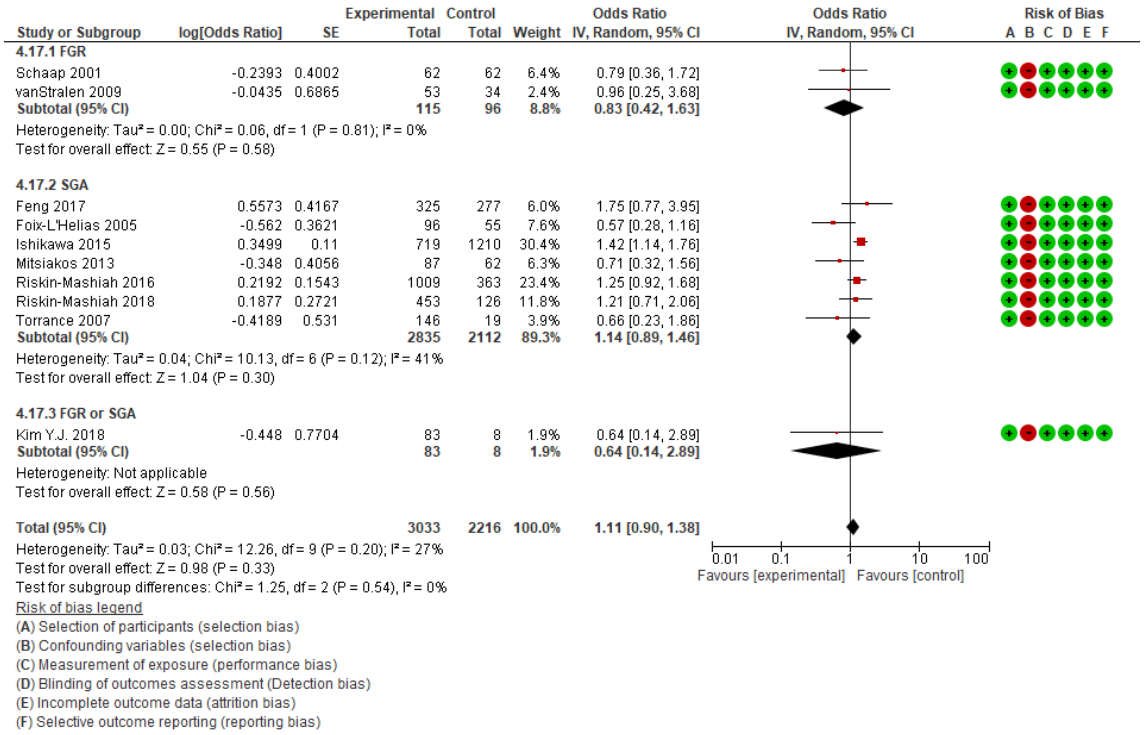
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

11) Patent ductus arteriosus



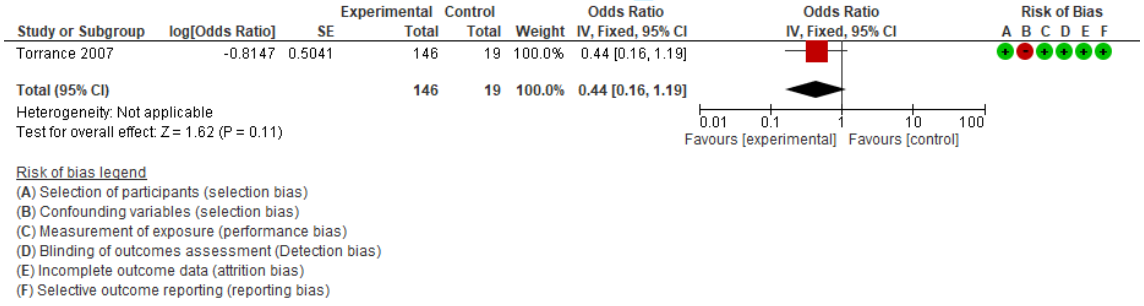
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



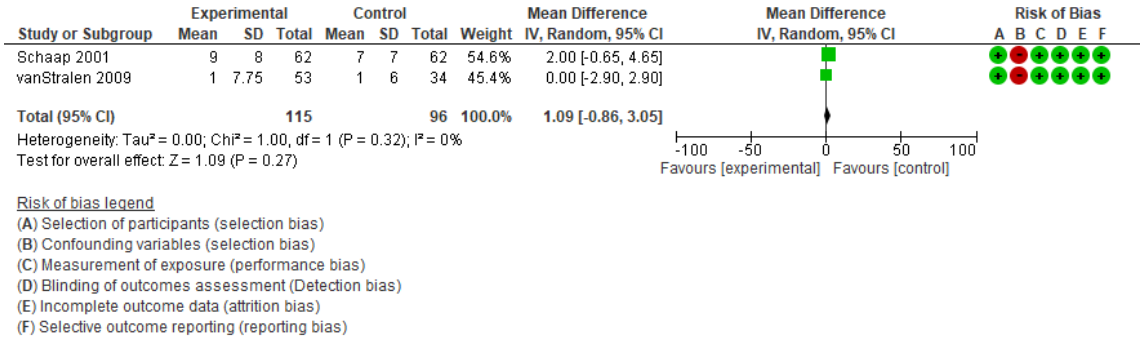
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

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



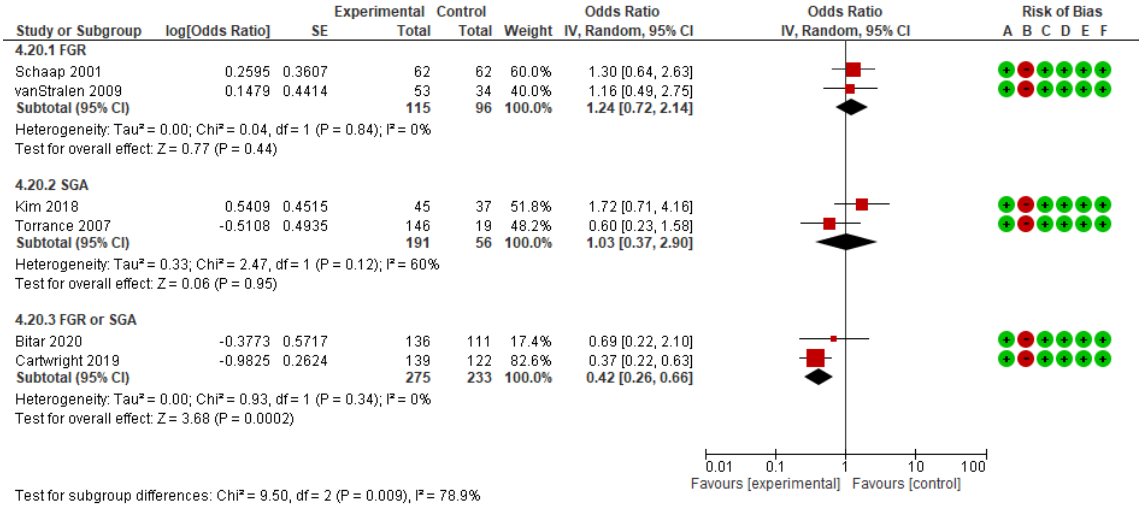
SE: Standard error; **CI:** Confidence interval

14) Duration of mechanical ventilation (FGR)



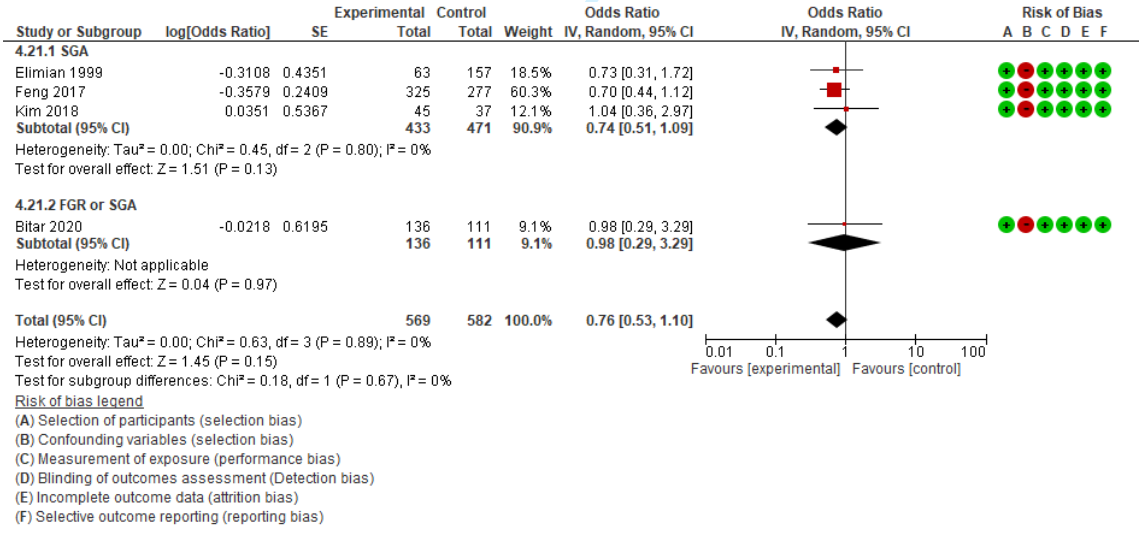
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

15) Use of mechanical ventilation



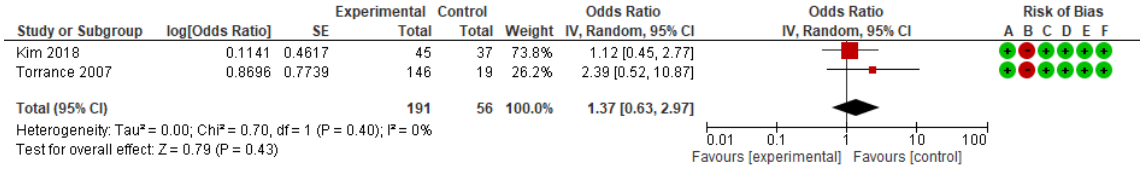
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

16) Apgar score < 7 at 5 minutes



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

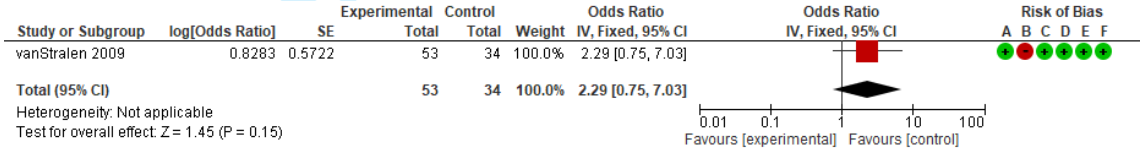
17) Apgar score < 5 at 1 minute (SGA)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

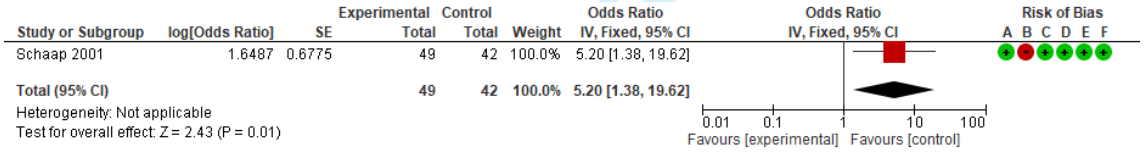
18) Hypotension (FGR)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

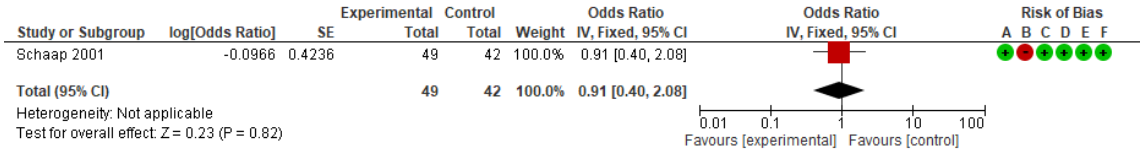
19) Growth < 10th percentile in early childhood (FGR)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

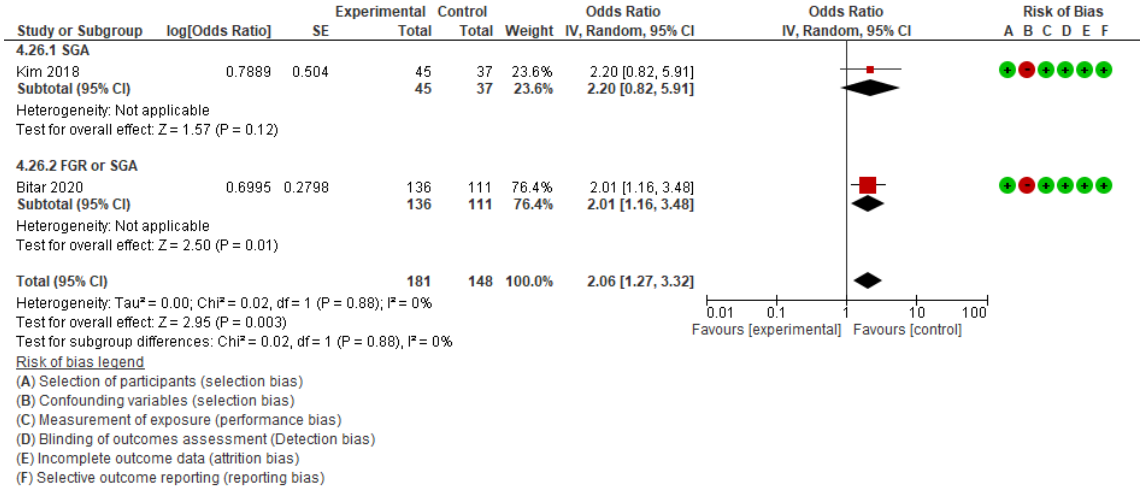
20) Abnormal behavior at long-term follow-up at school age (FGR)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

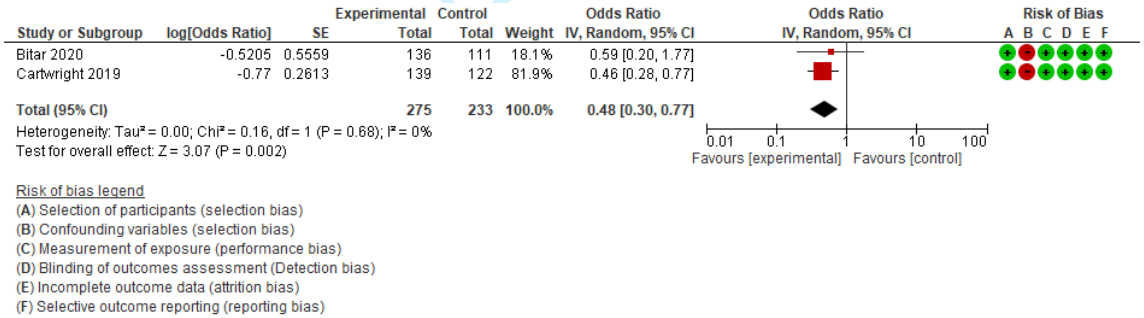
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

21) Neonatal hypoglycemia



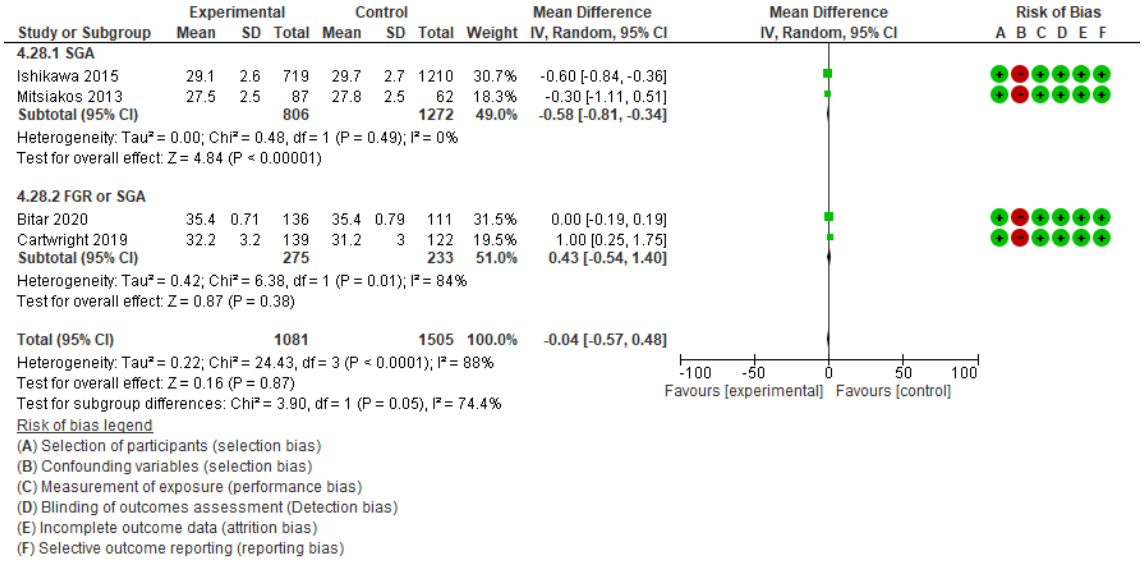
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

22) Oxygen therapy (FGR or SGA)



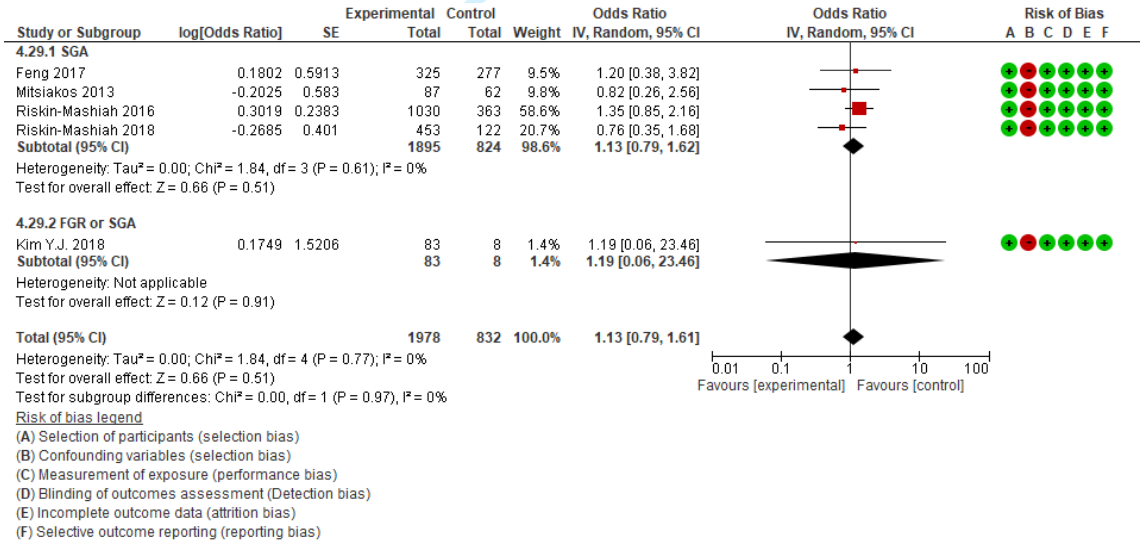
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

23) Gestational age at birth



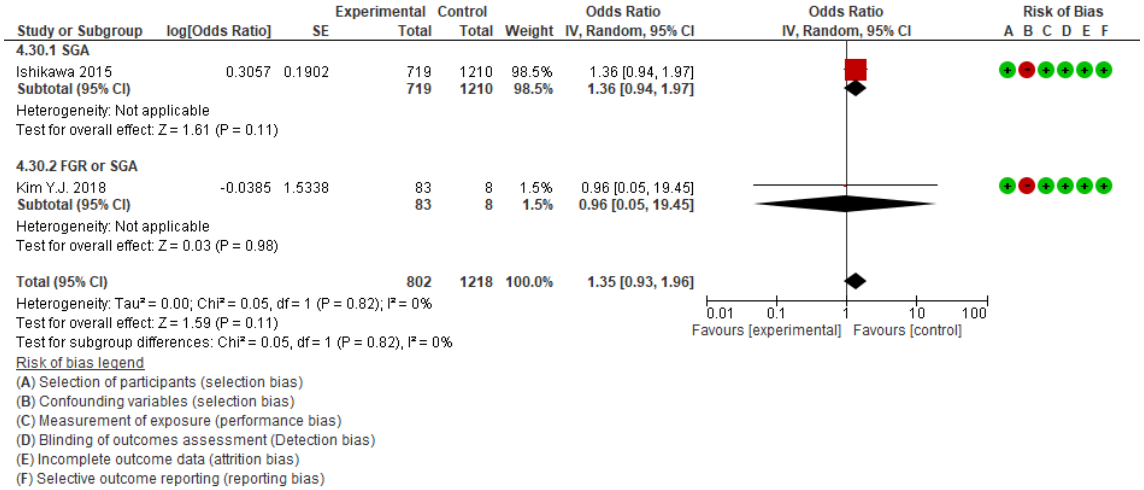
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

24) Retinopathy of prematurity



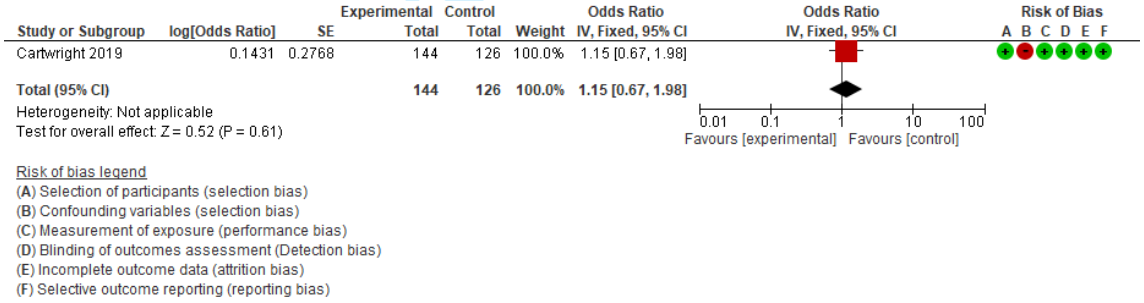
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

25) Neonatal adrenal insufficiency



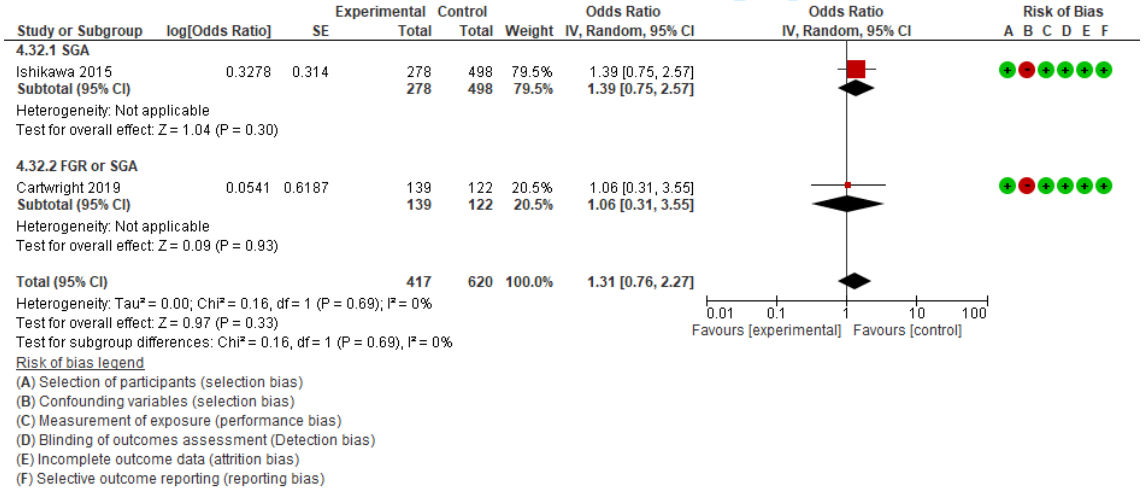
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

26) Survival free of disability (FGR or SGA)



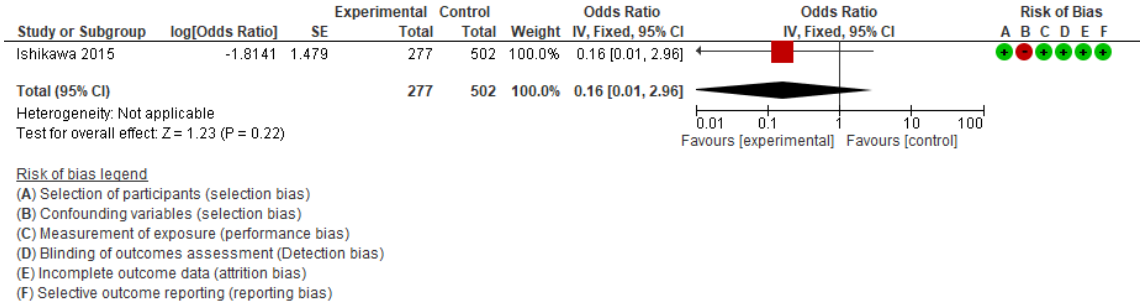
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

27) Cerebral palsy



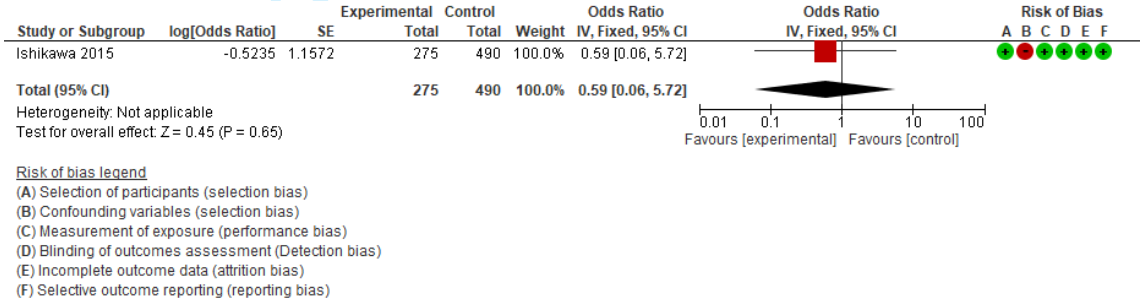
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

28) Severe hearing impairment (SGA)



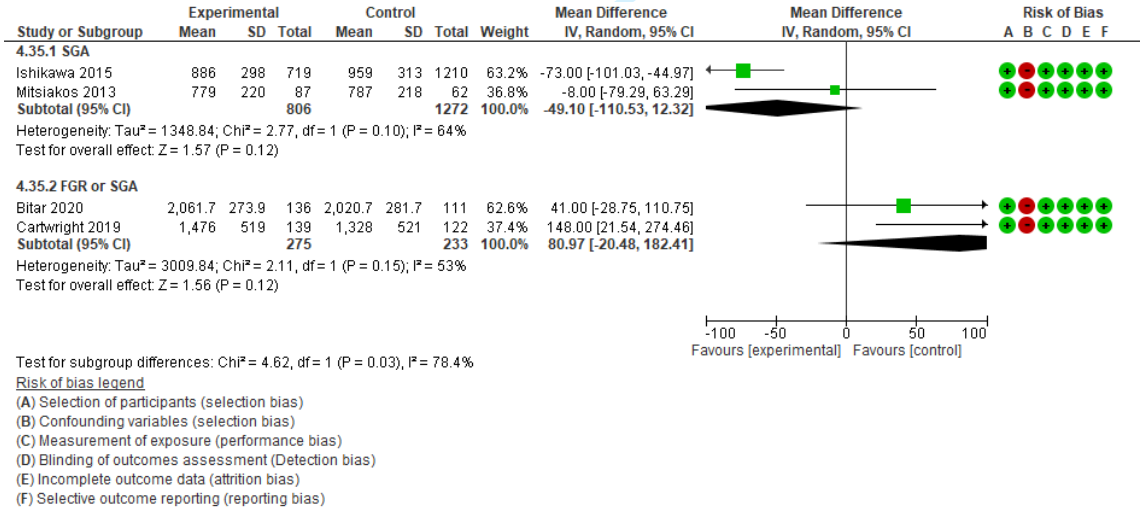
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

29) Visual impairment (SGA)



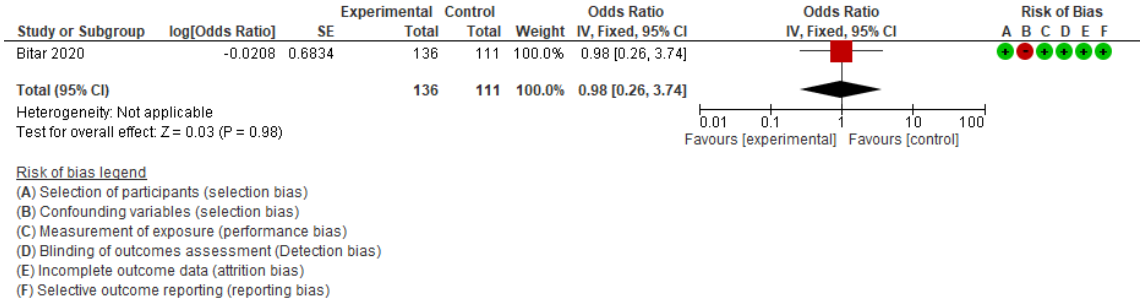
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

30) Birth weight



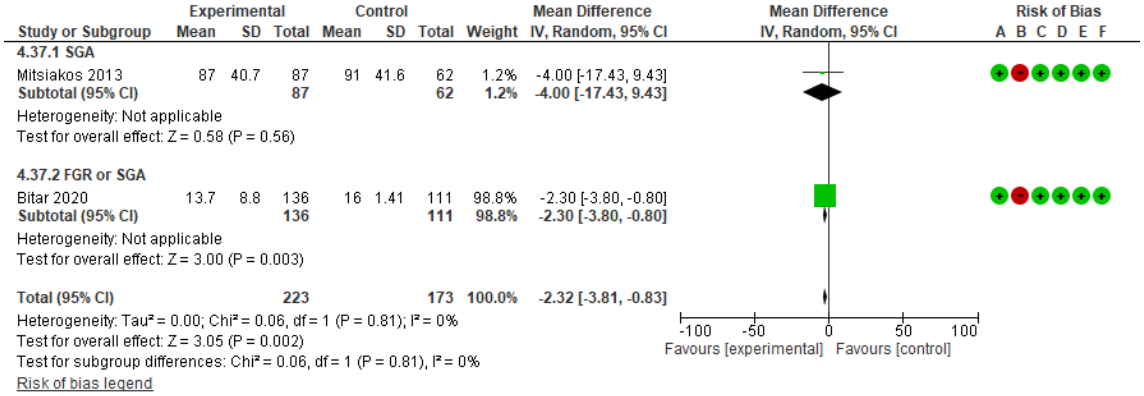
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

31) Admission to neonatal intensive care unit (FGR or SGA)



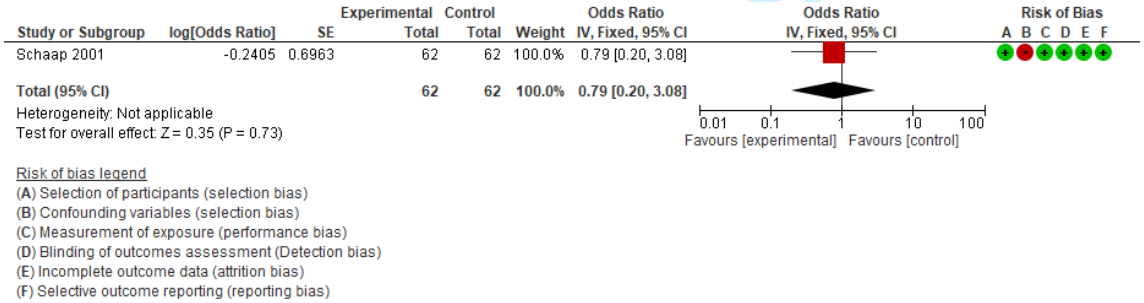
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

32) Duration of hospital stay



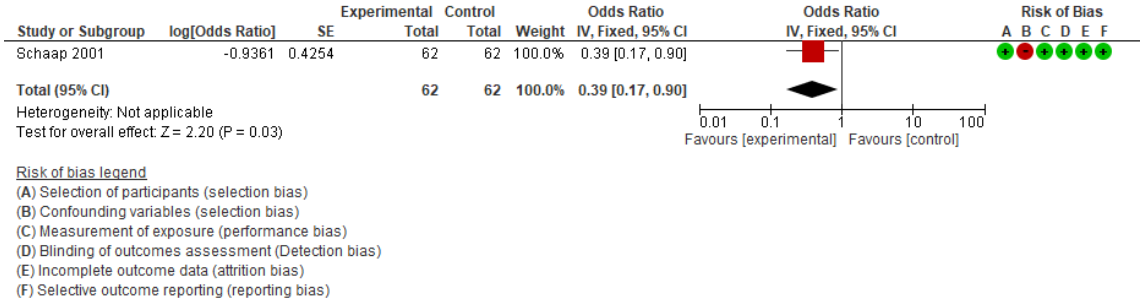
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

33) Death at long-term follow-up (school age) (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

34) Death or disability/handicap at 2yrs' corrected age (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

BMJ Open

ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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Secondary Subject Heading:	Obstetrics and gynaecology, Evidence based practice, Global health
Keywords:	OBSTETRICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, REPRODUCTIVE MEDICINE

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ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This study aimed to synthesize available evidence on the efficacy of antenatal corticosteroid (ACS) therapy among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period.

Methods: A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted for all comparative randomized or non-randomized interventional studies in the four subpopulations on June 6, 2021. Risk of Bias Assessment tool for Non-randomized Studies and the Cochrane Risk of Bias tool were used to assess the risk of bias. Grading of Recommendations, Assessment, Development, and Evaluations tool assessed the certainty of evidence.

Results: Thirty-two studies involving 5018 pregnant women and 10819 neonates were included. Data on women with diabetes were limited, and evidence on women undergoing planned CS was inconclusive. ACS use was associated with possibly reduced odds of neonatal death (pooled OR: 0.51; 95%CI: 0.31–0.85, low certainty), IVH (pooled OR: 0.41; 95%CI: 0.23–0.72, low certainty), and respiratory distress syndrome (pooled OR: 0.59; 95%CI: 0.45–0.77, low certainty) in women with chorioamnionitis. Among women with FGR, the rates of surfactant use (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate certainty), mechanical ventilation (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate certainty), and oxygen therapy (pooled OR: 0.48; 95%CI: 0.30–0.77, moderate certainty) were probably reduced; however, the rate of hypoglycemia probably increased (pooled OR: 2.06; 95%CI: 1.27–3.32, moderate certainty).

