

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065070
Article Type:	Original research
Date Submitted by the Author:	03-Jun-2022
Complete List of Authors:	Saito, KANA; Saitama Medical Center, Pediatrics Nishimura, Etsuko; St Luke's International University, Graduate School of Nursing Science Ota, Erika; St Luke's International University, Graduate School of Nursing Science; The Tokyo Foundation for Policy Research Namba, Fumihiko; Saitama Medical Center, Pediatrics Swa, Toshiyuki; Osaka University School of Medicine Graduate School of Medicine Ramson, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Lavin, Tina; World Health Organization, Department of Sexual and Reproductive Health and Research Cao, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Vogel, J; Burnet Institute, Maternal, Child and Adolescent Health Program
Keywords:	OBSTETRICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, REPRODUCTIVE MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 **ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF**
5 2 **PRETERM BIRTH: A SYSTEMATIC REVIEW**
6
7 3

8
9 4 Kana Saito^a, Etsuko Nishimura^b, Erika Ota^{b,c}, Fumihiko Namba^a, Toshiyuki Swa^d, Jenny
10 5 Ramson^e, Tina Lavin^f, Jenny Cao^e, Joshua P. Vogel^e
11 6

12 7
13 7 **Affiliations:**

14 8 ^a Saitama Medical Center, Saitama Medical University, Saitama, Japan

15 9 ^b St. Luke's International University, Tokyo, Japan

16 10 ^c Tokyo Foundation for Policy Research, Tokyo, Japan

17 11 ^d Osaka University, Graduate School of Medicine, Osaka, Japan

18 12 ^e Maternal, Child and Adolescent Health Program, Burnet Institute, Melbourne,
19 13 Australia

20 14 ^f UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research,
21 15 Development and Research Training in Human Reproduction, Department of Sexual
22 16 and Reproductive Health and Research, World Health Organization, Geneva,
23 17 Switzerland.
24 18

25 19 **Correspondence to:** Kana Saito

26 20 Department of Pediatrics, Saitama Medical Center, Saitama Medical University

27 21 1981 Kamoda, Kawagoe-city, Saitama 350-8550, Japan,

28 22 Phone: 81-49-228-3400

29 23 E-mail: kana988@live.jp

30 24 ORCID: 0000-0001-7781-1870
31 25

32 26 **Word count:** 3796 words
33 27

34 28 **Short title:** Systematic review: antenatal steroids in specific women
35 29
36 30
37 31
38 32
39 33
40 34
41 35
42 36
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 37 **ABSTRACT**
5
6 38

7 39 **Objective:** Synthesize available evidence on ACS effectiveness among women at risk
8 40 of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or
9 41 fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm
10 42 period.
11
12
13
14

15 44 **Methods:** A systemic search of MEDLINE, EMBASE, CINAHL, Cochrane Library,
16 45 Web of Science, Global Index Medicus was conducted for all comparative randomized
17 46 or non-randomized interventional studies in the four subpopulations. Data were
18 47 extracted independently by authors. Risk of Bias Assessment tool for Non-randomized
19 48 Studies (RoBANS) was used to assess risk in non-randomized studies. Grading of
20 49 Recommendations, Assessment, Development and Evaluations (GRADE) was used to
21 50 assess the certainty of evidence.
22
23
24
25

26 51
27 52 **Results:** Twenty-three studies with 18003 pregnant women/neonates were included. All
28 53 included articles were observational studies. Data on women with diabetes were limited
29 54 and evidence on women undergoing planned CS was inconclusive. ACS was associated
30 55 with possibly reduced odds of neonatal mortality (pooled OR 0.49, 95%CI 0.33-0.74,
31 56 low certainty), severe intraventricular hemorrhage (IVH) (pooled OR 0.41, 95%CI 0.23-
32 57 0.72, low), and IVH (pooled OR 0.41, 95%CI 0.19-0.87, low) in women with
33 58 histological chorioamnionitis. Among women with clinical chorioamnionitis, IVH
34 59 (pooled OR 0.39, 95%CI 0.15-0.99, low) and periventricular leukomalacia (pooled OR
35 60 0.30, 95%CI 0.11-0.86, low) odds were possibly reduced. Among women with FGR,
36 61 surfactant use (pooled OR 0.38, 95%CI 0.23-0.62, moderate), mechanical ventilation
37 62 (pooled OR 0.42, 95%CI 0.26-0.66, moderate), and oxygen therapy (pooled OR 0.48,
38 63 95%CI 0.30-0.77, moderate) were probably reduced, but hypoglycemia probably
39 64 increased (pooled OR 2.06, 95%CI 1.27-3.32, moderate). Definitional differences for
40 65 populations and outcomes complicated meta-analyses. Most studies were conducted in
41 66 high-income countries.
42
43
44
45
46
47
48
49

50 67
51 68 **Conclusions:** Evidence is lacking for women with diabetes or undergoing planned CS.
52 69 ACS might have benefits in women with chorioamnionitis. ACS is probably beneficial
53 70 in FGR but can increase neonatal hypoglycemia. Well-designed studies with adequate
54 71 follow-up are required.
55
56
57
58
59
60

1
2
3
4 **73 Protocol registration:**

5
6 74 PROSPERO (CRD42021267816; Supplementary File S1)

7
8 75

9 **76 Strengths and limitations:**

10 77 -This review included a broad search strategy.

11 78 -This review applied rigorous quality assessment and GRADE methodology.

12 79 -Definitional differences for population and outcomes complicated meta-analysis.

13 80 -Most studies were conducted in high-income countries.

14
15
16 81

17
18 82

19
20 **83 INTRODUCTION**

21
22
23 84 Antenatal corticosteroids (ACS), such as intramuscular dexamethasone or

24
25
26 85 betamethasone, have been shown to cross the placenta and can induce fetal lung

27
28
29 86 maturation.¹ When ACS is administered to women at risk of imminent preterm birth

30
31
32 87 prior to 34 weeks' gestation, the risk of perinatal death, neonatal death, and respiratory

33
34
35 88 distress syndrome (RDS) is significantly reduced.² ACS also probably decreases the risk

36
37
38 89 of intraventricular hemorrhage (IVH) and reduces developmental delay in childhood.²

39
40
41 90 As a result, the World Health Organization (WHO) and several obstetric and

42
43
44 91 gynecological societies internationally recommend ACS therapy in women up to 34

45
46
47 92 weeks' gestation for improving preterm newborn outcomes.³⁻⁶ Some national

48
49
50 93 organizations have recommended the use of ACS in women at risk of preterm birth up

51
52
53 94 to 36 weeks' gestation on the basis of the evidence that there may be some respiratory-

54
55
56 95 related benefits for the newborn.^{3,4}

1
2
3
4
5 96
6
78 97 However, the evidence regarding benefits and possible harms of ACS use in
910 98 subpopulations of women with specific complications of pregnancy, such as women
11
1213 99 with diabetes, chorioamnionitis or babies fetal growth restriction (FGR), is more
14
1516 100 controversial. Women with diabetes, chorioamnionitis, or babies with FGR are at higher
17
1819 101 risk of adverse perinatal outcomes, but they are generally excluded from ACS efficacy
20
2122 102 trials.² Consequently, any subgroup analyses to explore the effects of ACS in women
23
2425 103 with these complications is unlikely to provide direct evidence from which conclusions
26
2728 104 can be drawn.
29
3031
32 105
33
3435 106 While pregnant women with diabetes are at a higher risk of spontaneous preterm birth
36
3738 107 and may require ACS, glucocorticoids have hyperglycaemic effects; respiratory
39
4041 108 morbidities that affect preterm infants may be exacerbated in the setting of poor
42
4344 109 maternal glycaemic control.⁷⁻⁹ Chorioamnionitis is acute inflammation of the
45
4647 110 membranes and chorion of the placenta and is estimated to affect 3.9% of women giving
48
4950 111 birth.¹⁰ Chorioamnionitis treatment involves antibiotics and prompt delivery of the
51
5253 112 fetus; typically, ACS is avoided due to concerns that its immunosuppressive effects may
54
5556 113 worsen outcomes for the woman and her baby. However, the relative benefits and harms
57
58
59
60

1
2
3
4
5 114 of using ACS in this clinical situation are unclear. In many high-income countries, small
6
7
8 115 for gestational age (SGA) neonates account for approximately 10% of all babies; this
9
10
11 116 proportion is generally higher in low-to-middle income countries.¹¹⁻¹³ SGA is associated
12
13
14 117 with an increased risk of neonatal morbidity and mortality than those babies born
15
16
17 118 appropriate for gestational age (AGA).^{14,15} The term SGA is often used as a proxy
18
19
20 119 measure for FGR because most cases of SGA are caused by FGR.¹⁶ Clarifying ACS
21
22
23 120 effects in women at risk of imminent preterm birth with growth-restricted fetuses is
24
25
26 121 necessary.

27
28
29 122
30
31
32 123 An additional clinical scenario where there is uncertainty regarding ACS efficacy is in
33
34
35 124 women undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to
36
37
38 125 <37 weeks' gestation). Babies born in late preterm have lower risks of mortality and
39
40
41 126 morbidity compared with those born prior to 34 weeks' gestation; however, they have
42
43
44 127 higher risks of adverse outcomes than babies born at term.¹⁷⁻²⁰ In many countries, the
45
46
47 128 rate of provider-initiated late preterm birth is rising, which has been linked to the more
48
49
50 129 generalised increase in CS use.²¹ Regardless of gestational age, babies born via elective
51
52
53 130 CS do not have the usual physical and hormonal stimuli of passage through the birth
54
55
56 131 canal; thus, they tend to have higher rates of respiratory morbidity.²²⁻²⁴ Some studies
57
58
59
60

1
2
3
4
5 132 have suggested that the risk of neonatal hypoglycaemia is greater following CS
6
7
8 133 although this may be confounded by the underlying indication for CS.²⁵
9
10
11 134
12
13
14 135 In 2016, members of our team published a systematic review to assess the effectiveness
15
16
17 136 of ACS in these four clinical situations.²⁶ The review did not find any direct evidence
18
19
20 137 on the effects of ACS in pregnant women with diabetes at risk of preterm birth or for
21
22
23 138 those undergoing elective CS in the late preterm period. The review could not draw firm
24
25
26 139 conclusions regarding the effects of ACS in women with growth-restricted fetuses
27
28
29 140 although low-quality evidence suggested that ACS reduces neonatal IVH in women
30
31
32 141 with chorioamnionitis.²⁶ Findings of the previous review informed WHO's 2015 ACS
33
34
35 142 recommendations.²⁷ As part of WHO's living guidelines in maternal and perinatal
36
37
38 143 health program, the ACS recommendations are currently being updated.²⁸ Hence, our
39
40
41 144 aim is to update the 2016 systematic review and provide a contemporary evidence base
42
43
44 145 for researchers, clinicians, and maternal and newborn health stakeholders on safe and
45
46
47 146 effective clinical management in preterm birth.
48
49

50 147

53 148 **METHODS**

56 149 The specific review objectives are described in Box 1, comprising four related questions
57
58
59
60

1
2
3
4
5 150 on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or
6
7
8 151 gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm
9
10
11 152 period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA
12
13
14 153 infants. The review protocol was registered on PROSPERO (CRD42021267816) and
15
16
17 154 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-
18
19
20 155 Analyses (PRISMA) checklist (Supplementary File S1, S2).²⁹
21
22

23 156

25 157 Box 1. Four Participant, Intervention, Comparison, Outcome (PICO) questions for the
26
27 158 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

55 159
56
57
58
59
60

1
2
3
4
5 **160 Study eligibility criteria**
6

7
8 161 Eligible studies were randomized or nonrandomized primary research studies that
9
10 162 reported on the effects of ACS in the four subpopulations. This included published,
11
12 163 unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled
13
14 164 before-after studies, interrupted-time-series studies, historically controlled studies,
15
16 165 cohort studies, and cross-sectional studies comparing any ACS administration
17
18 166 (betamethasone, dexamethasone, or hydrocortisone) given either parentally or enterally
19
20 167 with placebo or no treatment. Study populations of interest were women at risk of
21
22 168 imminent preterm birth or provider-initiated preterm birth and where the study
23
24 169 population fulfilled one or more of the following conditions: women with pregestational
25
26 170 and/or gestational diabetes, women undergoing elective CS in the late preterm period,
27
28 171 women with chorioamnionitis, and women with a FGR fetus or SGA infant.
29
30
31
32
33
34
35
36
37
38
39
40
41 172
42
43
44 173 Articles in any language and from any country were eligible for inclusion if they
45
46 174 reported on one or more of the review outcomes of interest that reflected WHO's
47
48 175 priority outcomes for preterm birth guideline development.²⁷ Maternal outcomes were
49
50 176 death, maternal morbidity, and side effects of therapy. Newborn and child outcomes of
51
52 177 interest were perinatal mortality, fetal mortality, neonatal mortality, neonatal morbidity,
53
54
55
56
57
58
59
60

1
2
3
4
5 178 neurodevelopment, anthropometric status, and side effects of therapy (Supplementary
6
7
8 179 File S3).
9

10
11 180
12

13 14 181 **Data sources and search strategy** 15

16
17 182 An information specialist was consulted for developing the search strategy. A
18
19
20 183 systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of
21
22
23 184 Science, and Global Index Medicus was conducted with no date restrictions. Controlled
24
25
26 185 vocabularies supplemented with free keywords were used to search for the relevant
27
28
29 186 concept areas, with duplicates removed in the process to yield a total number of
30
31
32 187 abstracts for each database (Supplementary File S4). Reference lists of the included
33
34
35 188 articles, including any recent systematic reviews, were also hand-searched for further
36
37
38 189 potentially relevant studies. All citations were imported into a Rayyan
39
40
41 190 (<http://rayyan.qcri.org>) library for eligibility assessment.
42
43

44 191
45

46 47 192 **Study selection, data extraction, and quality assessment** 48

49
50 193 Two reviewers (KS, EN) independently assessed titles and abstracts of identified
51
52
53 194 citations for eligibility. Any disagreement resulted in automatic inclusion into the next
54
55
56 195 level of screening. Subsequently, full-text publications of potentially eligible studies
57
58
59
60

1
2
3
4
5 196 were obtained and assessed in duplicate by two reviewers independently, with
6
7
8 197 disagreements resolved through discussion or consulting a third reviewer. The two
9
10
11 198 reviewers also independently extracted baseline and outcome data and assessed the
12
13
14 199 quality, with these data compared and any discrepancies resolved through discussion or
15
16
17 200 consulting a third reviewer. Extracted data were entered into Review Manager version
18
19
20 201 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality,
21
22
23 202 observational studies were assessed using the Risk of Bias Assessment tool for Non-
24
25
26 203 randomized Studies (RoBANS).³⁰ If we identified any randomized trials, we planned to
27
28
29 204 use the Cochrane Risk of Bias tool.³¹ We planned to assess for potential publication bias
30
31
32 205 through visual inspection of funnel plots for asymmetry in situations where data for a
33
34
35 206 single outcome were available from 10 or more studies.
36
37

207

208 **Data synthesis and analysis**

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

1
2
3
4
5 214 using ORs when the numbers of events were available and using logarithms of the ORs
6
7
8 215 weighted by the inverse variance when events were not available. For continuous data,
9
10
11 216 mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was
12
13
14 217 determined for each meta-analysis using I^2 and Chi^2 statistics. Heterogeneity was
15
16
17 218 deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2 test for
18
19
20 219 heterogeneity. For the analysis on women with FGR fetuses and/or SGA babies, we
21
22
23 220 reported results for three subpopulations (SGA only, FGR only, SGA and FGR). Data
24
25
26 221 from the three populations were combined and pooled ORs were calculated if the
27
28
29 222 heterogeneity for that outcome was less than 60%.

30
31
32 223

33
34
35 224 All statistical analyses were performed using RevMan5. Statistical significance was set
36
37
38 225 at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each
39
40
41 226 research question using GRADEpro (<https://gradepro.org/>). Grading of
42
43
44 227 Recommendations Assessment, Development, and Evaluation (GRADE) is an approach
45
46
47 228 for grading the certainty of evidence in systematic reviews and clinical practice
48
49
50 229 guidelines and was used in this review.

51
52
53 230

54
55
56 231 **Patients and public involvement**
57
58
59
60

1
2
3
4
5 232 As this paper is a systematic review of previously published data, there was no direct
6
7
8 233 involvement from patients or the public.
9

10
11 234

12 13 14 235 **RESULTS**

15 16 17 236 **Effects of ACS in women with pregestational and/or gestational diabetes mellitus**

18
19
20 237 The search identified 179 citations, from which 11 potentially eligible studies were
21
22
23 238 evaluated, and five studies met the eligibility criteria, providing data for 8,067 pregnant
24
25
26 239 women/neonates (Figure 1).³²⁻³⁶ All studies were conducted in high-income countries
27
28
29 240 and collected data between 2006 and 2017 (Supplementary File S5). One study involved
30
31
32 241 women with pregestational diabetes only, two studies involved women with gestational
33
34
35 242 diabetes only, and two studies involved women with either pregestational or gestational
36
37
38 243 diabetes. Three studies used betamethasone only, one study used dexamethasone or
39
40
41 244 betamethasone, and in one study, the corticosteroid used was not specified. All included
42
43
44 245 studies were judged as low risk of bias across all domains, except for two studies judged
45
46
47 246 as high risk of selection bias (Figure 2; Supplementary File S6). Data were available for
48
49
50 247 5 outcomes (Table 1; Supplementary File S7). One retrospective cohort study found that
51
52
53 248 in women with gestational diabetes, the likelihood of neonatal intensive care unit
54
55
56 249 (NICU) admission is possibly increased (1 study, 2262 infants; OR 7.41, 95% CI 5.04
57
58
59
60

250 to 10.89, *low certainty evidence*)³²; however, the effect of ACS on neonatal
 251 hypoglycemia was uncertain (3 studies, 2376 infants; pooled OR 1.74, 95% CI 0.96 to
 252 3.16, *very low certainty evidence*). Certainty of evidence was also very low for other
 253 outcomes; hence, no meaningful conclusions could be drawn (Supplementary File S8).

254

255 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

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

258

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

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

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

270

271

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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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 \leq 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

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

274

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

276 The search identified 418 citations, from which 12 potentially eligible studies were

277 evaluated, and eight studies met the eligibility criteria (Figure 5).³⁹⁻⁴⁶ Two were

278 prospective cohort studies and six were retrospective cohorts, providing data on 1460

279 pregnant women/neonates (Supplementary File S5). All studies were conducted in high-

280 income countries and enrolled women between 1989 and 2014. One study evaluated

281 dexamethasone, four studies evaluated betamethasone, and three studies evaluated

1
2
3
4
5 282 either betamethasone or dexamethasone. Additional unpublished crude data from the
6
7
8 283 four included studies were extracted from a previous meta-analysis identified through
9
10
11 284 the search process.^{39,42-44,47} All included studies were judged as low risk of bias overall
12
13
14 285 although six studies were judged as high risk of bias for the domain regarding
15
16
17 286 confounding variables as adjusted analyses were not reported (Figure 6; Supplementary
18
19
20 287 File S6). Data for 25 outcomes were available, with data reported separately for women
21
22
23 288 with histological chorioamnionitis and women with clinical chorioamnionitis (Table 3;
24
25
26 289 Supplementary File S7). Amongst women with histological chorioamnionitis, ACS
27
28
29 290 administration was associated with a possible reduction in the odds of neonatal
30
31
32 291 mortality (6 studies, 1193 infants; pooled OR 0.49, 95% CI 0.33 to 0.74, *low certainty*
33
34
35 292 *evidence*), IVH (5 studies, 658 infants; pooled OR 0.41, 95% CI 0.23 to 0.72, *low*
36
37
38 293 *certainty evidence*), and severe IVH (4 studies, 528 infants; pooled OR 0.41, 95% CI
39
40
41 294 0.19 to 0.87, *low certainty evidence*). ACS might result in no difference in neonatal
42
43
44 295 sepsis; however, evidence was uncertain (6 studies, 1193 infants: pooled OR 1.03, 95%
45
46
47 296 CI 0.73 to 1.47, *very low certainty evidence*). The certainty of evidence was very low
48
49
50 297 for other outcomes (Supplementary File S8). In women with clinical chorioamnionitis,
51
52
53 298 ACS administration was associated with a possible reduction in the odds of IVH (3
54
55
56 299 studies, 318 infants, pooled OR 0.39, 95% CI 0.15 to 0.99, *low certainty evidence*), and
57
58
59
60

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).

304

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

Outcomes	No of study	No of patients		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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

306 *There is no maternal outcome in clinical chorioamnionitis.