Conclusions: There is a paucity of evidence on ACS for women who have diabetes. ACS therapy may have benefits in women with chorioamnionitis and is probably beneficial in FGR. There is limited direct trial evidence on ACS efficacy in women undergoing planned CS in the late preterm period, though the totality of evidence suggests it is probably beneficial.

Protocol registration:
PROSPERO (CRD42021267816)

Strengths and limitations of this study:
-This review included a broad search strategy.
-This review applied rigorous quality assessment and GRADE methodology.
-Most included studies were observational studies.
-Definitional differences between populations and outcomes complicated the meta-analysis.
-Most studies were conducted in high-income countries.

INTRODUCTION

Previous studies have demonstrated that antenatal corticosteroids (ACS), such as intramuscular dexamethasone or betamethasone, cross the placenta and can induce fetal lung maturation [1]. When administered to women at risk of imminent preterm birth before 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly reduced [2]. ACS therapy also probably decreases the risk of intraventricular hemorrhage (IVH) and reduces the rate of developmental delay in childhood [2]. Therefore, the World Health Organization (WHO) and several obstetric and gynecological societies internationally recommend ACS therapy in women before or up to 34 weeks' gestation for improving preterm newborns' outcomes [3-6]. Some national organizations have recommended ACS use in women at risk of preterm birth up to 36 weeks' gestation based on evidence of the existence of possible respiratory-related benefits for the newborn [3,5].

However, current evidence regarding the benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis, or fetal growth restriction (FGR), is controversial. Women with diabetes, chorioamnionitis, or FGR are at a higher risk of adverse perinatal outcomes; however, they are generally excluded from ACS efficacy trials [2]. Consequently, any subgroup analysis to explore the effects of ACS on women with these complications is unlikely to yield concrete evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycemic effects, and respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor

maternal glycemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women giving birth, causing 22.6–36.9% of stillbirths [9-11]. Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided due to concerns that its immunosuppressive effects may worsen outcomes for women and their babies. However, the relative benefits and harms of using ACS in clinical settings are unclear. FGR is associated with an increased risk of morbidity and mortality [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as SGA neonates are constitutionally, rather than pathologically, small [16]. In most cases, FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant women with both FGR fetuses and SGA neonates.

Another clinical scenario where there is uncertainty is around ACS efficacy is women undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37 weeks' gestation). Babies born in the late preterm period have lower risks of mortality and morbidity than those born before 34 weeks' gestation; however, they have higher risks of adverse outcomes than those born at term [18-21]. In many countries, the rising rate of provider-initiated late preterm birth has been linked to the generalized increase in the CS rate [22]. Regardless of gestational age, babies born via elective CS do not have the usual physical and hormonal stimuli of passage through the birth canal; thus, they tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested that the risk of neonatal hypoglycemia is greater following CS; however, this may be confounded by the underlying indication for CS [26].

In 2016, members of our team published a systematic review assessing the effectiveness of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for

those undergoing elective CS in the late preterm period was found. The review could not draw firm conclusions regarding the effects of ACS on women with growth-restricted fetuses, although low-quality evidence suggested that ACS reduced neonatal IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015 ACS recommendations [28]. Now, WHO's ACS recommendations are being updated as part of the WHO's living guidelines in maternal and perinatal health [29]. Our aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians, and maternal and newborn health stakeholders on safe, effective clinical management in preterm birth.

METHODS

The specific review objectives are presented in Box 1, comprising four related questions on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are explained in Supplementary table 1. SGA infants are all neonates with birth weights below the 10th percentile. In this study, FGR fetuses were defined using the operational definition used in eligible studies (Supplementary table 1). The review protocol was registered on PROSPERO (CRD42021267816) and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary file 1, Supplementary table 2) [30].

Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a systematic review

P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes
P: Women at risk of imminent preterm birth less than 37 weeks with pregestational diabetes mellitus and/or gestational diabetes mellitus
I: ACS administration
C: Placebo or no treatment
O: World Health Organization (WHO) priority outcomes for preterm birth

P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period
P: Women undergoing elective CS in the late preterm period between 34 weeks and 0 days and 36 weeks and 6 days
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P3: Effects of ACS therapy on women with chorioamnionitis
P: Women at risk of imminent preterm birth less than 37 weeks with chorioamnionitis
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants
P: Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or small-for-gestational-age infants
I: ACS administration
C: Placebo or no treatment
O: WHO priority outcomes for preterm birth

Study eligibility criteria

Eligible studies were randomized or non-randomized primary studies that reported on the effects of ACS therapy in the four subpopulations. This included published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-after studies, interrupted-time-series studies, historically controlled studies, cohort studies, and cross-sectional studies comparing any ACS (betamethasone, dexamethasone, or hydrocortisone) administered either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational

diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis, and women with FGR fetuses or SGA infants.

Articles in any language and from any country were eligible for inclusion if they reported on one or more of WHO's priority outcomes for preterm birth guideline development [28]. Maternal outcomes were death, maternal morbidity, and therapy side effects. Newborn and child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric status, and therapy side effects (Supplementary table 3).

Data sources and search strategy

An information specialist was consulted for the development of the search strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions on June 6, 2021. Controlled vocabularies supplemented with free keywords were used to search for the relevant concept areas, with duplicates removed in the process to yield a total number of abstracts for each database (Supplementary table 4). Reference lists of the included articles, including any recent systematic reviews, were also hand-searched for further potentially relevant studies. All citations were imported into a Rayyan (http://rayyan.qcri.org) library for eligibility assessment.

Study selection, data extraction, and quality assessment

Two reviewers (KS, EN) independently assessed the titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies

were obtained and assessed in duplicate by two reviewers working independently, with disagreements resolved through discussions or by consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through discussions or by consulting a third reviewer. Extracted data were entered into the Review Manager version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [31]. We used the Cochrane Risk of Bias tool for randomized trials [32]. Potential publication bias was inspected visually using funnel plots for asymmetry in situations where data for a single outcome were available from at least ten studies.

Data synthesis and analysis

Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs) were determined for dichotomous data using the random-effects model. Crude data were used when the numbers of events were available and crude OR were employed when events were not available. We integrated crude odds ratios to mitigate confounding bias associated with varying covariates, as using adjusted odds ratios would introduce potential bias. This approach follows the methodology outlined in Yoneoka et al. (2015, 2017) [33,34]. For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for heterogeneity. For the analysis of women with FGR fetuses and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only, and

SGA or FGR). Data from the three populations were combined, and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%. Based on the evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at high risk of bias. All statistical analyses were performed using RevMan5. The threshold for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development, and Evaluation (GRADE), an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines, was used in this review.

Patients and public involvement

Since this is a systematic review of previously published data, there was no direct involvement of patients or the public.

RESULTS

Associations of ACS therapy on women with pregestational and/or gestational diabetes mellitus

The search identified 179 citations: 11 potentially eligible studies were evaluated, and three studies met the eligibility criteria, providing data on 725 pregnant women and 830 neonates (Supplementary file 2) [35-37]. All studies were conducted in high-income countries and data collection was performed between 2008 and 2017 (Supplementary table 1). One study involved women with pregestational diabetes only, one study involved women with gestational diabetes only, and one study involved women with either pregestational or gestational diabetes. All included studies were judged as having

a low risk of bias across all domains except high risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). Data were available for six outcomes (Table 1). One retrospective cohort study found that in women with gestational diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (one study, 162 infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty evidence*); however, the effect of ACS therapy on neonatal hypoglycemia was uncertain (two studies, 215 infants; pooled OR: 1.44; 95%CI: 0.702.97, *very-low-certainty evidence*) [35]. The certainty of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn.

Table 1: Maternal and neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

Neonatal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Caesarean section	2	31/65 (47.7%)	58/150 (38.7%)	1.75 (0.63–4.82)	138 more per 1,000 (from 102 fewer to 366 more)	Very Low
Neonatal death within 48 h of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09–2.20)	14 fewer per 1000 (from 23 fewer to 29 more)	Very Low
RDS	2	179/583 (30.7%)	37/193 (19.2%)	2.79 (0.85–9.08)	207 more per 1000 (from 24 fewer to4 91 more)	Very Low
Neonatal hypoglycemia	2	14/65 (21.5%)	66/150 (44.0%)	1.44 (0.70–2.97)	91 more per 1000 (from 85 fewer to 260 more)	Very Low
Apgar score < 7 at 5 min	1	1/47 (2.1%)	21/114 (18.4%)	0.79 (0.10–5.89)	33 fewer per 1000 (from 162 fewer to 387 more)	Very Low
Admission to NICU	1	19/47 (40.4%)	36/114 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome.

Associations of ACS therapy on women undergoing elective CS in the late preterm period

The search identified 211 citations:17 potentially eligible studies were evaluated, and three studies were included (Supplementary file 2) [38,39,40]. These were two observational studies and a randomized controlled trial (RCT). All studies were conducted in high-income countries between 2010 and 2017, providing data on 205 pregnant women/neonates (Supplementary table 1). The two observational studies were judged as having a high risk of bias for confounding variables (Supplementary file 3,

Supplementary table 5). Data on eleven outcomes were available but all had very low certainty; so, no meaningful conclusions could be drawn (Table 2).

Table 2: Maternal and neonatal outcomes for women undergoing elective cesarean section in the late preterm period

Maternal outcomes	**No of studies**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09–1.21)	89 fewer per 1000 (from 126 fewer to 25 more)	Very Low
Gestational diabetes mellitus	1	3/30 (10.0%)	4/10 (40.0%)	0.17 (0.03-0.95)	298 fewer per 1000 (from 380 to 12 fewer)	Very Low
Neonatal outcomes	**No of studies**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29–2.24)	17 fewer per 1000 (from 65 fewer to 95 more)	Very Low
IVH	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Necrotizing enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02–15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very Low
Neonatal hypoglycemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81–2.78)	93 more per 1000 (from 44 fewer to 246 more)	Very Low
Use of mechanical ventilation	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.30–2.12)	17 fewer per 1000 (from 64 fewer to 86 more)	Very Low
Admission to NICU	2	10/88 (11.4%)	14/117 (12.0%)	0.78 (0.23–2.72)	24 fewer per 1000 (from 89 fewer to 150 more)	Very Low
Apgar score ≤ 7 at 5 min	1	2/58 (3.4%)	0/107 (0.0%)	9.51 (0.45–201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very Low
Mean duration of mechanical ventilation	1	30	10	-	MD 0.2 lower (1.35 lower to 0.95 higher)	Very Low
Oxygen requirement for at least 4 hours	1	13/58 (22.4%)	25/107 (23.4%)	0.95 (0.44-2.03)	9 fewer per 1000 (from 115 fewer to 149 more)	Very Low

*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS: Respiratory distress syndrome

Associations of ACS therapy on women with chorioamnionitis (histological or clinical)

The search identified 418 citations: 12 potentially eligible studies were evaluated, and eight were found to be eligible (Supplementary file 2) [41-48]. Two were prospective cohort studies and six were retrospective, providing data on 1372 pregnant women and 1460 neonates (Supplementary table 1). Four studies included pregnant women with clinical chorioamnionitis, and there were variations in the diagnostic criteria (Supplementary table 1). All studies were conducted in high-income countries between 1989 and 2014. Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process [41,44-46,49]. All included studies were judged as having a low risk of bias overall except high

risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). Data for 27 outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3; Supplementary file 4). Among women with histological chorioamnionitis, ACS administration was associated with a possible reduction in the odds of neonatal death (six studies, 1193 infants; pooled OR: 0.51; 95%CI: 0.31–0.85, *low-certainty evidence*), severe intraventricular hemorrhage (IVH) (four studies, 528 infants; pooled OR: 0.41; 95%CI: 0.19–0.87, *low-certainty evidence*), IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*), RDS (six studies, 1193 infants; pooled OR: 0.59; 95%CI: 0.45–0.77, *low-certainty*). ACS might result in no difference in neonatal sepsis; however, the evidence was uncertain (six studies, 1193 infants: pooled OR: 1.03; 95%CI: 0.73–1.47, *very-low-certainty evidence*). The certainty of evidence was very low for other outcomes (Supplementary table 6). In women with clinical chorioamnionitis, only very-low-certainty evidence was available for neonatal sepsis (two studies, 150 infants, pooled OR: 0.71; 95%CI: 0.13–3.89). The certainty of evidence was very low for all other outcomes (Supplementary table 6).

Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						
Caesarean section	1	42/97 (43.3%)	2/12 (16.7%)	3.82 (0.79–18.36)	266 fewer per 1000 (from 30 fewer to 619 more)	Very Low
Gestational diabetes mellitus	1	6/97 (6.2%)	2/12 (16.7%)	0.33 (0.06-1.86)	105 fewer per 1000 (from 155 fewer to 104 more)	Very Low
Preeclampsia or eclampsia	1	5/97 (5.2%)	1/12 (8.3%)	0.60 (0.06–5.59)	32 fewer per 1000 (from 78 fewer to 254 more)	Very Low
Neonatal outcomes (histological chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	0.51 (0.31–0.85)	75 fewer per 1000 (from 109 fewer to 22 fewer)	Low
Severe IVH	4	25/414 (6.0%)	13/114 (11.4%)	0.41 (0.19–0.87)	64 fewer per 1000 (from 90 fewer to 13 fewer)	Low
IVH	5	42/502 (8.4%)	26/156 (16.7%)	0.41 (0.23–0.72)	91 fewer per 1000 (from 123 fewer to 41 fewer)	Low
RDS	6	305/677 (45.1%)	289/516 (56.0%)	0.59 (0.45-0.77)	131fewer per 1000 (from 196 fewer to 65 fewer)	Low
Sepsis	6	112/677 (16.5%)	83/516 (16.1%)	1.03 (0.73–1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very Low
Neonatal outcomes (clinical chorioamnionitis)						
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	

Neonatal death	2	14/109 (12.8%)	14/81 (17.3%)	0.71 (0.32-1.60)	44 fewer per 1000 (from 110 fewer to 78 more)	Very Low
Severe IVH	3	5/163 (3.1%)	14/155 (9/0%)	0.32 (0.03–3.19)	60 fewer per 1000 (from 87 fewer to 150 more)	Very Low
IVH	3	13/163 (8.0%)	20/155 (12.9%)	0.43 (0.07–2.44)	69 fewer per 1000 (from 119 fewer to 136 more)	Very Low
RDS	4	99/209 (47.45)	99/208 (47.6%)	0.74 (0.48-1.12)	74 fewer per 1000 (from 172 fewer to 28 more)	Very Low
Sepsis	2	26/104 (25.0%)	12/46 (26.1%)	0.71 (0.13–3.89)	60 fewer per 1000 (from 271 fewer to 318 more)	Very Low

*There was no maternal outcome in clinical chorioamnionitis.
*ACS: Antenatal corticosteroid, CI: Confidence interval, IVH: Intraventricular hemorrhage, OR: Odds ratio, RDS: Respiratory distress syndrome

Associations of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The search identified 261 citations: 36 potentially eligible studies were assessed, and 18 studies were included (Supplementary file 2) [44,50-66]. Of these, twelve studies included women with SGA infants only, four studies included women with FGR or SGA infants, and two studies included women with FGR infants only (Supplementary table 1). Among the studies that included FGR fetuses, the definitions of FGR varied widely (Supplementary table 1). Since SGA status is insufficient to determine FGR, we separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three populations were combined, and the pooled OR in total was calculated. Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 [53,56,61]. These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event. All were observational studies conducted in high-income countries. Additional unpublished data from the study by Torrance et al. (2007) were extracted from a review paper published in 2009 identified through the search strategy [56,67]. We extracted crude data from the

included studies except Ley et al. (1997) [52]. The study by Ley et al. only provided the adjusted ORs, controlled by birthweight deviation, gestational age, pre-eclampsia, premature rupture of membranes, and mode of delivery [52]. Most of these studies were judged as having a low risk of bias across all domains except high risk of bias at confounding variables (Supplementary file 3, Supplementary table 5). For SGA infants only, 12 studies provided data on 30 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the odds of pre-eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95%CI: 0.66–0.94, *low-certainty evidence*), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–0.97, *low-certainty evidence*), periventricular leukomalacia (PVL) (four studies, 3955 infants; pooled OR: 0.54; 95%CI: 0.38–0.77, *low-certainty evidence*) were possibly reduced (Table 4). Two studies involving FGR infants only provided data for 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17–0.90, *low-certainty evidence*) were possibly reduced (Table 4). Four studies involved SGA or FGR infants, providing data for 25 outcomes (Supplementary file 4, Supplementary table 6). The administration of ACS for women with SGA or FGR was associated with a possible reduction in the odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62, *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants; pooled OR: 0.42; 95%CI: 0.26–0.66, *moderate-certainty evidence*), oxygen use (two studies, 508 infants; pooled OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*) although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01;

95%CI: 1.16–3.48, *low-certainty evidence*) (Table 4). Pooled ORs involving women and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be determined for 20 outcomes (Supplementary file 4, Supplementary table 6). ACS administration for women with SGA and/or FGR was associated with a possible reduction in severe IVH (nine studies, 4636 infants; pooled OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital stay (two studies, 396 infants; MD −2.23 days; 95%CI: −3.81–−0.83, *low-certainty evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were possibly increased (Table 4).

Table 4: Maternal and neonatal outcomes for women with growth-restricted fetuses and/or small-for-gestational-age infants

Maternal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Pregnancy induced hypertension						
Total	3	195/453 (43.0%)	99/322 (30.7%)	1.47 (1.07–2.01)	87 more per 1000 (from 15 more to 164 more)	Low
SGA	2	144/370 (38.9%)	94/314 (29.9%)	1.50 (1.08–2.07)	91 more per 1000 (from 16 more to 170 more)	Low
Pre-eclampsia						
SGA	2	359/806 (44.5%)	640/1271 (50.4%)	0.78 (0.66-0.94)	62 fewer per 1000 (from 103 fewer to 15 fewer)	Low
Neonatal outcomes	**No of study**	**No of the patients**		**Effect**		**Certainty**
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Neonatal death [a)]						
SGA	8	242/1544 (15.7%)	196/1116 (17.6%)	0.68 (0.47-0.97)	49 fewer per 1000 (from 85 fewer to 4 fewer)	Low
Severe IVH						
Total	9	190/3018 (6.3%)	171/1618 (10.6%) }	0.59 (0.41-0.85)	41 fewer per 1000 (from 59 fewer to 14 fewer)	Low
Neonatal hypoglycemia						
Total	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27–3.32)	155 more per 1000 (from 47 more to 273 more)	Moderate
FGR or SGA	1	55/136 (40.4%)	28/111 (25.2%)	2.01 (1.16-3.48)	152 more per 1000 (from 29 more to 288 more)	Low
Surfactants use						
FGR or SGA	3	61/358 (17.0%)	58/241 (24.1%)	0.38 (0.23–0.62)	133 fewer per 1000 (from 173 fewer to 76 fewer)	Moderate
PVL						
SGA	4	74/2219 (3.3%)	68/1736 (3.9%)	0.54 (0.38–0.77)	18 fewer per 1000 (from 24 fewer to 9 fewer)	Low
Use of mechanical ventilation						
FGR or SGA	2	73/275 (26.5%)	94/233 (40.3%)	0.42 (0.26–0.66)	182 fewer per 1000 (from 254 fewer to 95 fewer)	Moderate
Oxygen therapy						

FGR or SGA	2	79/275 (28.7%)	94/233 (40.3%)	0.48 (0.30–0.77)	158 fewer per 1000 (from 235 fewer to 61 fewer)	Moderate
Duration of hospital stay (days)						
Total	2	223	173		MD 2.32 lower (3.81 lower to 0.83 lower)	Low
Death or disability/handicap at 2years' corrected age						
FGR	1	11/62 (17.7%)	22/62 (35.5%)	0.39 (0.17-0.90)	178 fewer per 1000 (from 269 fewer to 24 fewer)	Low

*The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in total and calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH: Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, PVL: Periventricular leukomalacia, SGA: Small for gestational age. [a)] We calculated the numerators using the adjusted OR in the study by Ley et al. (1997).

DISCUSSION

This systematic review identified 31 observational studies and a RCT on the benefits and harms of using ACS in subgroups of women with specific pregnancy complications. In women with diabetes and those undergoing elective late preterm CS, the available evidence on the effects of ACS therapy was largely very-low-certainty; thus, conclusions could not be drawn. In women with histological and clinical chorioamnionitis, ACS therapy was associated with the benefit of neonatal death, IVH and RDS reduction. In women with FGR and/or SGA babies, ACS therapy possibly has benefits regarding neonatal morbidity and mortality, as well as the reduced use of respiratory support interventions for the newborn; however, neonatal hypoglycemia might be increased.

Associations of ACS therapy on women with pregestational and/or gestational diabetes

A clinical concern regarding ACS use in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycemia, which causes avoidable harm to the neonate. For example, in women with insulin-dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid

administration [68]. A 2002 Danish study conducted on 24 pregnant women with diabetes who received steroids suggested that insulin dose adjustment may be required for up to five days after ACS administration [69]. However, in the current review, there was insufficient evidence to determine whether ACS increased neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU admission; however, the authors noted that average birthweight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding [35]. Well-designed studies are needed that describe adjustments to maternal diabetic regimens at the time of ACS therapy and from the time of ACS administration to birth and report on important newborn health outcomes.

Associations of ACS therapy on women undergoing elective CS in the late preterm period

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from seven trials recruiting women in the late preterm period [2]. This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh et

al. reported that ACS reduced the need for respiratory support and increased the risk of hypoglycemia with moderate certainty in late preterm [70]. However, no subgroup analyses were conducted on CS [70]. Hence, these findings cannot be generalized to all women undergoing CS in the late preterm period. The trial by Gyamfi-Bannerman et al. reported that ACS in the late preterm period reduced their primary outcome and severe newborn respiratory complications [40]. Their subgroup analysis showed that these beneficial effects persisted among women admitted for planned CS only [40]. Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, mechanical ventilation, or the need for extracorporeal membrane oxygenation (ECMO) [40]. Severe respiratory complications were defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death within 72 hours after delivery, or the need for ECMO [40]. Their outcomes did not adequately fit our outcomes, and the study did not provide their outcome data. Our review suggests there is insufficient evidence to draw firm conclusions on the benefits

and possible harms of ACS when used in this subpopulation. At the same time, the multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective effects from ACS for neonatal respiratory morbidity amongst women with late preterm CS [40]. An ongoing randomized trial in New Zealand will provide further information on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and 39 weeks 6 days [71].

Associations of ACS on women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to concerns that the prolongation of pregnancy and/or immunosuppression may worsen outcomes for these women and their newborns. Although ACS appears to be associated with reduced neonatal death, IVH and RDS rates in women with histological chorioamnionitis, there was insufficient evidence of other important infection-related maternal and neonatal outcomes in this review. While these conclusions are similar to those of a 2011 review by Been et al., we do not consider that the available evidence supports the routine use of ACS therapy in women with chorioamnionitis, as clinical trials comparing ACS therapy to no ACS therapy in this population and reliable evidence regarding infection-related outcomes are still lacking [49]. Significant overlap

exists between clinical and histological chorioamnionitis [72]. Histological chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis [73]. However, since physicians must decide the indications for ACS therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant women with clinical chorioamnionitis should be encouraged.

Associations of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants

The totality of the evidence identified in this review suggests that ACS therapy should be used in the fetal growth restriction setting. Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes, and no harm was reported. The current review identified more substantial evidence than that identified in our 2016 systematic review, which was unable to draw solid conclusions about the effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected fetal growth restriction [74]. The current review did not identify the benefits regarding the outcome RDS, which might be attributable to

a single retrospective cohort study in Japan in which neonates in the ACS group were delivered significantly earlier than those in the control group [59]. A sensitivity analysis in which we excluded this study suggested that RDS is significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal hypoglycemia in this subpopulation, which warrants further exploration in future research. In this meta-analysis, two studies targeted pregnant women with FGR while the other 16 included pregnant women with SGA. SGA status does not perfectly represent FGR [16]. Since physicians must decide the indication for ACS therapy when FGR is detected, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.

Strengths and limitations

The strengths of this review were its broad search strategy, which included studies published in languages other than English, rigorous quality assessments, and the use of the GRADE methodology to assess the reliability of the review's findings. Thus, we consider the risk of missing potentially eligible studies to be low, although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified, or diagnosed the subgroup

conditions and outcomes of interest. These differences might have created a bias in the review conclusions. However, we explored and reported heterogeneity for meta-analyses. This analysis extracted all data from observational studies. Since adjusted confounding variables showed a wide variety in each included study, crude data were employed in our review. No included studies adequately considered their study design to adjust the confounding bias. Therefore, confounding bias should be cautiously considered in our results' interpretation. Another limitation is that most of the included studies were conducted in high-income countries, although over 60% of all preterm births globally occur in African and South Asian countries [75]. This review did not lead to any evidence of high certainty, and one reason for this observation is that all studies were observational. In 1990, Crowley P et al. reported a structured review of ACS for preterm birth [76]. The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity [76]. In 1995, the National Institutes of Health developed a consensus on recommending ACS treatment for preterm birth [77]. In our review, only one study targeting women with chorioamnionitis and two studies targeting women with FGR started before 1990 [43,52,55]. It would be challenging to conduct the RCTs on ACS efficacy even in these special populations after the review by Crowley P et al. [76]. The latest Cochrane review on ACS treatment for preterm birth

involved a subgroup analysis in the seven special conditions [2]. However, the review did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis, and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery [70]. Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes. Our search was last conducted in June 2021 and required time for publication. Despite scrutinizing additional sources between June 2021 and February 2023, we did not find any further relevant studies.

CONCLUSION

ACS has possible benefits in the setting of FGR and/or SGA; however, direct trial evidence of its efficacy and safety for pregnant women with pregestational and/or gestational diabetes mellitus and those undergoing elective CS in the late preterm period

is still lacking. Although ACS may have some benefits in the context of histological chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with adequate follow-up for long-term child outcomes are needed to confirm the upsides and downsides of ACS use in these subpopulations.

AUTHOR CONTRIBUTIONS

Dr. Saito participated in the conceptualization and design of the study, conducted title, abstract, and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, drafted the initial manuscript, and critically reviewed the manuscript. Ms. Nishimura conducted the title abstract and full-text screening, performed data extraction, analysis, and interpretation, assessed the risk of bias, and critically reviewed the manuscript. Dr. Swa conceptualized and designed the search strategy, conducted a systematic search, and critically reviewed the manuscript for important intellectual content. Dr. Ramson assisted in the interpretation of data and the assessment of the risk of bias and critically reviewed the manuscript for important intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel designed and planned the study, assisted with developing the literature search strategy

and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the execution of the study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DATA SHARING STATEMENT

Data were obtained from the published journal article, and extracts are available from the corresponding author upon reasonable request.

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COMPETING INTERESTS

None declared.

SUPPLEMENTARY FILES

Supplementary table 1: Characteristic tables

Supplementary table 2: PRISMA 2020 Checklist

Supplementary table 3: Review outcomes

Supplementary table 4: Database-specific search terms and strategies

Supplementary table 5: Risk of bias tables

Supplementary table 6: GRADE tables

Supplementary file 1: PROSPERO

Supplementary file 2: PRISMA flow diagrams

Supplementary file 3: Risk of bias figures

Supplementary file 4: Forest plots

ETHICS APPROVAL

This study is a systematic review of published studies; thus, ethical approval was not required.

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Supplementary table 1: Chracteristic tables

Table 1: Characteristics of included studies for women with pregestational and/or gestational diabetes mellitus

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	PGDM or GDM	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Battarbee et al., 2020	Retrospective cohort	Pregnant women 510 (439, 71) Infants 615 (536, 79)	2008–2011	USA	Women giving birth at GA 23–33weeks	Stillborn, nonresuscitated cases	PGDM or GDM	NS	NS	NS	Yes
Cassimatis et al., 2020	Retrospective cohort	Pregnant women=infants 54 (18, 36)	2014–2017	USA	Women giving birth in late preterm	Congenital anomalies, multiple pregnancy	PGDM	Beta	12	24	No
Krispin et al., 2018	Retrospective cohort	Pregnant women=infants 161 (47, 114) [1)]	2012–2016	Israel	Women giving birth in late preterm period	Preterm PROM, multiple gestations, PGDM, fetal anomaly, fetal chromosomal abnormalities	GDM	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, Dex: Dexamethasone, GA: Gestational age, GDM: Gestational diabetes mellitus, NS: Not stated, PGDM: Pregestational diabetes mellitus, PROM: Premature rupture of the membranes

[1)] This study included 2262 women who gave birth in the late preterm and term period. Data were extracted and reported for women in the late-preterm delivery group (n = 161) only.

Table 2: Characteristics of included studies for women undergoing elective cesarean section in the late preterm period

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	Antenatal corticosteroid course			
							Drug	Dose (mg)	Interval (h)	Repeat ACS
de la Huerga et al., 2019	Retrospective cohort	Pregnant women=infants 40 (30, 10)	2013–2017	Spain	Women undergoing elective CS between 35 weeks 0 days and 36 weeks 6 days	Congenital anomalies, transferred to other hospitals	Beta	NS	NS	NS
Kirshenbaum et al., 2018	Case-control	Pregnant women=infants 165 (58, 107)	2011–2013	Israel	Women undergoing elective CS between GA 34 weeks 0 days and 37 weeks 0 days	Multiple pregnancy, congenital anomalies, chromosomal abnormalities, chorioamnionitis	Beta	12	24	No

Gyamfi-Bannerman et al., 2016[a)]	RCT	Pregnant women=infants 2827 (1427, 1400)	2010-2015	USA	Women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation, who were high probability of delivery in the late preterm period	Received ACS previously during the pregnancy, Expected to deliver in less than 12 hours for any reasons, Lack of gestational dating based on ultrasonography before GA 32 weeks, Lack of gestational dating based on last menstrual period before GA 24 weeks	Beta	12	24	No

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CS: Cesarean section, GA: Gestational age, NS: Not stated, RCT: Randomized controlled trial
[a)]Gyamfi-Bannerman (2016) did not provide the data on our review outcomes.

Table 3-a: Characteristics of included studies for women with chorioamnionitis (histological or clinical)

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	HC CC	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Ryu et al., 2019	Retrospective cohort	Pregnant women=infants 109 (97, 12)	2007–2014	Republic of Korea	Women giving birth between GA 23weeks 0 days and 33 weeks 6 days	Multiple gestations, congenital anomalies, SGA or LGA, transferred to other hospitals, incomplete information	HC	Beta /Dex	NS	NS	No
Ahn et al., 2012	Prospective cohort	Pregnant women no data Infants 88 (52, 36)	2005–2010	Republic of Korea	Women giving birth at GA < 34 weeks	Congenital anomalies, transferred from other hospitals	HC	Dex	5	12	No
Been et al., 2009	Prospective cohort	Pregnant women=infants HC121 (89, 32) CC93 (64,29)	2001–2003	Netherlands	Women giving birth at GA < 32 weeks	Congenital anomalies	HC CC	Beta	12	24	No
Goldernberg et al., 2006	Retrospective cohort	Pregnant women=infants HC218 (182, 36) CC93 (64, 29)	1996–2001	USA	Women giving birth between GA 23 weeks 0 days and 32 weeks 6 days	Multiple gestations	HC CC	Beta	12	24	Yes
Dempsey et al., 2005	Retrospective cohort	Pregnant women=infants 130 (88, 42)	1989–1999	USA	Women giving birth at GA < 30 weeks	Multiple gestations	HC	Beta	12	24	NS
Foix-L'Helias et al., 2005	Retrospective cohort	Pregnant women=infants 97 (45, 52)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations	CC	Beta /Dex	NS	NS	Yes
Baud et al., 2000	Retrospective cohort	Pregnant women=infants 170 (60, 110)	1993–1997	France	Women giving birth at GA < 33 weeks	Multiple gestations, severe DM	CC	Beta /Dex	NS	NS	Yes
Elimian et al., 2000	Retrospective cohort	Pregnant women=infants 527 (169, 358)	1990–1997	USA	Birth weight: 500–1750 g	CC	HC	Beta	12	24	Yes

*ACS: Antenatal corticosteroid, Beta: Betamethasone, CC: Clinical chorioamnionitis, Dex: Dexamethasone, DM: Diabetes mellitus, GA: Gestational age, HC: Histological chorioamnionitis, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

Table 3-b: Diagnostic criteria on histological and clinical chorioamnionitis from individual studies

Author, year	HC, CC	Diagnostic criteria
Ryu et al., 2019	HC	Salafia et al.*2
Ahn et al., 2012	HC	No written diagnostic criteria
Been et al., 2009	HC/ CC	HC: Redline et al. *3 CC: maternal temperature greater than 38.0℃ in the absence of another focus for infection, with two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leucocytosis (WBC>15000cells/μL), raised serum C-reactive protein, maternal tachycardia (>100 beats/min), and fetal tachycardia (>160 beats/min)
Goldernberg et al., 2006	HC/ CC	HC: Redline et al.*3, Faye-Petersen et al.*4, Bendon et al.*5 CC: diagnosed by an obstetrician, usually for a combination of fever, abdominal pain, and elevated white count
Dempsey et al., 2005	HC	HC: the presence of abundant polymorphonuclear leukocytes in the chorion and amnion
Foix-L'Helias et al., 2005	CC	CC: defined by the association of preterm labor and at least two of the following criteria: a) maternal temperature greater than 38℃, b) maternal serum C reactive protein concentration >20mg/l, c) positive bacterial culture of amniotic fluid (amniocentesis), d) documented early onset neonatal sepsis
Baud et al., 2000	CC	CC: defined by the association of preterm labor and at least two pre and/ or intrapartum criteria of maternal fever (temperature > 38℃ on at least two occasions); blood inflammatory response (C-reactive protein plasma concentration > 40 ml/L or white blood count > 18000/mm3; or bacteriological evidence of infection in amnionic fluid obtained by amniocentesis
Elimian et al., 2000	HC	HC: Salafia et al. *2

*1 HC: Histological chorioamnionitis ,CC: Clinical chorioamnionitis

*2 Salafia CM, Weigl C, Silberman L. The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. *Obstet Gynecol*. 1989;73(3 Pt 1):383-389.
*3 Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003;6(5):435-448. doi:10.1007/s10024-003-7070-y.
*4 Faye-Petersen O, Heller DS, Joshi VV. Handbook of Placental Pathology. Oxford: Taylor and Francis Medical Publishers; 2005. 142-52.
*5 Bendon RW, Faye-Petersen O, Pavlova Z, et al. Histologic features of chorioamnion membrane rupture: development of methodology. Pediatr Pathol Lab Med. 1997;17(1):27-42.

Table 4-a: Characteristics of included studies for women with growth-restricted fetuses and/or small for gestational age infants

Author, year	Study design	N (treatment, control)	Study period	Location	Inclusion criteria	Exclusion criteria	FGR SGA	Antenatal corticosteroid course			
								Drug	Dose (mg)	Interval (h)	Repeat ACS
Bitar et al., 2020	Retrospective cohort	Pregnant women=infants 247 (136, 111)	2015–2019	USA	Women giving birth between GA 34 weeks 0 days and 36 weeks 6 days	Multiple gestations, mother age ≥ 18 years	SGA or FGR	Beta	NS	NS	NS
Cartwright et al., 2019	Retrospective cohort	Pregnant women 216 (118, 98) Infants 261 (139, 122)	1998–2004	Australia New Zealand	Women giving birth at GA < 32 weeks, single, twin, and triplet pregnancy	Chorioamnionitis requiring urgent delivery, labor at the second stage, mature fetal lung development, and further steroid therapy	SGA or FGR	Beta	13.8	NS	Yes
Kim WJ et al., 2018	Retrospective cohort	Pregnant women=infants 82 (45, 37)	2009–2016	Republic of Korea	Women giving birth between GA 29 weeks 0 days and 34 weeks 6 days	Multiple gestations, still birth, major congenital abnormality, ACS administration within 24 h before births, ACS administration >7 days before birth	SGA	Dex	5	12	NS
Kim YJ et al., 2018	Retrospective cohort	Pregnant women=infants 91 (83, 8)	2007–2014	Republic of Korea	Women giving birth between GA 23 weeks 0 days and 33 weeks 6 days	Multiple gestations, major congenital abnormality, fetal hydrops, incomplete information, LGA, repeated ACS, transfer to other hospitals, SGA without fetal umbilical artery Doppler abnormalities	FGR or SGA	Beta/ Dex	NS	24/ 12	No
Riskin-Mashiah et al., 2018	Retrospective cohort	Pregnant women=infants 784 (585,199)	1995–2012	Israel	Women giving birth to twins between GA 24 weeks 0 days and 31 weeks 6 days	Congenital anomalies	SGA	NS	NS	NS	NS
Feng et al., 2017	Retrospective cohort	Pregnant women No data Infants 602 (325, 277)	2013–2014	China	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days	Major congenital abnormality, inherited metabolic disease	SGA	Beta/ Dex	12/ 5–6	24/ 12	No
Riskin-Mashiah et al., 2016	Retrospective cohort	Pregnant women=infants 1771 (1246, 525)	1995–2012	Israel	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital malformation, incomplete data	SGA	NS	NS	NS	NS
Ishikawa et al., 2015	Retrospective cohort	Pregnant women=infants 1929 (719, 1210)	2003–2007	Japan	Birth weight < 1500 g	Multiple gestations, Women giving birth ≥34 weeks, major congenital malformation, incomplete information, out-of-hospital birth	SGA	NS	NS	NS	NS
Mitsiakos et al., 2013	Retrospective cohort	Pregnant women=infants 149 (87, 62)	NS	Canada	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	Multiple gestations, congenital anomalies	SGA	Beta	12	24	No

van Stralen et al, 2009	Retrospective cohort	Pregnant women=infants 88 (54,34)	2001–2005	Netherlands	Birth weight < 1500 g	Multiple gestations, major congenital malformation or infection, incomplete information	FGR	Beta	11.4	24	NS
Torrance et al., 2007	Retrospective cohort	Pregnant women 165 (146, 19) FGR140 (112,28), SGA165 (146, 19)	1999–2003	Netherlands	Women giving birth at GA < 34 weeks	Congenital, chromosomal or syndromic abnormalities	SGA	Beta	12	24	NS
Foix-L'Helias et al, 2005	Retrospective cohort	Pregnant women No data Infants 151 (96,55)	1993–1996	France	Women giving birth between GA 24 weeks 0 days and 31 weeks 6 days	NS	SGA	NS	NS	NS	NS
Schaap et al, 2001	Case-control	Pregnant women=infants 124 (62,62)	1984–1991	Netherlands	Women giving birth between GA 26 weeks 0 days and 31 weeks 6 days	ACS < 24 h before delivery, fetal death or fetal distress at admission to the hospital, abruptio placentae, lethal congenital abnormalities or infections, multiple gestations	FGR	Beta	12.5	24	NS
Bernstein et al, 2000 *1	Retrospective cohort	Pregnant women=infants 1258 (703,555)	1991–1996	USA, Canada	Women giving birth between GA 25 weeks 0 days and 30 weeks 6 days, white and African-American infants	Multiple gestations, major anomalies	SGA	NS	NS	NS	NS
Elimian et al, 1999	Retrospective cohort	Pregnant women No data Infants 220 (63,157)	1990–1997	USA	Birth weight ≤ 1750 g	NS	SGA	Beta	12	24	Yes
Ley et al, 1997	Retrospective cohort	Pregnant women No data Infants 234 (117, 117)	1984–1985	Sweden	Women giving birth at GA < 33 weeks	NS	SGA	NS	NS	NS	NS
Spinillo et al, 1995	Prospective cohort	Pregnant women No data Infants 96 (32,64)	1988–1993	Italy	Women giving birth between GA 24 weeks 0 days and 34 weeks 6 days, indetermined or immature lecithin/sphingomyelin ratio, planned delivery with medication complications, liveborn	Congenital anomalies	SGA	Beta/Dex	12/ 12	NS	NS
Lenardo et al, 1990	Retrospective cohort	Pregnant women=infants 72 (15,57)	NS	Italy	Women giving birth at GA ≤ 35 weeks	Twin gestations	SGA	Beta	12	24	NS

*ACS: Antenatal corticosteroid, Beta: Betamethasone, Dex: Dexamethasone, FGR: Fetal growth restriction, GA: Gestational age, LGA: Large for gestational age, SGA: Small for gestational age, NS: Not stated

*1: The data was obtained through personal communication.

Table 4-b: Diagnostic criteria on fetal growth restriction (FGR) from individual studies

Author, year	Diagnostic criteria on FGR
Bitar et al., 2020	Identified by International Classification of Diseases, Tenth Revision (ICD-10) codes..
Cartwright et al., 2019	Defined a priori as one or more of the following: obstetric diagnosis of FGR at trial entry; cesarean delivery for FGR; or customized birth weight of no greater than the third centile (GROW, version 6.7.8.3; Perinatal Institute).
Kim YJ et al., 2018	Defined as any fetal growth restriction (estimated fetal weight <10th percentile) documented from serial maternal medical records or a birth weight of less than the 10th percebtile based on the growth curve of Olsen et al. [*1]with absent or reverse umbilical artery end-diastolic flow in the fetal Doppler studies.
van Stralen et al, 2009	Defined id at least one measurement of the U/C ratio was higher than 0.725.[*2] U:umbilical artery, C:middle cerebaral artery
Schaap et al, 2001	Diagnosed by fundal height measurement and by sonographic fetal biometry. The FGR was due to placental dysfunction, as confirmed by pathological examination of placenta.

*1 Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010;125(2):e214-e224. doi:10.1542/peds.2009-0913

*2 Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol. 1993;169(1):169-175. doi:10.1016/0002-9378(93)90156-d

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplementary table 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4, 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7,8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6,7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6,7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8,9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8,9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8,9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8,9
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7,8

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8,9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9-15
Study characteristics	17	Cite each included study and present its characteristics.	Page 9-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9-15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 9-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 9-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 9-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16-21
	23b	Discuss any limitations of the evidence included in the review.	Page 21-23
	23c	Discuss any limitations of the review processes used.	Page 21-23
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23, 24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 25
Competing interests	26	Declare any competing interests of review authors.	Page 25
Availability of	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from	Page 25

Supplementary table 2: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
data, code and other materials		included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

Supplementary table 2: PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary table 3: Review outcomes

Table 1-a. Review outcomes

Maternal outcomes	Neonatal outcomes
Preeclampsia or eclampsia	Neonatal death
Preeclampsia	Neonatal death within 48 h after birth
Hypertensive disorders	Death before discharge home
Pregnancy induced hypertension (PIH)	Apgar score ≤ 7 at 5 min after birth
Chorioamnionitis	Apgar score < 7 at 5 min after birth
Gestational diabetes mellitus	Apgar score < 5 at 1 min after birth
	Respiratory distress syndrome (RDS)
	Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD)
	Pneumonia
	Use of mechanical ventilation
	Surfactant use
	Oxygen therapy
	Oxygen requirement for at least 4 h
	Mean duration of mechanical ventilations
	Duration of oxygen use
	Patent ductus arteriosus (PDA)
	Hypotension within 7 postnatal days
	Hypotension
	Intraventricular hemorrhage (IVH)
	Severe IVH

Periventricular leukomalacia (PVL)
Major brain lesion damage
Necrotizing enterocolitis (NEC)
Sepsis
Early onset sepsis
Systemic inflammatory response syndrome
Meningitis
Neonatal hypoglycemia
Neonatal adrenal insufficiency
Intrahepatic cholestasis
Retinopathy of prematurity (ROP)
Gestational age at birth
Birth weight
Neonatal intensive care unit (NICU) admission
Duration of hospital stay
Survival free from disability
Death at long-term follow up
Death or disability/handicap at 2 years
Cerebral palsy
Severe hearing impairment
Visual impairment

	Discharge with respiratory support
	Growth < 10%ile in early childhood
	Abnormal behavior at long-term follow up at school-age

Table 1-b. Outcome definition

Maternal outcomes	Definition
Preeclampsia or eclampsia	**P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].
Preeclampsia	**P4** Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Cartwright et al. (2019): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a systolic Blood pressure(BP) >160mmHg and a diastolic BP ≧ 90mmHg measured at least twice and proteinuria ≧0.3g/24g.
Hypertensive disorders	**P2** Kirshembaum et al. (2018): No data.
Pregnancy induced hypertension (PIH)	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as any maternal diagnoses of preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Feng et al. (2017): No data.
Chorioamnionitis	**P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): No data. Elimian et al. (1999): No data.
Gestational diabetes mellitus	**P2** de la Hueruga et al. (2019): No data. **P3** Ryu et al. (2019): Listed in the online supplementary Table1[*1].

	P4 Bitar et al. (2020): Identified by the medication administration record, ICD-10 coded, and chart review. Kim et al. (2018): No data. Kim YJ et al. (2018):No data. Ishikawa et al. (2015): No data.
Neonatal outcomes	**Definition**
Neonatal death	Deaths during the first 28 completed days of life.*[2]
Neonatal death within 48h after birth	**P1** Battarbee et al. (2020): Death within 48h after birth.
Death before discharge home	**P3** Foix-L'Helias et al. (2005): Death before discharge home. **P4** Riskin-Mashiah et al. (2016): Death before discharge home. Ishikawa et al. (2015): Death before discharge home. Foix-L'Helias et al. (2005): Death before discharge home. Schaap et al. (2001): Death before discharge home. Bernstein et al. (2000): Death before discharge home.
Apgar score ≤7 at 5 min after birth	**P2** Kishenbaum et al. (2018): Apgar score ≤7 at 5 min after birth.
Apgar score <7 at 5min after birth	**P1** Krispin et al. (2018): Apgar score <7 at 5 min after birth. **P3** Elimian et al. (2000): Apgar score <7 at 5 min after birth. **P4** Bitar et al. (2020): Apgar score <7 at 5 min after birth. Kim et al. (2018): Apgar score <7 at 5min after birth. Feng et al. (2017): Apgar score <7 at 5min after birth. Elimian et al. (1999): Apgar score <7 at 5min after birth.
Apgar score <5 at 1min after birth	**P4** Kim et al. (2018): Apgar score <5 at 1min after birth. Torrance et al. (2007): Apgar score <5 at 1min after birth.
Respiratory distress syndrome (RDS)	**P1** Battarbee et al. (2020): Defined as a clinical diagnosis of respiratory distress syndrome, hyaline

membrane disease, or respiratory insufficiency requiring oxygen therapy with FiO2 ≧0.40 started within the first 24 hours after birth and continued for ≧24 hours or until neonatal demise.

Krispin et al. (2018): No data.

P2

de la Huerga Lopez et al. (2019): Defined ad the presence of clinical signs of respiratory distress with oxygen requirement and chest X-ray with reticulonodular infiltrate.

Kishenbaum et al. (2018): Defined as early respiratory distress that comprised cyanosis, grunting, retraction and tachypnea combined with ground glass appearance and air bronchogram on chest X-ray.

P3

Ryu et al. (2019): Defined if the chest radiographic findings were consistent with RDS together with an oxygen requirement of >0.4 for the fraction of inspired oxygen.

Ahn et al. (2012): Diagnosed in infants with respiratory distress, an increased oxygen requirement and a radiological finding consistent with RDS.

Been et al. (2009): Diagnosed in a clinical presentation (expiratory grunting, sub- or intercostal or sternal retractions, nasal flaring, tachypnea, cyanosis in room air with or without apnea) and characteristic radiographic appearance according to Giedion et al. [*3]

Goldenberg et al. (2006): Defined as the documentation of any of three criteria: (1) oxygen requirement at 6 through 24 hours of life; (2) an abnormal chest radiograph consistent with RDS within the first 24 hours of life; and (3) need for surfactant.

Dempsey et al. (2005): Defined from a combination of three of the following: clinical signs, oxygen need greater than 30% from 12 to 72 hours, need for assisted ventilation (continuous positive airway pressure or mechanical ventilation), and typical chest X-ray appearance.

Foix-L'Helias et al. (2005): No data.

Baud et al. (2000): Diagnosed if any two criteria were present in the first 24 hours of life: clinical symptoms (respiratory failure requiring assisted ventilation and administration of exogenous surfactant), typical radiological feature, and biological evidence of lung immaturity (fetal lung maturity test on tracheal aspirates).

Elimian et al. (2018): Diagnosed clinically by need for mechanical ventilation and oxygen for at least 48 hours, and radiologic chest findings.

P4

Kim et al. (2018): No data.

Riskin-Mashiah et al. (2018): No data.

Riskin-Mashiah et al. (2016): Diagnosed by a chest radiography consistent with RDS together with supplementary oxygen or mechanical ventilation therapy.

Feng et al. (2017): No data.

Ishikawa et al. (2015): Diagnosed based on the clinical and radiographic finings.

Mitsiakos et al. (2013): Diagnosed based on clinical and radiological criteria and oxygen requirements

	≧30%. van Stralen et al. (2009): Based on radiological criteria (poor lung expansion) and clinical criterial (need for supplemental oxygen, sternal retraction, intercostal and subcostal recession, grunting and tachypnea). Torrance et al. (2007): Defined as clinical signs of RDS with oxygen requirement and typical findings on a chest X-ray. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as tachypnea, chest wall retractions, and oxygen requirement in the presence of a chest X-ray classified as RDS. Bernstein et al. (2000): Required both a PaO2 <50mmHg in room air plus central cyanosis in room air or a requirement for supplemental oxygen to maintain a PaO2 >50mmHg. Elimian et al. (1999): Diagnosed clinically and by the need for mechanical ventilation and oxygen for a least 48 hors and the presence of radiologic chest findings. Ley et al. (1997): No data. Spinillo et al. (1995): Diagnosed with physical signs of respiratory distress (grunting, chest retraction, tachypnea) and required ventilatory support for >48hr and radiologic chest findings. Di Lenardo et al. (1990): Based on the basis of radiological indications and worsening of the symptoms from a clinical point of view.
Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Based on National Institute of Child and Human Development criteria.[*4] Been et al. (2009): Diagnosed with a dependency on oxygen supplementation at a postmenstrual age of 36 weeks. Goldenberg et al. (2006): Defined as infant oxygen requirement at 28 days or oxygen requirement at 36 weeks of life. Foix-L'Helias et al. (2005): No data. **P4** Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): No data. Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed according to the criteria of Bancalari et al.[*5] including clinical and radiologic features. Together with the requirement for oxygen supplementation at 36 weeks post menstrual age. Ishikawa et al. (2015): Defined when an infant continued to receive supplemental oxygen on the 28th day after birth and at the 36th week based on postmenstrual age. Mitsiakos et al. (2013): Based on oxygen supplementation at 36 weeks postmenstrual age. van Stralen et al. (2009): No data.

	Torrance et al. (2007): Defined as the need for extra oxygen on day 28 of life with chronic abnormalities on a chest X-ray and symptoms of respiratory distress. Foix-L'Helias et al. (2005): No data. Schaap et al. (2001): Defined as the presence of chronic respiratory distress and oxygen requirement beyond 28 days of life accompanied by a chest radiograph that showed persistent streaks of increased density in both lungs interspersed with normal hyperlucent areas.
Pneumonia	**P3** Dempsey et al. (2005): Defined by a combination of X-ray changes, endotracheal tube aspirates, and positive inflammatory markers.
Use of mechanical ventilation	**P3** Been et al. (2009): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim et al. (2018): Mechanical ventilation within 48 hours after birth. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Schaap et al. (2001): No data.
Surfactant use	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Been et al. (2009): No data. Elimian et al. (2000): No data. **P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data. Kim YJ et al. (2018):Defined as the administration of any prophylactic or rescue surfactant. van Stralen et al. (2009): No data. Torrance et al. (2007): No data. Elimian et al. (1999): No data.
Oxygen therapy	**P4** Bitar et al. (2020): No data. Cartwright et al. (2019): No data.
Oxygen requirement for at least 4 h	**P2** Kishenbaum et al. (2018): Oxygen requirement for at least 4 hours.

Mean duration of mechanical ventilations	**P2** de la Huerga Lopez et al. (2019): No data. **P3** Ahn et al. (2012): No data.
Duration of oxygen use	**P3** Ahn et al. (2012): No data.
Patent ductus arteriosus (PDA)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Diagnosed by echocardiography and medical treatment or surgical ligation were performed when necessary. Been et al. (20009): Persistence of the open ductus arteriosus postnatally, as demonstrated by ultrasonographic examination. Elimian et al. (2000): Required medical or surgical intervention. **P4** Kim YJ et al. (2018): No data. Feng et al. (2019): No data. Ishikawa et al. (2015): Diagnosed based on both echocardiographic findings and clinical evidence of a volume overload due toa left-to-right shunt. Mitsiakos et al. (2013): No data. van Stralen et al. (2009): No data. Elimian et al. (1999): No data.
Hypotension within 7 postnatal days	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1]
Hypotension	**P4** van Stralen et al. (2009): Defined as a mean arterial pressure ≤30mmHg requiring treatment with volume expanders and/or inotropic support.
Intraventricular hemorrhage (IVH)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): Defined as grade ≧3 and listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined according to the IVH grading by Papile et al.[*6] Been et al. (2009): Defined according to Volpe. [*7] Goldenberg et al. (2006): Defined as grade 3 or 4 by ultrasound criteria.[*7] Dempsey (2005): Graded according to the Papile classification [*6] Baud et al. (2000): Defined as grade 3 or 4 of Papile classification. [*6]

	P4 Kim et al. (2018): Defined as grade 3 or 4. Kim YJ et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Ishikawa et al. (2015): Defined as Papile grade 1 or more. Schaap et al. (2001): Defined as grade 3 or 4. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Severe IVH	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined as grade 3 or 4 of Papile classification. *6 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): No data. Baud et al. (2000): No data. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): No data. Riskin-Mashiah et al. (2018): Defined as grade 3 or 4 of Papile classification. *6 Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Diagnosed by ultrasound examination and graded according to Papile et al. *6 Mitsiakos et al. (2013): Defined as grade 3 or 4. Schaap et al. (2001): No data. Bernstein et al. (2000): Diagnosed according to the criteria by Papile. *6 Spinillo et al. (1995): Defined as grade 3 or 4 of Papile classification. *6
Periventricular leukomalacia (PVL)	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1 Ahn et al. (2012): Defined according to Volpe. *7 Been et al. (2009): Defined according to Volpe. *7 Goldenberg et al. (2006): Defined according to Volpe. *7 Baud et al. (2000): Diagnosed on cerebral ultrasound scan.

	P4 Riskin-Mashiah et al. (2018): No data. Riskin-Mashiah et al. (2016): Diagnosed by the presence of multiple periventricular cysts identified by cranial ultrasound examination after 28 days of life. Ishikawa et al. (2015): Based on either head ultrasound or cranial MRI scan performed at 2 weeks of age or later. Mitsiakos et al. (2013): No data.
Major brain lesion damage	**P4** van Stralen et al. (2009): Defined as the presence of a least one of the following findings: IVH ≧grade3 or ventricular dilatation or cystic PVL. Schaap et al. (2001): No data. Elimian et al. (1999): Defined as IVH grade 3 and 4, IVH with PVL, and PVL. Ley et al. (1997): Defined ad IVH grade 3, IVH grade 4, or PVL. Spinillo et al. (1995): No data.
Necrotizing enterocolitis (NEC)	**P2** Kishenbaum et al. (2018): No data. **P3** Ryu et al. (2019): NEC stage ≧2b. [*8] Been et al. (2009): Defined as stage 2 or higher according to Bell et al.[*8] Goldenberg et al. (2006): Defined as stage 2 or higher. Dempsey et al. (2005): Classified as the presence of intramural gas on X-ray, perforation or evidence of intestinal necrosis at surgery or autopsy. Elimian et al. (2000): Diagnosed clinically and radiologically, and confirmed by surgery or autopsy. **P4** Kim et al. (2018): No data. Kim YJ et al. (2018): Defined as stage 2b or higher according to Bell et al.[*8] Riskin-Mashiah et al. (2018): Defined as stage 2 or higher according to Bell et al.[*8] Feng et al. (2017): No data. Riskin-Mashiah et al. (2016): Presence of clinical and radiologic features according to the criteria of Bell et al. [*8] Ishikawa et al. (2015): Defined as stage 2 or higher according to Bell et al.[*8] Mitsiakos et al. (2013): No data. Bernstein et al. (2010): No data. van Stralen et al. (2009): Defined as stage 2 or higher. Elimian et al. (1999): Diagnosed clinically and radiologically and confirmed at surgery or autopsy.

Sepsis	**P3** Ryu et al. (2019): Defined as culture proven sepsis. The presence of clinical symptoms, and signs with proven causative organisms documented from blood cultures. Ahn et al. (2012): Defined as a positive blood culture. Been et al. (2009): Clinical sepsis or culture-proven sepsis. Clinical sepsis was clinical presentation of sepsis with raised CRP. Culture-proven sepsis was any systemic bacterial infection documented by a positive blood or cerebrospinal fluid culture. Goldenberg et al. (2006): No data. Dempsey et al. (2005): Defined as a positive blood culture. Elimian et al. (2000): Defined as positive blood or cerebrospinal fluid cultures. **P4** Kim et al. (2018): Included both suspected infections (with clinical findings suggesting infection) and proven infections. Kim YJ et al. (2018): Defined as the presence of clinical symptoms and signs with proven causative organisms documented from blood cultures. Feng et al. (2017): No data. Ishikawa et al. (2015): No data. Mitsiakos et al. (2013): Defined as a positive blood culture and the need for intravenous antibiotics for minimum of 7 days. van Stralen (2009): Based on the need for intravenous antibiotics administration for more than 7 days. Schaap et al. (2001): Defined as neonatal septicemia or meningitis confirmed by positive cultures. Elimian et al. (1999): Defined as positive blood or cerebrospinal fluid cultures.
Early onset sepsis	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.[*1] Ahn et al. (2012): Defined as a positive blood culture occurring within the first 72 hours. Been et al. (2009): Neonatal sepsis occurring during the first 72 hours of life. Dempsey et al. (2005): Defined as a positive blood culture in the first 72 hours.
Systemic inflammatory response syndrome	**P3** Goldenberg et al. (2006): Defined as clinically suspected sepsis with negative cerebrospinal fluid and blood cultures or a band: band + polymorphonuclear cell ratio of 0.15 or greater.
Meningitis	**P3** Dempsey et al. (2005): Defined as a positive cerebrospinal fluid culture.
Neonatal hypoglycemia	**P1** Cassimatis et al. (2020): Defined as Blood sugar <40mg/dL within 4 hours of birth. Krispin et al. (2018): No data.

	P2 De la Huerga Lopez et al. (2019): No data. Kishenbaum et al. (2018): Defined as glucose level ≤45 mg/dl. **P4** Bitar et al. (2020): Defined as glucose level <40 mg/dl. Kim et al. (2018): Defined as glucose level <40 mg/dl.
Neonatal adrenal insufficiency	**P4** Kim YJ et al. (2018): Defined as the requirement of hydrocortisone treatment. Ishikawa et al. (2015): No data.
Intrahepatic cholestasis	**P3** Ahn et al. (2012): Defined when conjugated bilirubin exceed 2.0mg/dl.
Retinopathy of prematurity (ROP)	**P3** Ryu et al. (2019): Defined as requiring treatment. **P4** Kim YJ et al. (2018): Defined as requiring treatment. Riskin-Mashiah et al. (2018): No data. Feng et al (2017): No data. Riskin-Mashiah et al. (2016): Defined as grade 3-4 in international standard classification.[*9] Mitsiakos et al. (2013): No data.
Gestational age at birth	**P4** Bitar et al. (2020): Defined as gestational age birth. Cartwright et al. (2019): Defined as gestational age at birth. Ishikawa et al. (2015): Defined as gestational age at birth. Mitsiakos et al. (2013): Defined as gestational age birth.
Birth weight	**P4** Bitar et al. (2020): Defined as birth weight. Cartwright et al. (2019): Defined as birth weight. Ishikawa et al. (2015): Defined as birth weight. Mitsiakos et al. (2013): Defined as birth weight.
Neonatal intensive care unit (NICU) admission	**P1** Krispin et al. (2018): Defined as NICU admission. **P2** de la Huerga Lopez et al. (2019): Defined as NICU admission. Kishenbaum et al. (2018): Defined as NICU admission.

	P4 Bitar et al. (2020): Defined as NICU admission.
Duration of hospital stay	**P4** Bitar et al. (2020): No data. Mitsiakos et al. (2013): No data.
Survival free from disability	**P4** Cartwright et al. (2019): No data
Death at long-term follow up	**P4** Schaap et al. (2001): No data.
Death or disability/handicap at 2 years	**P4** Schaap et al. (2001): No data.
Cerebral palsy	**P4** Ishikawa et al. (2015): Defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Cartwright et al. (2019): Defined as a nonprogressive loss of motor function with disordered muscle tone or tendon reflexes.
Severe hearing impairment	**P4** Ishikawa et al. (2015): Defined as the need for hearing aids.
Visual impairment	**P4** Ishikawa et al. (2015): Defined as unilateral or bilateral blindness diagnosed by an ophthalmologist.
Discharge with respiratory support	**P3** Ryu et al. (2019): Listed in the online supplementary Table1.*1
Growth<10%ile in early childhood	**P4** Schaap et al. (2001): Defined by using standard deviation to adjust for discrepancies in age and sex at school age.*10
Abnormal behavior at long-term follow up at school-age	**P4** Schaap et al. (2001): Defined by the DuPaul-score. *11

*1. www.karger.com/doi/10.1159/000502650.
*2. Neonatal mortality rate (0 to 27 days) per 1000 live births) (SDG 3.2.2) (who.int).
*3. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol*. 1973;1(3):145-152. doi:10.1007/BF00974058.
*4. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-1729. doi:10.1164/ajrccm.163.7.2011060.
*5. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95(5 Pt 2):819-823. doi:10.1016/s0022-3476(79)80442-4.
*6. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-534. doi:10.1016/s0022-3476(78)80282-0.

*7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
*8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7. doi:10.1097/00000658-197801000-00001.
*9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol. 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
*10. Frederiks AM, Nederlandes groeidoagrammen 1997 in historisch persepectief. In: Wit JM, ed. De Vierde Landelijke Groeistidie 1997. Presentatie nieuwe groepidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
*11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.

Supplementary table 4: Database-specific search terms and strategies

MEDLINE (via Ovid) 2021/6/6

#	Searches	Annotations
1	exp *Adrenal Cortex Hormones/ad, tu	
2	exp *Adrenal Cortex Hormones/ and (ci or de or dt).fs.	
3	exp Adrenal Cortex Hormones/ae, po, to	
4	or/1-3	
5	exp Pregnancy/	
6	exp Pregnancy Outcome/	
7	Fetal Death/	
8	Maternal Death/	
9	Obstetric Labor Complications/	
10	exp Obstetric Labor, Premature/	
11	Pregnancy, Prolonged/	
12	Fetus/	
13	exp Infant, Newborn/	
14	Prenatal Care/	
15	exp Fetal Development/	
16	exp Birth Weight/	
17	Prenatal Exposure Delayed Effects/	
18	or/5-17	
19	4 and 18	
20	limit 19 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactivetutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
21	limit 20 to meta analysis	
22	20 not 21	
23	19 not 22	
24	limit 23 to humans	
25	("*corticosteroid" or "*corticoid").mp.	
26	(pregnan* or labor or labour or gestation* or delivery* or preterm* or fetus or fetal or baby or babies or newborn* or neonat* or antenat* or prenat* or birth*).mp.	
27	25 and 26	
28	MEDLINE.st.	
29	27 not 28	
30	(biograph* or case report* or comment or congress* or conference* or editor* or tutorial* or interview* or lecture* or news* or handout* or guideline* or (review* not (meta analys* or metaanalys*))).mp.	

31	29 not 30	
32	exp Diabetes Mellitus/	
33	exp Hyperglycemia/	
34	or/32-33	
35	34 and 18	
36	exp Diabetes, Gestational/	
37	Pregnancy in Diabetics/	
38	or/36-37	
39	or/5-17	
40	38 and 39	
41	or/35,40	
42	4 and 41	
43	limit 42 to (biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or editorial or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or news or newspaper article or overall or patient education handout or practice guideline or "review" or "scientific integrity review" or systematic reviews)	
44	limit 43 to meta analysis	
45	43 not 44	
46	42 not 45	
47	limit 46 to humans	
48	diabet*.mp.	
49	31 and 48	
50	or/47,49	
51	remove duplicates from 50	
52	exp epidemiologic study/	
53	(trial* or comparative or meta analysis or metaanalysis or multicenter or observational or randomized or randomised or rct or cct or cohort or cross sectional or longitudinal or evaluation or prospective or retrospective or control*).mp.	
54	or/52-53	
55	51 and 54	P1-1
56	51 not 55	P1-2
57	exp Cesarean Section/	
58	(cesarean or cesarian or caesarean or caesarian).mp.	
59	or/57-58	
60	or/24,31	
61	60 and 59	
62	remove duplicates from 61	
63	62 and 54	P2-1
64	62 not 63	P2-2
65	exp "Bacterial Infections and Mycoses"/	
66	Pregnancy Complications, Infectious/	

67	or/65-66	
68	24 and 67	
69	(infect* or chorioamnionitis).mp.	
70	31 and 69	
71	or/68,70	
72	remove duplicates from 71	
73	72 and 54	P3-1
74	72 not 73	P3-2
75	exp *Fetal Development/	
76	(growth adj3 restrict*).mp.	
77	or/75-76	
78	24 and 77	
79	((fetal or fetus or baby or babies or restricted) adj3 (development or growth or maturity or weight)).mp.	
80	31 and 79	
81	or/78,80	
82	remove duplicates from 81	
83	82 and 54	P4-1
84	82 not 83	P4-2

Embase (via embase.com) 2021/6/6

set	query	Annotations
#1	'corticosteroid'/exp/mj/dd_do,dd_cm,dd_dt,dd_ad,dd_to,dd_ct,dd_it	
#2	'corticosteroid'/exp/dd_ae	
#3	#1 OR #2	
#4	#3 AND 'human'/de	
#5	#4 AND [embase]/lim NOT [medline]/lim	
#6	'parameters concerning the fetus, newborn and pregnancy'/exp	
#7	'fetus death'/exp	
#8	'labor complication'/exp	
#9	'prolonged pregnancy'/de	
#10	'fetus'/de	
#11	'newborn'/de	
#12	'prenatal care'/exp	
#13	'prenatal development'/exp	
#14	'prenatal exposure'/de	
#15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	
#16	#5 AND #15	
#17	'editorial'/de OR 'erratum'/exp OR 'note'/de OR 'review'/de	
#18	'meta analysis'/exp	
#19	#17 NOT #18	
#20	#16 NOT #19	
#21	'case report'/exp	
#22	#20 NOT #21	

#23	'diabetes mellitus'/exp	
#24	'hyperglycemia'/de	
#25	#23 OR #24	
#26	#22 AND #25	P1
#27	'cesarean section'/de	
#28	#22 AND #27	P2
#29	'infection'/exp	
#30	'chorioamnionitis'/de	
#31	#29 OR #30	
#32	#22 AND #31	P3
#33	'prenatal development'/exp/mj	
#34	#22 AND #33	P4

Cochrane Library (via Wiley) 2021/6/8

ID	Search	Annotations
#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	
#2	*corticosteroid* or *corticoid*	
#3	#1 or #2	
#4	MeSH descriptor: [Pregnancy] explode all trees	
#5	pregnan* or labor or labour	
#6	MeSH descriptor: [Pregnancy Outcome] explode all trees	
#7	stillbirth or livebirth	
#8	MeSH descriptor: [Fetal Death] explode all trees	
#9	MeSH descriptor: [Maternal Death] explode all trees	
#10	MeSH descriptor: [Obstetric Labor, Premature] explode all trees	
#11	MeSH descriptor: [Pregnancy, Prolonged] explode all trees	
#12	MeSH descriptor: [Obstetric Labor Complications] this term only	
#13	MeSH descriptor: [Fetus] this term only	
#14	fetus or fetal	
#15	MeSH descriptor: [Infant, Newborn] explode all trees	
#16	infant* or newborn* or neonate* or baby or babies	
#17	MeSH descriptor: [Prenatal Care] explode all trees	
#18	prenatal or antenatal or perinatal	
#19	MeSH descriptor: [Fetal Development] explode all trees	
#20	matur* or immatur* or prematur*	
#21	MeSH descriptor: [Birth Weight] explode all trees	
#22	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees	
#23	gestation* or birth* or offspring	
#24	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	
#25	#3 and #24	
#26	MeSH descriptor: [Diabetes Mellitus] explode all trees	P1
#27	diabet* or dm	

#28	MeSH descriptor: [Hyperglycemia] explode all trees	
#29	hyperglycem*	
#30	MeSH descriptor: [Diabetes, Gestational] explode all trees	
#31	MeSH descriptor: [Pregnancy in Diabetics] explode all trees	
#32	#26 or #27 or #28 or #29 or #30 or #31	
#33	#25 and #32	
#34	handsrch	
#35	#33 and #34	P1
#36	MeSH descriptor: [Cesarean Section] explode all trees	
#37	cesarean or cesarian or caesarean or caesarian	
#38	#36 or #37	
#39	#25 and #38	
#40	#39 and #34	P2
#41	MeSH descriptor: [Bacterial Infections and Mycoses] explode all trees	
#42	infect*	
#43	MeSH descriptor: [Pregnancy Complications, Infectious] explode all trees	
#44	chorioamnionitis	
#45	#41 or #42 or #43 or #44	
#46	#25 and #45	
#47	#46 and #34	P3
#48	growth near restrict*	
#49	#25 and #48	
#50	#49 and #34	P4

CINAHL (via EBSCOhost) 2021/6/6

ID#	Search Terms	Search Options	Annotations
S1	(MM "Adrenal Cortex Hormones+/AD/DE/TU")		
S2	(MH "Adrenal Cortex Hormones+/AE")		
S3	S1 or S2		
S4	(MH "Pregnancy+")		
S5	(MH "Expectant Mothers")		
S6	(MH "Pregnancy Outcomes")		
S7	(MH "Perinatal Death")		
S8	(MH "Maternal Mortality")		
S9	(MH "Labor Complications+")		
S10	(MH "Labor, Premature")		
S11	(MH "Pregnancy, Prolonged")		
S12	(MH "Fetus+")		
S13	(MH "Infant, Newborn+")		
S14	(MH "Prenatal Care")		
S15	(MH "Fetal Development+")		
S16	(MH "Birth Weight")		

S17	(MH "Prenatal Exposure Delayed Effects")		
S18	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17		
S19	S3 and S18		
S20	S19	Limiters - Human	
S21	S20	Limiters - Research Article; Exclude MEDLINE records	
S22	(MH "Metabolic Diseases") OR (MH "Diabetes Mellitus+")		
S23	(MH "Hyperglycemia")		
S24	(MH "Pregnancy in Diabetes+")		
S25	S22 or S23 or S24		
S26	S21 and S25		P1
S27	(MH "Cesarean Section+")		
S28	S21 and S27		P2
S29	(MH "Bacterial and Fungal Diseases+")		
S30	S21 and S29		P3
S31	(MM "Fetal Development+")		
S32	restrict* N3 (growth or development or matur*)		
S33	S31 or S32		
S34	S21 and S33		P4

WHO Global Index Medicus (via WHO-GIM site) 2021/6/8

	Search Terms	Annotations
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (diaebet* OR DM OR hyperglycem*)	P1
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (elective caesarean)	P2
	cortico AND (labor OR labour OR prematur* OR immatur* OR matur*) AND (infect*)	P3
	cortico AND restrict* AND growth	P4

Web of Science Core Collection (via Web of Science) 2021/6/8

Set	Searches	Annotations
# 1	CITED AUTHOR: (amiya r*) AND CITED YEAR: (2016)	Cited Reference Search

Supplementary table 5: Risk of bias

Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cassimatis 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants from three institutions had PGDM (type 1 or type 2) with singleton pregnancies and delivered in late preterm between April 2014 and May 2017.	**High** -Study design No consideration -Analysis No consideration	**Low** Data obtained from an obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements	**Low** No missing data	**Low** All predefined outcomes reported	-
Krispin 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single, university-affiliated, tertiary medical center had GDM and delivered after 34 weeks of gestation between 2012 and 2016.	**High** -Study design No consideration -Analysis The following potential confounders were adjusted: primiparity, birth weight, gestational age at delivery, gravidity, parity, hypertensive disorders, and body mass index.	**Low** Data obtained from a comprehensive computerized perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Battarbee 2020 (Retrospective cohort study)	N/A	N/A	**Low** A cohort study included 115,502 participants from 25 hospitals in the United States between March 2008 and February 2011. To avoid overrepresentation of participants from larger hospitals, up to one-third of participants had spent days at hospitals with annual delivery volumes from 2,000 to 7,000 and up to one-sixth had spent days in hospitals with annual deliveries > 7,000.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** Eleven sets of missing data (11 women and 12 neonates) were excluded from the data for steroids, but the proportion of missing data was very small (less than 1%).	**Low** All predefined outcomes reported	-

N/A: Not Applicable; **PGDM:** Pregestational diabetes mellitus; **GDM:** gestational diabetes mellitus; **ACS:** Antenatal corticosteroid

*Krispin (2018) and Battarbee (2020) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

Risk of bias assessments for studies of antenatal corticosteroids in women undergoing elective cesarean section in the late preterm period

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kirshenbaum 2018 (Case-control study)	N/A	N/A	**Low** All participants, from a single tertiary medical center, delivered by elective cesarean section at 34 + 0–37 + 0 weeks of gestation between January 2011 and December 2013.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
de la Huerga López 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported	-

N/A: Not Applicable

Cochrane Risk of Bias tool

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Gyamfi-Bannerman 2016 (Randomized controlled trial)	**Low** The randomization sequence was developed using the simple urn method.	**Low** The randomization sequences were generated by an independent data coordinating center using the simple urn method.	**Low** Neither the participants nor the investigators were informed of the study group assignments.	**Low** All outcome reviewers were unaware of study-group assignments.	**Low** Only two participants in each of the two groups were lost to follow-up.	**Low** The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes have been reported.	**Low** No other bias is found.