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

310

311 **Effects of ACS in women with growth-restricted fetuses and/or small for**

312 **gestational age infants**

1
2
3
4
5 313 The search identified 261 citations, from which 36 potentially eligible studies were
6
7
8 314 assessed, and 18 studies were included (Figure 7).^{42,48-64} Of these, 12 studies included
9
10
11 315 women with SGA infants only, 4 studies included women with FGR or SGA infants,
12
13
14 316 and 2 studies included women with FGR infants only (Supplementary File S5). All were
15
16
17 317 observational studies conducted in high-income countries. Data were available from
18
19
20 318 8271 pregnant women/neonates enrolled between 1984 and 2019. Additional
21
22
23 319 unpublished data from the study by Torrance et al. (2007) were extracted from a review
24
25
26 320 paper published in 2009, which was identified through the search strategy.^{54,65} Most of
27
28
29 321 the included studies (17 of 18 studies) were judged as low risk of bias across all
30
31
32 322 domains. Five studies were judged as high risk of bias for the domain regarding
33
34
35 323 confounding variables. Four studies were judged as high risk of bias regarding
36
37
38 324 incomplete outcome data (Figure 8; Supplementary File S6). For SGA infants only, 12
39
40
41 325 studies provided data on 27 outcomes (Supplementary File S7, S8). The administration
42
43
44 326 of ACS for women with SGA was associated with the increasing odds of pregnancy-
45
46
47 327 induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95% CI 1.08 to
48
49
50 328 2.07, *low certainty evidence*) although the odds of neonatal mortality (8 studies, 2710
51
52
53 329 infants; pooled OR: 0.61, 95% CI: 0.49 to 0.78, *low certainty evidence*) and severe IVH
54
55
56 330 (6 studies, 3235 infants; pooled OR 0.60, 95% CI 0.45 to 0.80, *low certainty evidence*)
57
58
59
60

1
2
3
4
5 331 were possibly reduced (Table 4; Supplementary File S7, S8). Two studies involving
6
7
8 332 FGR infants only provided data for 19 review outcomes; however, all outcomes were
9
10
11 333 assessed as very low certainty evidence (Supplementary File S7, S8). Four studies
12
13
14 334 involved SGA or FGR infants, providing data for 24 outcomes (Supplementary File S7,
15
16
17 335 S8). The administration of ACS for women with SGA or FGR was associated with a
18
19
20 336 possible reduction in the odds of surfactant use (3 studies, 599 infants; pooled OR 0.38,
21
22
23 337 95% CI 0.23 to 0.62, *moderate certainty evidence*), use of mechanical ventilation (2
24
25
26 338 studies, 508 infants; pooled OR 0.42, 95% CI 0.26 to 0.66, *moderate certainty*
27
28
29 339 *evidence*), oxygen use (2 studies, 508 infants; pooled OR 0.48, 95% CI 0.30 to 0.77,
30
31
32 340 *moderate certainty evidence*), and duration of hospital stay (1 study, 247 infants; MD
33
34
35 341 -2.3 days, 95% CI -3.8 to -0.8 , *low certainty evidence*) (Table 4; Supplementary File
36
37
38 342 S7, S8). Pooled ORs involving women and newborns from all three populations (i.e.,
39
40
41 343 FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be
42
43
44 344 determined for 18 outcomes (Supplementary File S7, S8). The administration of ACS
45
46
47 345 for women with SGA and/or FGR was associated with a possible reduction in severe
48
49
50 346 IVH (8 studies, 3450 infants; pooled OR 0.62, 95% CI 0.47 to 0.82, *low certainty*
51
52
53 347 *evidence*) and in duration of hospital stay (2 studies, 396 infants; MD -2.23 days, 95%
54
55
56 348 CI -3.81 to -0.83 , *low certainty evidence*). However, the odds of PIH (3 studies, 775
57
58
59
60

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

352

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

Maternal outcomes	No of study	No of patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

1
2
3
4
5
6 359 **DISCUSSION**
7
8

9 360 This systematic review identified 33 observational studies pertaining to the benefits and
10
11
12 361 possible harms of using ACS in subgroups of women with specific complications of
13
14
15 362 pregnancy. In women with diabetes and those undergoing elective late preterm CS, the
16
17
18 363 available evidence on effects of ACS was largely very low certainty and conclusions
19
20
21 364 could not be drawn. In women with histological and clinical chorioamnionitis, ACS was
22
23
24 365 associated with some benefits. In women with FGR and/or SGA babies, ACS possibly
25
26
27 366 has benefits for neonatal morbidity and mortality, as well as reduced use of respiratory
28
29
30 367 support interventions for the newborn, although neonatal hypoglycemia might be
31
32
33 368 increased.
34

35
36 369

37
38
39 370 **Effects of ACS in women with pregestational and/or gestational diabetes**
40

41
42 371 A clinical concern regarding the use of ACS in women with diabetes is the possibility of
43
44
45 372 steroid-induced insulin resistance and consequent hyperglycemia causing avoidable
46
47
48 373 harm to the neonate. For example, in women with insulin-dependent diabetes,
49
50
51 374 ketoacidosis may occur if insulin dosing is not increased following steroid
52
53
54 375 administration.⁶⁶ A 2002 Danish study on 24 pregnant women with diabetes who
55
56
57 376 received steroids suggested that insulin dose adjustment may be required for up to 5
58
59
60

1
2
3
4
5
6 377 days after ACS administration.⁶⁷ However, in the current review, there was insufficient
7
8
9 378 evidence to assess whether ACS increased neonatal hypoglycemia, respiratory
10
11
12 379 morbidity, or mortality. One retrospective study suggested that ACS use in women with
13
14
15 380 gestational diabetes increases the risk of NICU admission³²; however, the authors noted
16
17
18 381 that neonatal birthweight in the ACS group was significantly lower than that in the
19
20
21 382 unexposed group, which may explain this finding. Further well-designed studies are
22
23
24 383 needed on this clinical question and would ideally describe any adjustments to maternal
25
26
27 384 diabetic regimens at the time of ACS therapy and the time from ACS administration to
28
29
30 385 birth and report on important newborn health outcomes.

31
32
33 386

34 35 36 387 **Effects of ACS in women undergoing elective CS in late preterm period**

37
38
39 388 The 2020 Cochrane review on ACS efficacy identified 27 trials; however, the subgroup
40
41
42 389 analysis on gestational age at trial entry reported on findings from seven trials (4142
43
44
45 390 women) recruiting women at ≥ 34 weeks 0 days gestation.² This subgroup analysis
46
47
48 391 suggested that ACS reduces RDS and increases neonatal hypoglycemia when used in
49
50
51 392 the late preterm period. Two systematic reviews (2018 and 2021) on trials of ACS in the
52
53
54 393 late preterm period drew similar conclusions.^{68,69} However, the CS rate (only reported
55
56
57 394 in five trials) was less than 30% in four of these trials⁷⁰⁻⁷³; hence, these findings cannot

1
2
3
4
5
6 395 be generalized to all women undergoing CS in the late preterm period. Our review
7
8
9 396 demonstrates there is currently insufficient evidence to draw conclusions on the benefits
10
11
12 397 and possible harms of ACS when used in this subpopulation although an ongoing
13
14
15 398 randomized trial in New Zealand is assessing the effects of ACS in women with CS
16
17
18 399 planned between 35 weeks 0 days and 39 weeks 6 days.⁷⁴
19
20

21 400

22 23 24 401 **Effects of ACS in women with chorioamnionitis**

25
26
27 402 Women with chorioamnionitis are typically excluded from ACS efficacy trials due to
28
29
30 403 concerns that prolongation of pregnancy and/or immunosuppression may worsen
31
32
33 404 outcomes for women and newborns. While ACS appears to be associated with reduced
34
35
36 405 neonatal mortality, IVH, and severe IVH in women with histological chorioamnionitis,
37
38
39 406 there was insufficient evidence for other important infection-related maternal and
40
41
42 407 newborn outcomes. While these conclusions are broadly similar to a 2011 review by
43
44
45 408 Been et al.,⁴⁷ we do not consider that the available evidence supports the routine use of
46
47
48 409 ACS in women with chorioamnionitis as clinical trials comparing ACS therapy with no
49
50
51 410 ACS in this population and reliable evidence for infection-related outcomes are still
52
53
54 411 lacking. It is unlikely that such trials will be performed although well-conducted
55
56
57 412 observational studies could provide useful additional evidence.
58
59
60

1
2
3
4
5
6 413

7
8
9 414 **Effects of ACS in women with growth-restricted fetuses and/or small for**
10
11
12 415 **gestational age infants**

13
14
15 416 The totality of evidence identified in this review suggests that ACS should be used in
16
17
18 417 the setting fetal growth restriction. While the evidence was largely low or very low
19
20
21 418 certainty, benefits were observed for several outcomes (including neonatal death, severe
22
23
24 419 IVH, and use of respiratory support interventions) and an absence of harms. The current
25
26
27 420 review identified more substantive evidence (18 studies) than that identified in our 2016
28
29
30 421 systematic review (8 studies) that was unable to draw conclusions of the effects of ACS
31
32
33 422 in this subpopulation.²⁶ It is also noteworthy that the largest trial of ACS in low-
34
35
36 423 resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported
37
38
39 424 preterm newborn mortality and morbidity benefits, recruited 189 women with known or
40
41
42 425 suspected fetal growth restriction.⁷⁵ The current review did not identify benefits for the
43
44
45 426 outcome RDS, which might be attributable to a single retrospective cohort study in
46
47
48 427 Japan in which neonates in the ACS group were delivered significantly earlier than
49
50
51 428 those in the control group.⁵⁷ A sensitivity analysis in which we excluded this study
52
53
54 429 suggests that RDS is significantly lower for SGA babies exposed to ACS. It cannot be
55
56
57 430 ruled out that ACS increases neonatal hypoglycemia in this subpopulation, which
58
59
60

1
2
3
4
5
6 431 warrants further exploration in future research.
7
8

9 432

10
11
12 433 **Strengths and limitations**
13

14
15 434 Strengths of this review included a broad search strategy, which included studies
16
17
18 435 published in languages other than English, rigorous quality assessment, and use of
19
20
21 436 GRADE methodology to assess the reliability of the review findings. We thus consider
22
23
24 437 the risk of missing potentially eligible studies to be low although we acknowledge that
25
26
27 438 publication bias may affect these results. One limitation of the present review is the
28
29
30 439 difference in how studies defined, identified, or diagnosed the subgroup conditions and
31
32
33 440 outcomes and interest. These differences might have created bias in the review
34
35
36 441 conclusions. However, we explored and reported heterogeneity for meta-analyses, as
37
38
39 442 well as downgrading for imprecision. Another limitation is that most included studies
40
41
42 443 were conducted in high-income countries although over 60% of all preterm births
43
44
45 444 globally occur in African and South Asian countries.⁷⁶
46
47

48 445

49
50
51 446 **CONCLUSION**
52

53
54 447 ACS has possible benefits in the setting of FGR and/or SGA; however, direct evidence
55
56
57 448 on its effectiveness and safety for pregnant women with pregestational and/or
58
59
60

1
2
3
4
5
6 449 gestational diabetes mellitus and those undergoing elective CS in late preterm is
7
8
9 450 lacking. While ACS might have some benefits in the context of histological
10
11
12 451 chorioamnionitis, more evidence is required. Well-designed studies, ideally trials, with
13
14
15 452 adequate follow-up for long-term child outcomes are needed to confirm the effects and
16
17
18 453 harms of ACS use in these subpopulations.
19

20
21 454

22
23
24 455 **Author contributions**

25
26
27 456 Dr Saito participated in the conceptualization and design of the study; conducted title,
28
29
30 457 abstract, and full-text screening; performed data extraction, analysis, and interpretation;
31
32
33 458 assessed the risk of bias; drafted the initial manuscript; and critically revised the
34
35
36 459 manuscript. Ms Nishimura conducted title, abstract, and full-text screening; performed
37
38
39 460 data-extraction, analysis, and interpretation; assessed the risk of bias; and critically
40
41
42 461 revised the manuscript. Dr Swa conceptualized and designed the search strategy,
43
44
45 462 conducted a systematic search, and critically reviewed the manuscript for important
46
47
48 463 intellectual content. Dr Ramson assisted in the interpretation of data and the assessment
49
50
51 464 of risk of bias, and critically reviewed the manuscript for important intellectual content.
52
53
54 465 Drs Namba, Cao and Lavin critically reviewed the protocol and manuscript for
55
56
57 466 important intellectual content. Prof. Ota and Associate Prof. Vogel designed and
58
59
60

1
2
3
4
5
6 467 planned the study, assisted with developing the literature search strategy and resolving
7
8
9 468 inclusion conflicts, critically revised the manuscript, and supervised the execution of the
10
11
12 469 study. All authors approved the final manuscript as submitted and agree to be
13
14
15 470 accountable for all aspects of the work.
16
17

18 471

21 472 **Data sharing statement**

23
24 473 Data were obtained from published journal articles: extracts are available upon
25
26
27 474 reasonable request.
28
29

30 475

33 476 **Funding**

35
36 477 This work was supported by UNDP/UNFPA/ UNICEF/WHO/World Bank Special
37
38
39 478 Program of Research (WBSPR), Development and Research Training in Human
40
41
42 479 Reproduction (HRP), WHO (Grand Number: not applicable) and Research Program on
43
44
45 480 Rare and Intractable Diseases co-sponsored program supported with grants from the
46
47
48 481 Japanese Ministry of Health, Labor and Welfare Science (JMoH) (Grant Number:
49
50
51 482 JPMH22FC117).
52
53

54 483

57 484 **Competing interest**

1
2
3
4
5
6 485 None declared.
7
8
9

10 486
11

12 487 **Supplementary Files**
13
14

15 488 Supplementary File S1: PROSPERO
16

17
18 489 Supplementary File S2: PRISMA 2020 Checklist
19

20
21 490 Supplementary File S3: Review outcomes
22

23
24 491 Supplementary File S4: Database-specific search terms and strategies
25

26
27 492 Supplementary File S5: Characteristic tables
28

29
30 493 Supplementary File S6: Risk of bias
31

32
33 494 Supplementary File S7: Forest plots
34

35
36 495 Supplementary File S8: GRADE tables
37

38
39 496
40

41
42 497 **Ethics approval**
43
44

45 498 As this study is a systematic review of published studies, ethical approval was not
46

47
48 499 required.
49

50 500
51

52 501
53

54 502
55

56 503
57

58 504
59

60 505

506 **REFERENCES**

- 507 [1] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for
508 prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.
509 1972;50:515-525. <https://doi:10.1542/peds.50.4.515>.
- 510 [2] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating
511 fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*.
512 2020;12:CD004454. <https://doi:10.1002/14651858.CD004454.pub.4>
- 513 [3] Skoll A, Boutin A, Bujold E, et al. No. 364-antenatal corticosteroid therapy for
514 improving neonatal outcomes. *J Obstet Gynaecol Can*. 2018;40:1219-1239.
515 <https://doi:10.1016/j.jogc.2018.04.018>.
- 516 [4] Committee on Obstetric Practice. Committee opinion no. 713 summary: antenatal
517 corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130:493-494.
518 <https://doi:10.1097/AOG.0000000000002231>.
- 519 [5] Japan Society of Obstetrics and Gynecology. Obstetrics and gynecology clinical
520 guideline 2020. https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf(accessed 24 Mar
521 2022).
- 522 [6] World Health Organization. Managing complications in pregnancy and childbirth: a
523 guide for midwives and doctors, 2nd ed.
524 2017. <https://apps.who.int/iris/handle/10665/255760> (accessed 24 Mar2022).
- 525 [7] McGillick EV, Morrison JL, McMillen IC et al. Intrafetal glucose infusion alters
526 glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of
527 the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol*. 2014;307:R538-
528 R545. <https://doi:10.1152/ajpregu.00053.2014>.
- 529 [8] Kawakita T, Bowers K, Hazrati S, et al. Increased neonatal respiratory morbidity
530 associated with gestational and pregestational diabetes: a retrospective study. *Am J*
531 *Perinatol*. 2017;34:1160-1168. <https://doi:10.1055/s-0037-1604414>.
- 532 [9] Battarbee AN, Venkatesh KK, Aliaga S, et al. The association of pregestational and
533 gestational diabetes with severe neonatal morbidity and mortality. *J Perinatol*.
534 2020;40:232-239. <https://doi:10.1038/s41372-019-0516-5>.
- 535 [10] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection:
536 a systematic review and meta-analysis. *PLoS Med*. 2019;16:e1002984.
537 <https://doi:10.1371/journal.pmed.1002984>.
- 538 [11] Hediger ML, Overpeck MD, Kuczumski RJ, et al. Muscularity and fatness of infants
539 and young children born small- or large-for-gestational-age. *Pediatrics*. 1998;102:E60.
540 <https://doi:10.1542/peds.102.5.e60>.
- 541 [12] Lim JS, Lim SW, Ahn JH, et al. New Korean reference for birth weight by gestational

- 1
2
3
4
5
6 542 age and sex: data from the Korean Statistical Information Service (2008-2012). *Ann*
7 543 *Pediatr Endocrinol Metab*. 2014;19:146-153. <https://doi:10.6065/apem.2014.19.3.146>.
- 8
9 544 [13] Lee AC, Kozuki N, Cousens S, et al. Estimates of burden and consequences of infants
10 545 born small for gestational age in low and middle income countries with
11 546 INTERGROWTH-21st standard: analysis of CHERG datasets. *BMJ*. 2017;358:j4229.
12 547 <https://doi:10.1136/bmj.j4229>.
- 13
14 548 [14] Liu J, Wang XF, Wang Y, et al. The incidence rate, high-risk factors, and short- and
15 549 long-term adverse outcomes of fetal growth restriction: a report from Mainland China.
16 550 *Medicine (Baltimore)*. 2014;93:e210. <https://doi:10.1097/MD.0000000000000210>.
- 17
18 551 [15] Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-
19 552 age infants in low-income and middle-income countries: a pooled country analysis.
20 553 *Lancet*. 2013;382:417-425. [https://doi:10.1016/S0140-6736\(13\)60993-9](https://doi:10.1016/S0140-6736(13)60993-9).
- 21
22 554 [16] Bakketeig LS. Current growth standards, definitions, diagnosis and classification of
23 555 fetal growth retardation. *Eur J Clin Nutr*. 1998;52:S1-S4.
- 24
25 556 [17] Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants.
26 557 *Pediatrics*. 2004;114:372-376. <https://doi:10.1542/peds.114.2.372>.
- 27
28 558 [18] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm
29 559 birth and maternal medical conditions on newborn morbidity risk. *Pediatrics*.
30 560 2008;121:e223-e232. <https://doi:10.1542/peds.2006-3629>.
- 31
32 561 [19] Leone A, Ersfeld P, Adams M, et al. Neonatal morbidity in singleton late preterm
33 562 infants compared with full-term infants. *Acta Paediatr*. 2012;101:e6-e10.
34 563 <https://doi:10.1111/j.1651-2227.2011.02459.x>.
- 35
36 564 [20] Mitha A, Chen R, Altman M, et al. Neonatal morbidities in infants born late preterm
37 565 at 35-36 weeks of gestation: a Swedish nationwide population-based study. *J Pediatr*.
38 566 2021;233:43-50 e5. <https://doi:10.1016/j.jpeds.2021.02.066>.
- 39
40 567 [21] Richards JL, Kramer MS, Deb-Rinker P, et al. Temporal trends in late preterm and
41 568 early term birth rates in 6 high-income countries in North America and Europe and
42 569 association with clinician-initiated obstetric interventions. *JAMA*. 2016;316:410-419.
43 570 <https://doi:10.1001/jama.2016.9635>
- 44
45 571 [22] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of
46 572 delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol*.
47 573 1995;102:101-106. <https://doi:10.1111/j.1471-0528.1995.tb09060.x>.
- 48
49 574 [23] Zanardo V, Simbi AK, Franzoi M, et al. Neonatal respiratory morbidity risk and
50 575 mode of delivery at term: influence of timing of elective caesarean delivery. *Acta*
51 576 *Paediatr*. 2004;93:643-647. <https://doi:10.1111/j.1651-2227.2004.tb02990.x>.
- 52
53 577 [24] Hansen AK, Wisborg K, Uldbjerg N, et al. Risk of respiratory morbidity in term
54
55
56
57
58
59
60