Risk of bias assessments for studies of antenatal corticosteroids in women with chorioamnionitis (histological or clinical)

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Ahn 2012 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at Ewha Women's University between 2005 and 2010.	**High** -Study design No consideration -Analysis Multiple logistic regression model was used but controlled only by gestational age.	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All expected outcomes reported	-
Been 2009 (Prospective cohort study)	N/A	N/A	**Low** All participants admitted/born at the Erasmus University Medical Center-Sophia Children's Hospital between May 2001 and February 2003.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from direct measurements and clinical assessments	**Low** No statement to indicate blinding, but unlikely to affect outcome. Measurements . .	**Low** No missing data	**Low** All expected outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Goldenberg 2006 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution during the same period (December 5, 1996–June 13, 2001).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements .	**Low** No missing data	**Low** All expected outcomes were reported	-
Dempsey 2005 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1989 and January 1999.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records (obstetrical and neonatal database and pathology database, cross-referenced with data from pathology database and from maternal and neonatal chart review).	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All expected outcomes were reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from different institutions between 1993 and 1996.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential the underestimation.
Baud 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted to Antoine Beclere University Hospital between 1993 and 1997.	**High** -Study design No consideration -Analysis Multiple logistic regression model was used, controlled for causes of delivery, antenatal antibiotics administration, mode of delivery, gestational age, origin (inborn or out born), and hemodynamic failure.	**Low** Data obtained from computerized database	**Low** No statement to indicate blinding, but unlikely to affect outcome measurements . .	**Low** No missing data	**Low** All predefined outcomes reported	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 2000 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered at the same institution between January 1990 and December 1997.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low.** All expected outcomes were reported.	-
Ryu 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single university hospital, admitted to the same institution (Seoul National University Hospital) between 2007 and 2014.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, sex, and cesarean section.	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** At the beginning of the study incomplete information was excluded.	**Low** All predefined outcomes reported.	-

N/A: Not applicable**; RDS:** Respiratory distress syndrome; **BPD:** Bronchopulmonary dysplasia; **IHC:** Intrahepatic cholestasis; **IVH:** Intraventricular hemorrhage; **PVL:** Periventricular leukomalacia; **NEC:** Necrotizing enterocolitis; **PDA:** Patent ductus arteriosus; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis; **IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **GA:** Gestational age; **CS:** Cesarean section

*Baud (2000), Ahn (2012) and Ryu (2019) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

Risk of bias assessments for of studies of antenatal corticosteroids in women with growth-restricted fetuses and/or small-for-gestational-age infants

Risk of bias assessments (RoBANS)

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
van Stralen 2009 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (Leiden University Medical Center) over the same period (January 2001–December 2005).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric electronic database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Although equally divided, the difference in origin, i.e., referral pattern, may also have influenced the results.
Torrance 2007 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single tertiary referral center admitted to the same institution (neonatal intensive care unit at the University Medical Centre Utrecht, the Netherlands) over the same period (from January 1, 1999, to December 31, 2003). Cases and controls were selected from same pool (e.g., same gestational age, same birth weight).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data was obtained from an electronic database.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No loss to follow-up	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Foix-L'Helias 2005 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from different institutions during the same period (1993–1996).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	Survey limited to inborn babies, possibly overestimating the impact of ACS. However, no distinction was made between completed and uncompleted ACS courses, so there is potential underestimation.
Schaap 2001 (Case-control study)	N/A	N/A	**Low** Participants drawn from different two institutions during the same period (1984–1991).	**High** -Study design Matched by birth weight, sex and year of birth. -Analysis No consideration on confounding variables	**Low** Data obtained from medical records. Because all mothers had been admitted at least 24 h before delivery, a difference in fetal condition on admission was unlikely.	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Nine losses at school age follow-up (4 in steroid group, 5 in control group) but no significant difference in sociodemographic details between those lost and retained at follow-up.	**Low** All predefined outcomes reported.	Hypertensive mothers less often treated with corticosteroids. Further, matching notwithstanding, birth weight and gestational age were significantly lower in the AGA group, although magnitude of the difference is small.

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Elimian 1999 (Retrospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (January 1990–July 1997)	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Ley 1997 (Retrospective cohort study)	N/A	N/A	**Low** All participants admitted/delivered and treated at the same institution (University Hospital of Lund) during the same period (1985–1994).	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for birthweight deviation, gestational age, pre-eclampsia, premature rupture of membranes and mode of delivery.	**Low** Data obtained from hospital records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Spinillo 1995 (Prospective cohort study)	N/A	N/A	**Low** All participants from the same institution during the same period (1988–1993)	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, birth weight and sex.	**Low** Data obtained from hospital records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** Missing data was less than 10%.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Di Lenardo 1990 (Retrospective cohort study)	N/A	N/A	**Unclear** All participants admitted/delivered and treated at the same institution (Prenatal Care Ward of Univ. of Padua's Gynecology & Obstetrics Institution) but unclear if over the same period.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Bitar 2020 (Retrospective cohort study)	N/A	N/A	**Low** All participants, from a single hospital, who delivered at 34.0–36.6 weeks of gestation, with small-for-gestational-age or fetal-growth-restriction infants between January 2015 and December 2019.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for parity and preeclampsia.	**Low** Data obtained from electronic medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes were reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Cartwright 2019 (Retrospective cohort study)	N/A	N/A	**Low** All participants from 23 collaborating hospitals, 16 in Australia and 7 in New Zealand, with a single, twin, or triplet pregnancy at less than 32 weeks of gestational age from April 1998 to July 2004.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age at trial entry, antepartum hemorrhage, preterm pre-labor rupture of membranes, and country of birth.	**Low** Data obtained from case notes	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** The predefined outcomes were described as planned.	-
Riskin-Mashiah 2018 (Retrospective cohort study)	NA	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, ethnicity, infertility treatment, maternal hypertensive disorder, preterm labor, premature rupture of membranes and/or amnionitis, gestational age, delivery mode, birth weight z-score, gender, birth order, delivery room resuscitation and year of birth.	**Low** Data obtained from the national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants from a single hospital between 2009 and 2016	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for gestational age, parity, mode of delivery, maternal diabetes, gestational hypertensive disorder, and preterm premature rupture of membrane.	**Low** Data obtained from medical records and perinatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
Ishikawa 2015 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Research Network Database in Japan between 2003 and 2007	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, parity, preeclampsia, preterm rupture of membranes, non-reassuring fetal status, mode of delivery, gestational age at delivery, birth weight, gender of the infant, and histological chorioamnionitis (≥ stage 2).	**Low.** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Riskin-Mashiah 2016 (Retrospective cohort study)	N/A	N/A	**Low** The data of all participants from the National Very Low Birth Weight Infant database from 1995 to 2012	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for maternal age, ethnicity, infertility treatment, maternal diabetes, maternal hypertensive disorder, preterm labor, premature rupture of membranes, amnionitis, antepartum hemorrhage, gestational age, delivery mode, birthweight z-score, gender, delivery room resuscitation and year of birth.	**Low** Data obtained from national network	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No missing data	**Low** All predefined outcomes reported.	-
Mitsiakos 2013 (Retrospective cohort study)	N/A	N/A	**Low** All participants between 24 and 31 6/7 weeks of gestational age from a single hospital. The study period was not specifically mentioned, but intervention and control groups seem to be selected from the same population groups.	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from obstetric and neonatal database	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** There are missing data, but this is unlikely to have affected the study outcome.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Kim YJ 2018 (Retrospective cohort study)	N/A	N/A	**Low** All participants born at 23 + 0 to 33 + 6 weeks of gestation between January 2007 and December 2014 in a single university hospital in South Korea.	**High** -Study design No consideration -Analysis Multiple logistic regression was used, controlled for birth weight and Apgar score at 5 minutes.	**Low** Data obtained from medical records and perinatal databases	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-
The collaborative study group for respiratory distress syndrome in preterm infants 2017 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from 14 hospitals during the same period (2013–2014).	**High** -Study design No consideration -Analysis Multiple logistic regression was used, but their confounding factors were not specified.	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

Study ID	Sequence generation	Allocation concealment	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcomes assessment	Incomplete outcome data	Selective outcome reporting	Other
Bernstein 2000 (Retrospective cohort study)	N/A	N/A	**Low** Participants drawn from North American hospitals during the same period (1991–1996).	**High** -Study design No consideration -Analysis No consideration on confounding variables	**Low** Data obtained from medical records	**Low** No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.	**Low** No statement of missing data, but the possibility of data loss is low.	**Low** All predefined outcomes reported.	-

N/A: Not Applicable**; IUGR:** Intrauterine growth restriction; **ACS:** Antenatal corticosteroid; **AGA:** Appropriate for gestational age

*****Spinillo (1995), Ishikawa (2015), Riskin-Mashiah (2016), Feng (2017), Riskin-Mashiah (2018), Kim (2018), Kim YJ (2018), Cartwright (2019), and Bitar (2020) reported the data by their multiple logistic regression models, but we used crude data in the analysis. Hence, confounding variables were at high risk of bias in all included studies.

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							№ of patients		Effect		Certainty	Importance
№ 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[b]	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[b]	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[b]	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[b]	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[b]	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[c]	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

a. Heterogeneity is high (I-square=>60%).
b. Estimate based on wide confidence interval crossing the line of no effect.
c. 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							№ of patients		Effect		Certainty	Importance
№ 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 =<7 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							№ of patients		Effect		Certainty	Importance
№ 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[c]	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[b]	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[b]	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[b]	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[b]	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 ≥ 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							№ of patients		Effect		Certainty	Importance
№ 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[a]	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[a]	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[a]	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[c]	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[a]	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[c]	not serious	serious[a]	non e	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[c]	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[c]	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[a,b]	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[a,b]	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[a,b]	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[c]	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[a,b]	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							№ of patients		Effect		Certainty	Importance
№ 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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[b]	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
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Setting: 18 studies (observational studies in Italy, the USA, France, Sweden, the Netherlands, Australia & New Zealand, Israel, Republic of Korea, and Japan)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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	**not serious**	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[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	
Neonatal sepsis (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious[a,b]	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[a,b]	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[a,b]	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[a,b]	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[a,b]	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[c]	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[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	
Neonatal adrenal insufficiency (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious[a,b]	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[a,b]	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[a,b]	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[a,b]	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

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%).

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ 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[c]	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[c]	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[a]	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[a]	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[a]	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[c]	not serious	serious[a]	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[a]	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[a]	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[a]	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%).

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

06/06/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2021

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

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Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Kana Saito

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Kana Saito

7. * Named contact email.

Give the electronic email address of the named contact.

kana988@saitama-med.ac.jp

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

1981, Kamoda, Kawagoe-city, Saitama, Japan

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

81-49-228-3400

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Saitama Medical University

Organisation web address:

http://www.saitama-med.ac.jp/

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr KANA SAITO. Saitama Medical University, Neonatology Department
Ms Etsuko Nishimura. St. Luke's International University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Non funded research

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Toshiyuki Swa. Osaka University Graduate School of Medicine
Dr Fumihiko Namba. Saitama Medical University
Dr Erika Ota. St. Luke's International University
Dr Joshua P. Vogel. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Ramson. Child and Adolescent Health Program, Burnet Institute, Melbourne
Dr Jenny Cao. Child and Adolescent Health Program, Burnet Institute, Melbourne

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

This study aims to synthesize available evidence on antenatal corticosteroid (ACS) use among specific subgroups of women at risk of imminent preterm birth.

The primary objective is to determine the effects of ACS administration for four subgroups of pregnant women at risk of imminent preterm birth on maternal and child outcomes. These subgroups are as follows.

1) women with pregestational or gestational diabetes mellitus

2) women undergoing elective CS in the late preterm period (from 34 weeks 0 days to 36 weeks 6 days)

3) women with an intrapartum inflammation, infection, or both (eg: chorioamnionitis)

4) women with growth-restricted fetuses

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search electronic databases (e.g. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP).

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

We will search electronic databases (i.e. MEDLINE, EMBASE, CINAHL, Cochrane Library, POPLINE, and Global Index medicus for publications). Our search is not limited by language or geographic restrictions. Relevant unpublished material will be identified through key term searches of the following databases: Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN), and the International Clinical Trial Registry Platform (ICTRP). Search terms include “adrenal cortex hormones”, “pregnancy”, “pregnancy outcome”, “fetal death”, “maternal death”, “obstetric labor complications”, “obstetric labor, premature”, “pregnancy, prolonged”, “fetus”, “infant, newborn”, “prenatal care”, “fetal development”, “birth weight”, “prenatal exposure delayed effects”, “diabetes mellitus”, “hyperglycemia”, “diabetes, gestational”, “pregnancy in diabetics”, “cesarean section”, “bacterial infections and mycoses”, “chorioamnionitis“, “pregnancy complications, infectious”, “fetal development”.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Pregnancy

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: We will not restrict the population to pregnant women who gave birth after 20 completed weeks gestation and their babies.
Exclusion: None

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

We will include women who received at least one dose of antenatal corticosteroid, either betamethasone, dexamethasone, or hydrocortisone after 20 weeks of gestation.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Women and babies who did not receive antenatal corticosteroids.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all published, unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled before-and-after studies, interrupted-time-series studies, historical controlled studies, cohort studies, and cross-sectional studies comparing ACS administration (betamethasone, dexamethasone, or hydrocortisone), given parenterally or enterally, compared with placebo or no treatment in women at risk of imminent preterm birth as a result of either spontaneous preterm labor, preterm rupture of the membranes, or elective preterm delivery, and where all (or at least a well-defined sub-sample) of the women under study also fulfilled one or more of the following conditions:

1. having pregestational or gestational diabetes mellitus;
2. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
3. having intrauterine inflammation, infection, or both; or
4. having a growth-restricted infant (or, more broadly, one that was at least small for gestational age).

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

We aim to establish the existing evidence that examines the implications of using or not using ACS in cases of imminent preterm birth in these subgroups of women. This evidence-based effort will be the source for the World Health Organization’s (WHO) updated recommendations on interventions to improve preterm birth outcomes.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a) maternal outcomes

-maternal death or severe morbidity (e.g. organ dysfunction, intensive care unit admission, chorioamnionitis)

-maternal morbidity(e.g. puerperal sepsis, pregnancy-induced hypertension, gestational diabetes mellitus, placental abruption, postpartum haemorrhage, or as defined by the author)

-route of delivery

-side effects of therapy

b) neonatal outcomes

-perinatal mortality

-fetal mortality

-neonatal mortality

-respiratory distress syndrome (RDS) and moderate/severe RDS

-surfactant use

-interventricular haemorrhage (IVH)

-periventricular leukomalacia (PVL)

-sepsis; early onset sepsis

-necrotizing enterocolitis (NEC)

-mechanical ventilation use and mean duration

-patent ductus arteriosus (PDA)

-chronic lung disease (CLD)/ bronchopulmonary dysplasia (BPD)

-Apgar scores seven at 5 minutes

-neurodevelopment

-anthropometric status; birth weight, height, and head circumference

-NICU admission and mean duration

-side effects of therapy

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

We will conduct the sub-group analysis; extremely preterm (less than GA 28weeks), very preterm (GA28 to 32weeks) and moderate to late preterm (GA 32 to 37weeks) on each predetermined outcome.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference (MDs) with 95% CIs will be used.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

At least two researchers will work independently to assess each title and abstract for eligibility. Disagreement will yield automatic inclusion into the next level of screening. After the initial screening of titles and abstracts, full-text publications of studies with the potential for inclusion will be obtained and assessed. The same reviewers will independently evaluate studies under consideration for inclusion without consideration of their results. Any disagreement will be resolved through discussion to reach a consensus. Finally, the reviewers independently will extract baseline and outcome data and assess the quality of the included studies. Any discrepancies will be resolved through discussion to reach a consensus.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Study quality will be assessed independently by the aforementioned reviewers at the outcome level using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS). Randomized control trials will be assessed with Risk of Bias 2 (RoB2). Potential publication bias will be assessed by visual inspection of funnel plots for asymmetry, subject to a sufficient number of included studies. Any disagreement will be resolved by discussion to reach a consensus.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Aggregate odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated for dichotomous data using Mantel-Haenszel analysis (fixed-effect model). Where between-study clinical or methodological heterogeneity will undermine the compatibility of the quantitative results, or if substantial statistical heterogeneity is detected, random-effect meta-analysis will be used. Data will be pooled using ORs when the

number of events is available and using logarithms of the ORs weighted by the inverse variance when the event is not available. For continuous data, mean difference with 95% CIs will be used.

The heterogeneity of studies will be assessed using both qualitative and quantitative measures. Statistical heterogeneity will be determined for each meta-analysis using T2, I², and ?² statistics.

Heterogeneity will be deemed substantial if T2 will be greater than zero and either I² will be greater than 50% or p0.10 in the ?² test for heterogeneity. To further assess potential heterogeneity, both fixed- and random-effects models will be compared for each outcome, where possible.

All statistical analyses will be performed using RevMan 5. Existing meta-analyses will be reviewed for relevance and completeness, and new meta-analyses will be performed where deemed necessary.

Statistical significance will be set at an alpha level of 0.05 for all analyses, except when testing study heterogeneity, where p0.10 will be regarded as significant.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat

No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
Yes

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Japan

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

We will disseminate the finding with a relevant medical journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Antenatal corticosteroid

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal corticosteroids for reducing adverse maternal and child outcomes in special populations of women at risk of imminent preterm birth: a systematic review and meta-analysis. PLoS ONE. 2016; 11(2): e0147604.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Supplementary file 2: PRISMA flow diagrams

Figure 1: Flow diagram of search results and study selection for women with pregestational and/or gestational diabetes

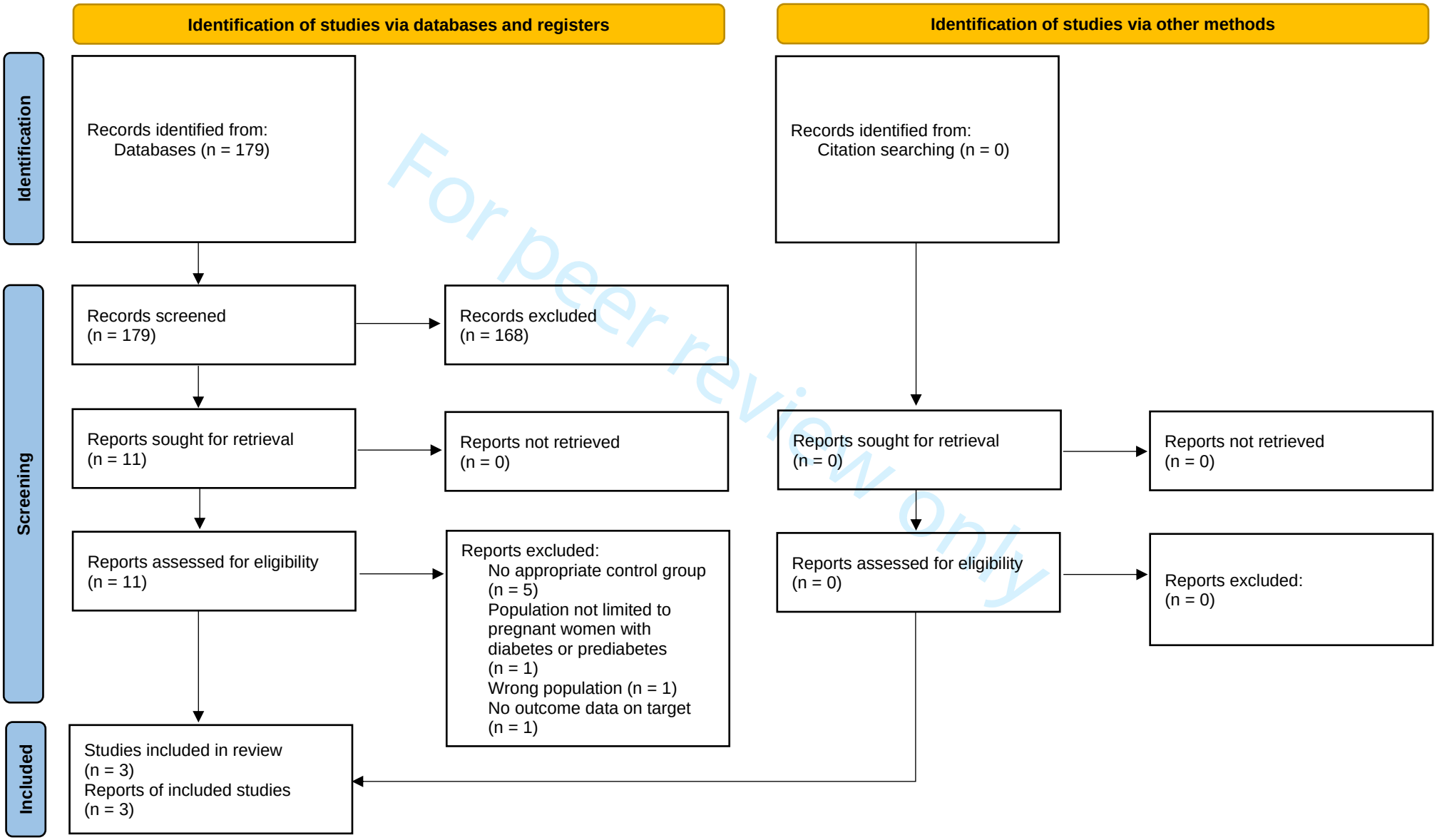


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

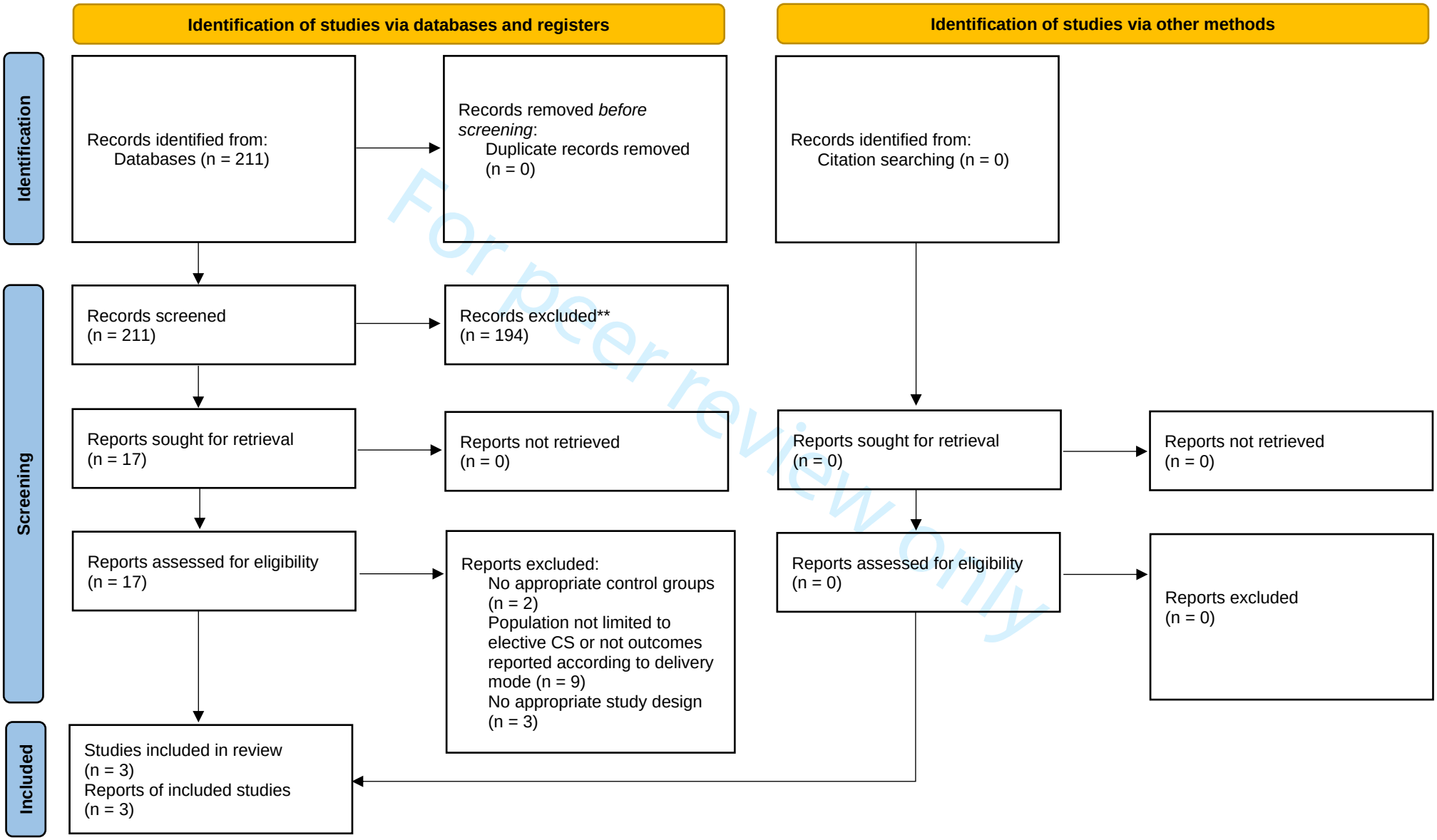


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

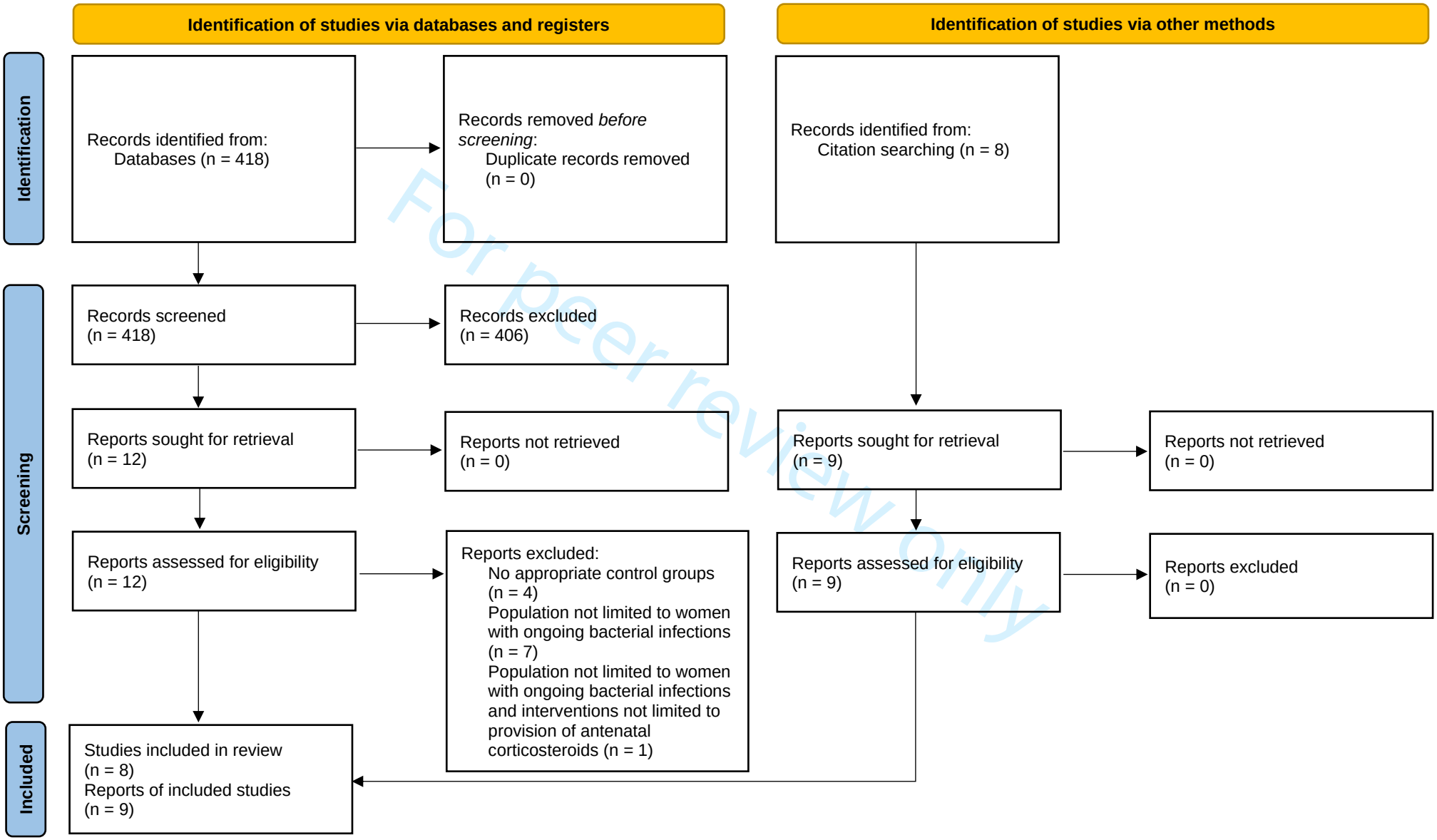
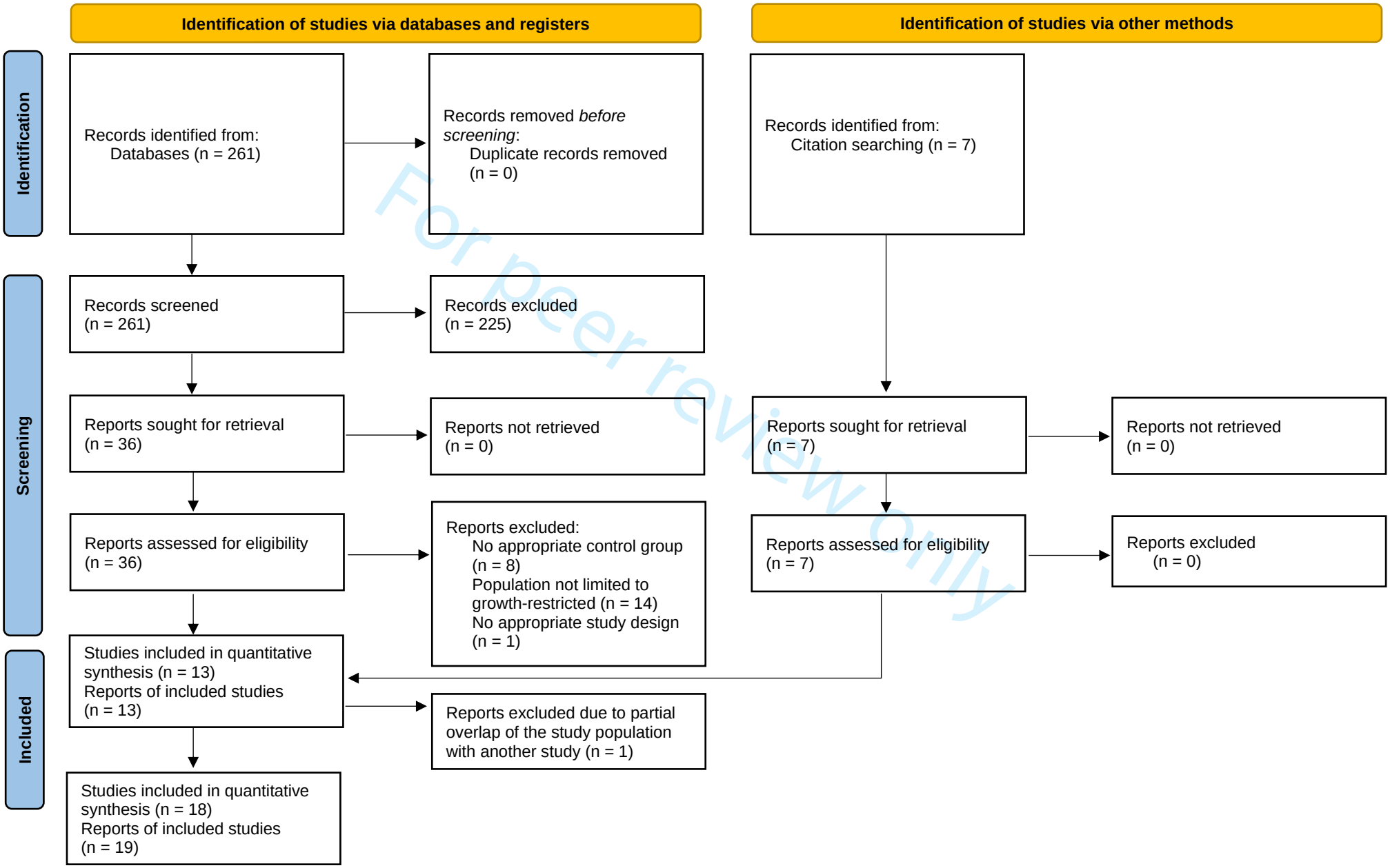


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure1: Summary of risk of bias for each trial for women with pregestational and/or gestational diabetes
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

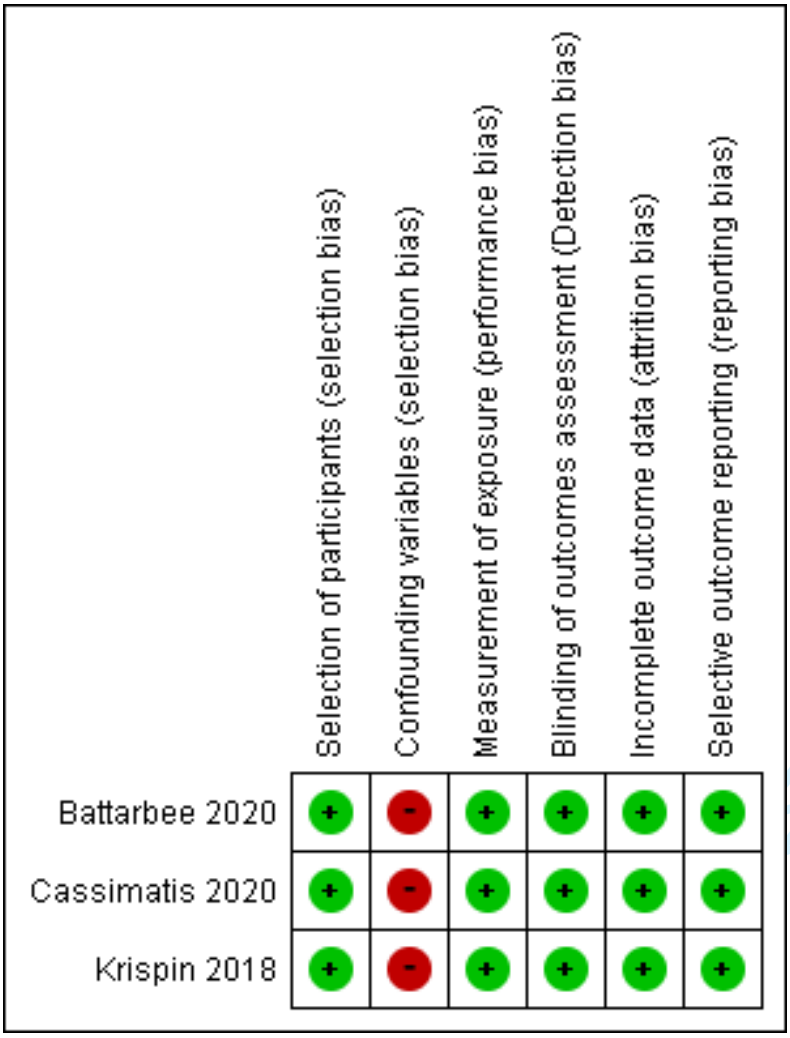
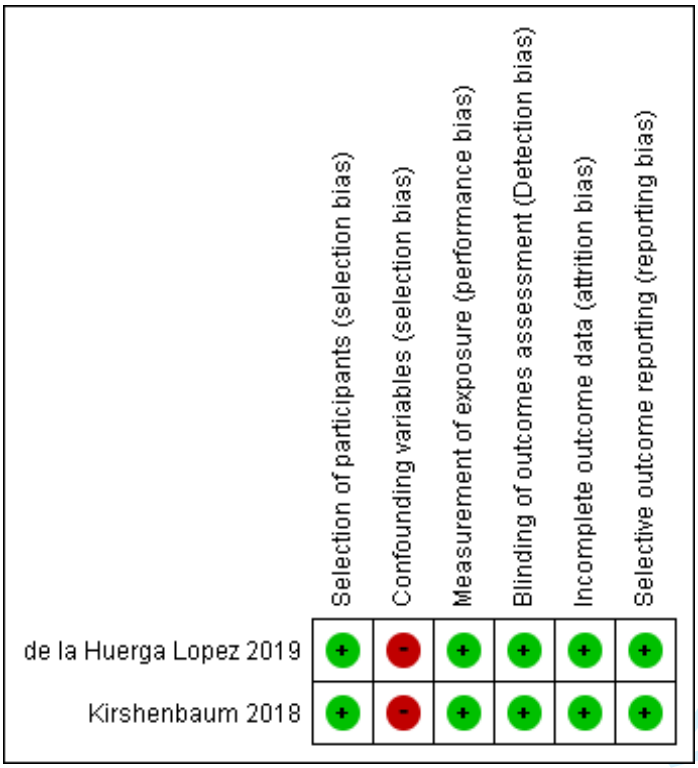


Figure 2: Summary of risk of bias for each trial for women undergoing elective Cesarean section in late preterm period
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



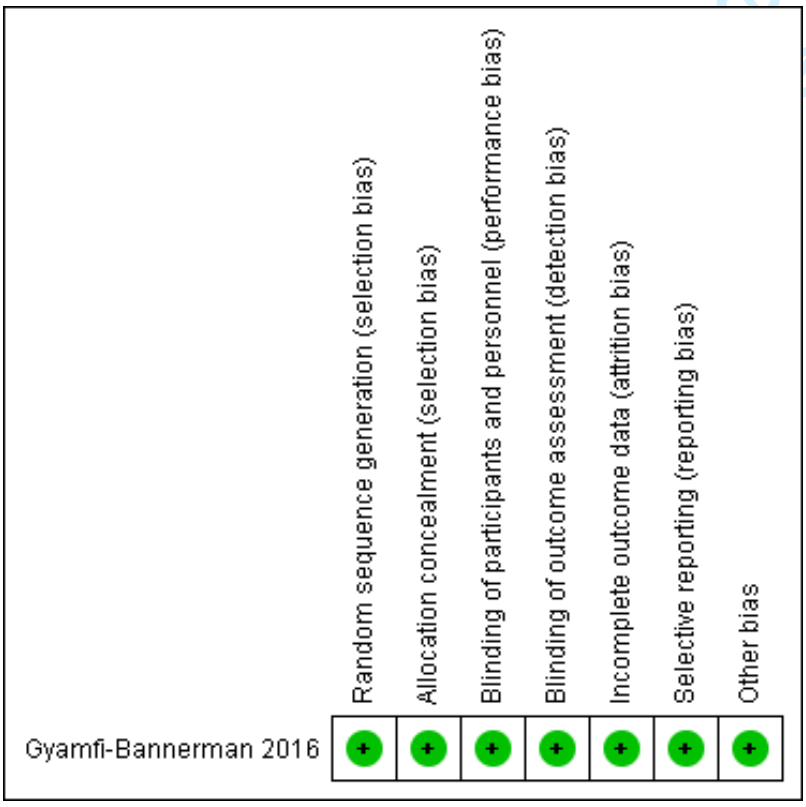


Figure 3: Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical)
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

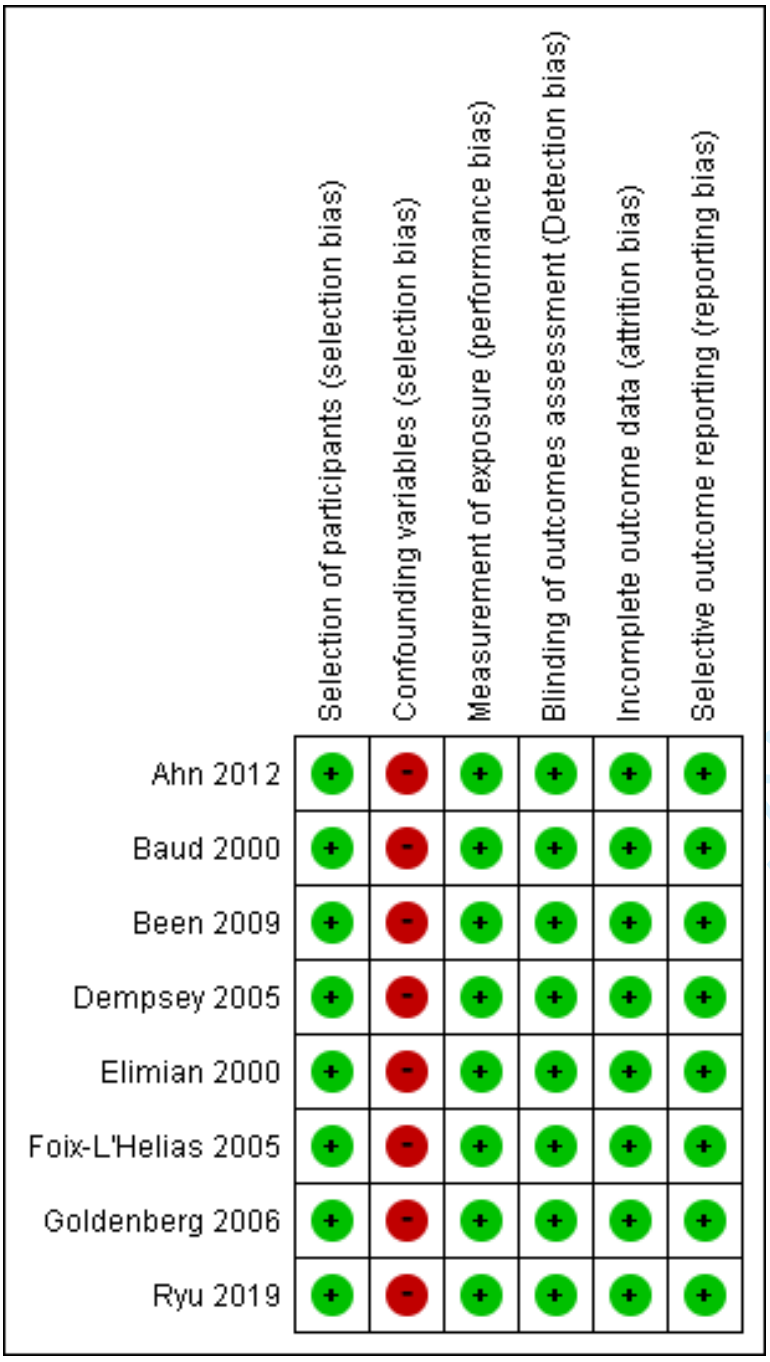
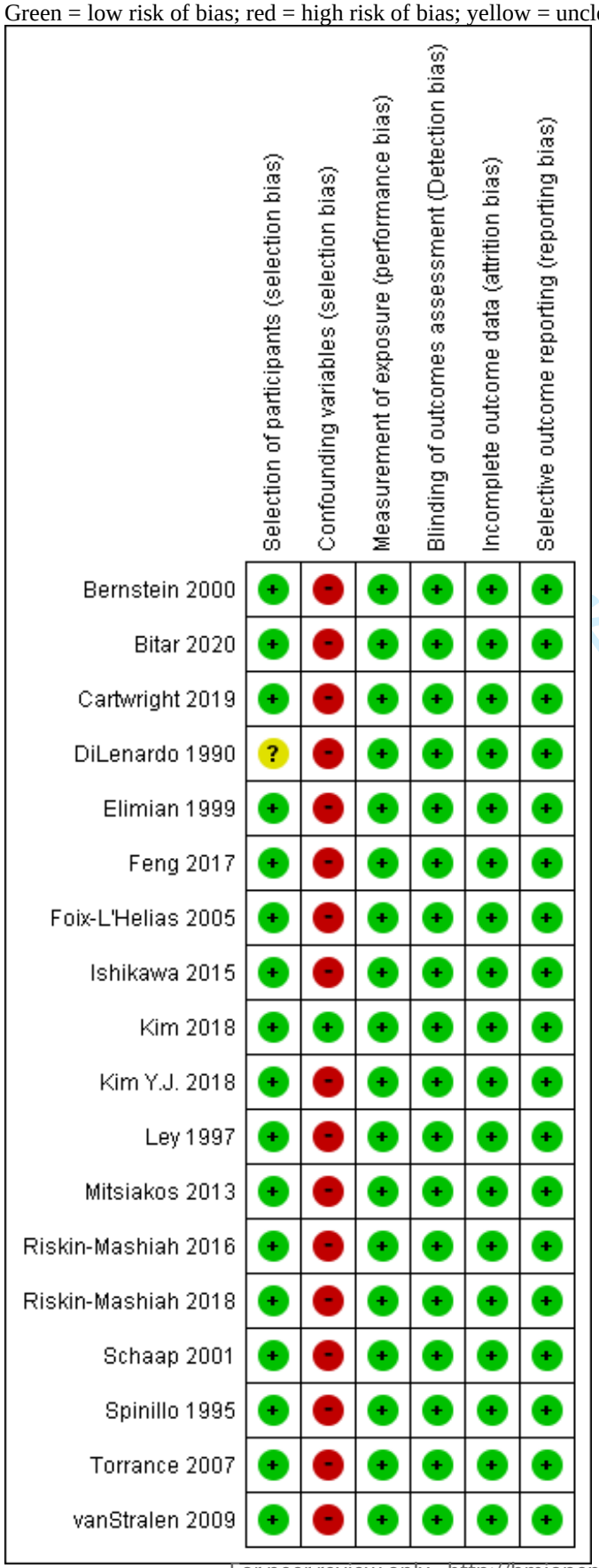


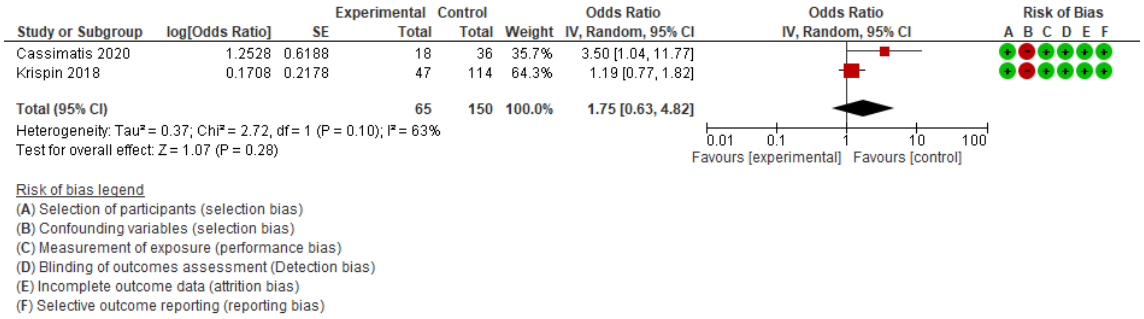
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias



Supplementary file 4: Forest plots

Maternal outcomes for women with pregestational and/or gestational diabetes mellitus

1) Caesarean section

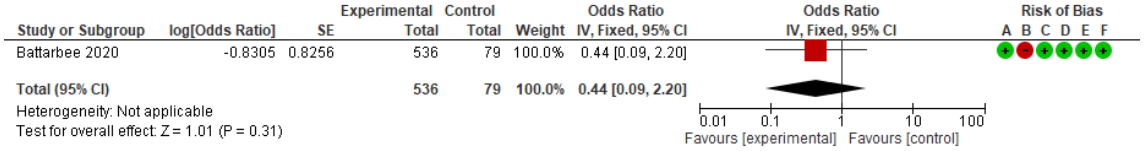


Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

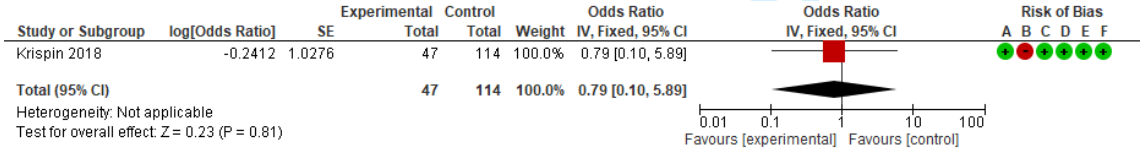
1) Neonatal death within 48 h of birth



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

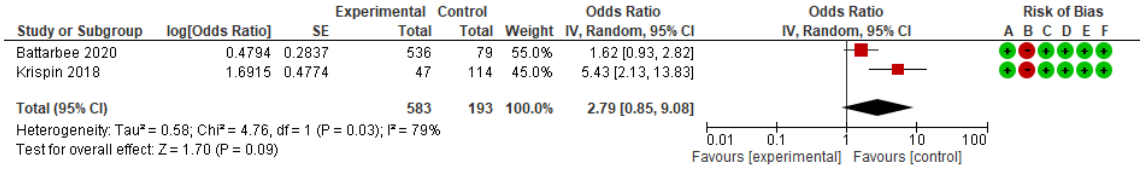
2) Apgar score < 7 at 5 min



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

3) Respiratory distress syndrome (RDS)



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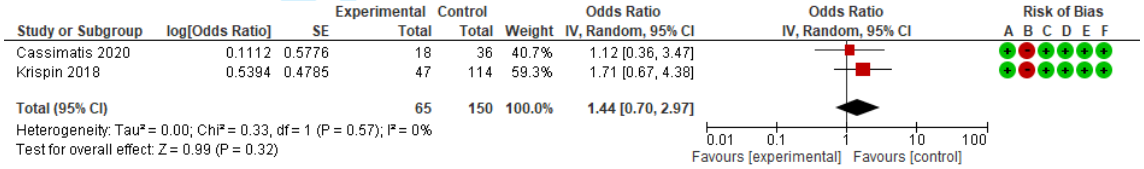
SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia



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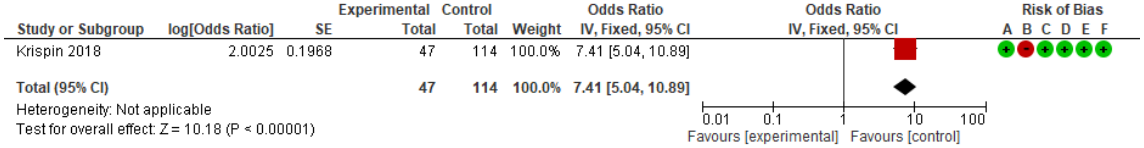
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

5) Admission to neonatal intensive care unit (NICU)



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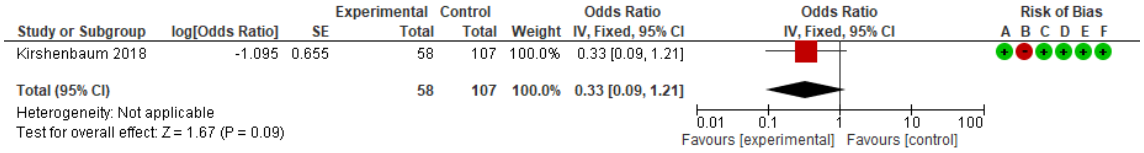
SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders



Risk of bias legend
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(E) Incomplete outcome data (attrition bias)
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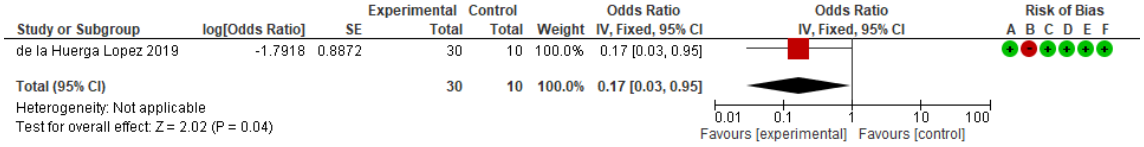
SE: Standard error; **CI:** Confidence interval

2) Gestational diabetes mellitus



Risk of bias legend
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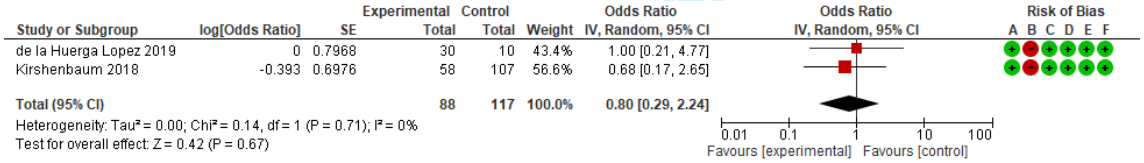
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

Neonatal outcomes for women undergoing elective cesarean section in late preterm period

1) Respiratory distress syndrome (RDS)



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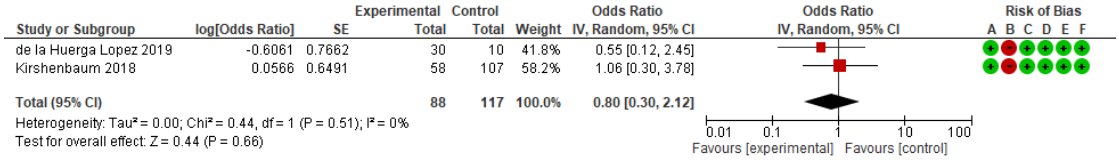
SE: Standard error; **CI:** Confidence interval

2) Use of mechanical ventilation



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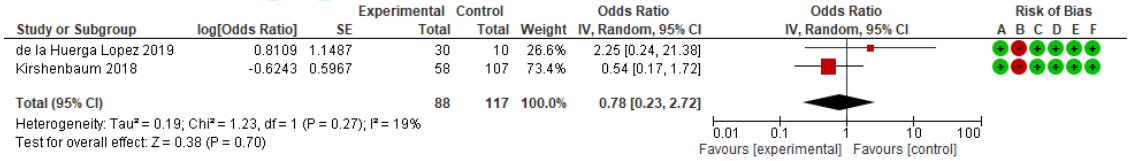
SE: Standard error; **CI:** Confidence interval

3) Admission to neonatal intensive care unit (NICU)



Risk of bias legend
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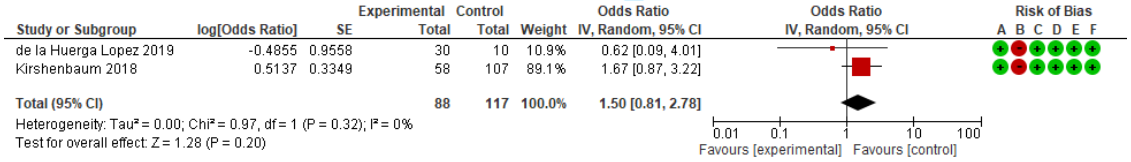
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

4) Neonatal hypoglycemia



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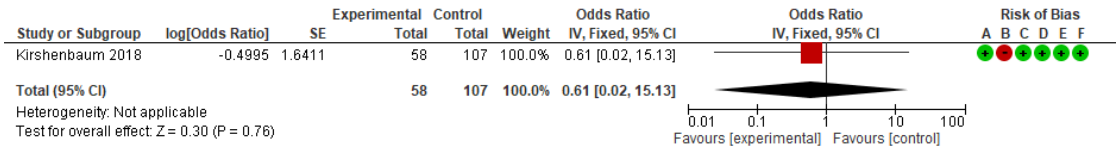
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

5) Intraventricular hemorrhage (IVH)



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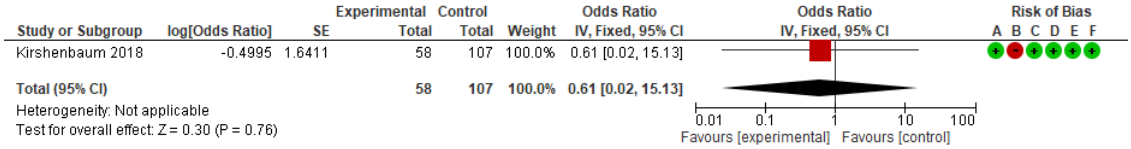
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

6) Necrotizing enterocolitis (NEC)



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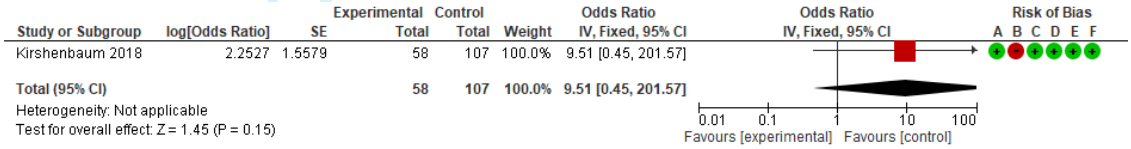
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

7) Apgar score ≤ 7 at 5min



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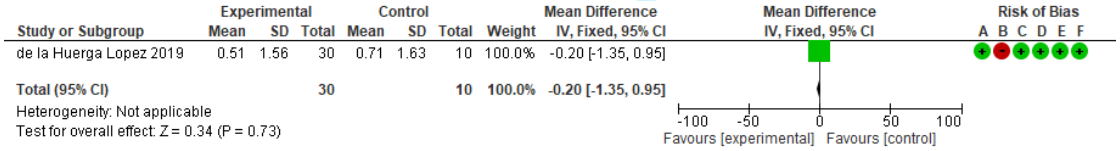
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval

8) Mean duration of mechanical ventilation, days



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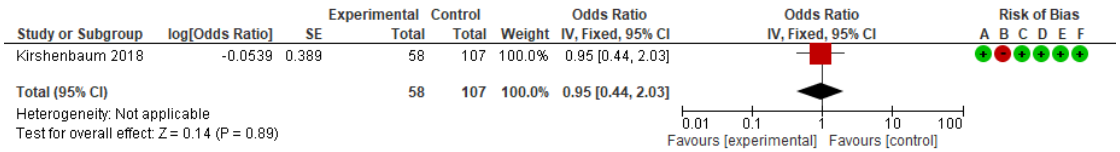
SE: Standard error; **CI:** Confidence interval

9) Oxygen requirement for at least 4 hours



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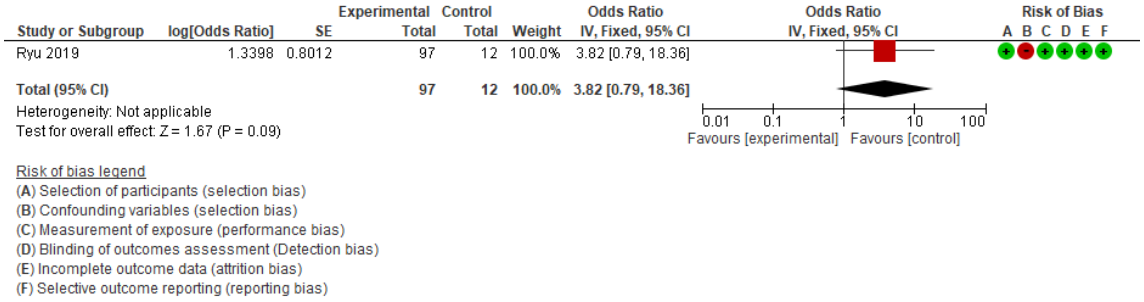
SE: Standard error; **CI:** Confidence interval

Maternal outcomes for women with histological chorioamnionitis

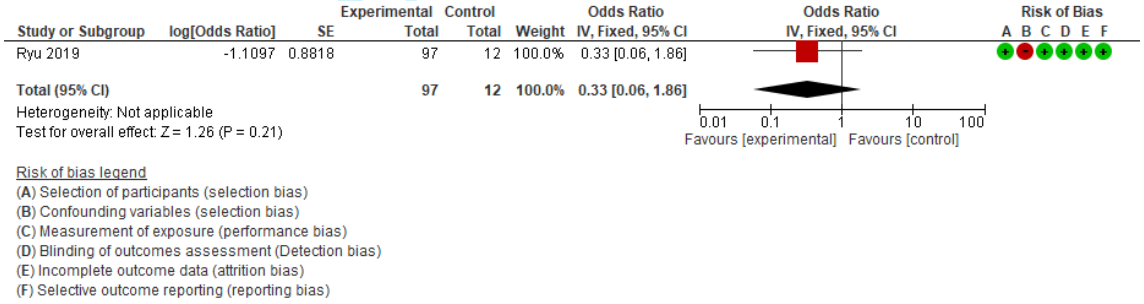
*There is no maternal outcome in clinical chorioamnionitis.