- 1
2
3
4
5
6 578 infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336:85-87.
7 579 <https://doi:10.1136/bmj.39405.539282.BE>.
- 8
9 580 [25] Groom KM. Antenatal corticosteroids after 34 weeks' gestation: do we have the
10 581 evidence? *Semin Fetal Neonatal Med*. 2019;24:189-
11 582 196.<https://doi:10.1016/j.siny.2019.03.001>.
- 12
13 583 [26] Amiya RM, Mlunde LB, Ota E, et al. Antenatal corticosteroids for reducing adverse
14 584 maternal and child outcomes in special populations of women at risk of imminent preterm
15 585 birth: a systematic review and meta-analysis. *PLoS One*. 2016;11:e0147604.
16 586 <https://doi:10.1371/journal.pone.0147604>.
- 17
18 587 [27] World Health Organization. WHO recommendations on interventions to improve
19 588 preterm birth outcomes. World Health Organization; 2015.
- 20
21 589 [28] Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines'
22 590 approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health*.
23 591 2019;4:e001683. <https://doi:10.1136/bmjgh-2019-001683>
- 24
25 592 [29] PRISMA. PRISMA Checklist. 2020. [http://prisma-](http://prisma-statement.org/PRISMAStatement/Checklist)
26 593 [statement.org/PRISMAStatement/Checklist](http://prisma-statement.org/PRISMAStatement/Checklist) (accessed 24 Mar2022).
- 27
28 594 [30] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for
29 595 nonrandomized studies showed moderate reliability and promising validity. *J Clin*
30 596 *Epidemiol*. 2013;66:408-414. <https://doi:10.1016/j.jclinepi.2012.09.016>.
- 31
32 597 [31] Cochrane Methods. Risk of Bias 2 (RoB 2) tool.
33 598 2020.<https://methods.cochrane.org/risk-bias-2> (accessed 24 Mar 2022).
- 34
35 599 [32] Krispin E, Hochberg A, Chen R, et al. Neonatal outcome in gestational-diabetic
36 600 mothers treated with antenatal corticosteroids delivering at the late preterm and term.
37 601 *Arch Gynecol Obstet*. 2018;298:689-695. <https://doi:10.1007/s00404-018-4848-8>.
- 38
39 602 [33] Paul R, Muruges C, Chepulis L, et al. Should antenatal corticosteroids be
40 603 considered in women with gestational diabetes before planned late gestation caesarean
41 604 section. *Aust N Z J Obstet Gynaecol*. 2019;59:463-466. <https://doi:10.1111/ajo.12963>.
- 42
43 605 [34] Battarbee AN, Sandoval G, Grobman WA, et al. Antenatal corticosteroids and
44 606 preterm neonatal morbidity and mortality among women with and without diabetes in
45 607 pregnancy. *Am J Perinatol*. 2022;39:67-74. <https://doi:10.1055/s-0040-1714391>.
- 46
47 608 [35] Cassimatis IR, Battarbee AN, Allshouse AA, et al. Neonatal outcomes associated
48 609 with late preterm betamethasone administration in women with pregestational diabetes.
49 610 *Pediatr Neonatol*. 2020;61:645-646. <https://doi:10.1016/j.pedneo.2020.07.002>.
- 50
51 611 [36] Tuohy JF, Bloomfield FH, Harding JE, et al. Patterns of antenatal corticosteroid
52 612 administration in a cohort of women with diabetes in pregnancy. *PLoS One*.
53 613 2020;15:e0229014. <https://doi:10.1371/journal.pone.0229014>.
- 54
55
56
57
58
59
60

- 1
2
3
4
5
6 614 [37] Kirshenbaum M, Mazaki-Tovi S, Amikam U, et al. Does antenatal steroids treatment
7 615 prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal morbidity?
8 616 Evidence from a case control study. *Arch Gynecol Obstet*. 2018;297:101-107.
9 617 <https://doi:10.1007/s00404-017-4557-8>.
11 618 [38] de la Huerza Lopez A, Sendarrubias Alonso M, Jimenez Jimenez AP, et al.
12 619 [Antenatal corticosteroids and incidence of neonatal respiratory distress after elective
13 620 caesarean section in late preterm and term neonates]. *An Pediatr (Engl Ed)*. 2019;91:371-
14 621 377. Corticoides antenatales e incidencia de distres respiratorio del recién nacido en las
15 622 cesareas programadas del pretermino tardio y termino precoz.
16 623 <https://doi:10.1016/j.anpedi.2018.12.004>.
17 624 [39] Baud O, Zupan V, Lacaze-Masmonteil T, et al. The relationships between antenatal
18 625 management, the cause of delivery and neonatal outcome in a large cohort of very preterm
19 626 singleton infants. *BJOG*. 2000;107:877-884. <https://doi:10.1111/j.1471->
20 627 [0528.2000.tb11086.x](https://doi:10.1111/j.1471-0528.2000.tb11086.x).
21 628 [40] Elimian A, Verma U, Beneck D, Cipriano R, Visintainer P, Tejani N. Histologic
22 629 chorioamnionitis, antenatal steroids, and perinatal outcomes. *Obstet Gynecol*.
23 630 2000;96:333-336. [https://doi:10.1016/s0029-7844\(00\)00928-5](https://doi:10.1016/s0029-7844(00)00928-5).
24 631 [41] Dempsey E, Chen MF, Kokottis T, Vallerand D, Usher R. Outcome of neonates less
25 632 than 30 weeks gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22:155-
26 633 159. <https://doi:10.1055/s-2005-865020>.
27 634 [42] Foix-L'heliass L, Baud O, Lenclen R, et al. Benefit of antenatal glucocorticoids
28 635 according to the cause of very premature birth. *Arch Dis Child Fetal Neonatal Ed*.
29 636 2005;90:F46-F48. <https://doi:10.1136/adc.2003.042747>.
30 637 [43] Goldenberg RL, Andrews WW, Faye-Petersen OM, et al. The Alabama preterm birth
31 638 study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various
32 639 markers of intrauterine infection. *Am J Obstet Gynecol*. 2006;195:1020-1024.
33 640 <https://doi:10.1016/j.ajog.2006.06.033>.
34 641 [44] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal
35 642 involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am*
36 643 *J Obstet Gynecol*. 2009;201:587.e1-8. <https://doi:10.1016/j.ajog.2009.06.025>.
37 644 [45] Ahn HM, Park EA, Cho SJ, et al. The association of histological chorioamnionitis
38 645 and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four
39 646 weeks' gestation. *Neonatology*. 2012;102:259-264. <https://doi:10.1159/000339577>.
40 647 [46] Ryu YH, Oh S, Sohn J, Lee J. The associations between antenatal corticosteroids
41 648 and in-hospital outcomes of preterm singleton appropriate for gestational age neonates
42 649 according to the presence of maternal histologic chorioamnionitis. *Neonatology*.
43 650
44 651
45 652
46 653
47 654
48 655
49 656
50 657
51 658
52 659
53 660

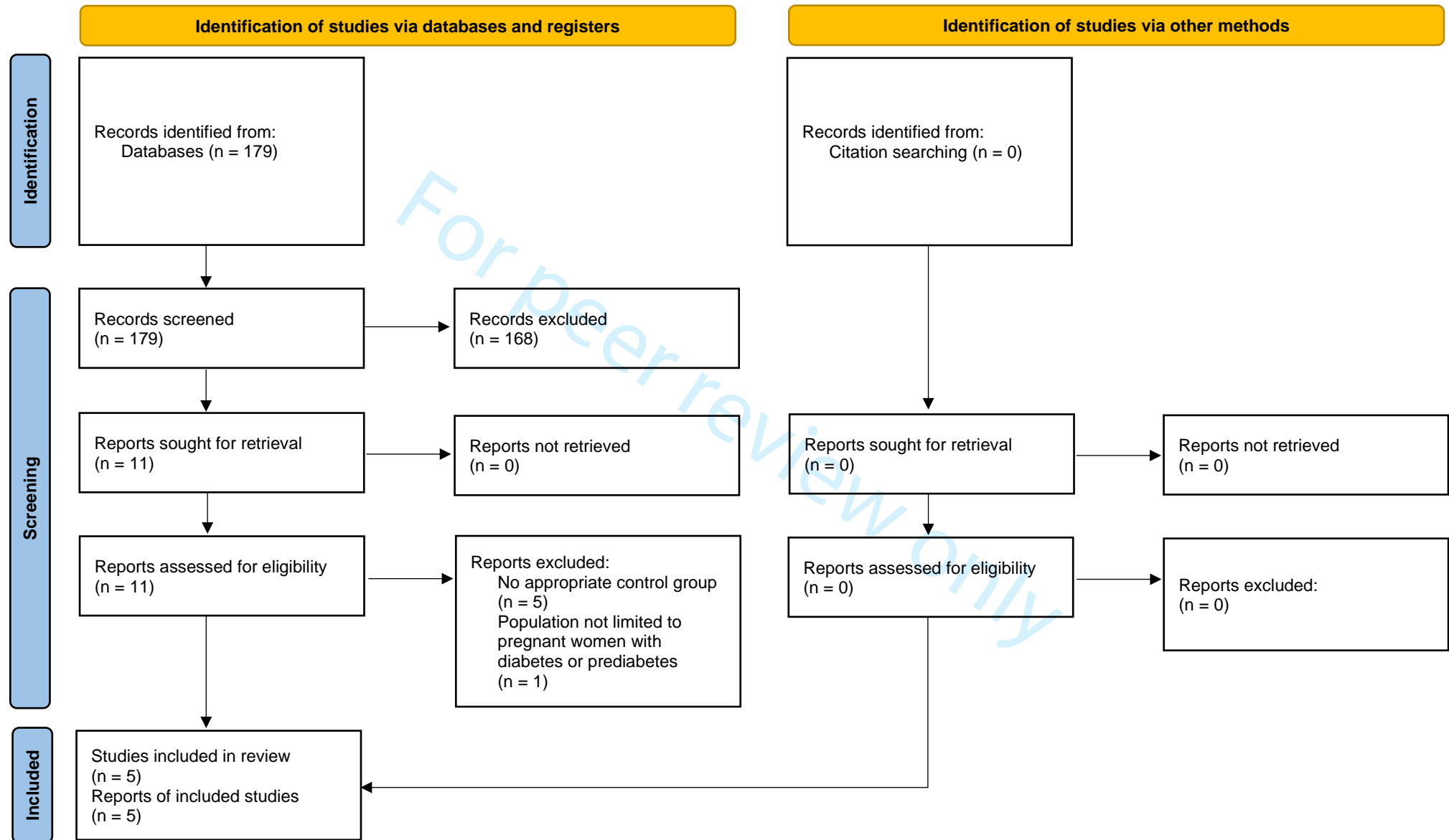
- 1
2
3
4
5
6 650 2019;116:369-375. <https://doi:10.1159/000502650>.
- 7 651 [47] Been JV, Degraeuwe PL, Kramer BW, et al. Antenatal steroids and neonatal outcome
8 652 after chorioamnionitis: a meta-analysis. *BJOG*. 2011;118:113-122.
9 653 <https://doi:10.1111/j.1471-0528.2010.02751.x>.
- 10 654 [48] Di Lenardo D, Piermarocchi P, Cazzaro L, et al. Betamethasone and theophylline in
11 655 the prevention of the Respiratory Distress Syndrome (RDS). *J FOET Med*. 1990;1-4:27-
12 656 31.
- 13 657 [49] Spinillo A, Capuzzo E, Ometto A,. Value of antenatal corticosteroid therapy in
14 658 preterm birth. *Early Hum Dev*. 1995;42:37-47. [https://doi:10.1016/0378-3782\(95\)01638-](https://doi:10.1016/0378-3782(95)01638-j)
15 659 [j](https://doi:10.1016/0378-3782(95)01638-j).
- 16 660 [50] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in infants
17 661 with impaired intrauterine growth. *Acta Paediatr*. 1997;86:1090-1096.
18 662 <https://doi:10.1111/j.1651-2227.1997.tb14814.x>.
- 19 663 [51] Elimian A, Verma U, Canterino J, Shah J, Visintainer P, Tejani N. Effectiveness of
20 664 antenatal steroids in obstetric subgroups. *Obstet Gynecol*. 1999;93:174-179.
21 665 [https://doi:10.1016/s0029-7844\(98\)00400-1](https://doi:10.1016/s0029-7844(98)00400-1).
- 22 666 [52] Bernstein IM, Horbar JD, Badger GJ, et al. Morbidity and mortality among very-
23 667 low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford
24 668 Network. *Am J Obstet Gynecol*. 2000;182:198-206. [https://doi:10.1016/s0002-](https://doi:10.1016/s0002-9378(00)70513-8)
25 669 [9378\(00\)70513-8](https://doi:10.1016/s0002-9378(00)70513-8).
- 26 670 [53] Schaap AH, Wolf H, Bruinse HW, et al. Effects of antenatal corticosteroid
27 671 administration on mortality and long-term morbidity in early preterm, growth-restricted
28 672 infants. *Obstet Gynecol*. 2001;97:954-960. [doi:10.1016/s0029-7844\(01\)01343-6](https://doi:10.1016/s0029-7844(01)01343-6)
- 29 673 [54] Torrance HL, Mulder EJ, Brouwers HA, et al. Respiratory outcome in preterm small
30 674 for gestational age fetuses with or without abnormal umbilical artery Doppler and/or
31 675 maternal hypertension. *J Matern Fetal Neonatal Med*. 2007;20:613-621.
32 676 <https://doi:10.1080/14767050701463662>.
- 33 677 [55] van Stralen G, van der Bos J, Lopriore E, et al. No short-term benefits of antenatal
34 678 corticosteroid treatment in severely preterm growth restricted fetuses: a case-control
35 679 study. *Early Hum Dev*. 2009;85:253-257. <https://doi:10.1016/j.earlhumdev.2008.10.010>.
- 36 680 [56] Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial to
37 681 severely growth restricted fetuses? *J Matern Fetal Neonatal Med*. 2013;26:1496-1499.
38 682 <https://doi:10.3109/14767058.2013.789852>.
- 39 683 [57] Ishikawa H, Miyazaki K, Ikeda T, et al. The effects of antenatal corticosteroids on
40 684 short- and long-term outcomes in small-for-gestational-age infants. *Int J Med Sci*.
41 685 2015;12:295-300. <https://doi:10.7150/ijms.11523>.
- 42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 686 [58] Riskin-Mashiah S, Riskin A, Bader D, et al. Antenatal corticosteroid treatment in
7 687 singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-
8 688 based study. *BJOG*. 2016;123:1779-1786. doi:10.1111/1471-0528.13723
- 9
10 689 [59] Collaborative Study Group for Respiratory Distress Syndrome in Preterm I. [Effect
11 690 of antenatal corticosteroids therapy on the mortality and morbidity of small for gestational
12 691 age infants born at 24-34 completed weeks: a retrospective multicenter study]. *Zhonghua*
13 692 *Er Ke Za Zhi*. 2017;55:613-618. <https://doi:10.3760/cma.j.issn.0578-1310.2017.08.013>.
- 14 693 [60] Kim WJ, Han YS, Ko HS, Park IY, Shin JC, Wie JH. Antenatal corticosteroids and
15 694 outcomes of preterm small-for-gestational-age neonates in a single medical center. *Obstet*
16 695 *Gynecol Sci*. 2018;61:7-13. <https://doi:10.5468/ogs.2018.61.1.7>.
- 17 696 [61] Riskin-Mashiah S, Reichman B, Bader D, et al. Population-based study on antenatal
18 697 corticosteroid treatment in preterm small for gestational age and non-small for gestational
19 698 age twin infants. *J Matern Fetal Neonatal Med*. 2018;31:553-559.
20 699 <https://doi:10.1080/14767058.2017.1292242>.
- 21 700 [62] Kim YJ, Choi SH, Oh S, et al. Antenatal corticosteroids and clinical outcomes of
22 701 preterm singleton neonates with intrauterine growth restriction. *Neonatal Med*.
23 702 2018;25:161-169. <https://doi:10.5385/nm.2018.25.4.161>.
- 24 703 [63] Cartwright RD, Crowther CA, Anderson PJ, et al. Association of fetal growth
25 704 restriction with neurocognitive function after repeated antenatal betamethasone treatment
26 705 vs placebo: secondary analysis of the ACTORDS randomized clinical trial. *JAMA Netw*
27 706 *Open*. 2019;2:e187636. <https://doi:10.1001/jamanetworkopen.2018.7636>.
- 28 707 [64] Bitar G, Merrill SJ, Sciscione AC, et al. Antenatal corticosteroids in the late preterm
29 708 period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM*. 2020;2:100153.
30 709 <https://doi:10.1016/j.ajogmf.2020.100153>.
- 31 710 [65] Torrance HL, Derks JB, Scherjon SA, et al. Is antenatal steroid treatment effective
32 711 in preterm IUGR fetuses? *Acta Obstet Gynecol Scand*. 2009;88:1068-1073.
33 712 <https://doi:10.1080/00016340903176784>.
- 34 713 [66] Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic
35 714 ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am*. 1996;23:87-107.
36 715 [https://doi:10.1016/s0889-8545\(05\)70246-1](https://doi:10.1016/s0889-8545(05)70246-1).
- 37 716 [67] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid
38 717 treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction
39 718 of analgoritm]. *Acta Obstet Gynecol Scand*. 2002;81:835-839. <https://doi:10.1034/j.1600-0412.2002.810906.x>.
- 40 719
41 720 [68] Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-
42 721 36+6 weeks) deliveries-a systematic review and meta-analysis of RCTs. *PLoS One*.
- 43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 722 2021;16:e0248774. <https://doi:10.1371/journal.pone.0248774>
- 7 723 [69] Sotiriadis A, Makrydimas G, Papatheodorou S, et al. Corticosteroids for preventing
8 724 neonatal respiratory morbidity after elective caesarean section at term. *Cochrane*
9 725 *Database Syst Rev.* 2018;8:CD006614. <https://doi:10.1002/14651858.CD006614.pub3>.
- 10 726 [70] Balci O, Ozdemir S, Mahmoud AS, et al. The effect of antenatal steroids on fetal
11 727 lung maturation between the 34th and 36th week of pregnancy. *Gynecol Obstet Invest.*
12 728 2010;70:95-99. <https://doi:10.1159/000295898>.
- 13 729 [71] Porto AM, Coutinho IC, Correia JB, et al. Effectiveness of antenatal corticosteroids
14 730 in reducing respiratory disorders in late preterm infants: randomised clinical trial. *BMJ.*
15 731 2011;342:d1696. doi:10.1136/bmj.d1696
- 16 732 [72] Attawattanakul N, Tansupswatdikul P. Effects of antenatal dexamethasone on
17 733 respiratory distress in late preterm infant: a randomized controlled trial. *Thai J Obstet*
18 734 *Gynaecol.* 2015;23:25-33.
- 19 735 [73] Ontela V, Dorairajan G, Bhat VB, et al. Effect of antenatal steroids on respiratory
20 736 morbidity of late preterm newborns: a randomized controlled trial. *J Trop Pediatr.*
21 737 2018;64:531-538. <https://doi:10.1093/tropej/fmy001>.
- 22 738 [74] University of Auckland. The C*Steroid trial.
23 739 [https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html)
24 740 [studies-pregnancy/c-steroid-trial.html](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html) (accessed 24 Mar 2022).
- 25 741 [75] Collaborators WAT, Oladapo OT, Vogel JP, et al. Antenatal dexamethasone for early
26 742 preterm birth in low-resource countries. *N Engl J Med.* 2020;383:2514-2525.
27 743 <https://doi:10.1056/NEJMoa2022398>.
- 28 744 [76] World Health Organization. Born too soon: the global action report on preterm birth.
29 745 World Health Organization; 2012.
30 746
31 747
32 748
33 749
34 750
35 751
36 752
37 753
38 754
39 755
40 756
41 757
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 758 **Figure 1.** Flow diagram of search results and study selection for women with
7 759 pregestational and/or gestational diabetes
8
9 760 **Figure 2.** Summary of risk of bias for each trial for women with pregestational and/or
10 761 gestational diabetes. Green=low risk of bias; red=high risk of bias; yellow=unclear risk
11 762 of bias.
12
13 763 **Figure 3.** Flow diagram of search results and study selection for women undergoing
14 764 elective Cesarean section in late preterm period
15
16 765 **Figure 4.** Summary of risk of bias for each trial for women undergoing elective Cesarean
17 766 section in late preterm period. Green=low risk of bias; red=high risk of bias;
18 767 yellow=unclear risk of bias.
19
20 768 **Figure 5.** Flow diagram of search results and study selection for women with
21 769 chorioamnionitis (histological or clinical)
22
23 770 **Figure 6.** Summary of risk of bias for each trial for women with chorioamnionitis
24 771 (histological or clinical). Green=low risk of bias; red=high risk of bias; yellow=unclear
25 772 risk of bias.
26
27 773 **Figure 7.** Flow diagram of search results and study selection for women with growth-
28 774 restricted fetuses and/or small-for-gestational-age infants
29
30 775 **Figure 8.** Summary of risk of bias for each trial for women with growth-restricted fetuses
31 776 and/or small-for-gestational-age infants. Green=low risk of bias; red=high risk of bias;
32 777 yellow=unclear risk of bias.
33
34 778
35 779
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