1) Caesarean section (HC)



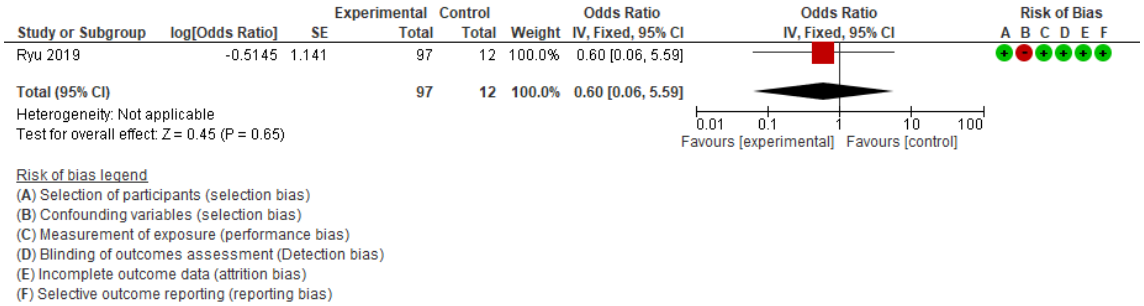
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

2) Gestational diabetes mellitus (HC)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

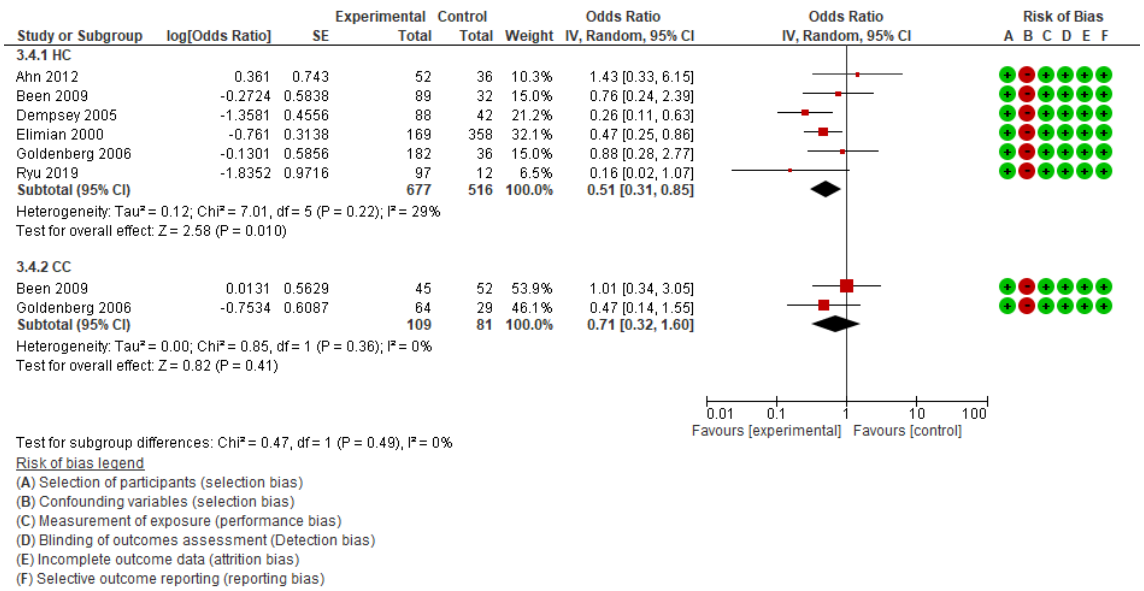
3) Preeclampsia or eclampsia (HC)



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

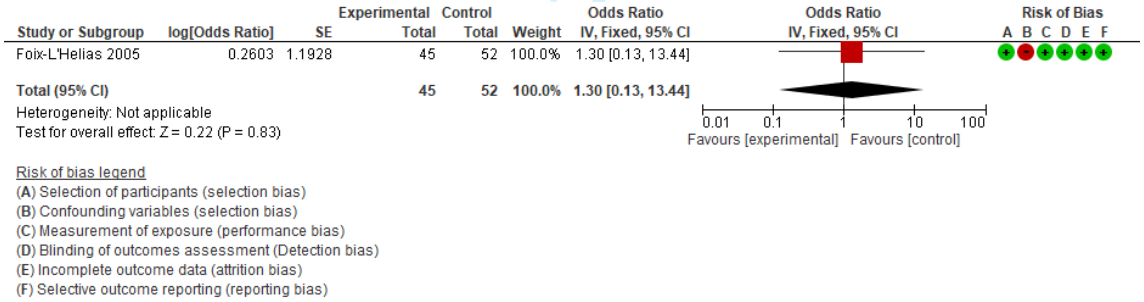
Neonatal outcomes for women with histological chorioamnionitis (HC) and clinical chorioamnionitis (CC)

1) Neonatal death



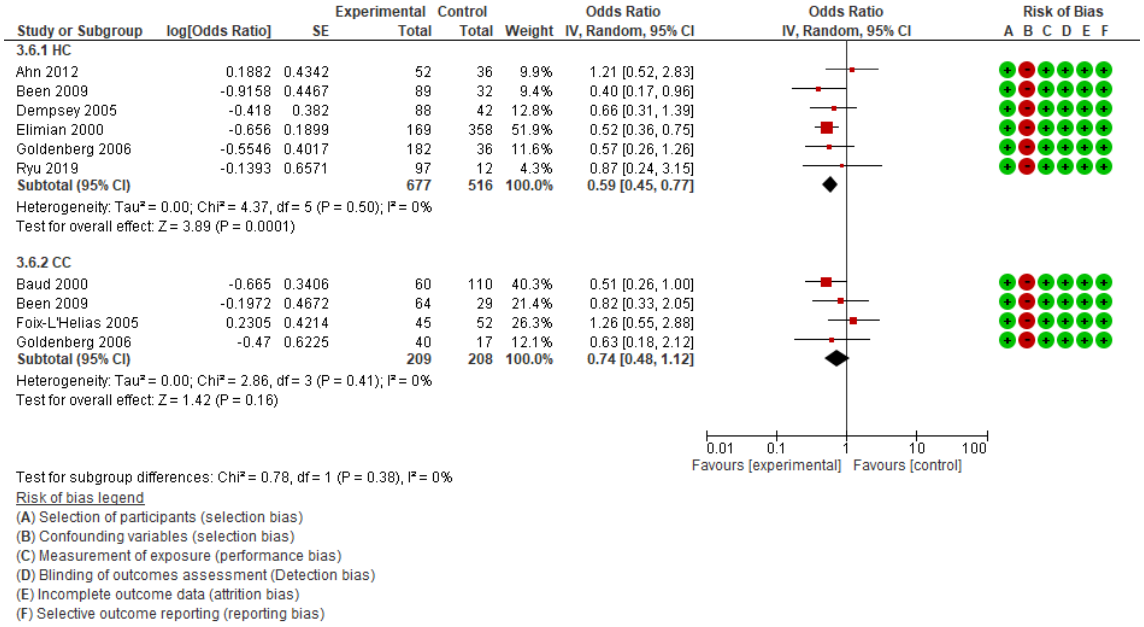
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

2) Death before discharge home (CC)



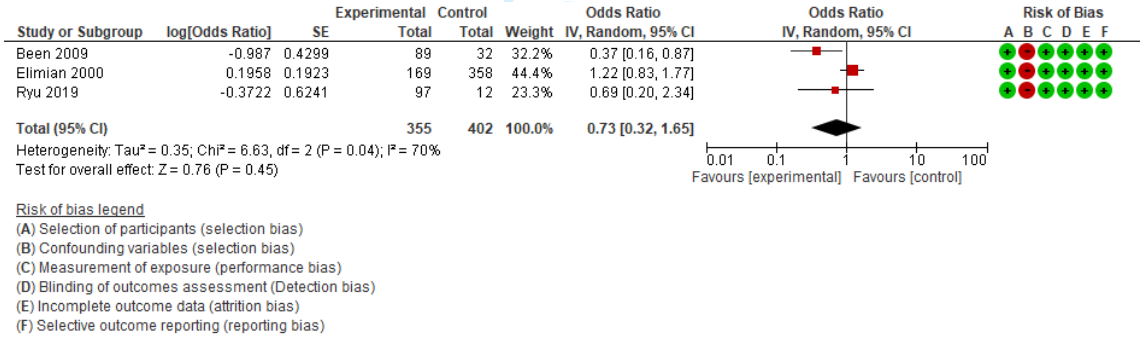
SE: Standard error; **CI:** Confidence interval; **CC:** Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



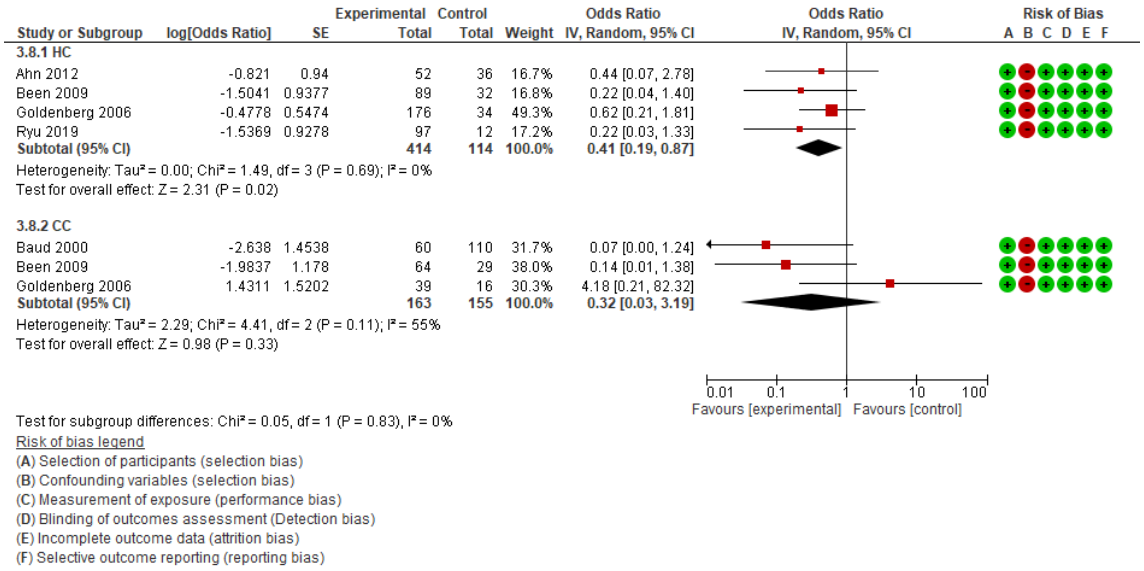
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

4) Surfactant use (HC)



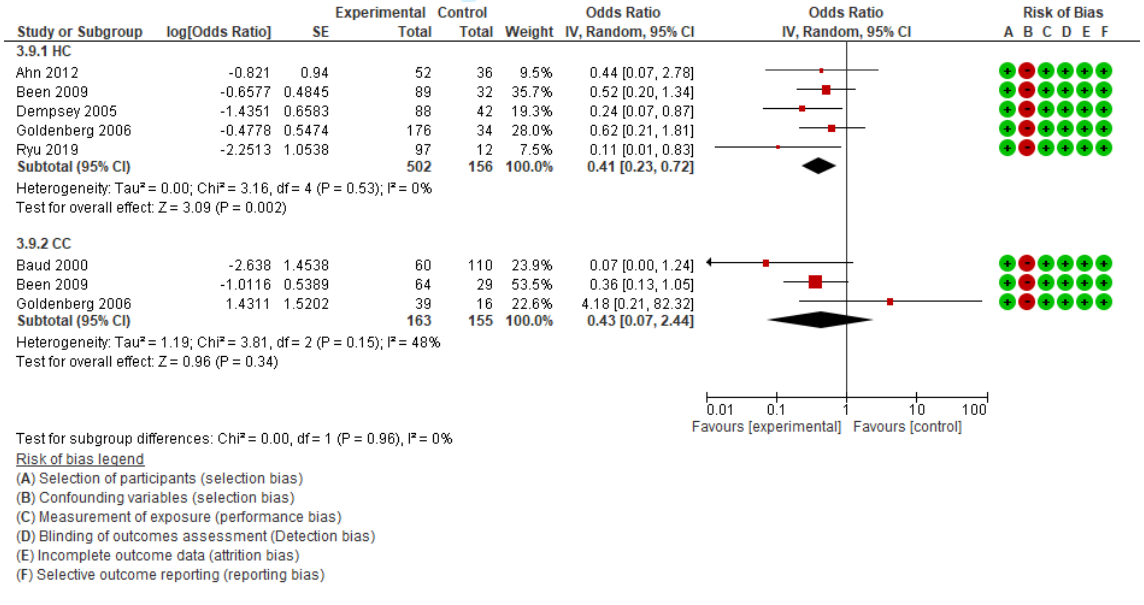
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

5) Severe intraventricular hemorrhage (IVH)



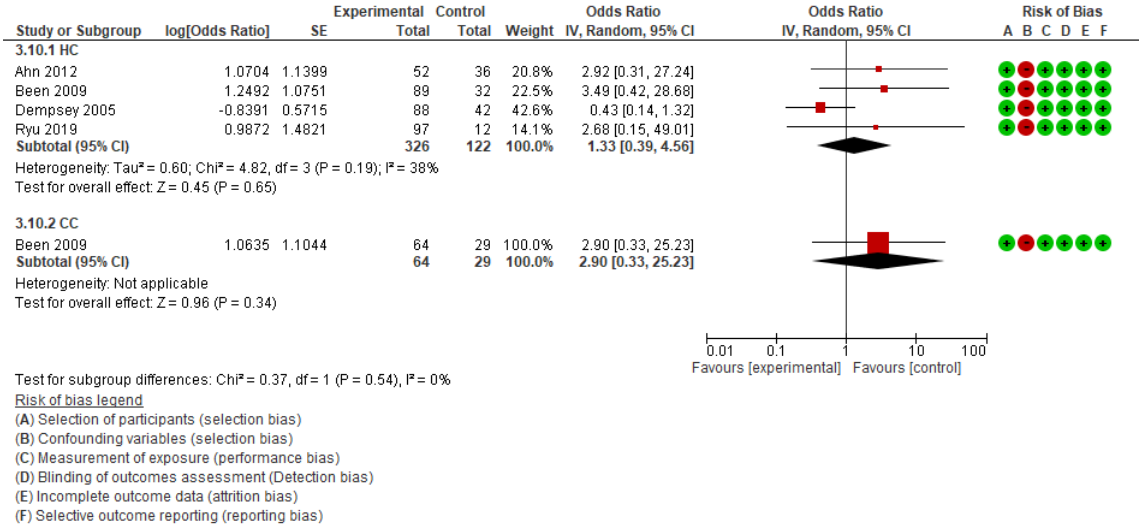
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



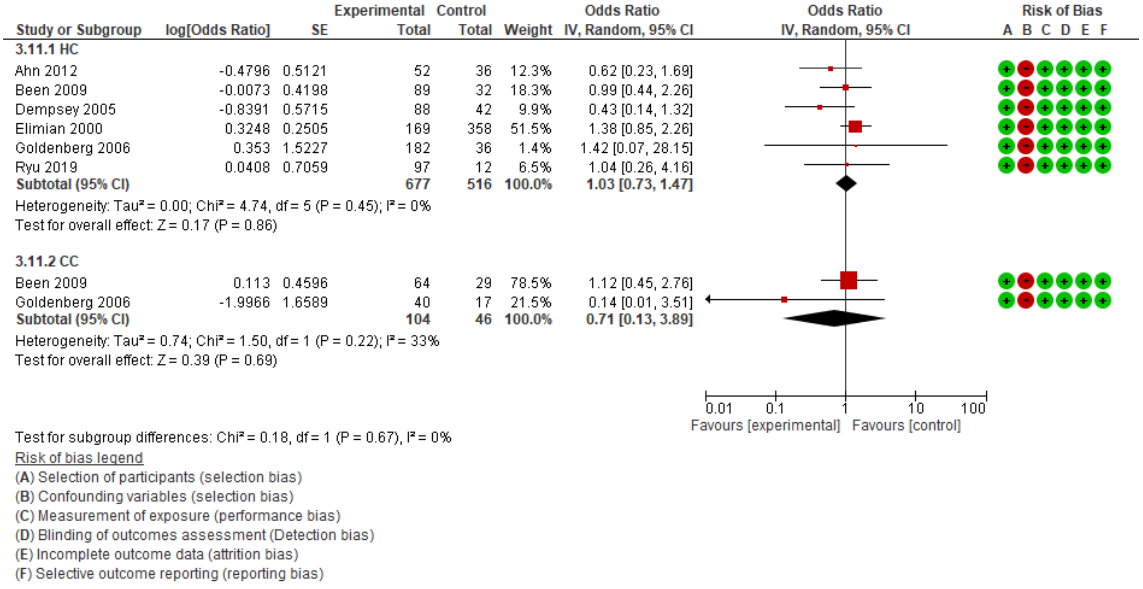
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

7) Early-onset sepsis



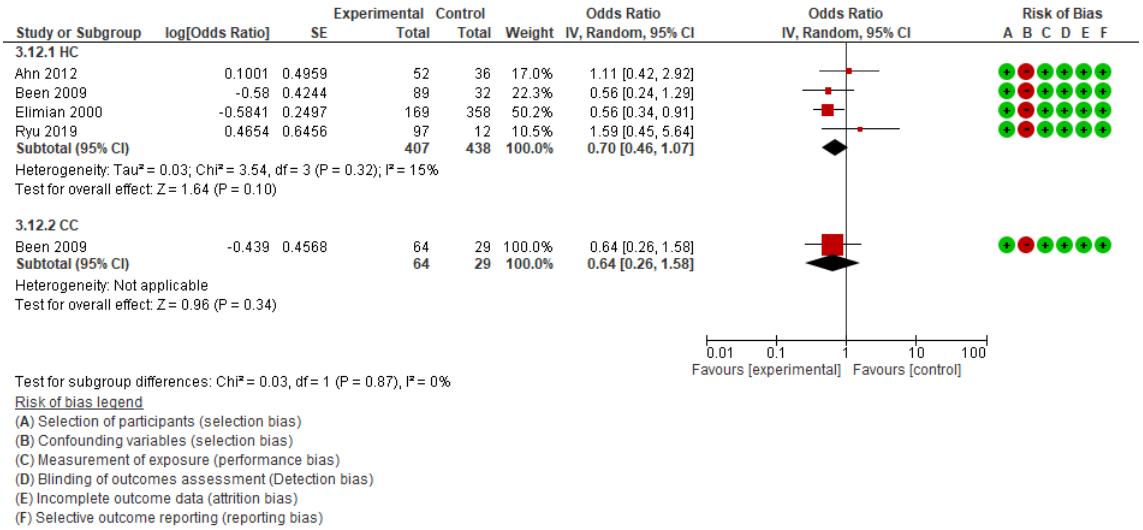
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

8) Sepsis



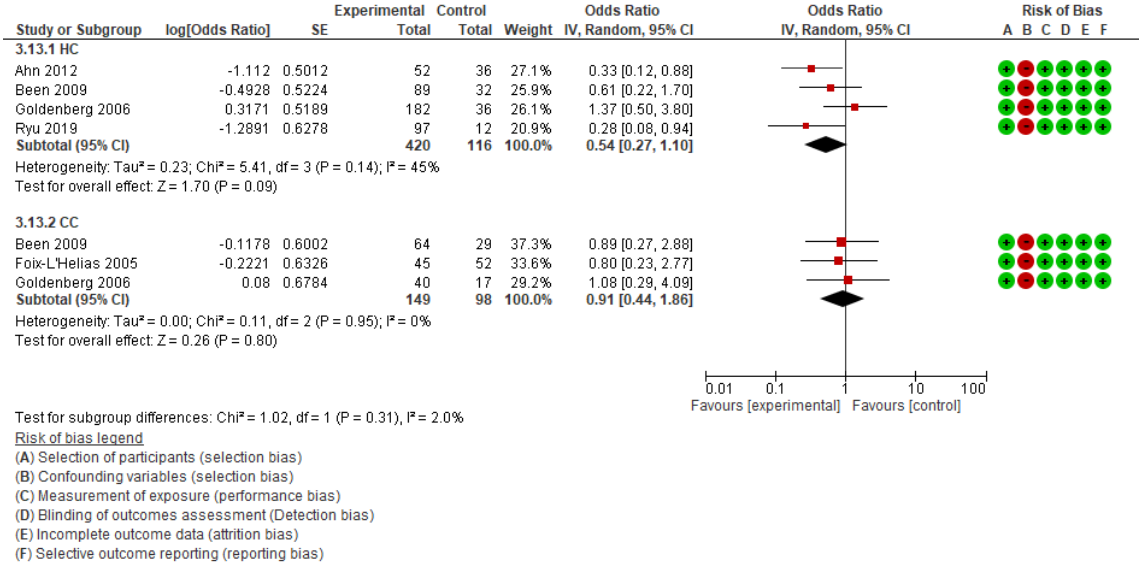
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



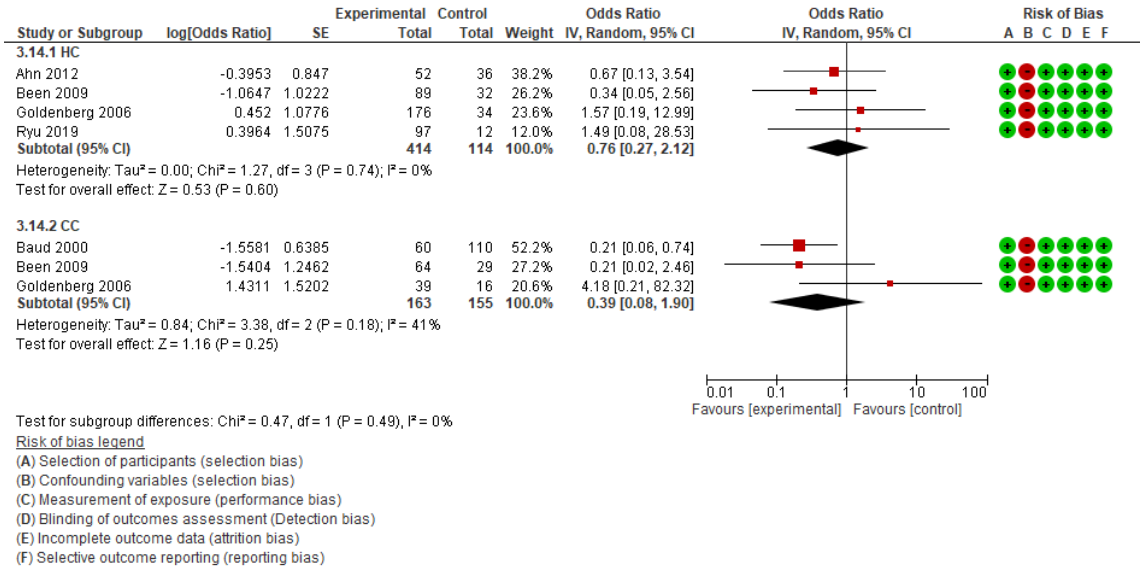
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

10) Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)



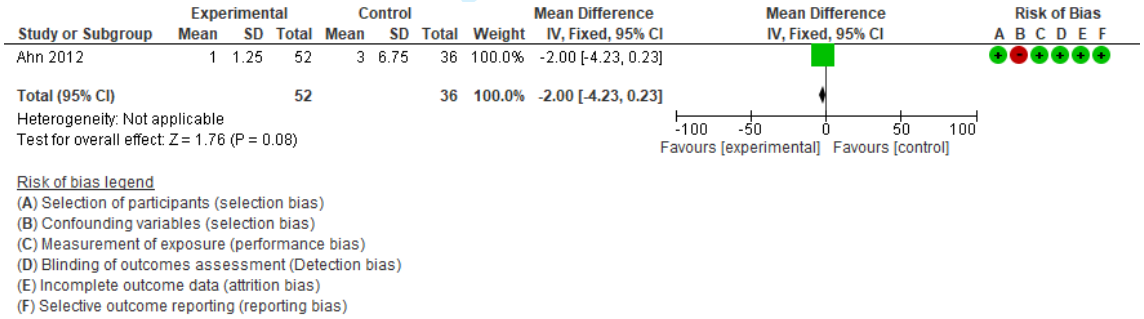
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

11) Periventricular leukomalacia (PVL)



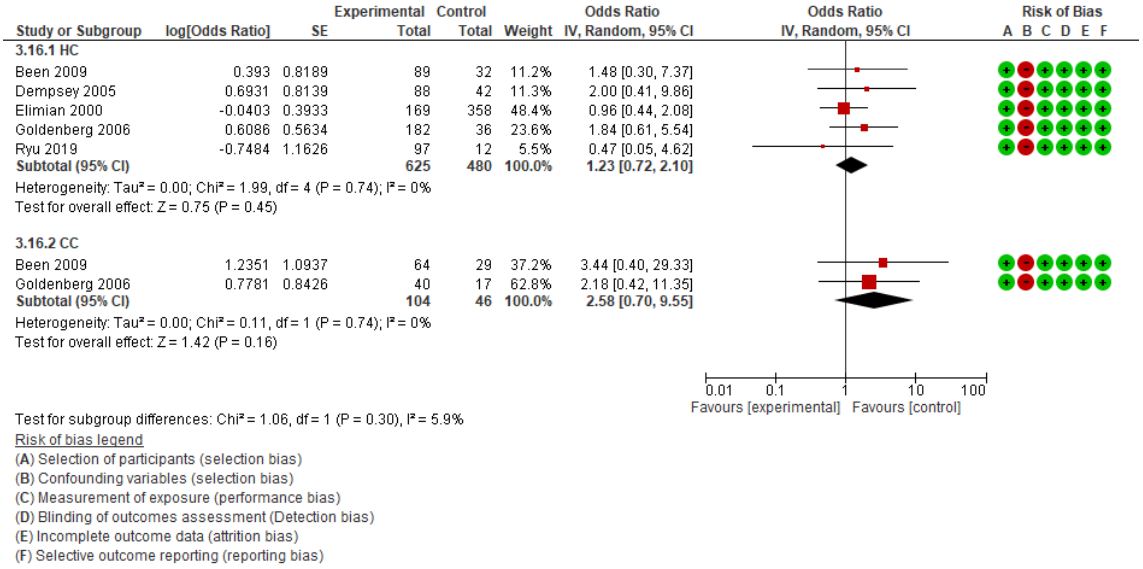
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

12) Mean duration of mechanical ventilation, days (HC)



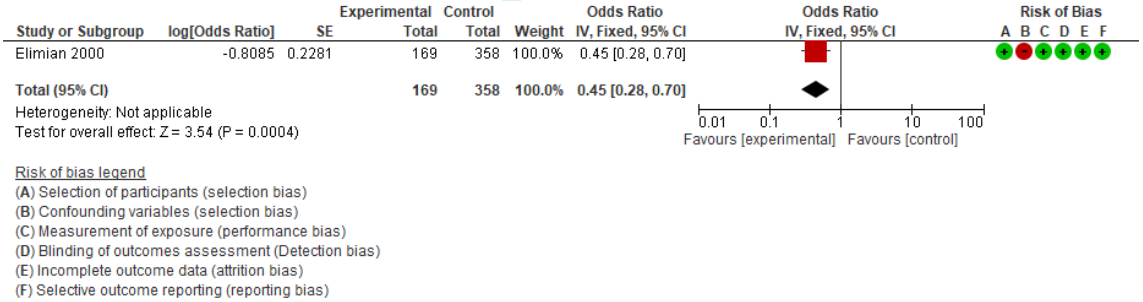
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

13) Necrotizing enterocolitis (NEC)



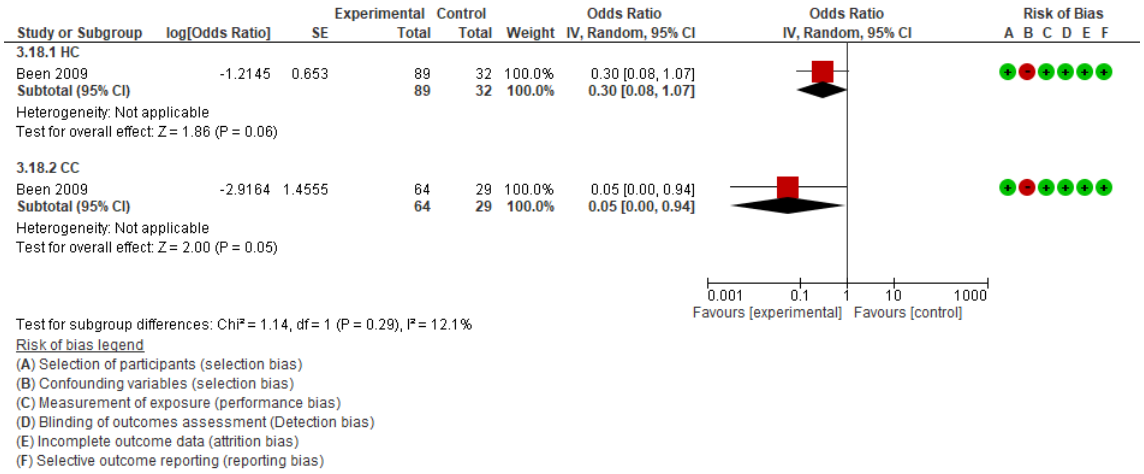
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

14) Apgar score < 7 at 5 minutes (HC)



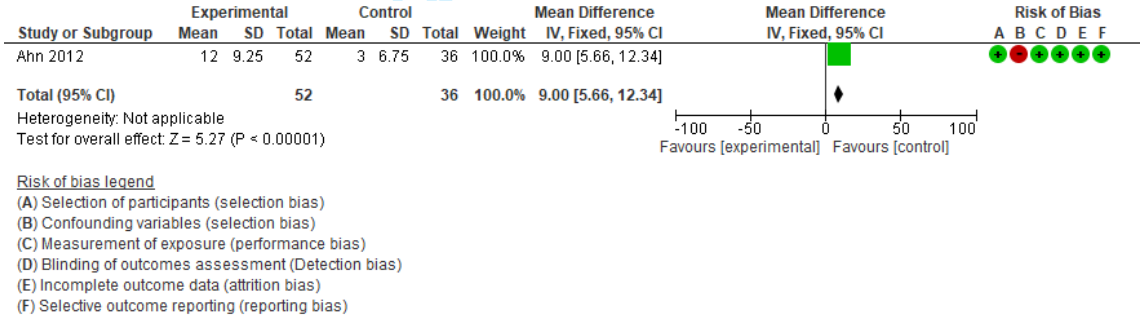
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

15) Use of mechanical ventilation



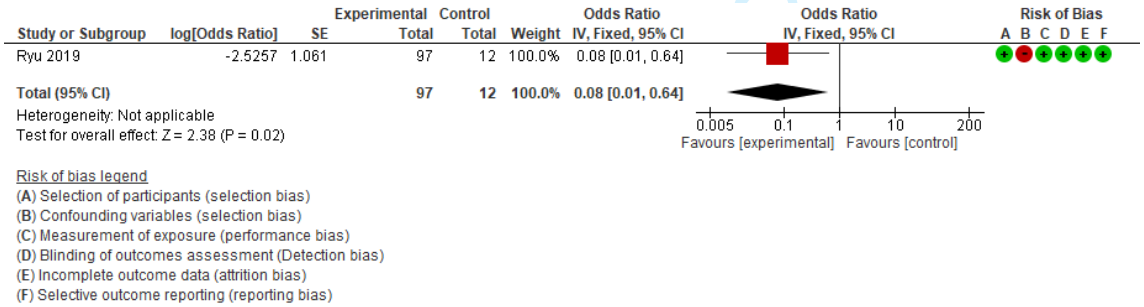
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)



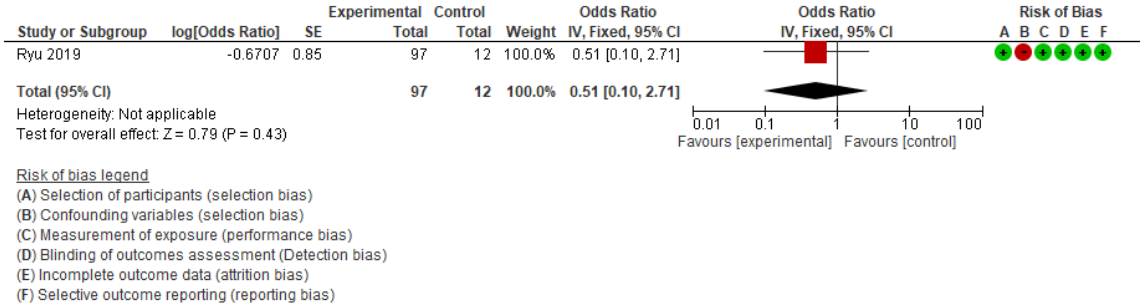
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

17) Hypotension within 7 postnatal days (HC)



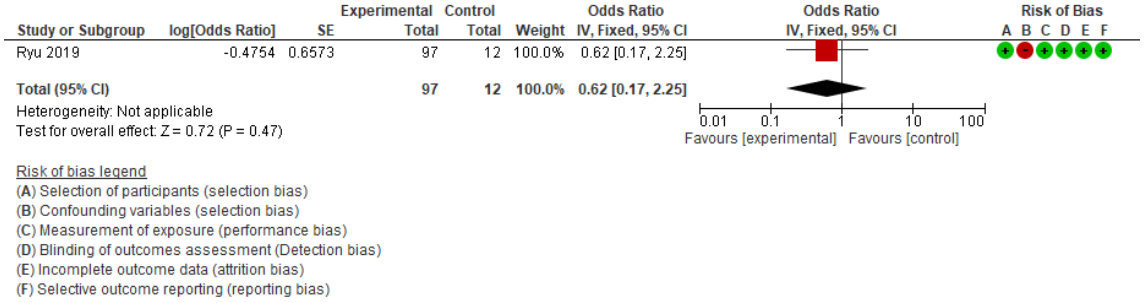
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Retinopathy of prematurity requiring treatment (HC)



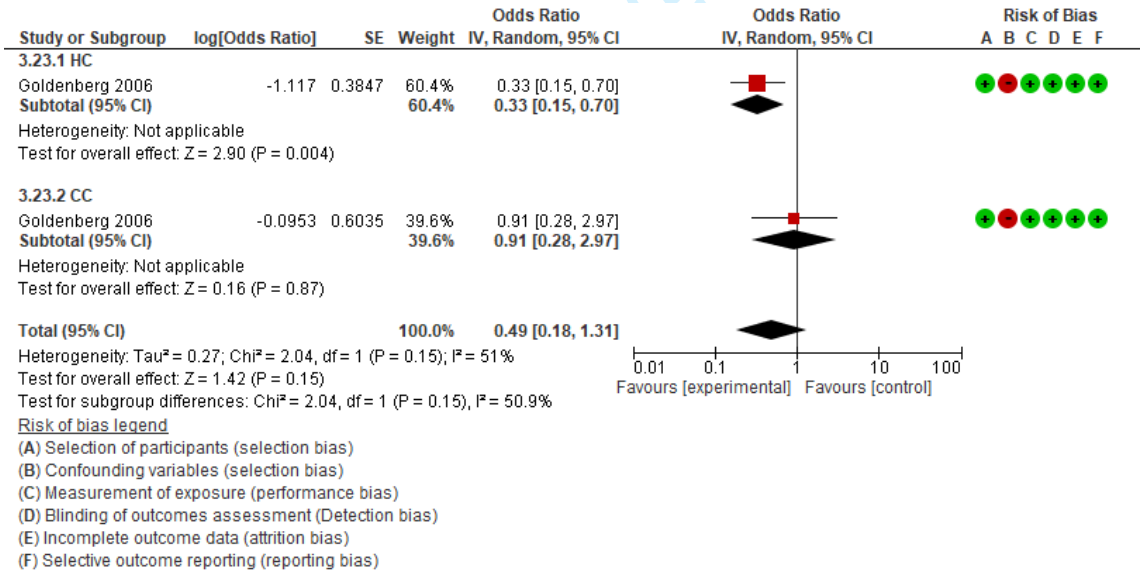
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

19) Discharge with respiratory support (HC)



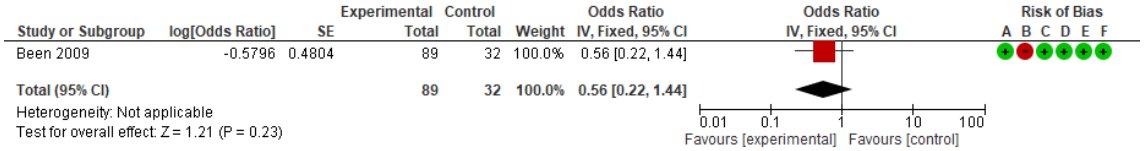
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

20) Systemic inflammatory response syndrome



SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis; **CC:** Clinical chorioamnionitis

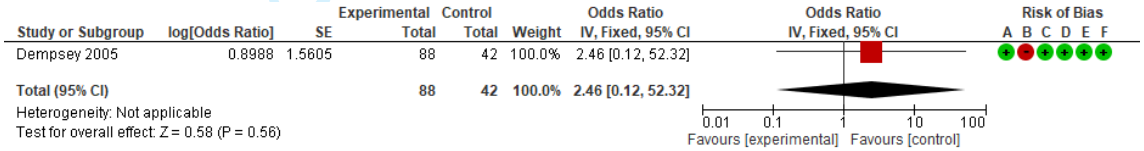
21) Severe respiratory distress syndrome (RDS) (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

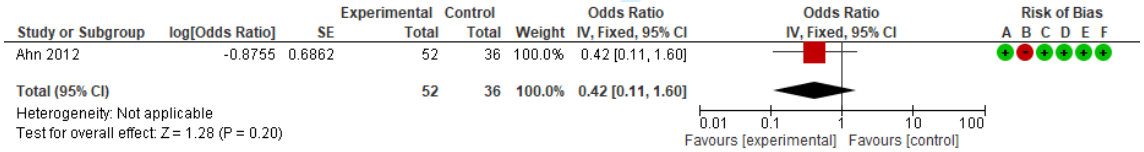
22) Meningitis (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

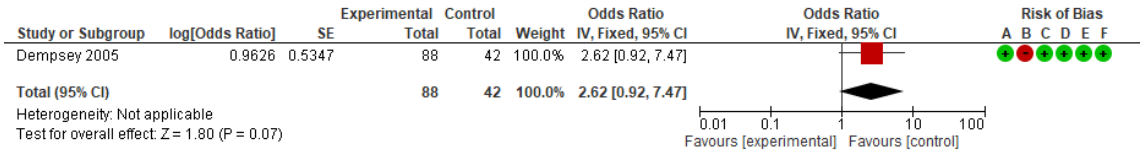
23) Intrahepatic cholestasis (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

24) Pneumonia (HC)



Risk of bias legend
(A) Selection of participants (selection bias)
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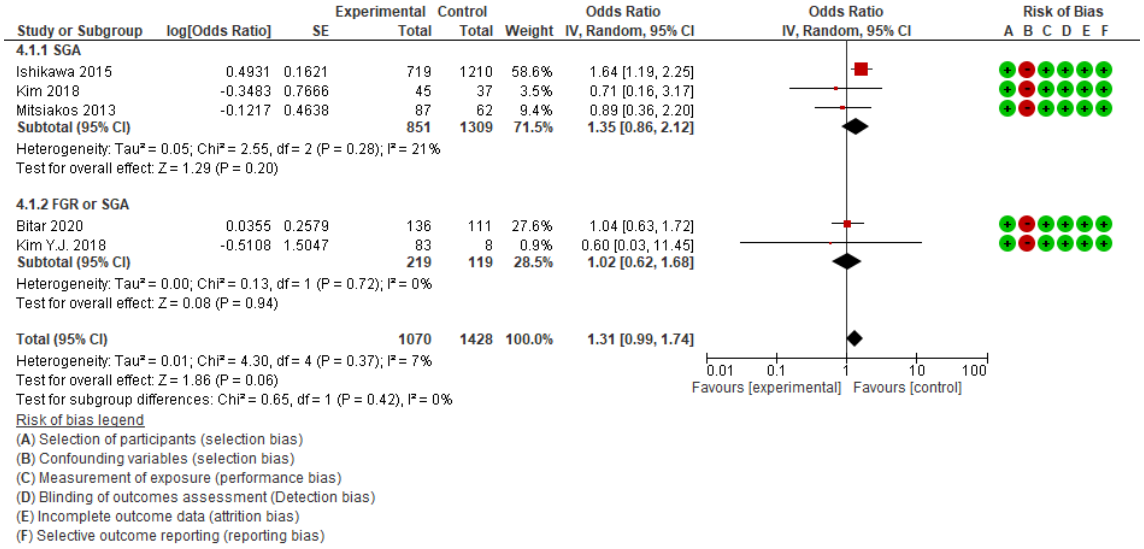
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

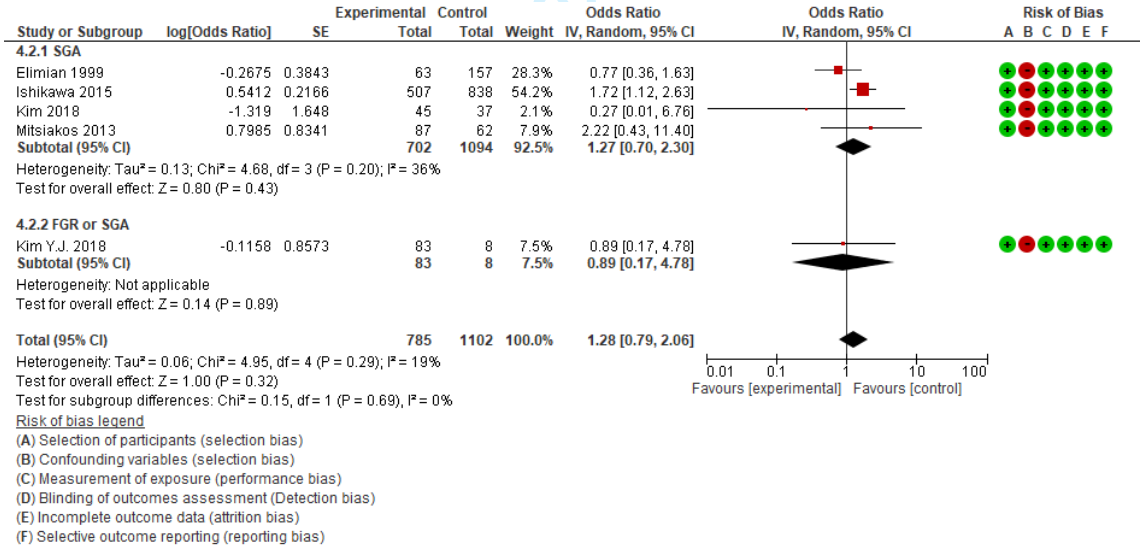
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



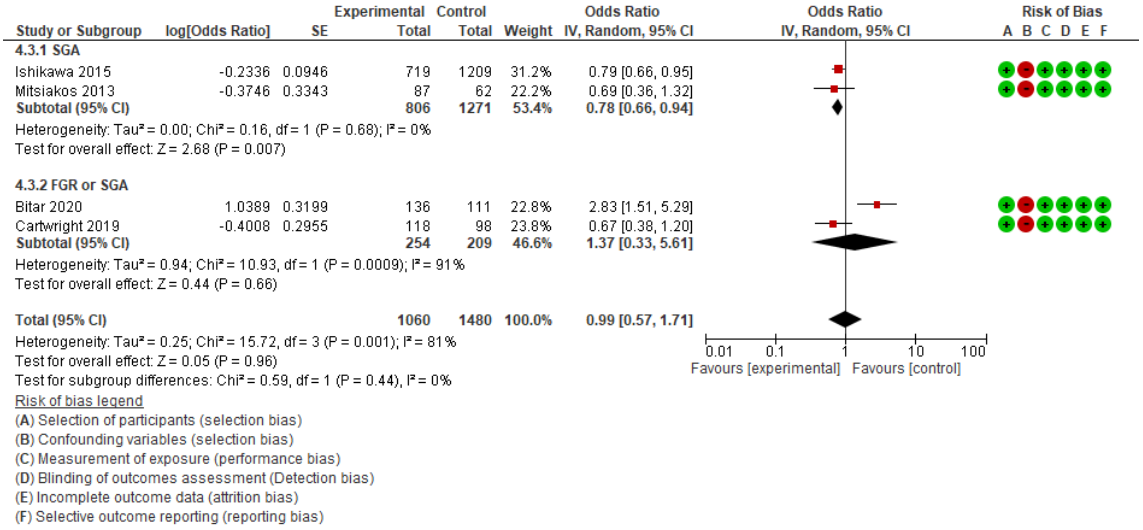
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Chorioamnionitis (histologic and /or clinical)



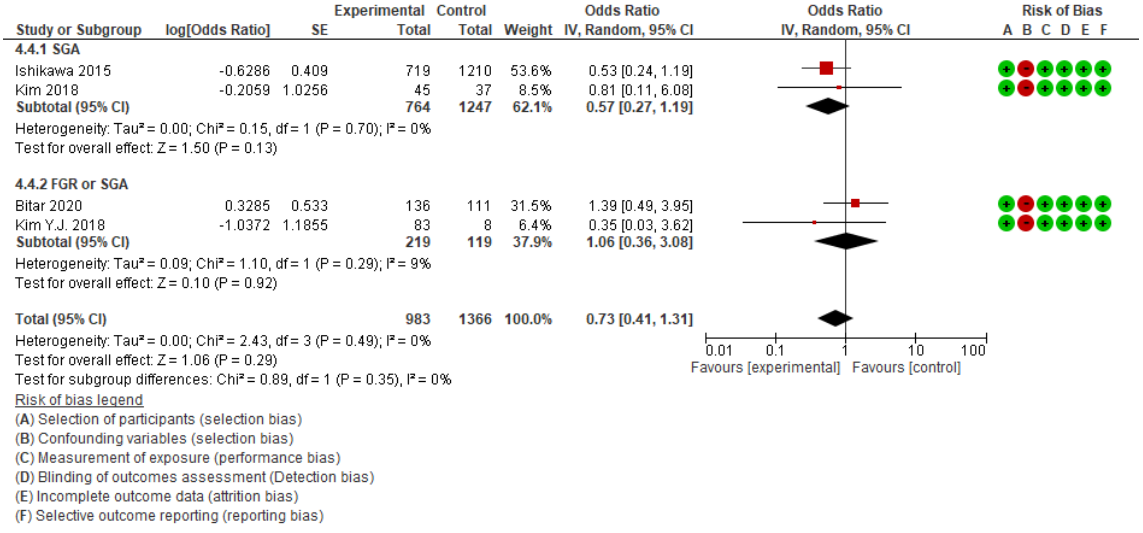
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Preeclampsia.



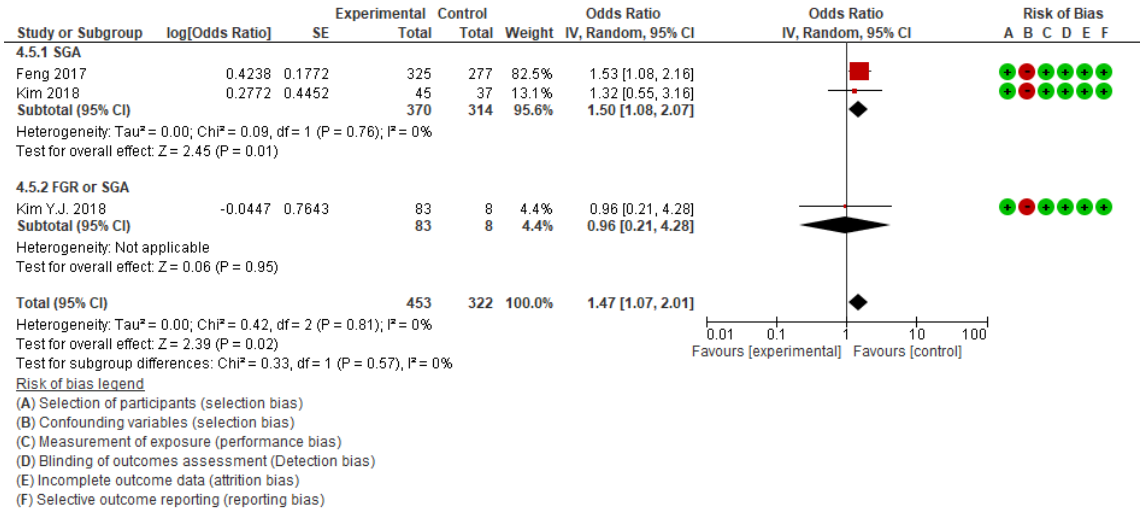
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Gestational diabetes mellitus.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

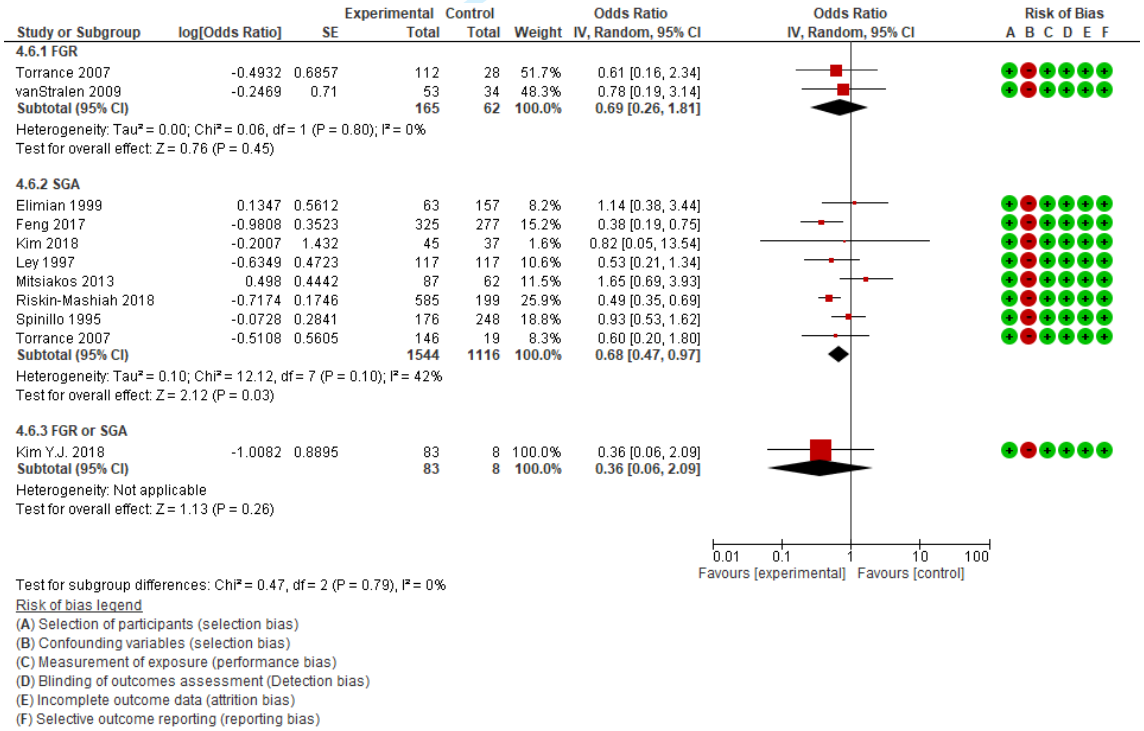
5) Pregnancy induced hypertension.



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

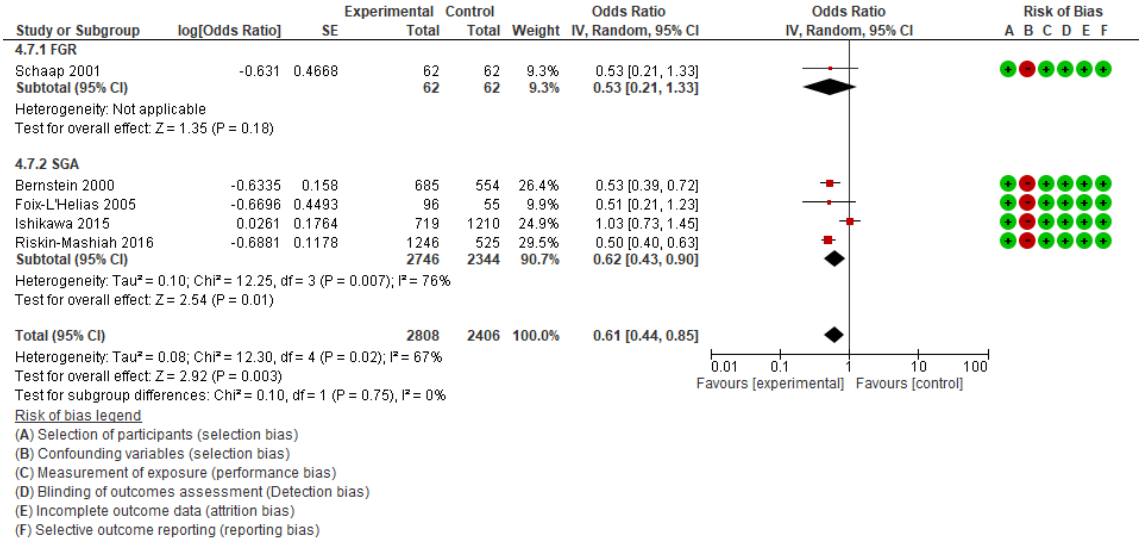
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



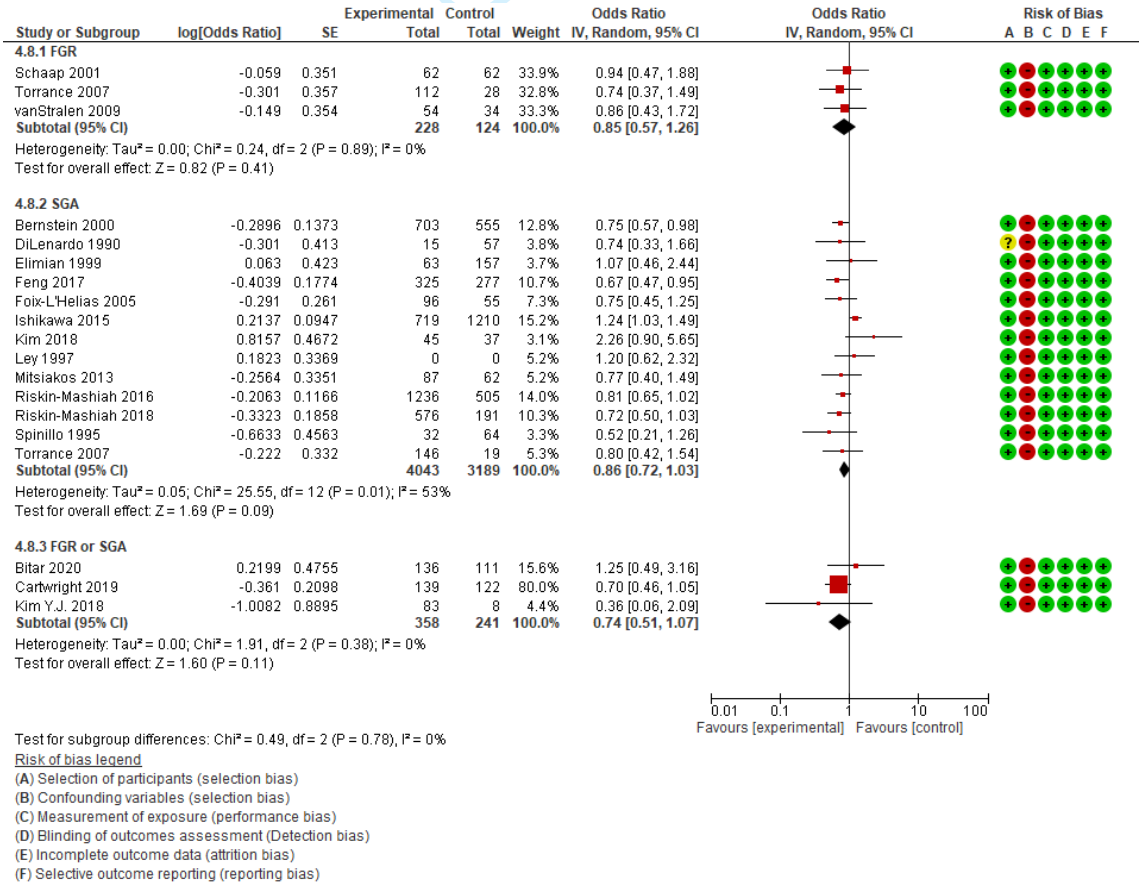
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

2) Death before discharge home



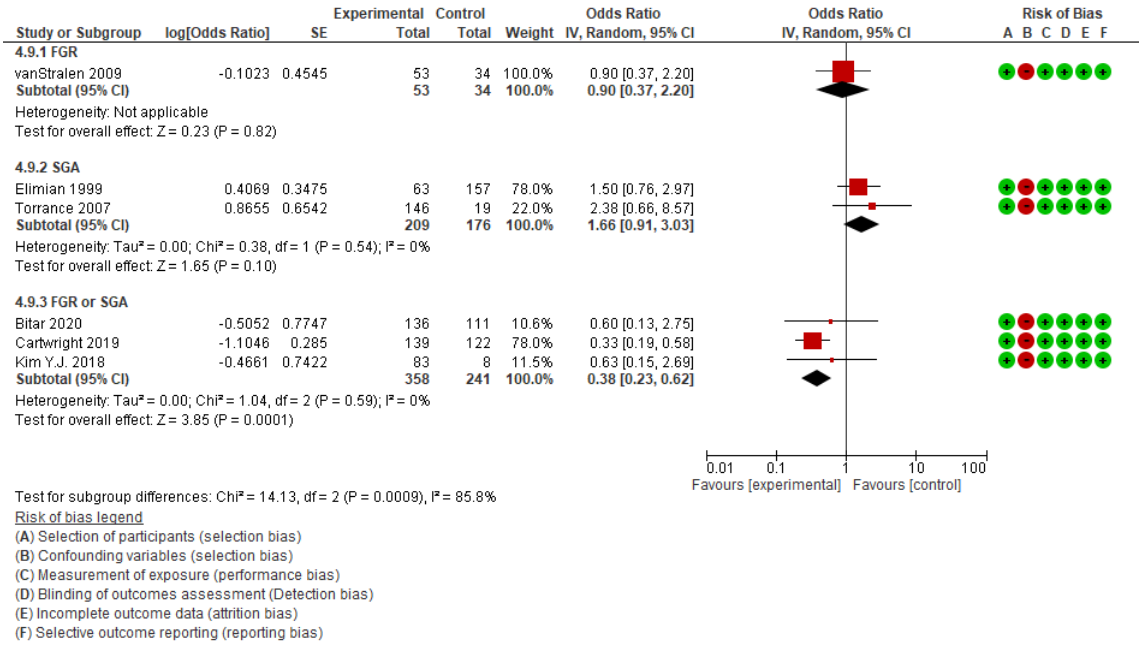
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

3) Respiratory distress syndrome (RDS) and moderate / severe RDS



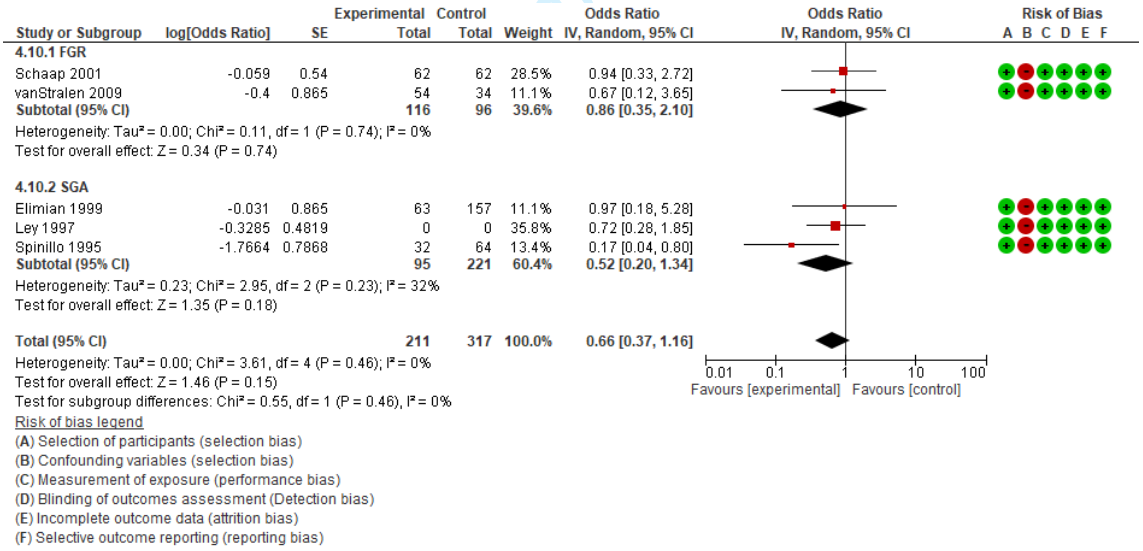
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

4) Surfactant use



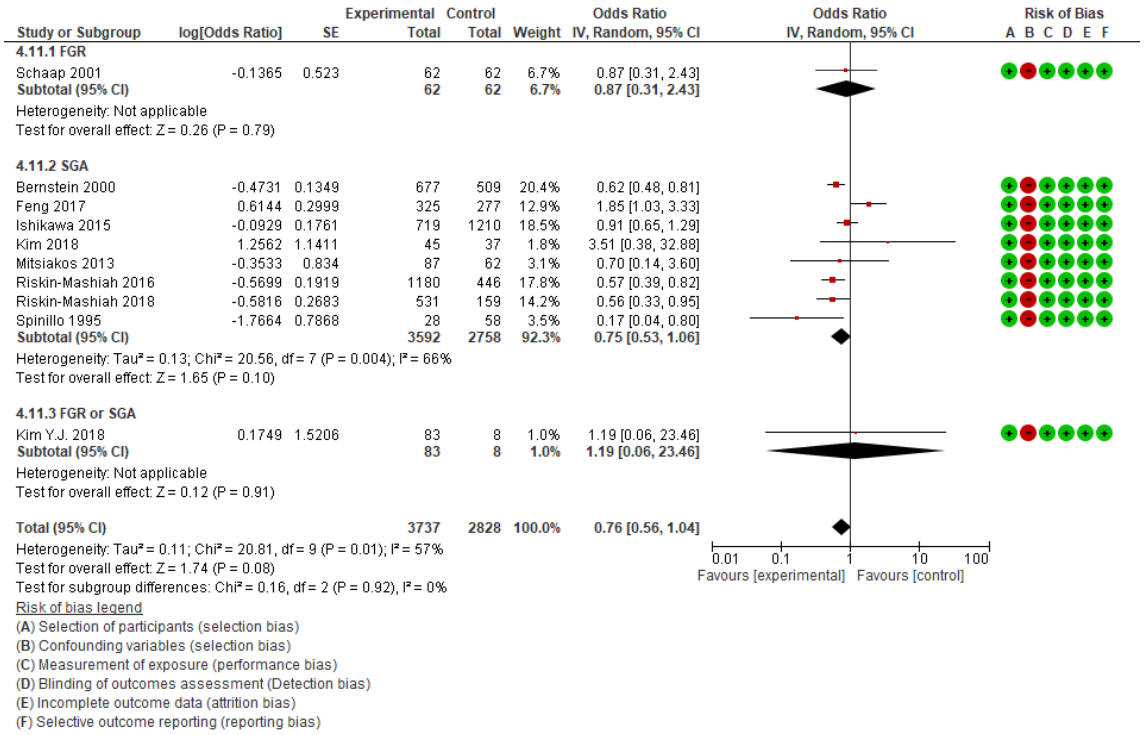
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

5) Major brain lesion (IVH, ICH, PVH, PVL)



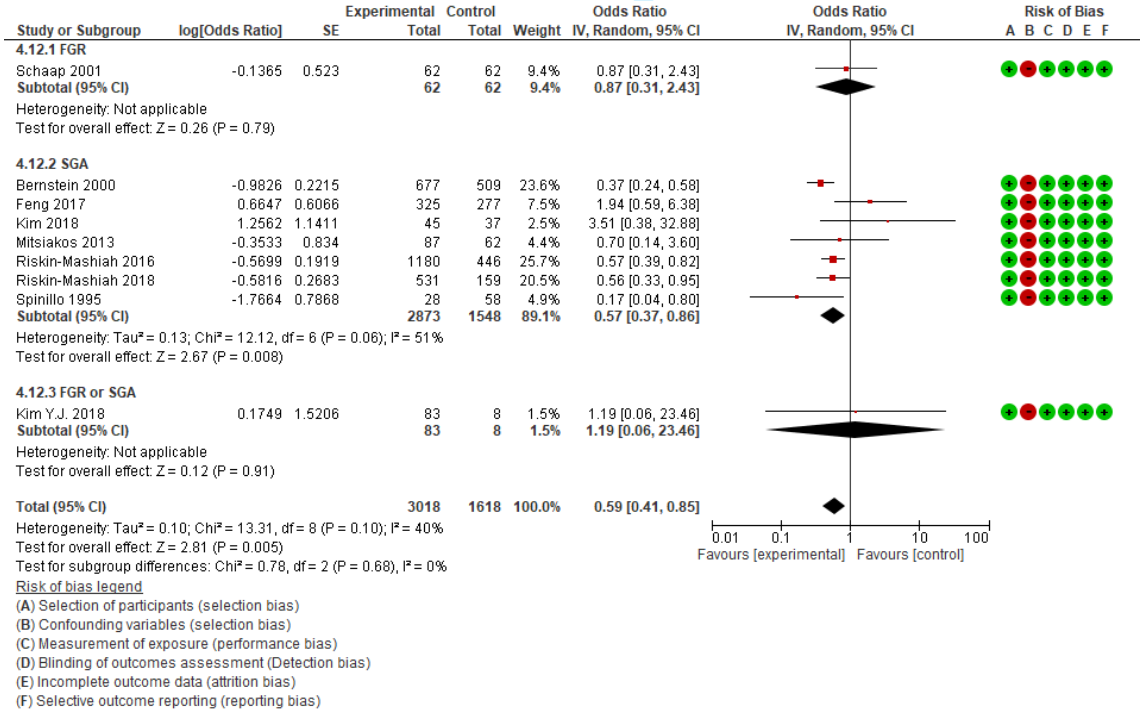
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

6) Interventricular haemorrhage



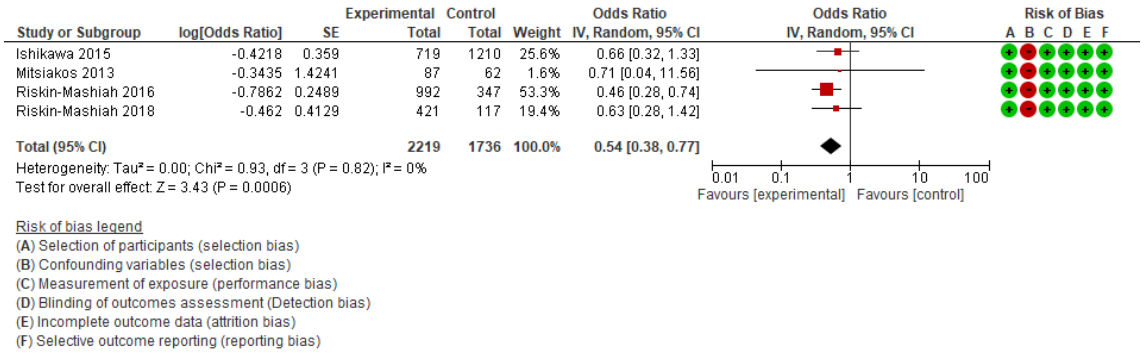
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

7) Severe interventricular haemorrhage (grade3-4)



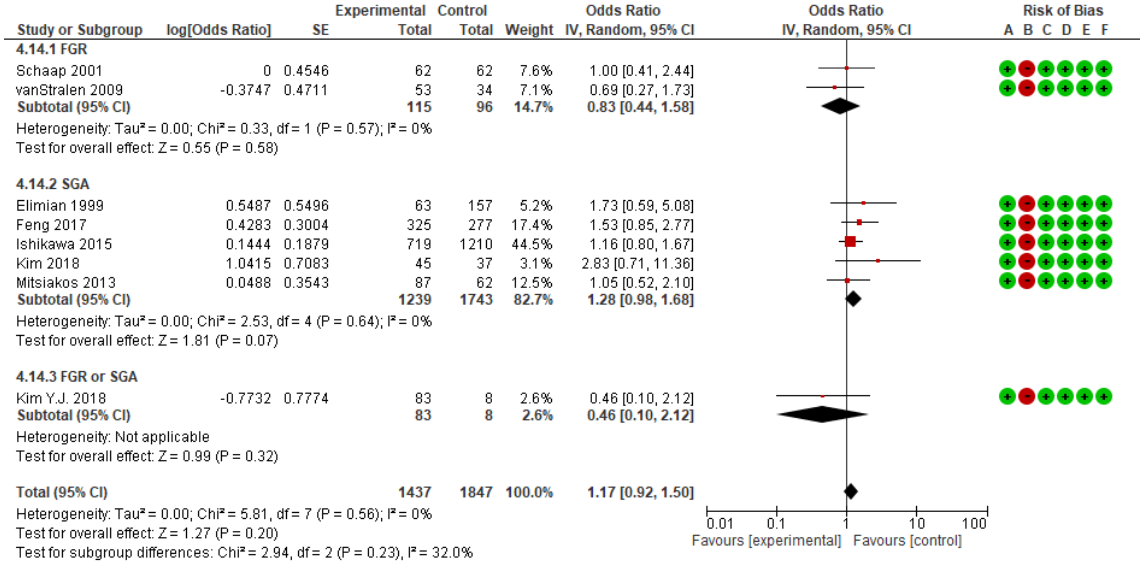
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

8) Periventricular leukomalacia (SGA)



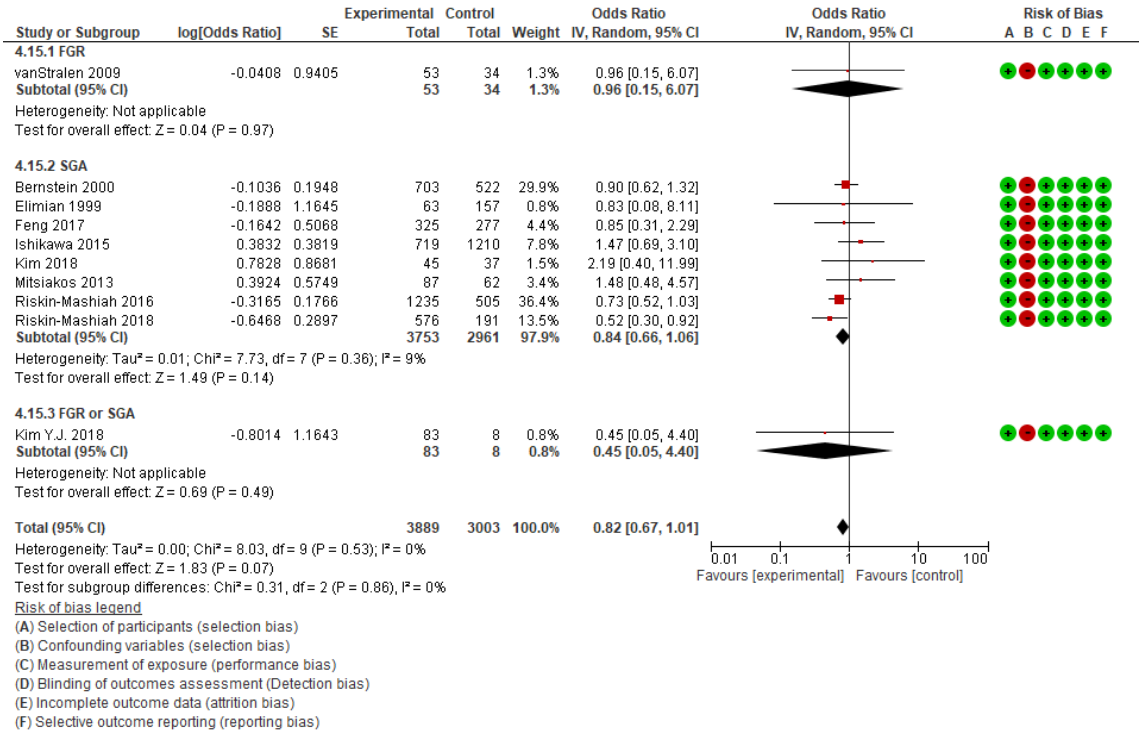
SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