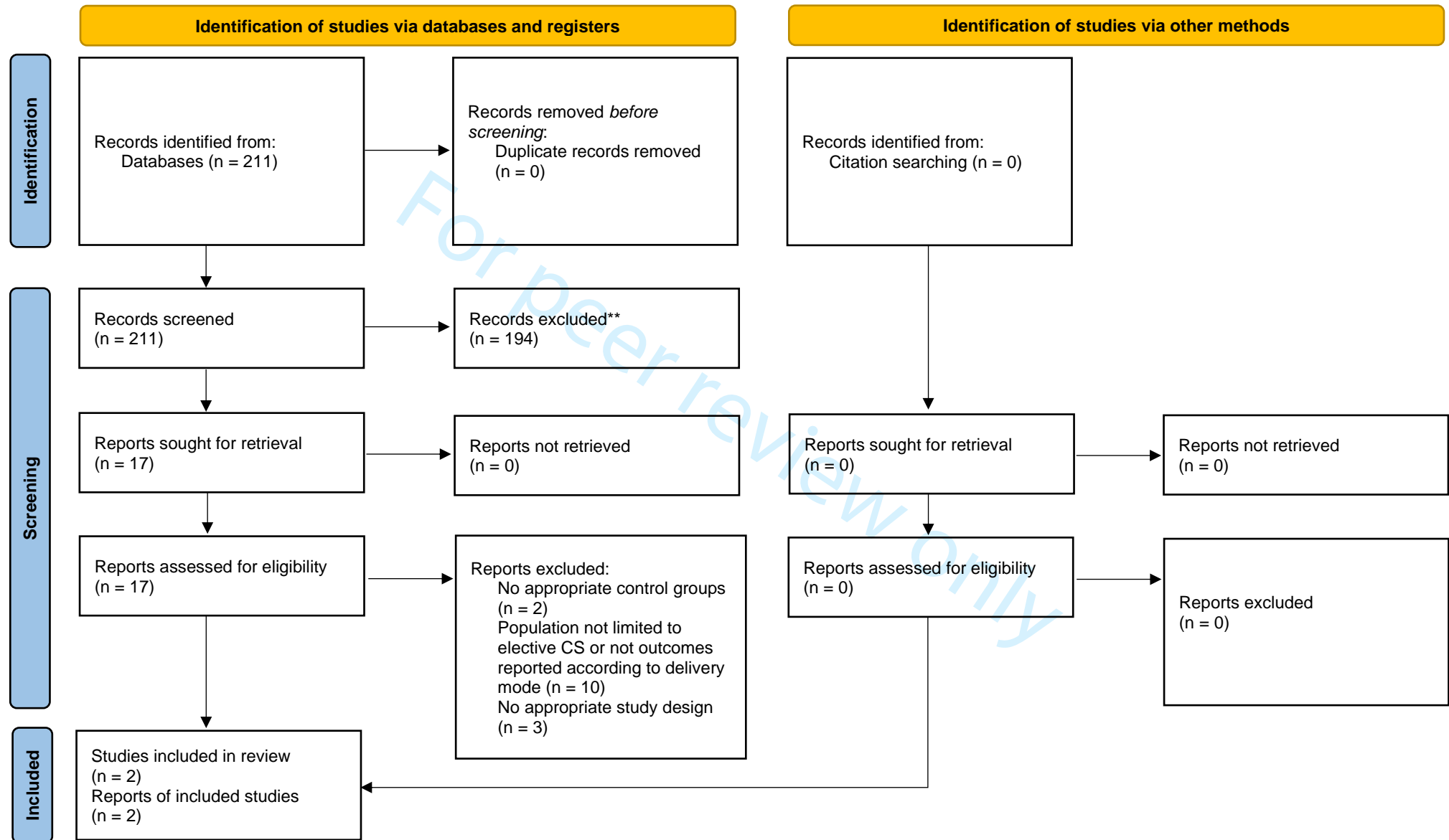


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

	Tuohy 2020	Paul 2019	Krispin 2018	Cassimatis 2020	Battarbee 2020	
	+	+	+	+	+	Selection of participants (selection bias)
	+	-	+	-	+	Confounding variables (selection bias)
	+	+	+	+	+	Measurement of exposure (performance bias)
	+	+	+	+	+	Blinding of outcomes assessment (Detection bias)
	+	+	+	?	+	Incomplete outcome data (attrition bias)
	+	+	+	+	+	Selective outcome reporting (reporting bias)

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



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

	Kirshenbaum 2018	de la Huerga Lopez 2019	
	+	-	Selection of participants (selection bias)
	+	-	Confounding variables (selection bias)
	+	+	Measurement of exposure (performance bias)
	+	+	Blinding of outcomes assessment (Detection bias)
	+	?	Incomplete outcome data (attrition bias)
	+	+	Selective outcome reporting (reporting bias)

view only

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

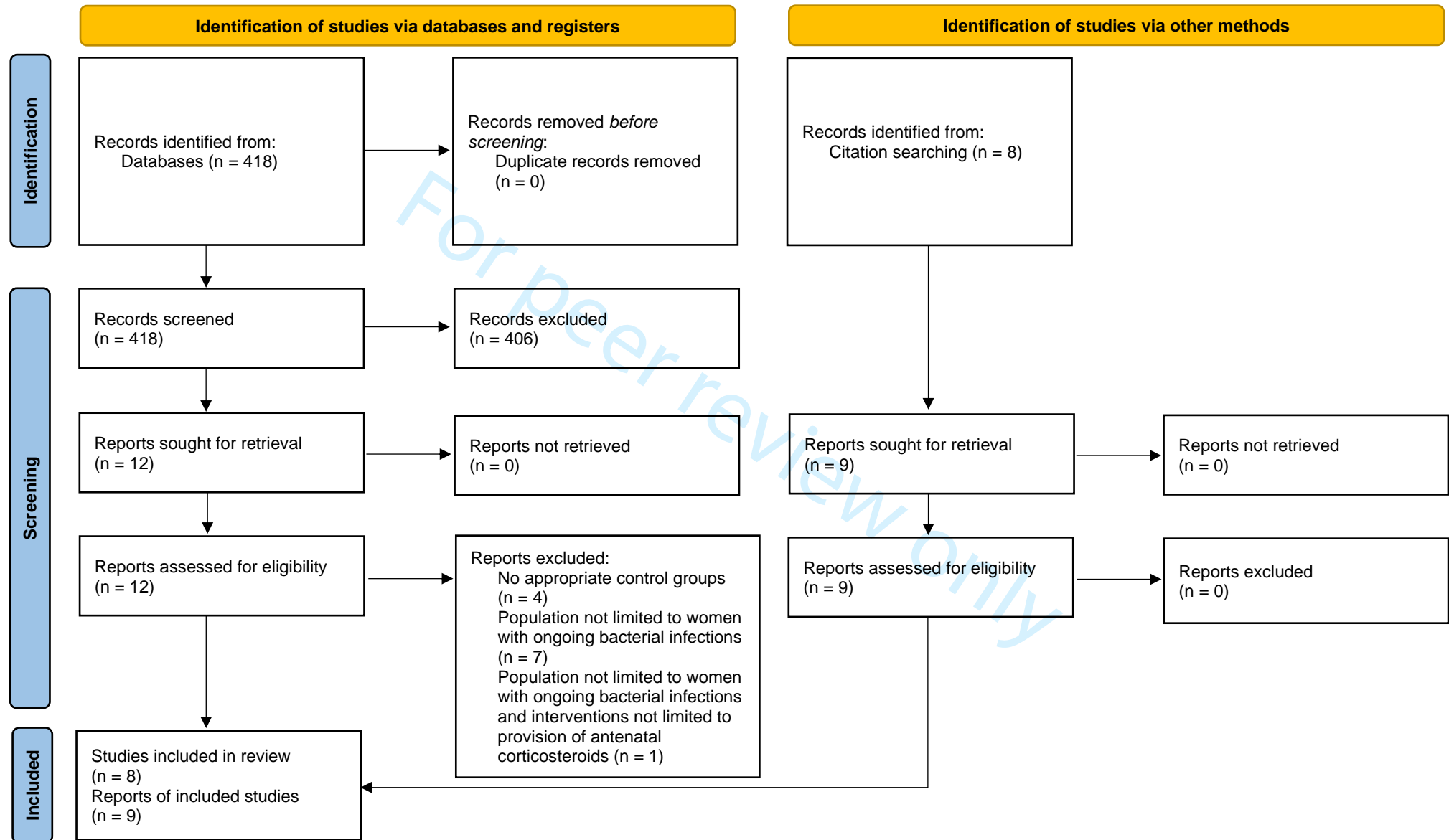


Figure 6: Summary of risk of bias for each trial for women with chorioamnionitis (histological or clinical)
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

	Ryu 2019	Goldenberg 2006	Foix-L'Helias 2005	Elimian 2000	Dempsey 2005	Been 2009	Baud 2000	Ahn 2012	
	+	+	?	+	+	+	+	+	Selection of participants (selection bias)
	+	-	-	-	-	-	+	-	Confounding variables (selection bias)
	+	+	+	+	+	+	+	+	Measurement of exposure (performance bias)
	+	+	+	+	+	+	+	+	Blinding of outcomes assessment (Detection bias)
	+	?	?	?	?	+	?	?	Incomplete outcome data (attrition bias)
	+	+	+	+	+	+	?	+	Selective outcome reporting (reporting bias)

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

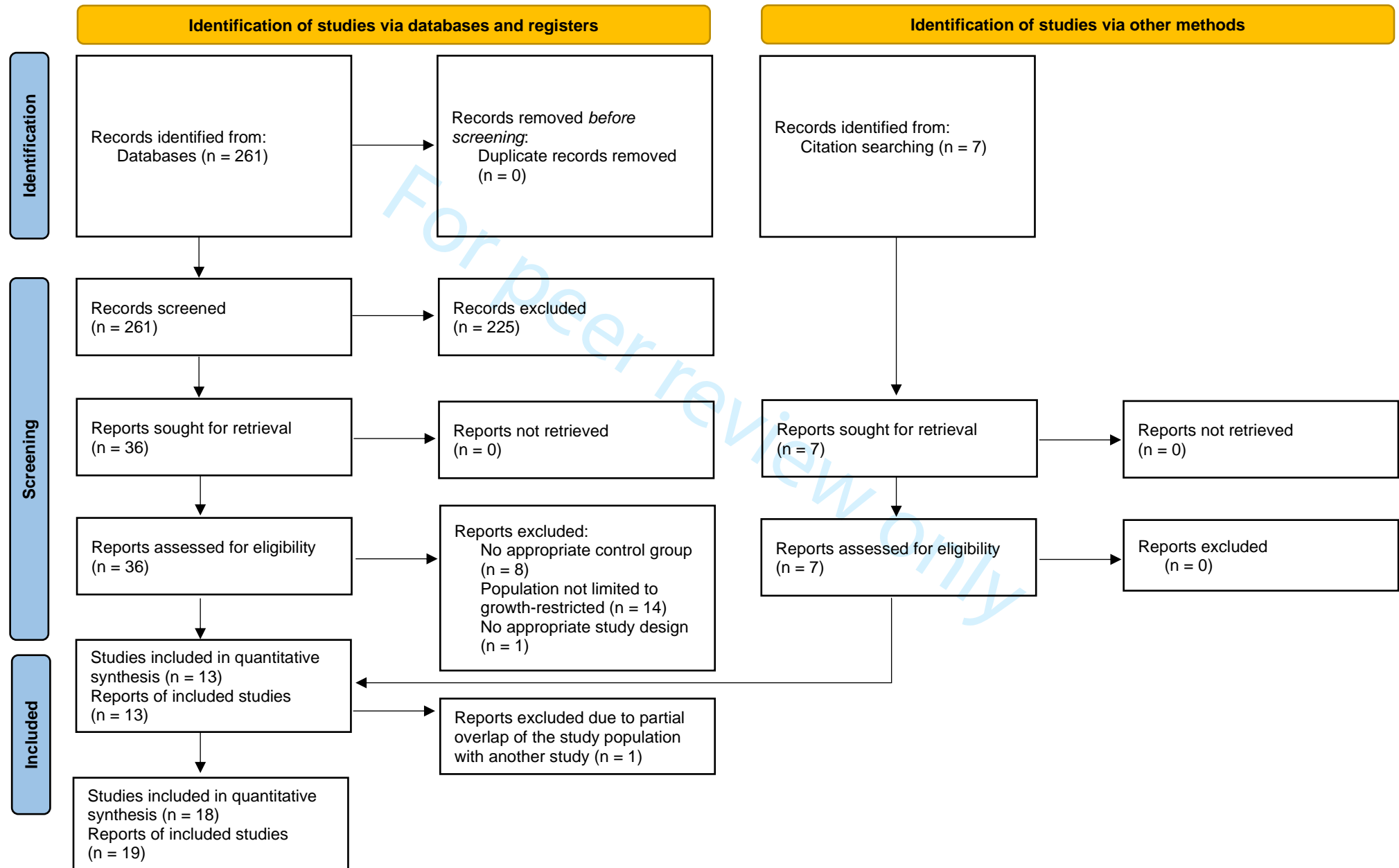


Figure 8: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

vanStralen 2009	+	-	+	+	?	+
Torrance 2007	-	+	+	?	+	+
Spinillo 1995	?	+	+	+	?	+
Schaap 2001	?	+	+	+	+	+
Riskin-Mashiah 2018	+	+	+	+	-	+
Riskin-Mashiah 2016	+	+	+	+	-	+
Mitsiakos 2013	+	-	+	+	-	+
Ley 1997	+	?	+	+	?	+
Kim Y.J. 2018	-	+	+	+	+	+
Kim 2018	+	+	+	+	+	+
Ishikawa 2015	+	+	+	+	-	+
Foix-L'Hellias 2005	?	-	+	+	?	+
Feng 2017	+	?	+	+	?	+
Elimian 1999	?	-	+	+	?	+
Dilenardo 1990	?	-	+	+	?	+
Cartwright 2019	+	+	+	+	+	+
Bitar 2020	+	+	+	+	+	+
Bernstein 2000	+	+	+	+	+	+
	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)

PROSPERO**International prospective register of systematic reviews**

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

PROSPERO

International prospective register of systematic reviews

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

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.

PROSPERO

International prospective register of systematic reviews

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.

Exclusion: Pregnant women with the population at 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.

PROSPERO

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 fulfil one or more of the following conditions:

1. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
2. having intrauterine inflammation, infection, or both; or
3. 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.

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)

PROSPERO

International prospective register of systematic reviews

- 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.

PROSPERO

International prospective register of systematic reviews

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

PROSPERO

International prospective register of systematic reviews

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 T^2 , I^2 , and τ^2 statistics.

Heterogeneity will be deemed substantial if T^2 will be greater than zero and either I^2 will be greater than 50% or $p < 0.10$ in the τ^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 $p < 0.10$ 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

PROSPERO**International prospective register of systematic reviews**

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

PROSPERO**International prospective register of systematic reviews**1
2
3
4 No

5 Education

6 No

7
8 Endocrine and metabolic disorders

9 No

10 Eye disorders

11 No

12
13 General interest

14 No

15 Genetics

16 No

17 Health inequalities/health equity

18 No

19 Infections and infestations

20 No

21 International development

22 No

23 Mental health and behavioural conditions

24 No

25 Musculoskeletal

26 No

27 Neurological

28 No

29 Nursing

30 No

31 Obstetrics and gynaecology

32 No

33 Oral health

34 No

35 Palliative care

36 No

37 Perioperative care

38 No

39 Physiotherapy

40 No

41 Pregnancy and childbirth

42 Yes

43 Public health (including social determinants of health)

44 No

45 Rehabilitation

46 No

47 Respiratory disorders

48 No

49
50
51
52
53
54
55
56
57
58
59
60

PROSPERO

International prospective register of systematic reviews

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?

PROSPERO

International prospective register of systematic reviews

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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/>

For peer review only

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

1
2
3
4
5 Periventricular leukomalacia (PVL)
6 Major brain lesion damage
7 Necrotizing enterocolitis (NEC)
8 Sepsis
9
10 Early onset sepsis
11 Systemic inflammatory response syndrome
12
13 Meningitis
14 Neonatal hypoglycemia
15 Neonatal adrenal insufficiency
16
17 Intrahepatic cholestasis
18
19 Retinopathy of prematurity (ROP)
20 ROP requiring treatment
21
22 Gestational age at birth
23
24 Birth weight
25
26 Small for gestational age
27 Neonatal intensive care unit (NICU) admission
28
29 Duration of hospital stay
30
31 Survival free from disability
32
33 Death at long-term follow up
34
35 Death or disability/handicap at 2 years
36
37 Cerebral palsy
38
39 Severe hearing impairment
40
41
42
43
44
45
46
Visual impairment

1
2
3
4
5 Discharge with respiratory support
6 Growth < 10%tile in early childhood
7
8 Abnormal behavior at long-term follow up at school-age
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

For peer review only

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	(MH "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: Characteristic 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 23–33 weeks	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 Hueriga 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 ⁴⁰	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	Beta /Dex	NS	NS	No	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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
Goldenberg 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 \geq 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 ³⁹	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 ³⁶	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

1											
2											
3											
4											
5											
6											
7	Schaap et al, 2001	124			Women giving birth between GA 26 weeks	ACS < 24 h before delivery, fetal death or fetal					
8	⁵³	(62,62)	1984–1991	Netherlands	0 days and 31 weeks 6 days	distress at admission to the hospital, abruptio	FGR	Beta	12.5	24	NS
9						placentae, lethal congenital abnormalities or					
10						infections					
11											
12											
13											
14											
15	Bernstein et al,				Women giving birth between GA 25 weeks						
16	2000 ⁵²	1258 (703,555)	1991–1996	USA, Canada	0 days and 30 weeks 6 days, white and	Multiple gestations, major anomalies	SGA	NS	NS	NS	NS
17					African-American infants						
18											
19											
20											
21	Elimian et al, 1999	220			Birth weight ≤ 1750 g						
22	⁵¹	(63,157)	1990–1997	USA		NS	SGA	Beta	12	24	Yes
23											
24	Ley et al, 1997 ⁵⁰	234			Women giving birth at GA < 33 weeks						
25		(117, 117)	1984–1985	Sweden		NS	SGA	NS	NS	NS	NS
26											
27											
28											
29											
30											
31	Spinillo et al, 1995	96			Women giving birth between GA 24 weeks						
32	⁴⁹	(32,64)	1988–1993	Italy	0 days and 34 weeks 6 days, indetermined						
33					or immature lecithin/sphingomyelin ratio,	Congenital anomalies	SGA	Beta/Dex	12 12	NS	NS
34					planned delivery with medication						
35					complications, liveborn						
36											
37											
38											
39											
40											
41											
42											
43											
44											
45											
46											

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

*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

For peer review only

1 **Supplementary File S6: Risk of bias**

2
3 **Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes**

4
5
6 ***Risk of bias assessments (RoBANS)***

7
8

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.	-

9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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	Seque nce genera tion	Allocat ion concea lment	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	<p>High.</p> <p>All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017).</p> <p>Newborns with congenital malformations or those transferred to another hospital were excluded from the study.</p> <p>Cases and controls were selected from the same gestational age. However, the control group was defined only by no-steroid treatment without further specification.</p> <p>The percentage of planned cesarean sections was higher in SGA newborns, with statistical significance (34/38 89% vs. 174/245 71%; $p = 0.016$).</p> <p>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; $p < 0.001$).</p>	<p>High.</p> <p>No confirmation or consideration in either design or analysis phase.</p>	<p>Low.</p> <p>Data obtained from medical records.</p>	<p>Low.</p> <p>No statement to indicate that blinding was performed, but unlikely to affect outcome measurements</p>	<p>Unclear.</p> <p>No information about missing data.</p>	<p>Low.</p> <p>All predefined outcomes reported.</p>	

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	Sequencing 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	Sequencing 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

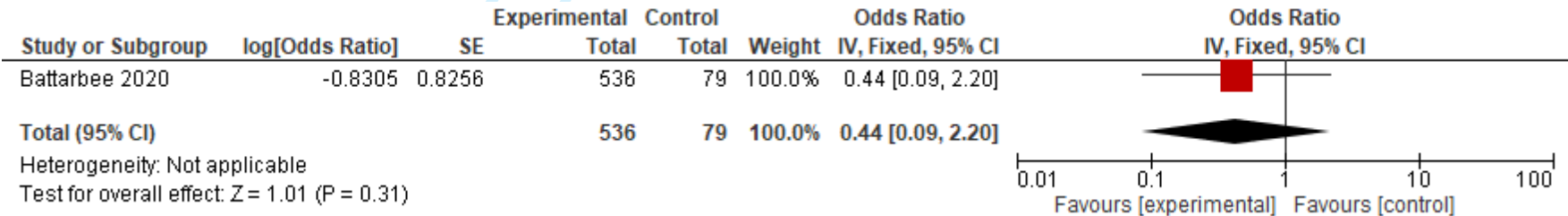
Supplementary File S7: Forest plots

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

*There is no maternal outcome.