9) Neonatal sepsis



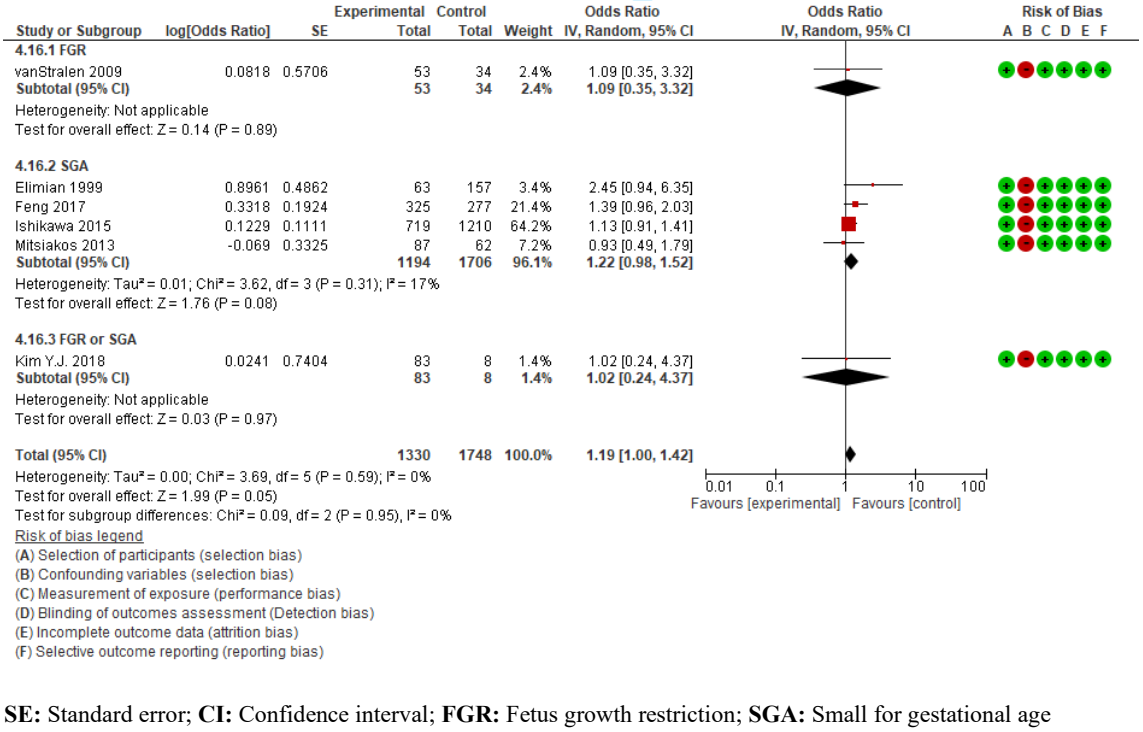
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

10) Necrotizing enterocolitis



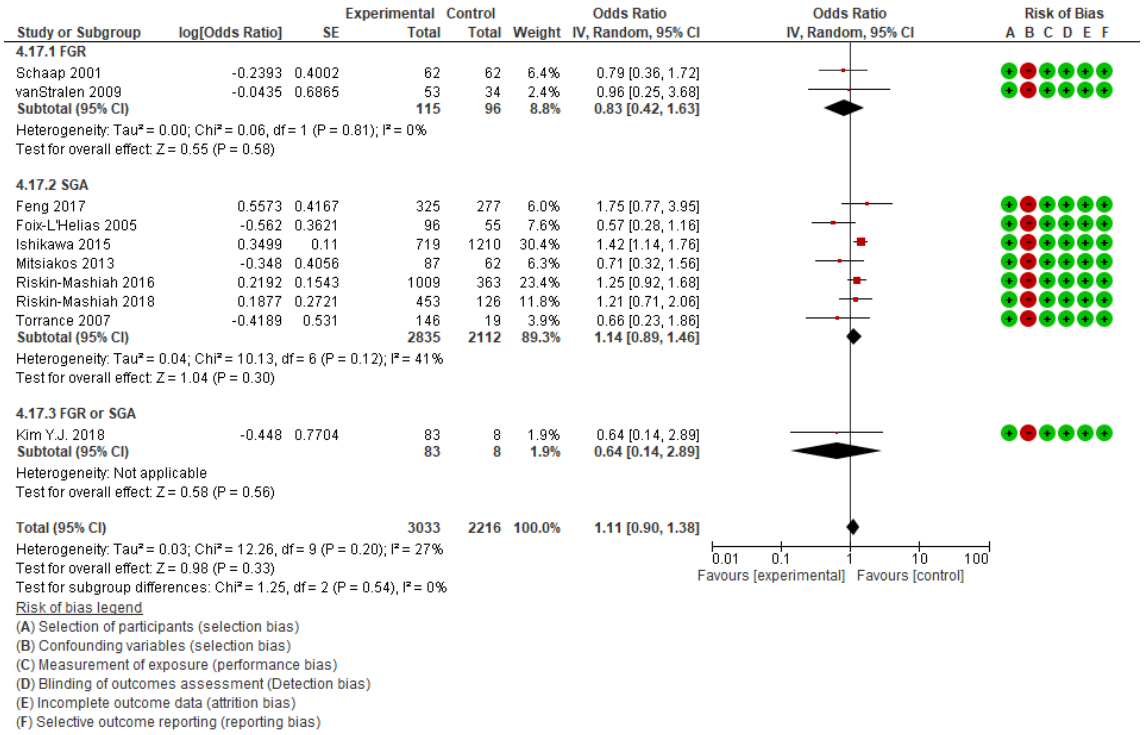
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

11) Patent ductus arteriosus



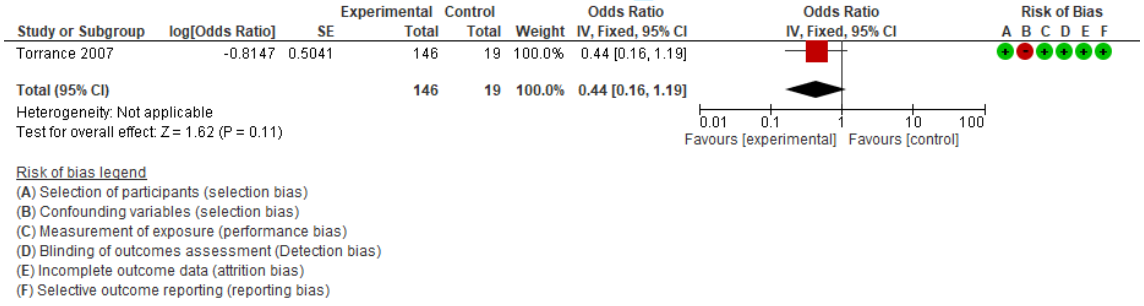
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



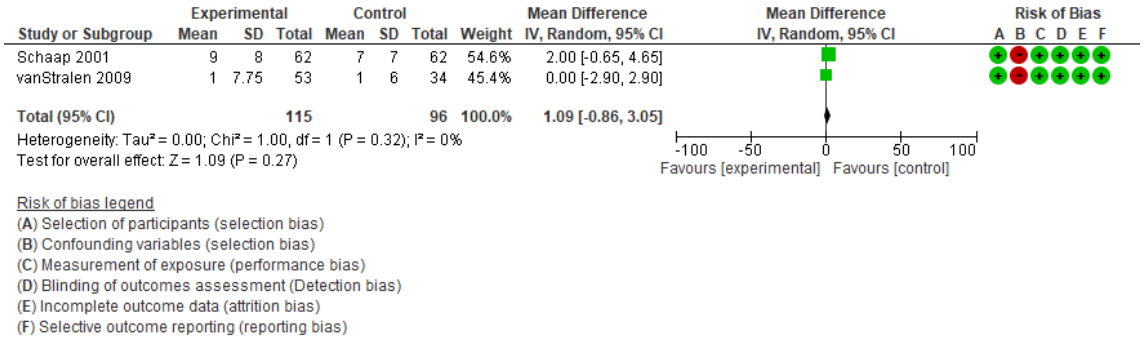
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

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



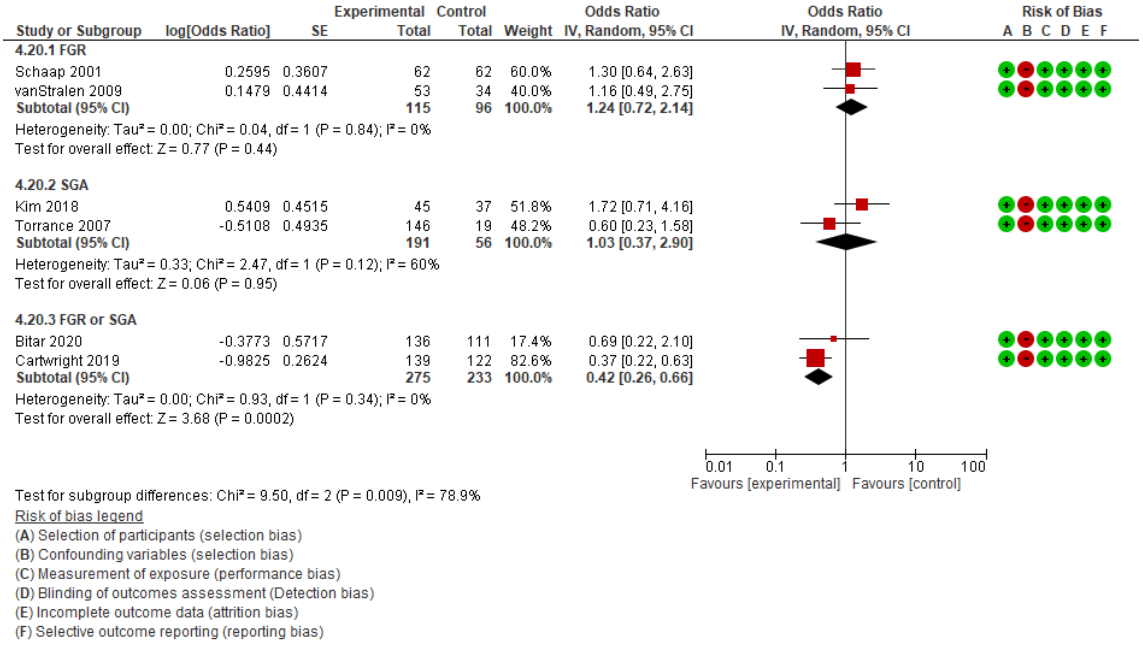
SE: Standard error; **CI:** Confidence interval

14) Duration of mechanical ventilation (FGR)



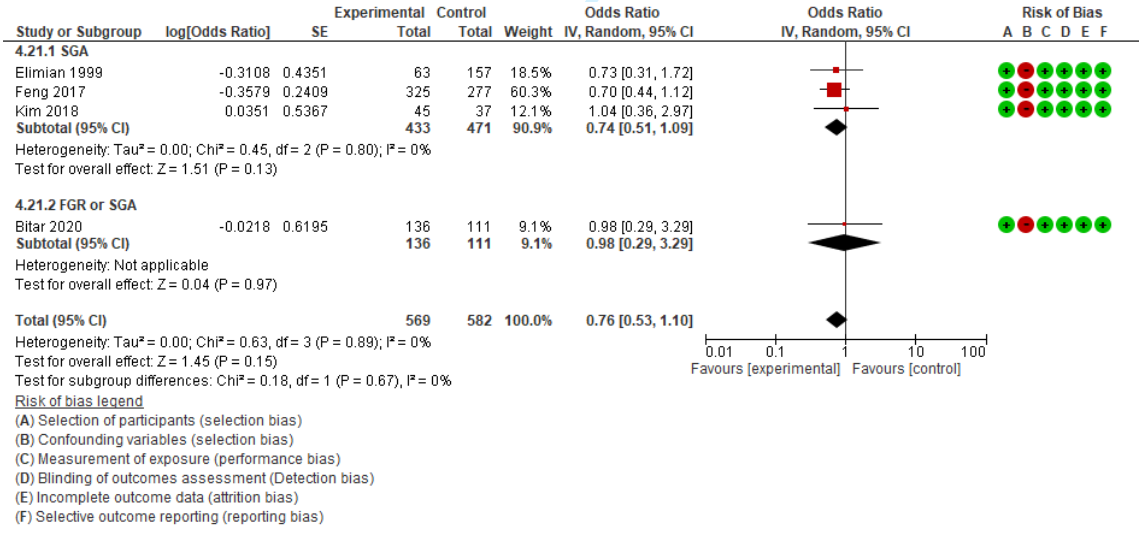
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

15) Use of mechanical ventilation



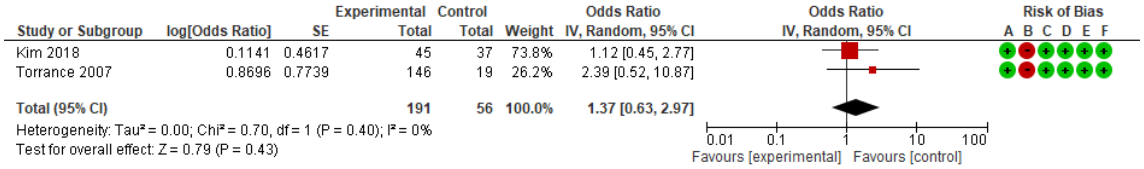
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

16) Apgar score < 7 at 5 minutes



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

17) Apgar score < 5 at 1 minute (SGA)



Risk of bias legend
(A) Selection of participants (selection bias)
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(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
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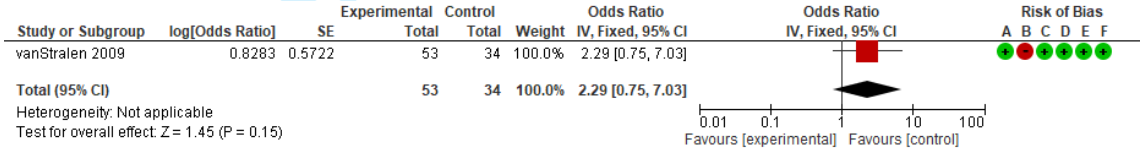
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

18) Hypotension (FGR)



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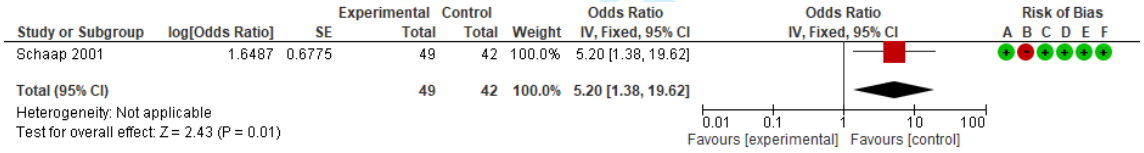
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

19) Growth < 10th percentile in early childhood (FGR)



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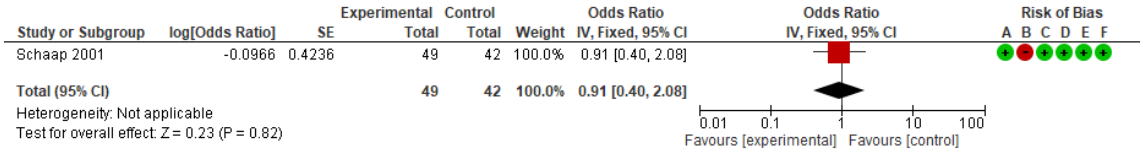
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

20) Abnormal behavior at long-term follow-up at school age (FGR)



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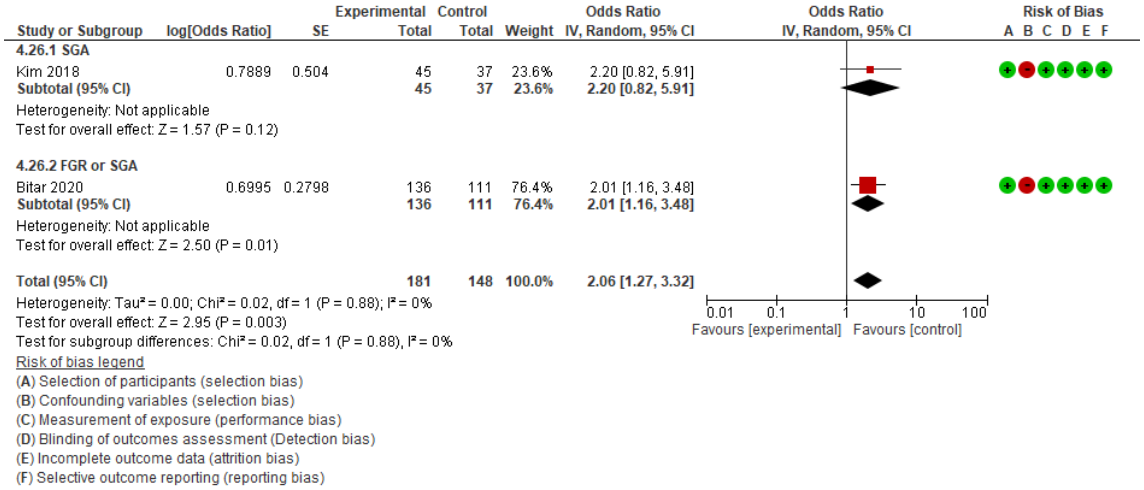
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

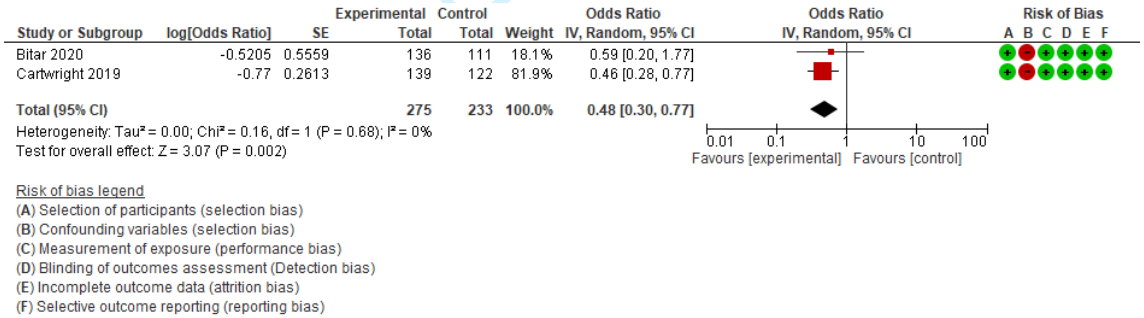
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

21) Neonatal hypoglycemia



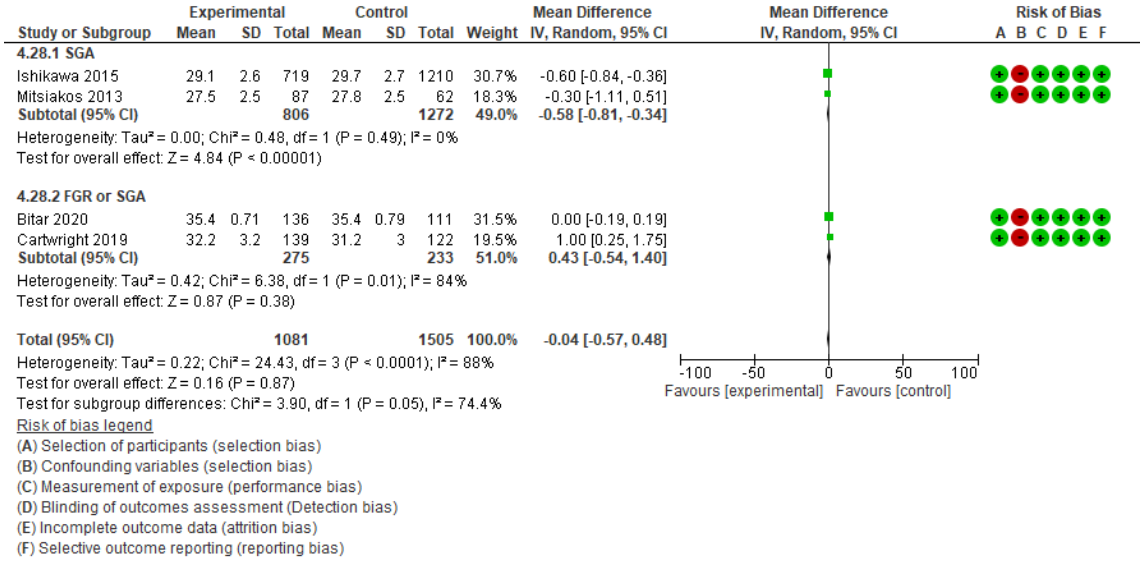
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

22) Oxygen therapy (FGR or SGA)



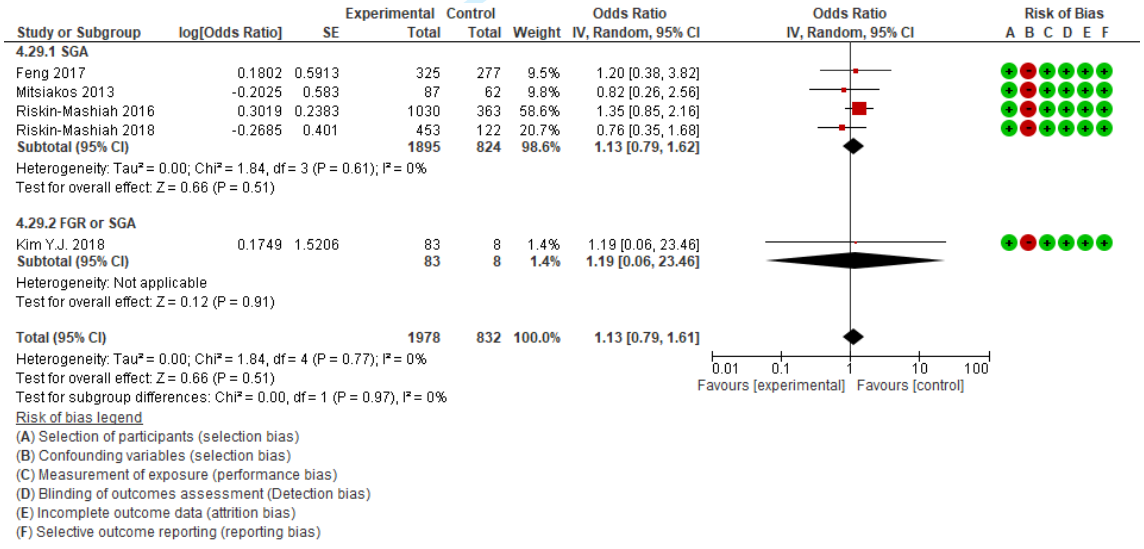
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

23) Gestational age at birth



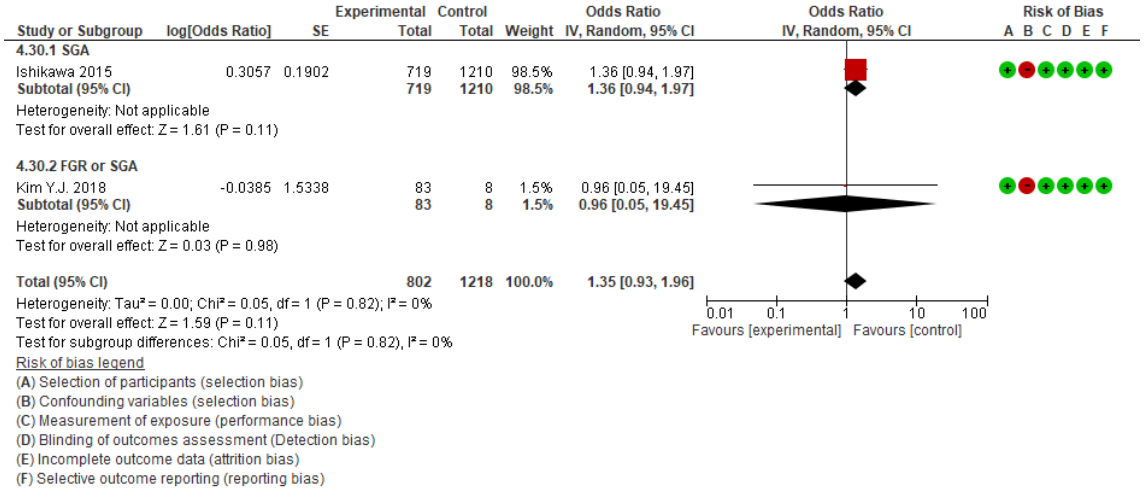
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

24) Retinopathy of prematurity



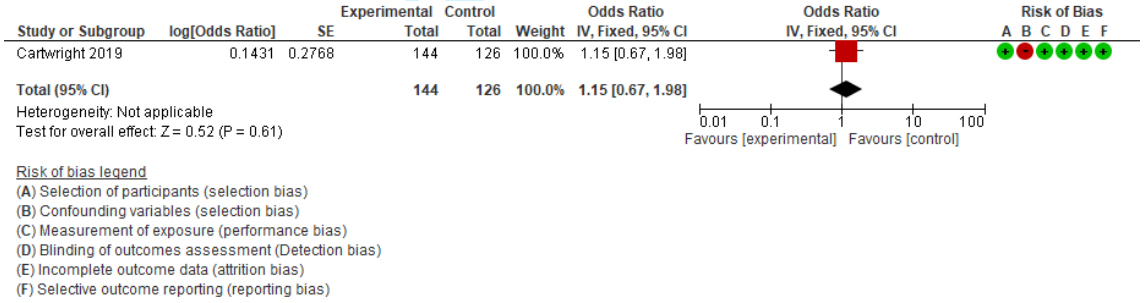
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

25) Neonatal adrenal insufficiency



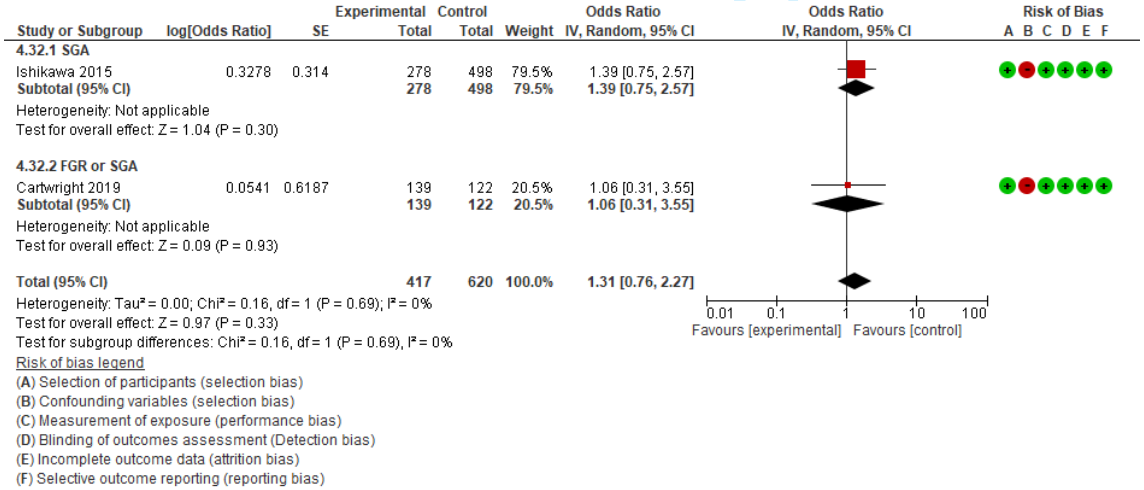
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

26) Survival free of disability (FGR or SGA)



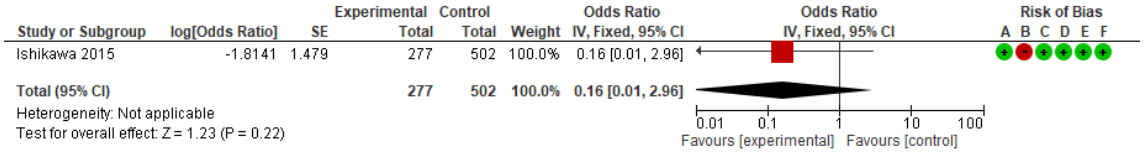
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

27) Cerebral palsy



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

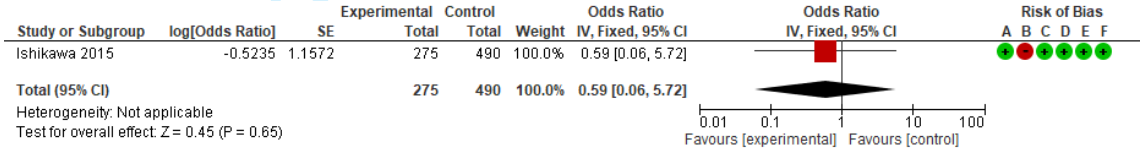
28) Severe hearing impairment (SGA)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

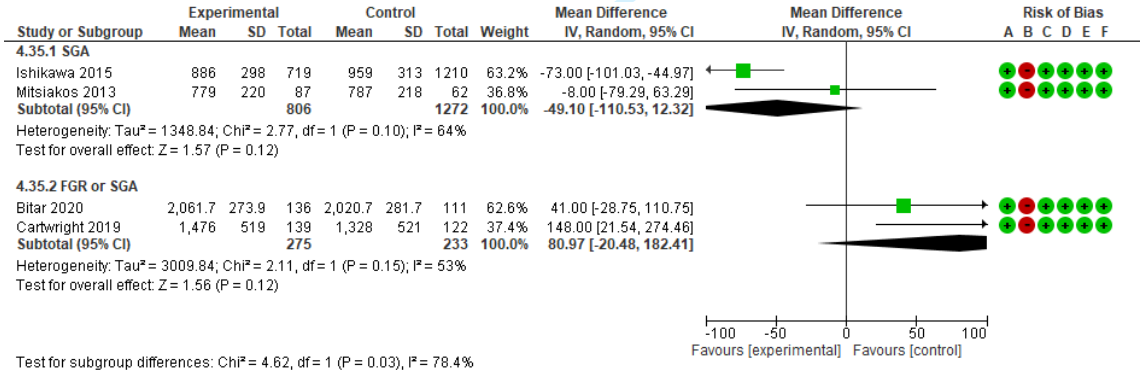
29) Visual impairment (SGA)



Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

SE: Standard error; **CI:** Confidence interval; **SGA:** Small for gestational age

30) Birth weight

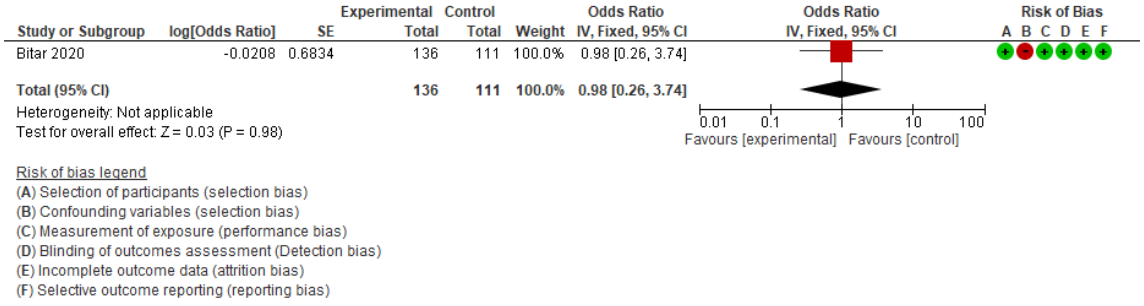


Test for subgroup differences: Chi² = 4.62, df = 1 (P = 0.03), I² = 78.4%

Risk of bias legend
(A) Selection of participants (selection bias)
(B) Confounding variables (selection bias)
(C) Measurement of exposure (performance bias)
(D) Blinding of outcomes assessment (Detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective outcome reporting (reporting bias)

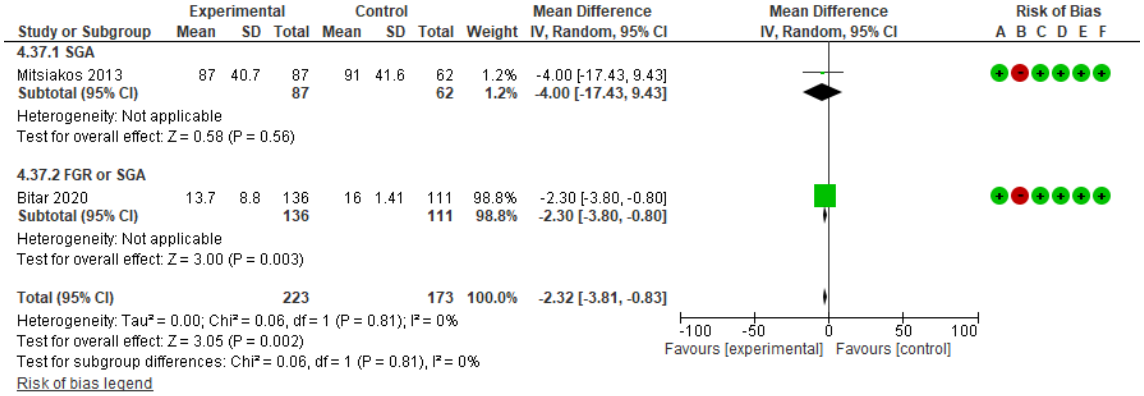
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

31) Admission to neonatal intensive care unit (FGR or SGA)



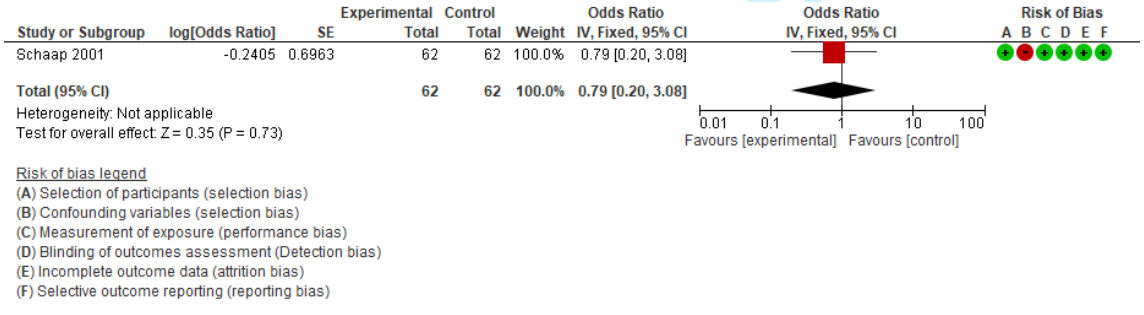
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

32) Duration of hospital stay



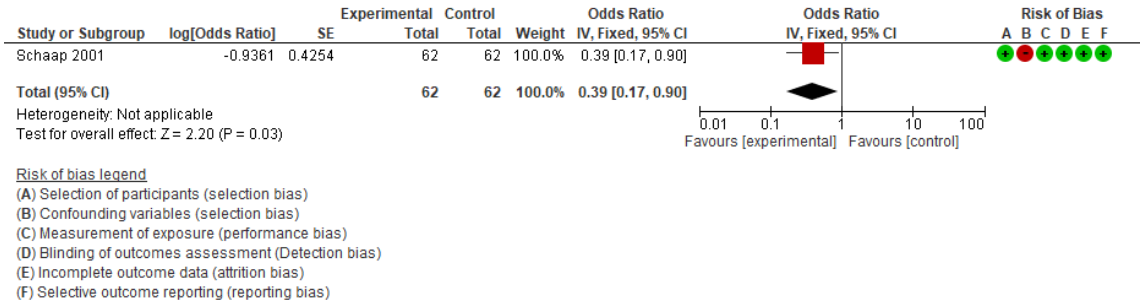
SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction; **SGA:** Small for gestational age

33) Death at long-term follow-up (school age) (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction

34) Death or disability/handicap at 2yrs' corrected age (FGR)



SE: Standard error; **CI:** Confidence interval; **FGR:** Fetus growth restriction