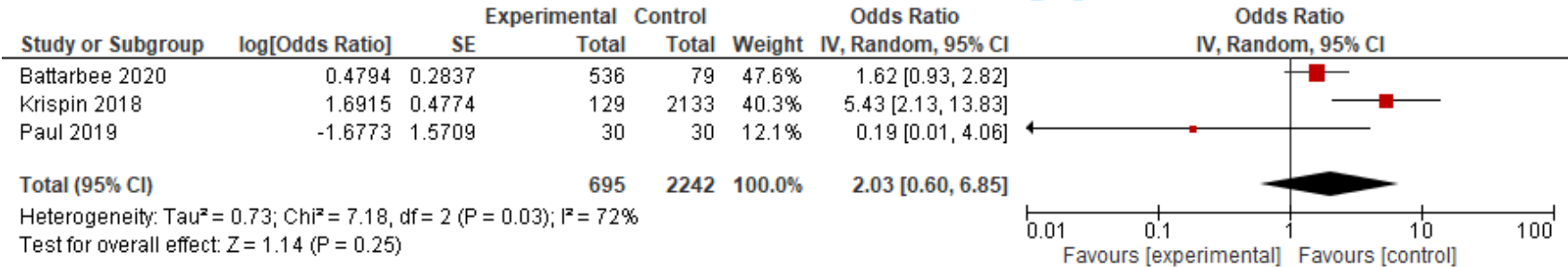
Neonatal outcomes for women with pregestational and/or gestational diabetes mellitus

1) Neonatal death within 48 h of birth



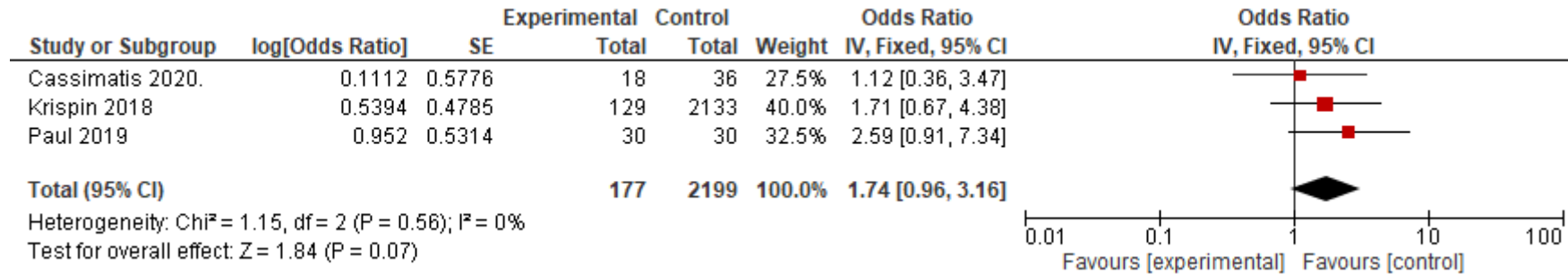
SE: Standard error; CI: Confidence interval

2) Respiratory distress syndrome (RDS)



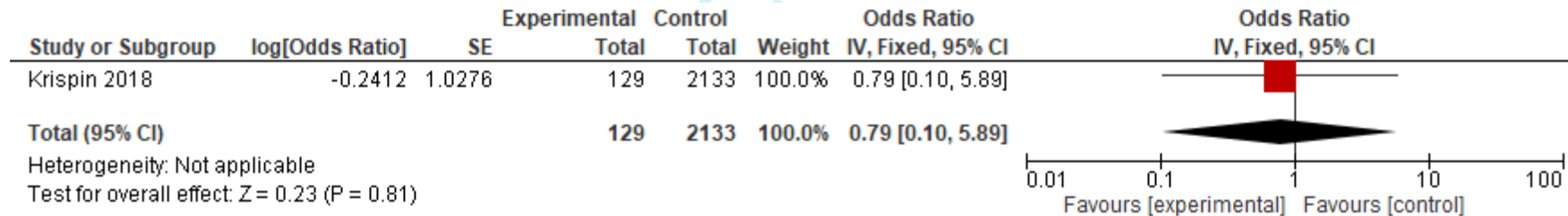
SE: Standard error; CI: Confidence interval

3) Neonatal hypoglycemia



SE: Standard error; CI: Confidence interval

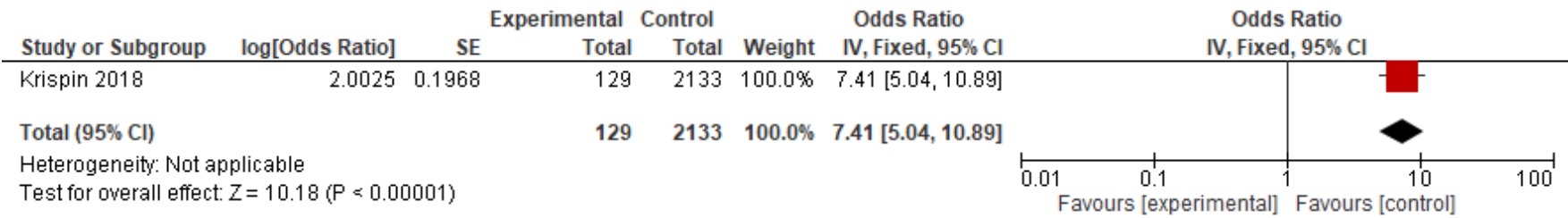
4) Apgar score < 7 at 5 min



SE: Standard error; CI: Confidence interval

5) Admission to neonatal intensive care unit (NICU)

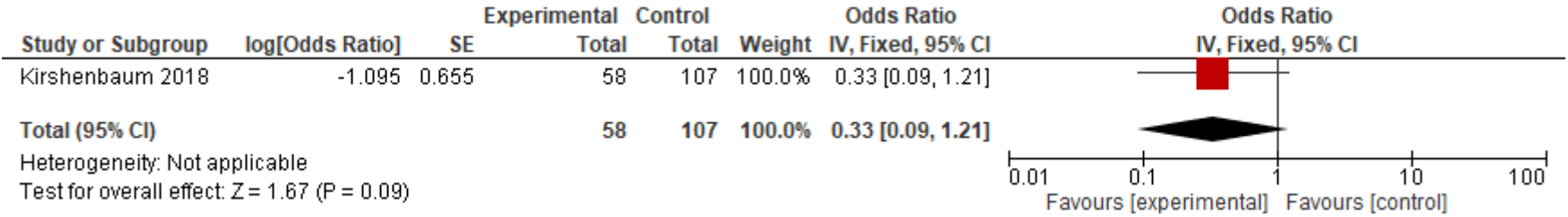
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



SE: Standard error; CI: Confidence interval

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

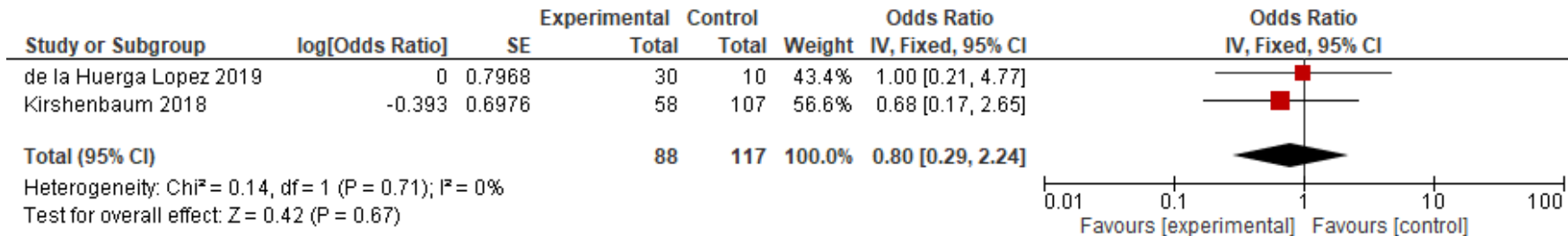
1) Hypertensive disorders



SE: Standard error; CI: Confidence interval

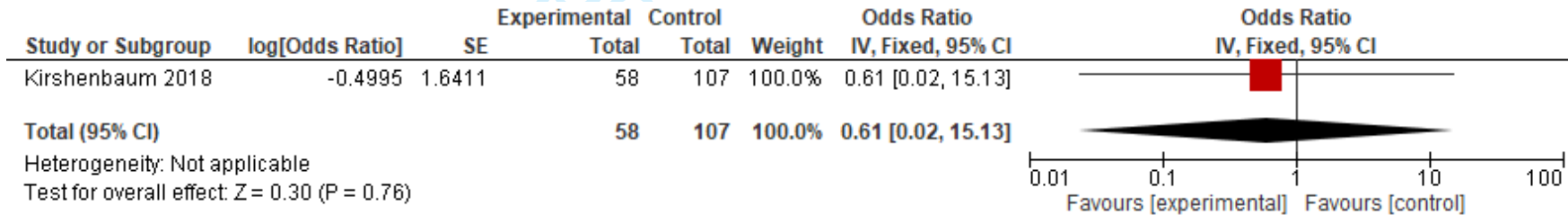
Neonatal outcomes for women undergoing elective cesarean section in late preterm period

1) Respiratory distress syndrome (RDS)



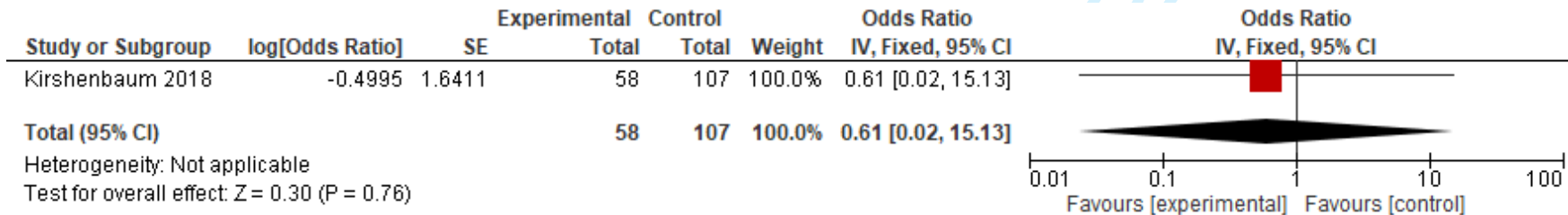
SE: Standard error; CI: Confidence interval

2) Intraventricular hemorrhage (IVH)



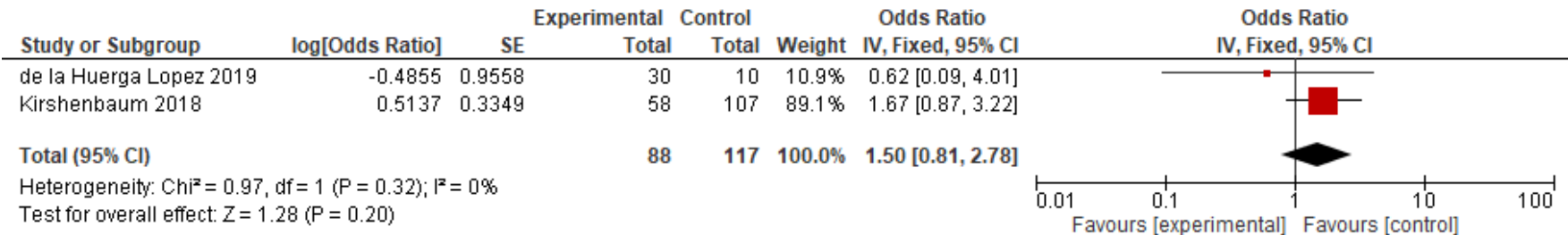
SE: Standard error; CI: Confidence interval

3) Necrotizing enterocolitis (NEC)



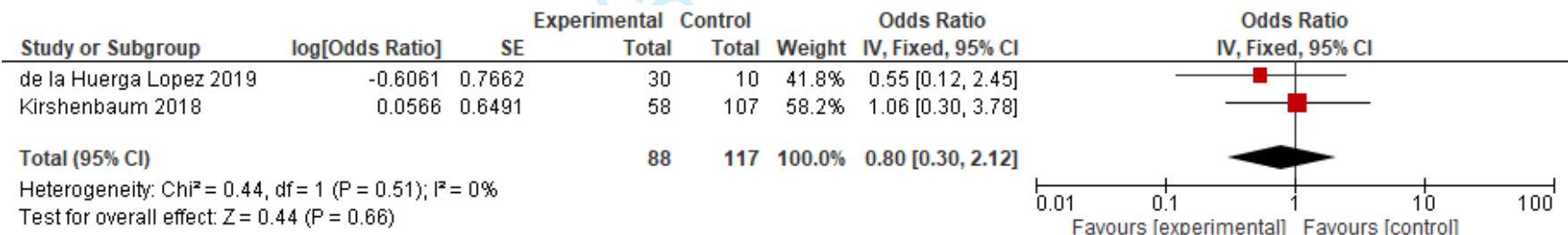
SE: Standard error; CI: Confidence interval

4) Neonatal hypoglycemia



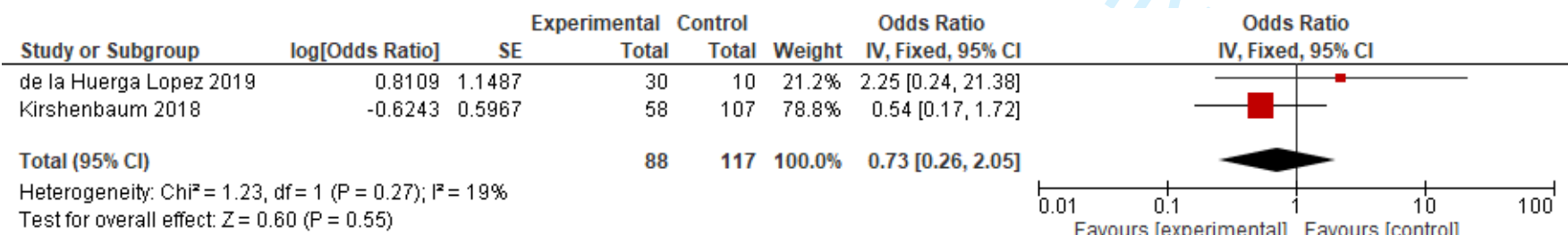
SE: Standard error; CI: Confidence interval

5) Use of mechanical ventilation



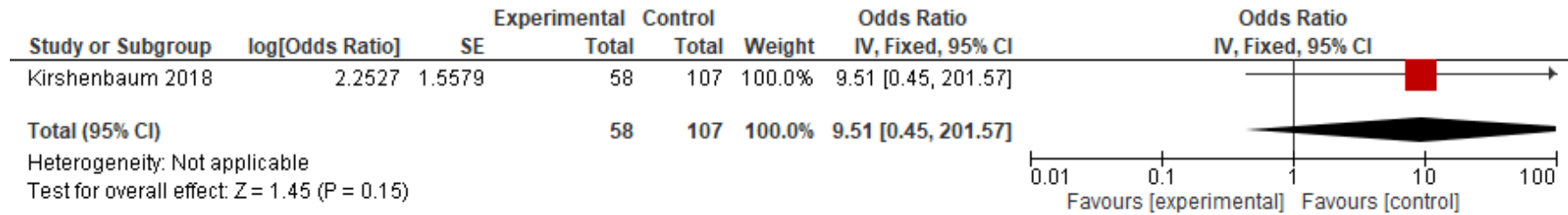
SE: Standard error; CI: Confidence interval

6) Admission to neonatal intensive care unit (NICU)



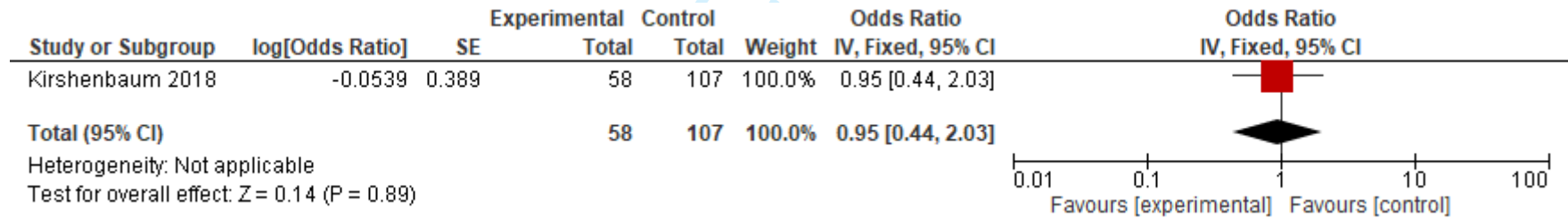
SE: Standard error; CI: Confidence interval

7) Apgar score ≤ 7 at 5min



SE: Standard error; CI: Confidence interval

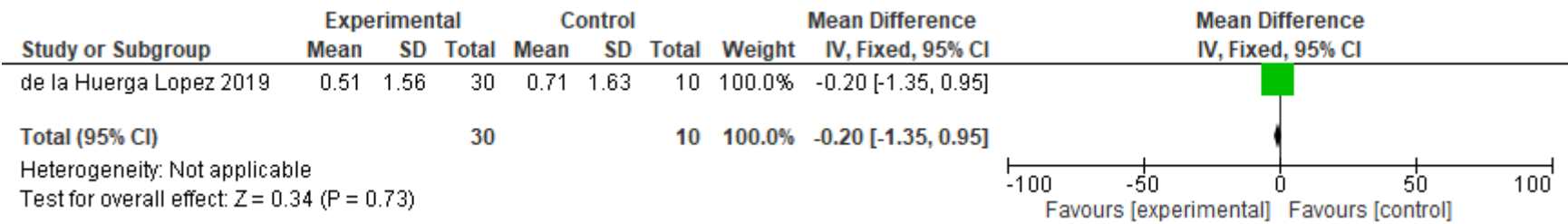
8) Oxygen requirement for at least 4 hours



SE: Standard error; CI: Confidence interval

9) Mean duration of mechanical ventilation, days

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

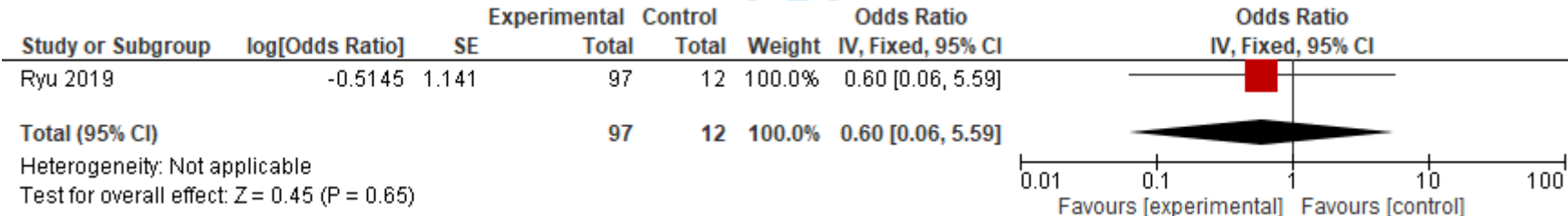


SD: Standard Deviation; CI: Confidence interval

Maternal outcomes for women with histological chorioamnionitis

*There is no maternal outcome in clinical chorioamnionitis.

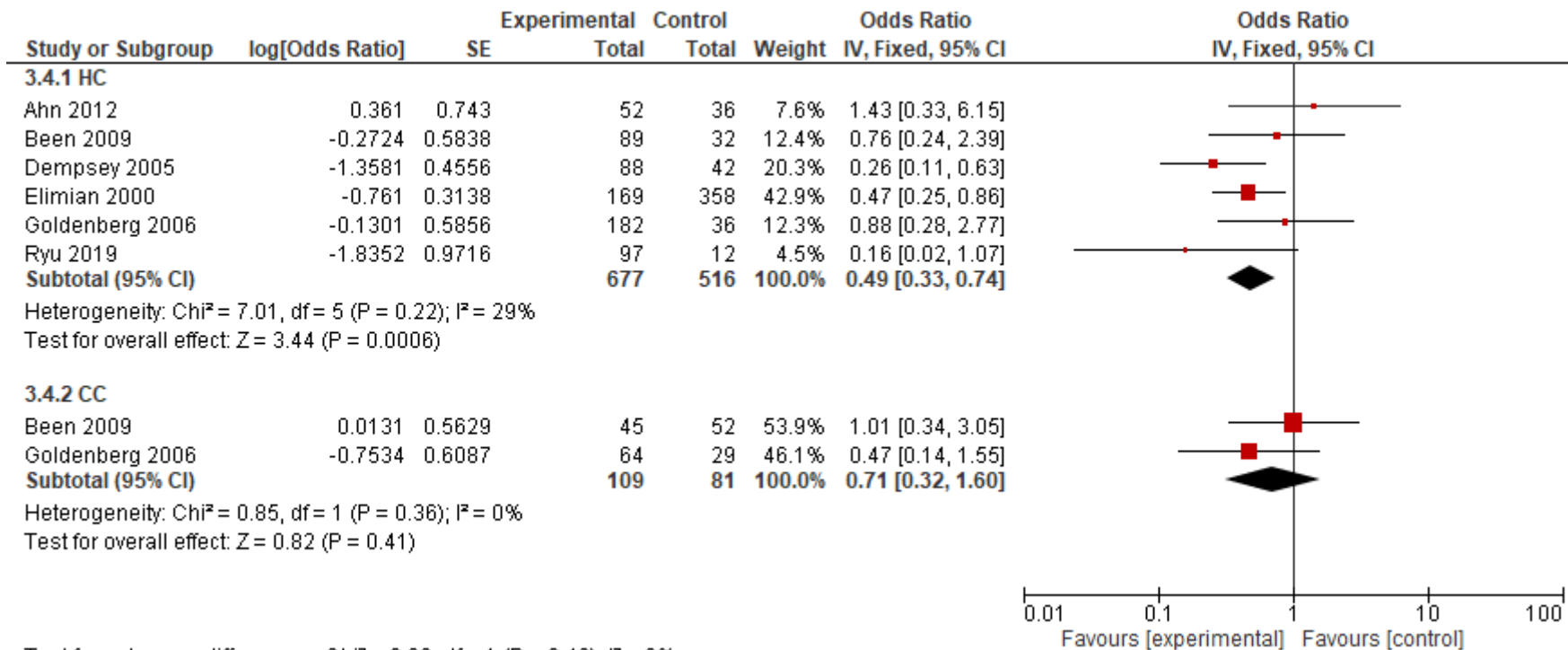
1) Preeclampsia or eclampsia (HC)



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

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

1) Neonatal death

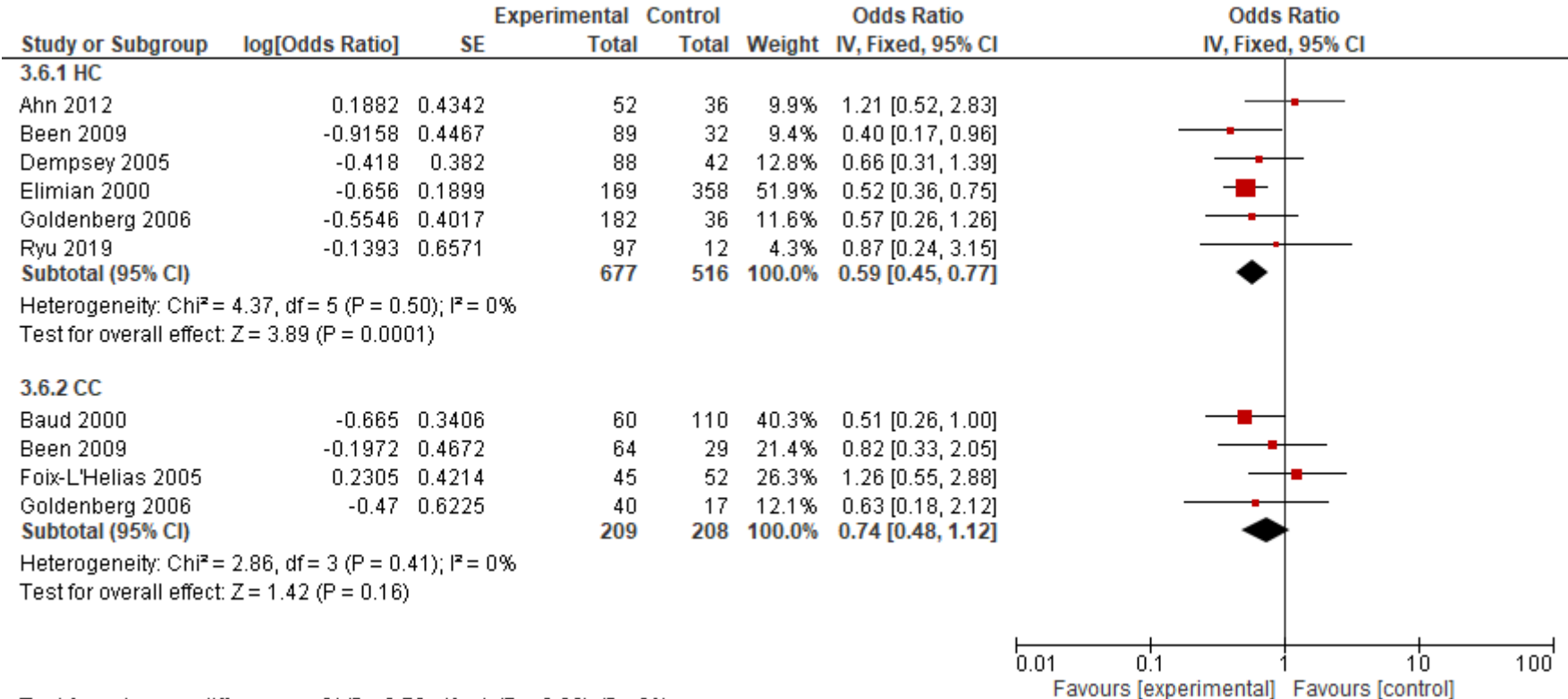


Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%

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

2) Respiratory distress syndrome (RDS)

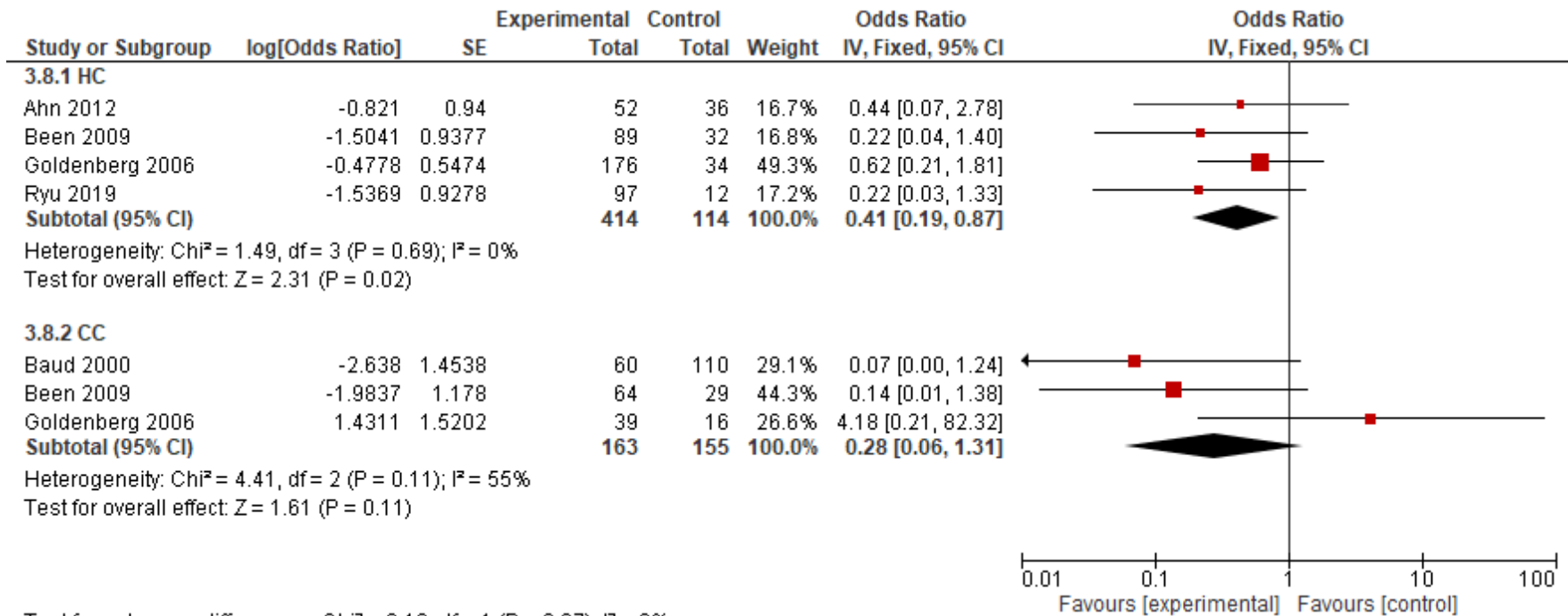
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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)

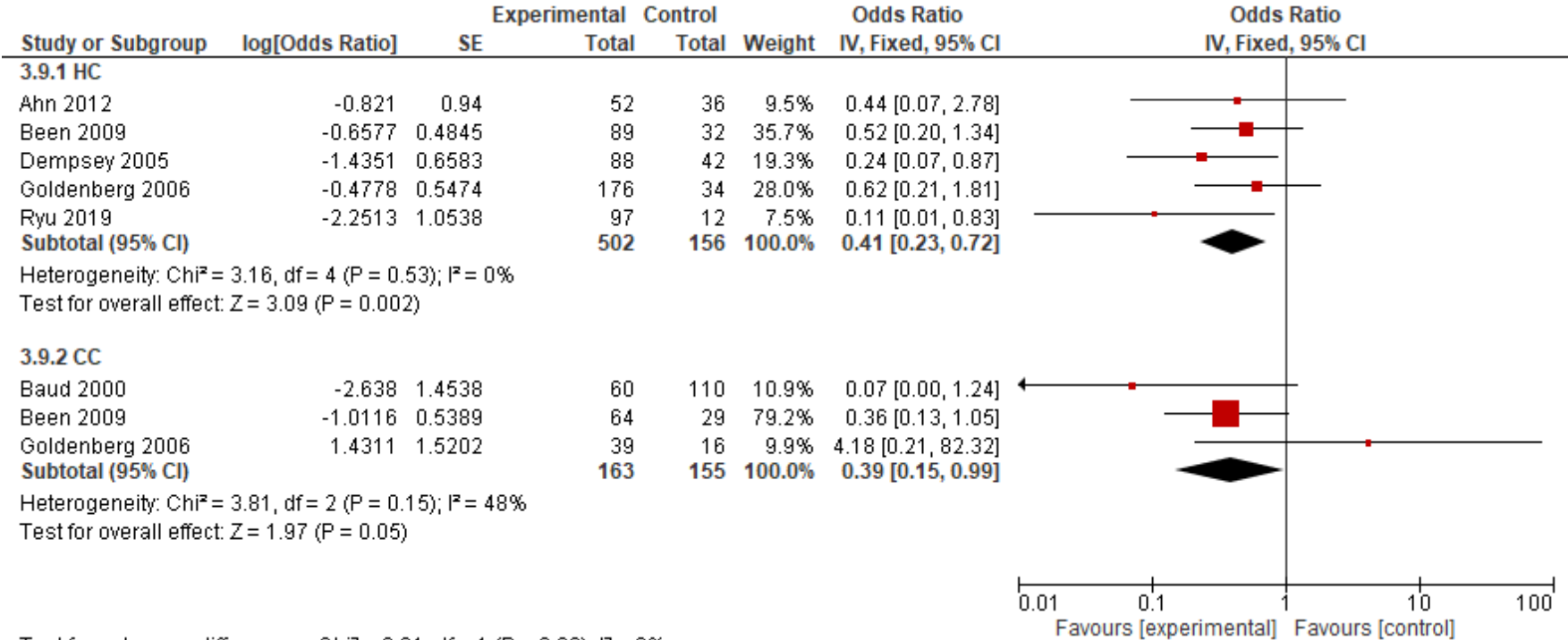


Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%

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

4) Intraventricular hemorrhage (IVH)

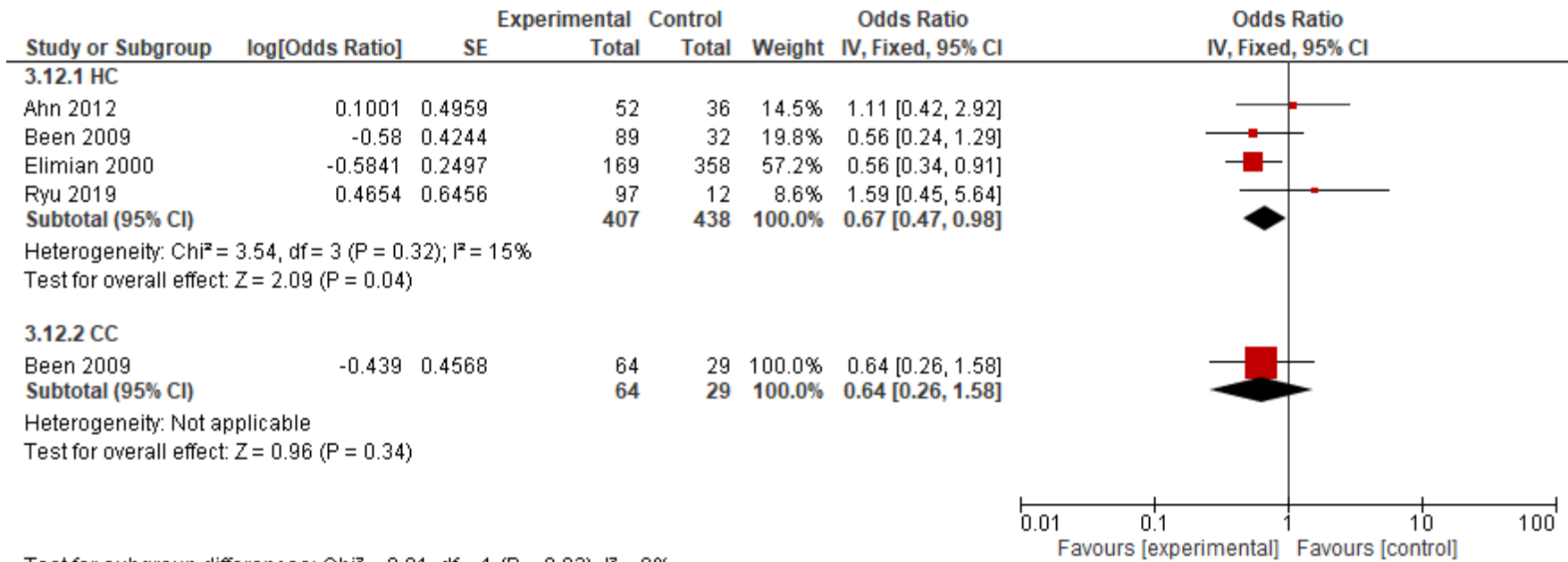
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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)

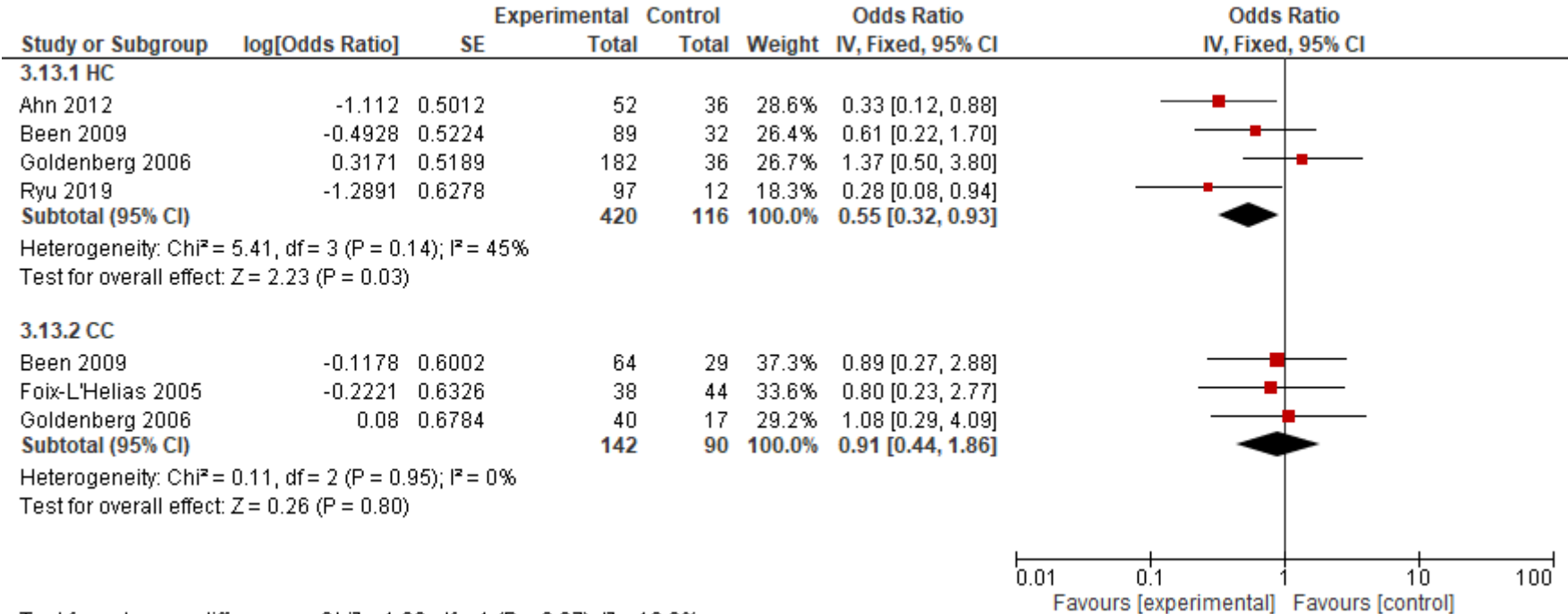


Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

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

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

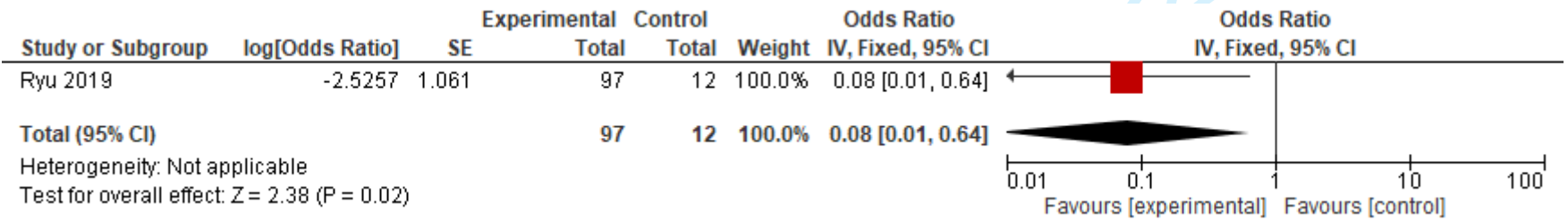
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



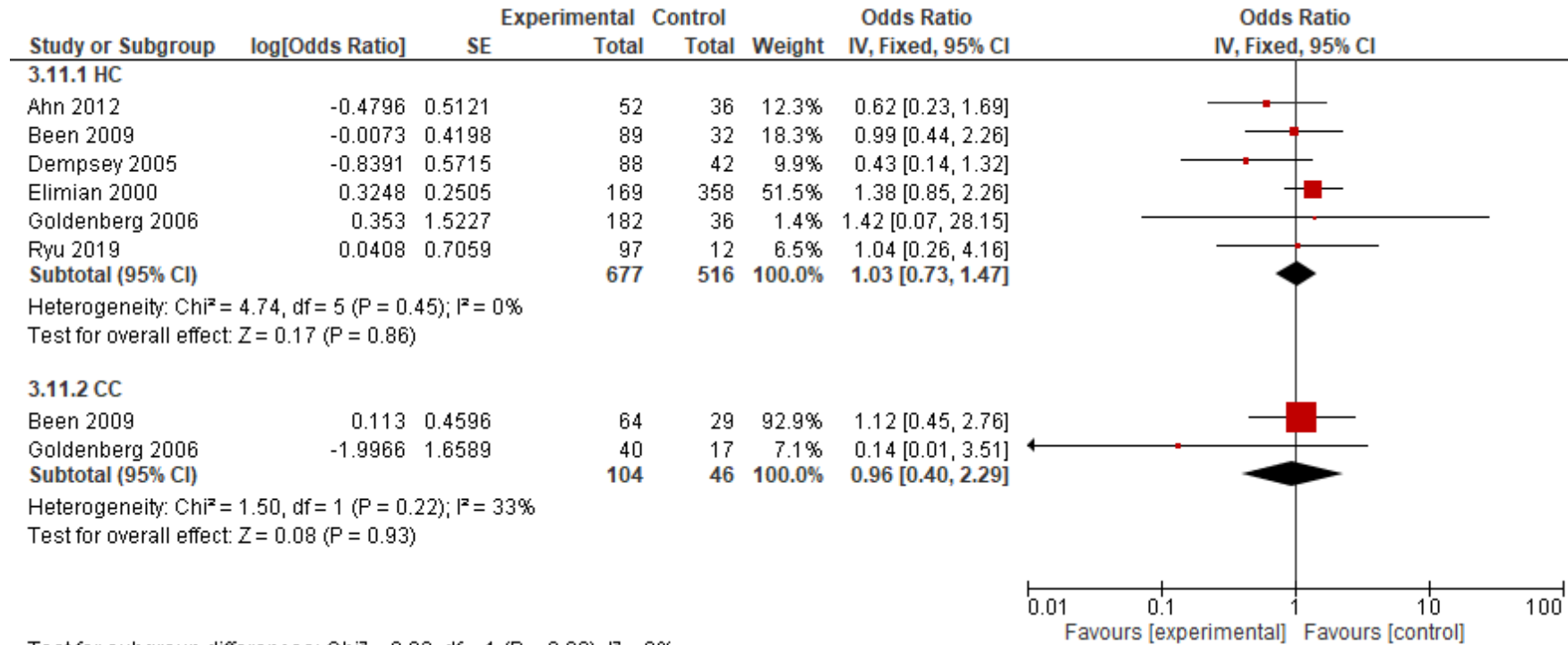
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.8%

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

7) Hypotension within 7 days postnatal



8) Sepsis

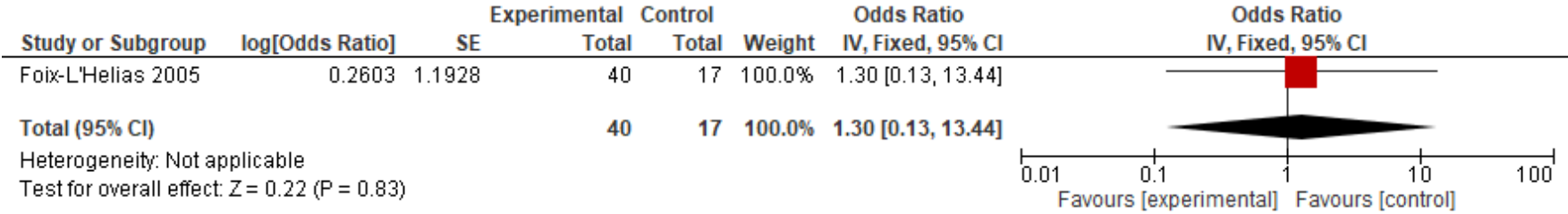


Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%

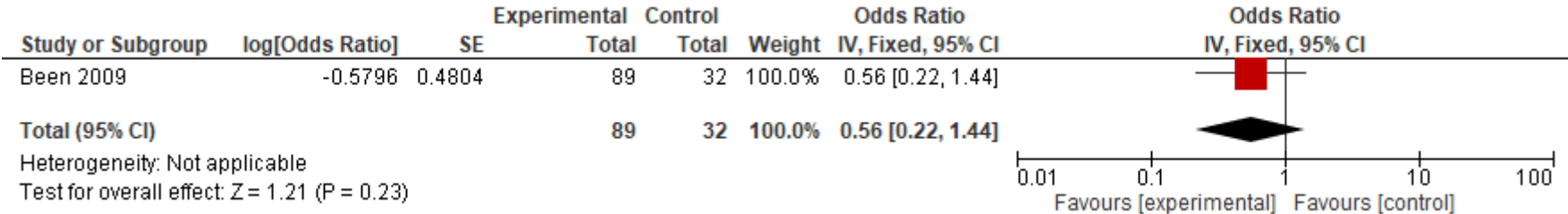
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

9) Death before discharge home (CC)

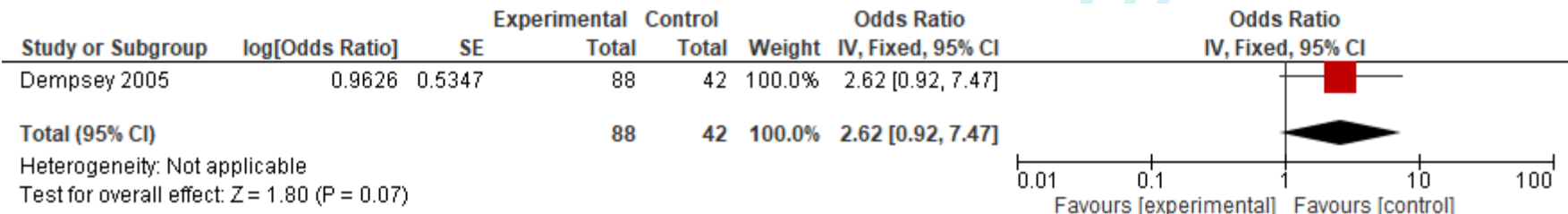
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



SE: Standard error; CI: Confidence interval; CC: Clinical chorioamnionitis
10) Severe respiratory distress syndrome (RDS) (HC)

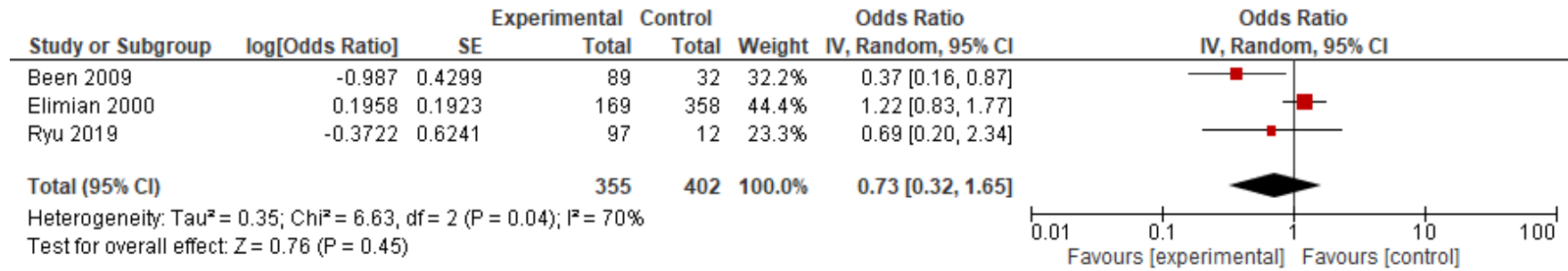


SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis
11) Pneumonia (HC)



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

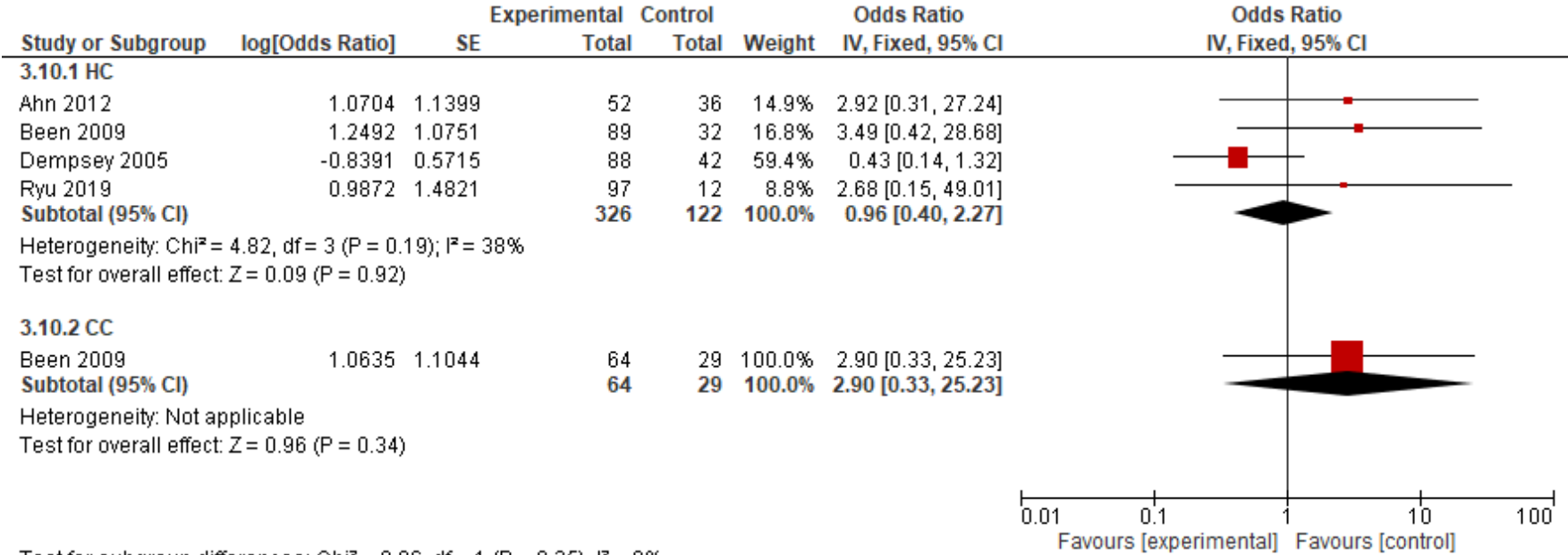
12) Surfactant use (HC)



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

13) Early-onset sepsis

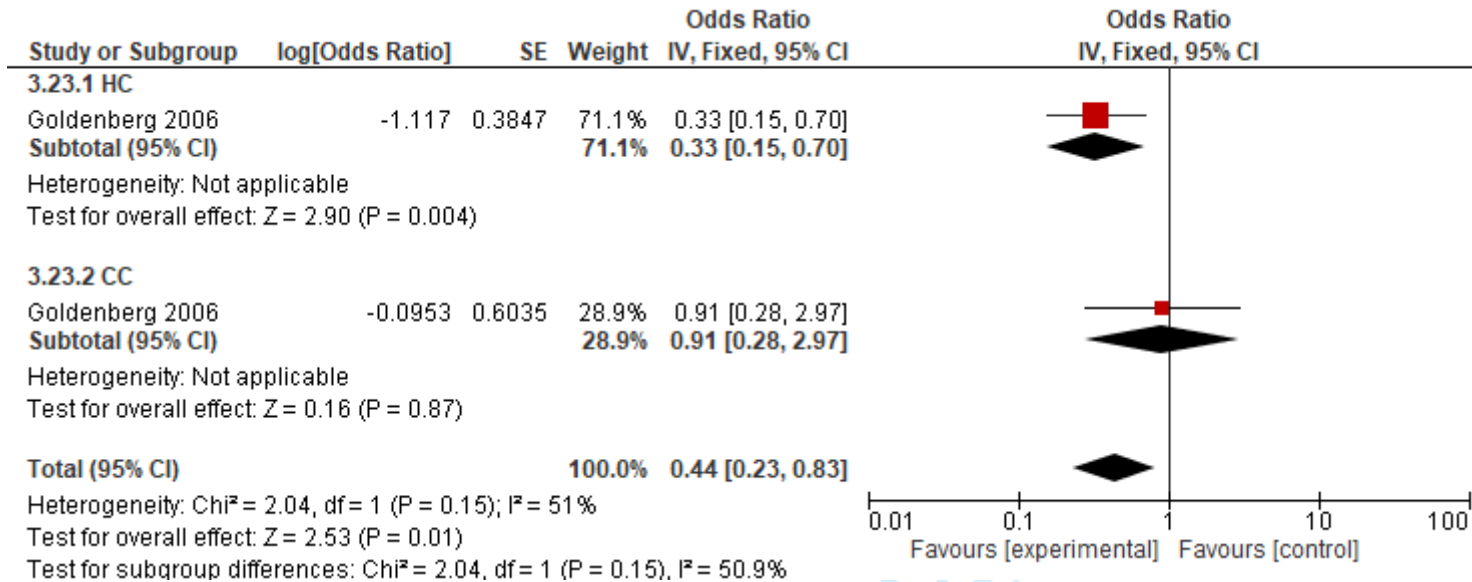
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

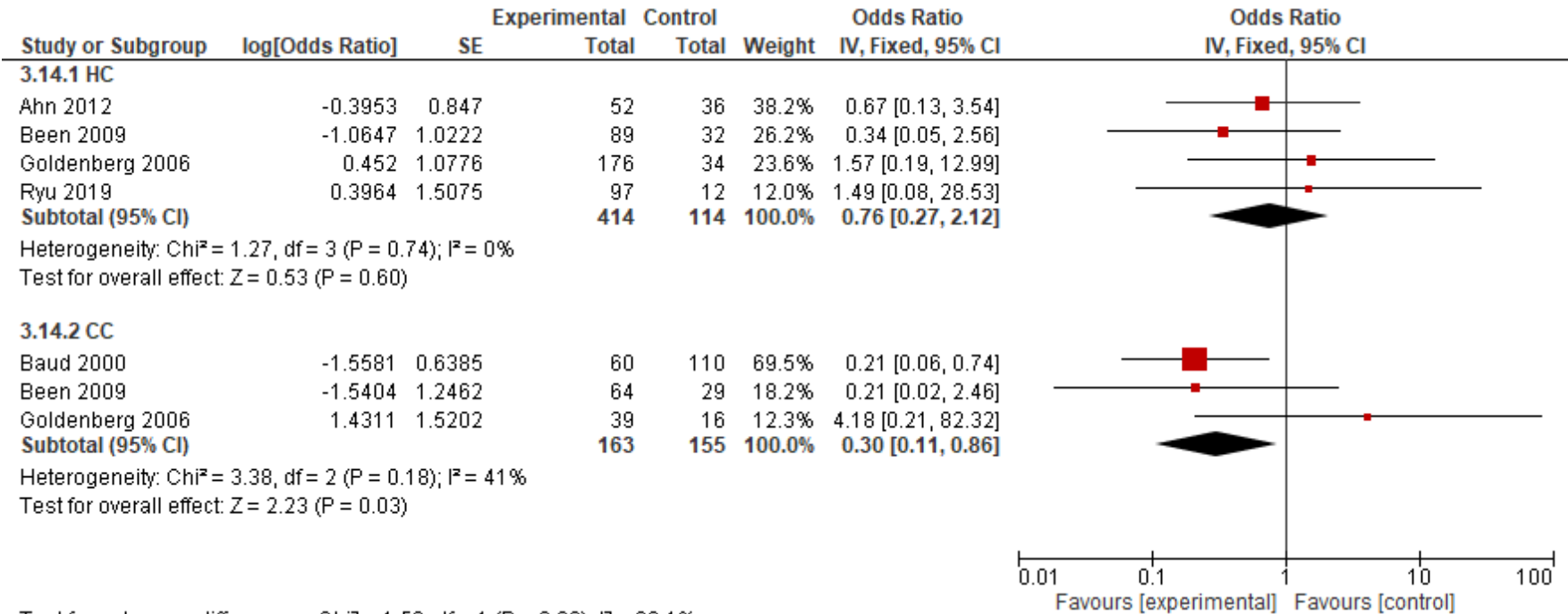
14) Systemic inflammatory response syndrome



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

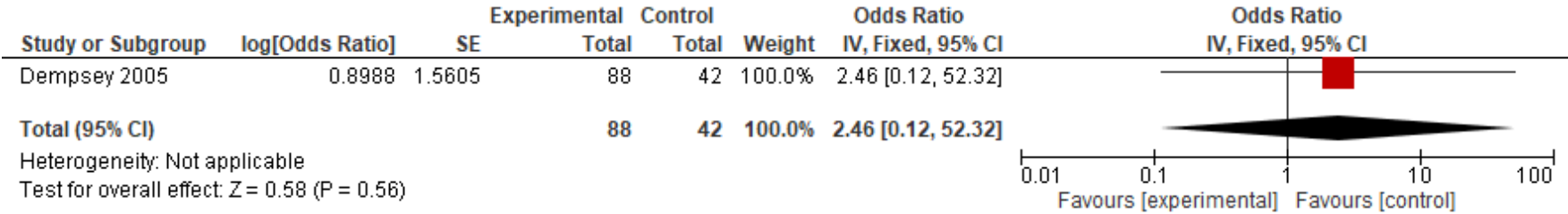
15) Periventricular leukomalacia (PVL)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



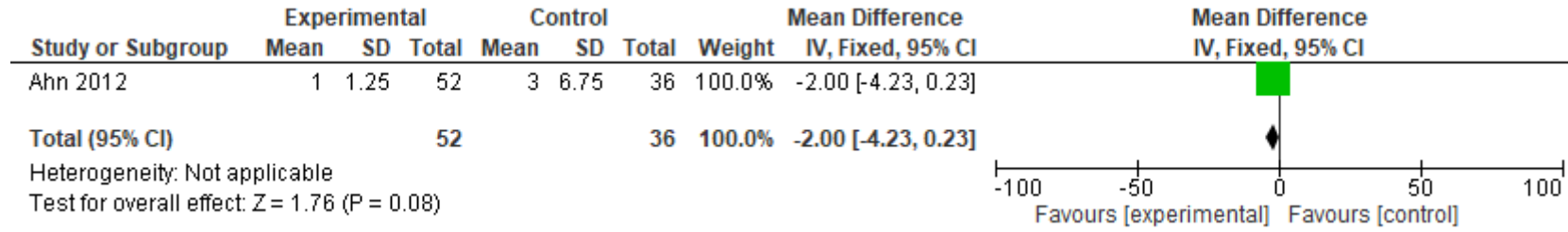
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

16) Meningitis (HC)



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

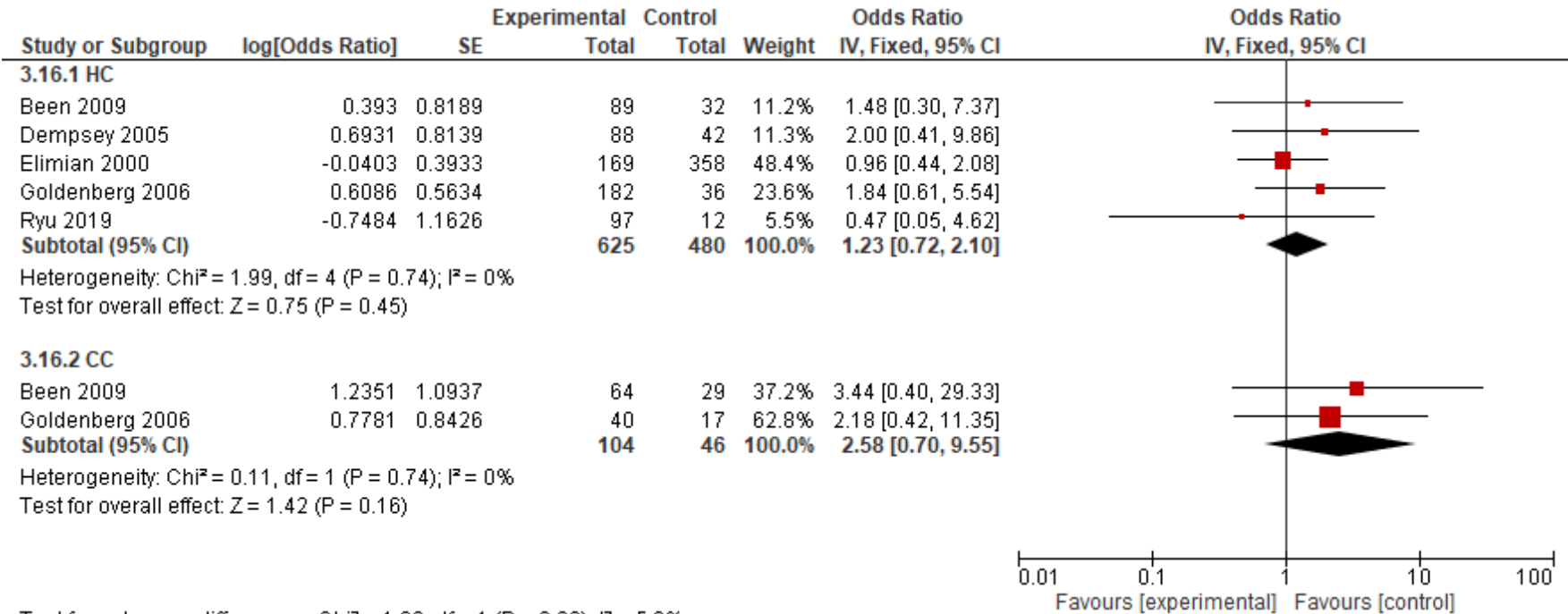
17) Mean duration of mechanical ventilation, days (HC)



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

18) Necrotizing enterocolitis (NEC)

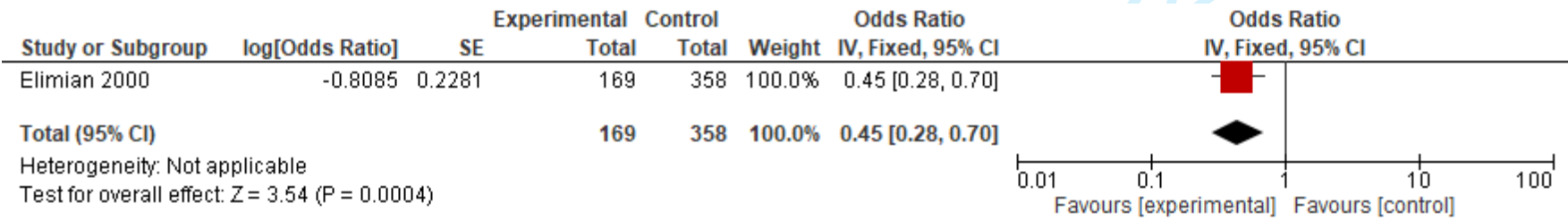
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.9%

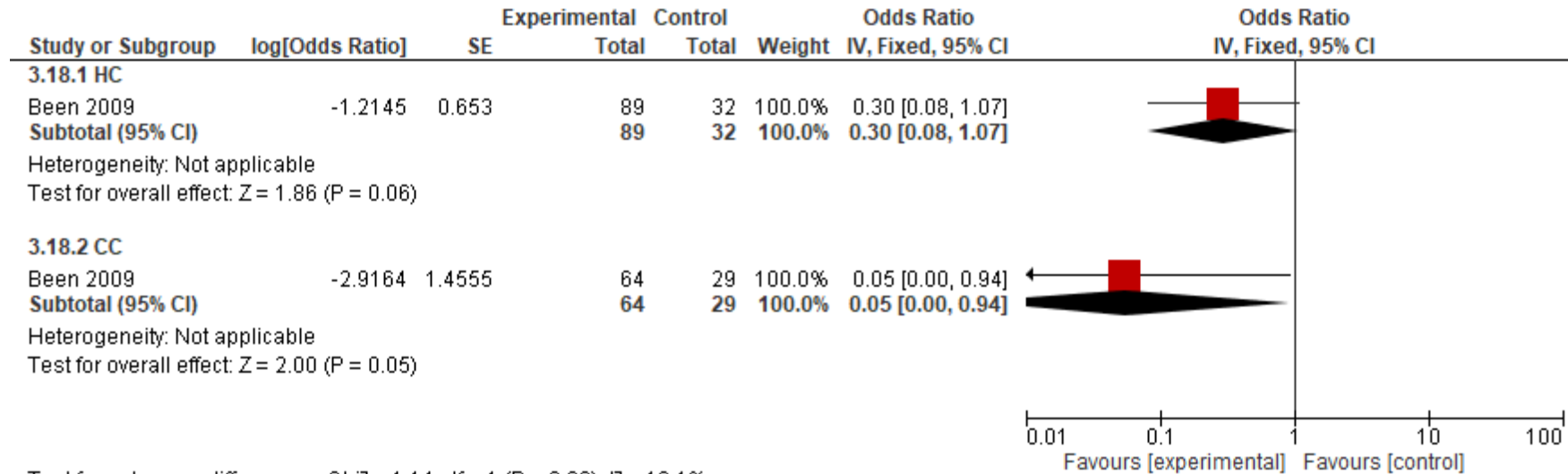
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



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

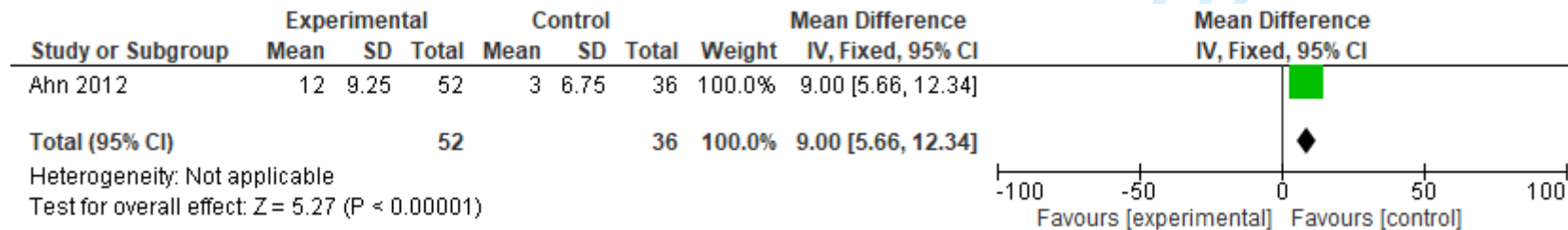
20) Use of mechanical ventilation



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

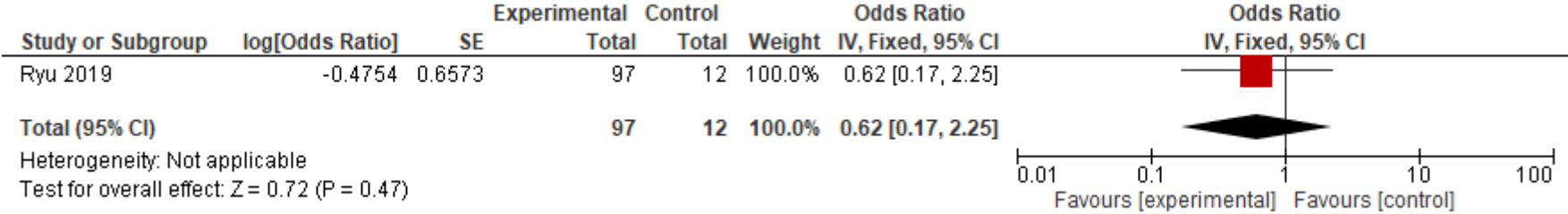
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

21) Duration of oxygen use, days (HC)



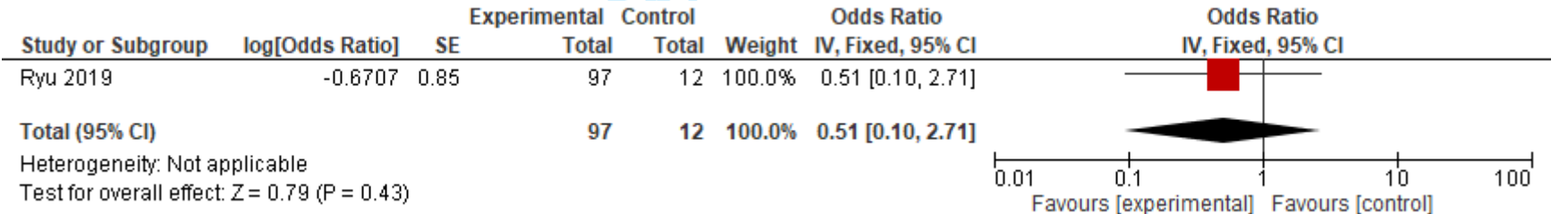
SD: Standard Deviation; CI: Confidence interval; HC: Histological chorioamnionitis

22) Discharge with respiratory support (HC)



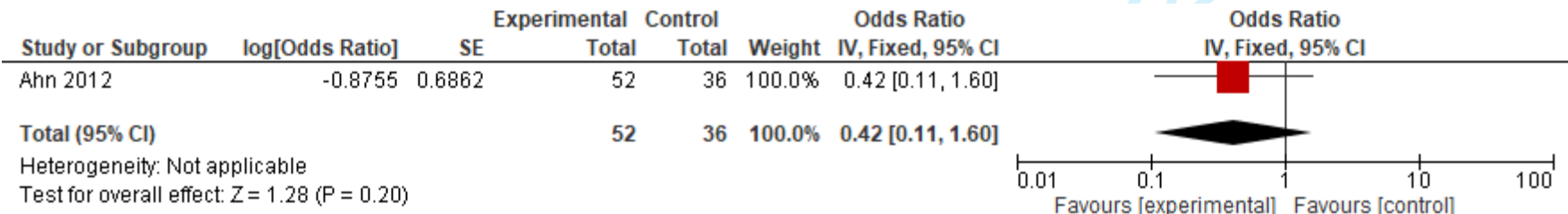
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

23) Retinopathy of prematurity requiring treatment (HC)



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

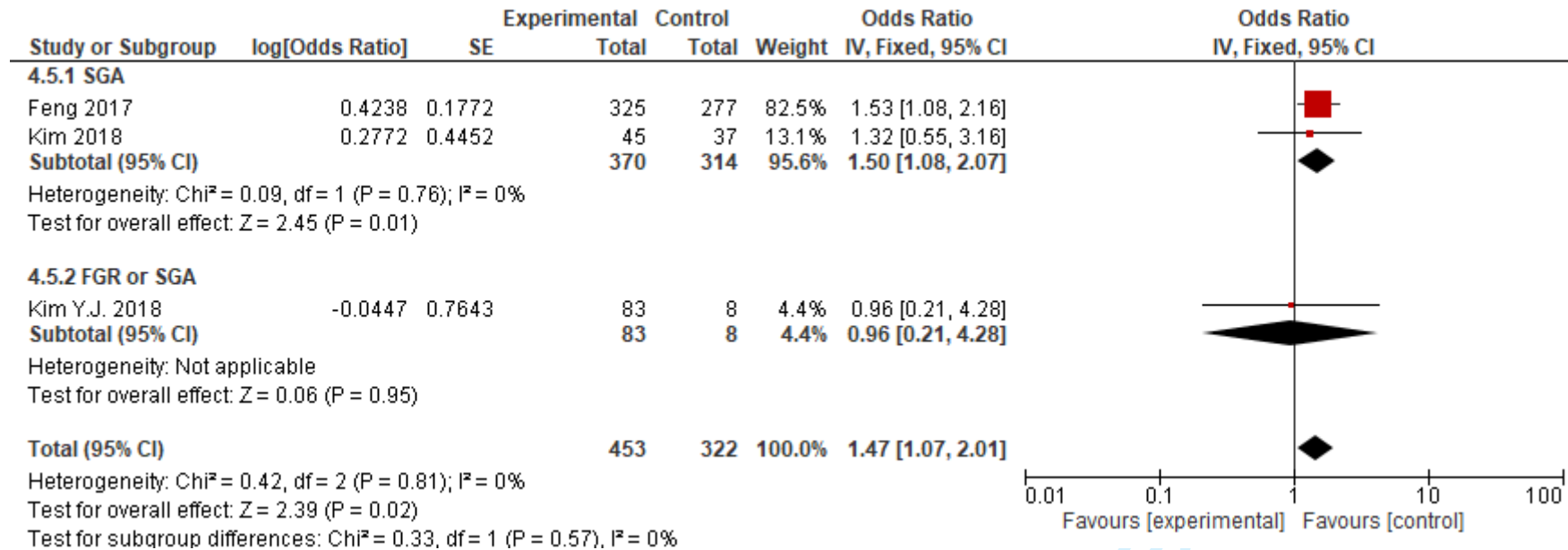
24) Intrahepatic cholestasis (HC)



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

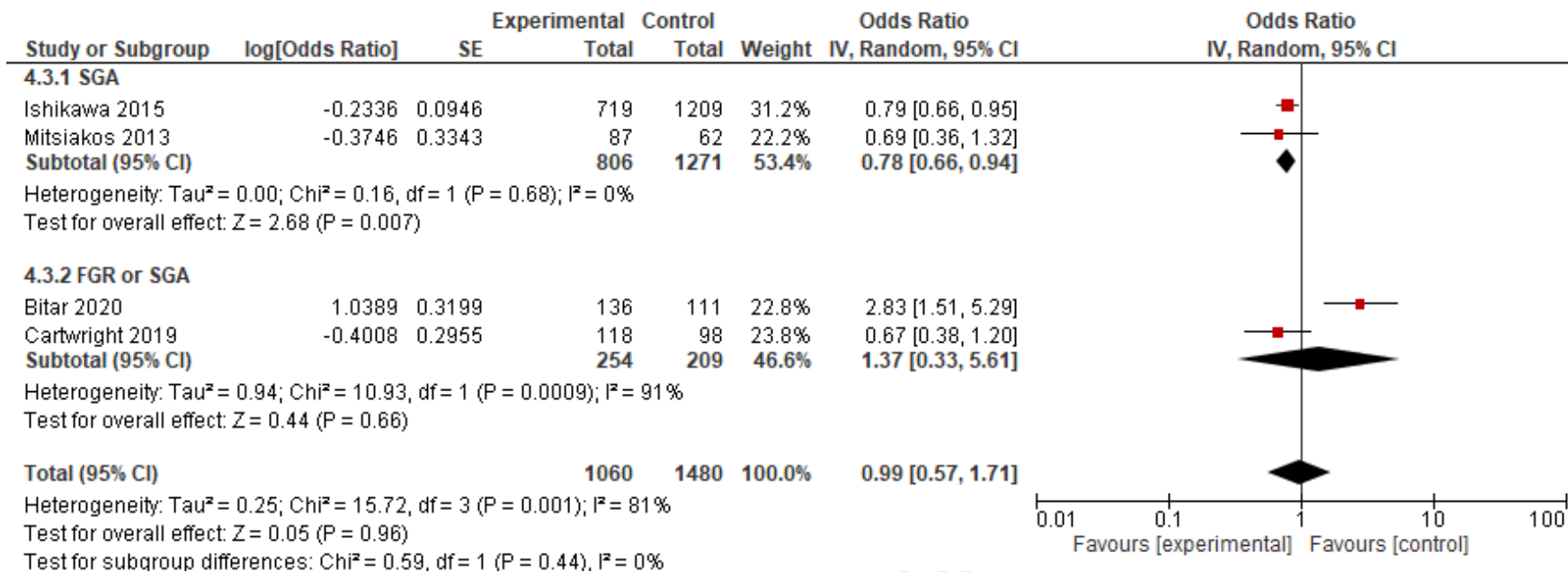
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Pregnancy-induced hypertension (PIH)



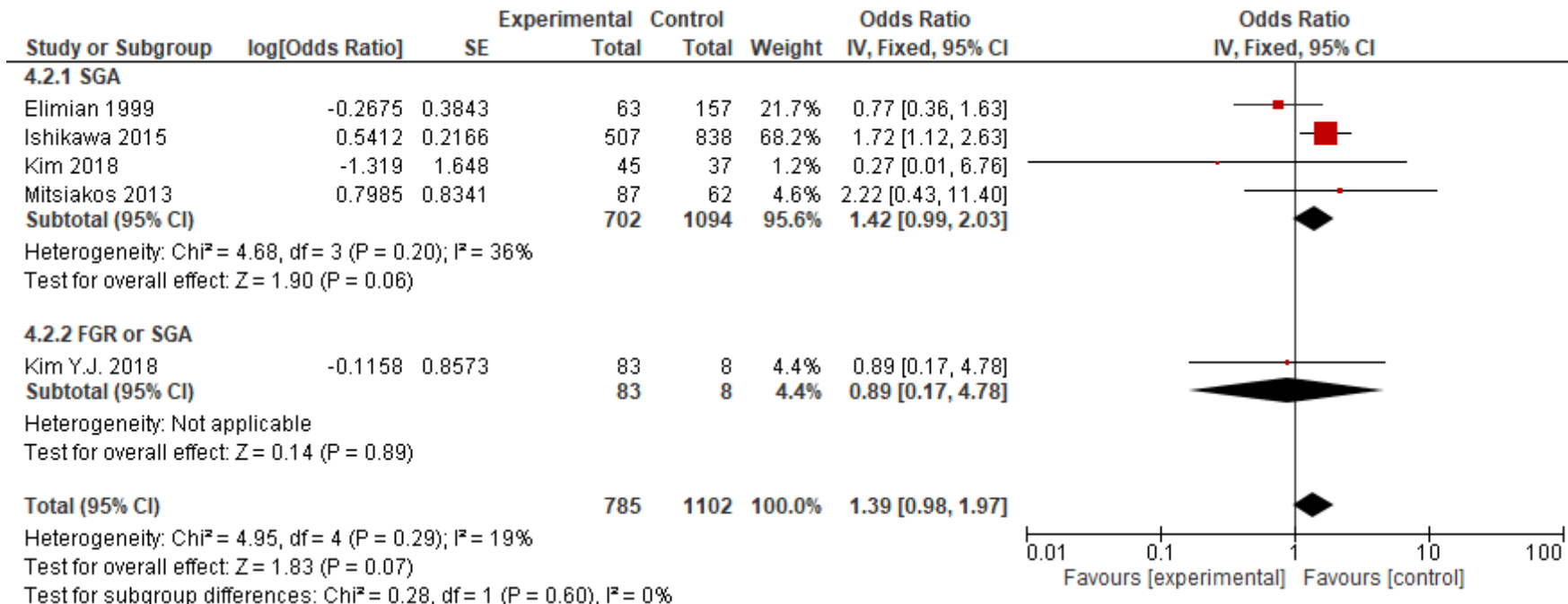
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

2) Preeclampsia



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

3) Chorioamnionitis

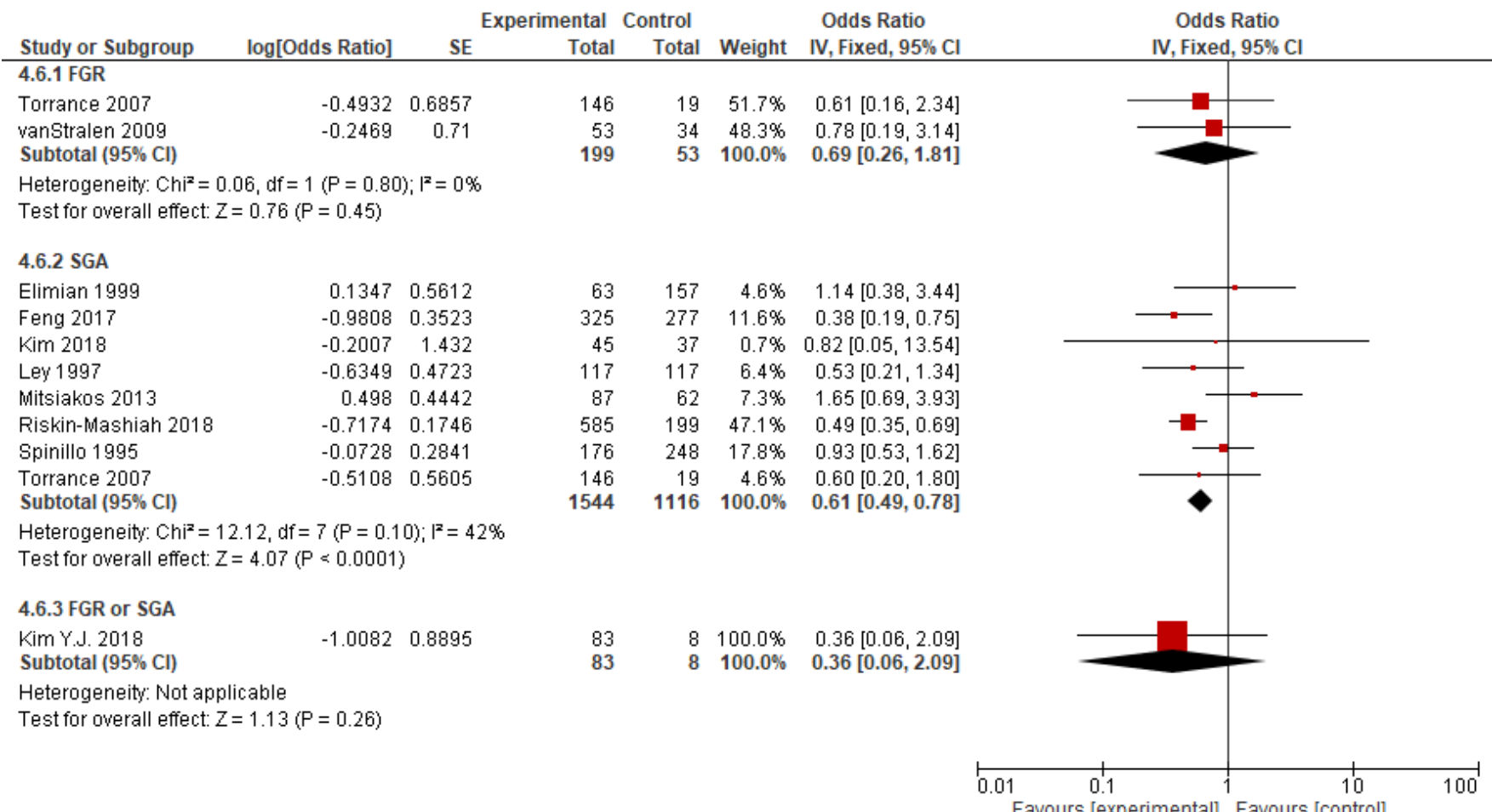


SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

Neonatal outcomes for women with growth-restricted fetuses

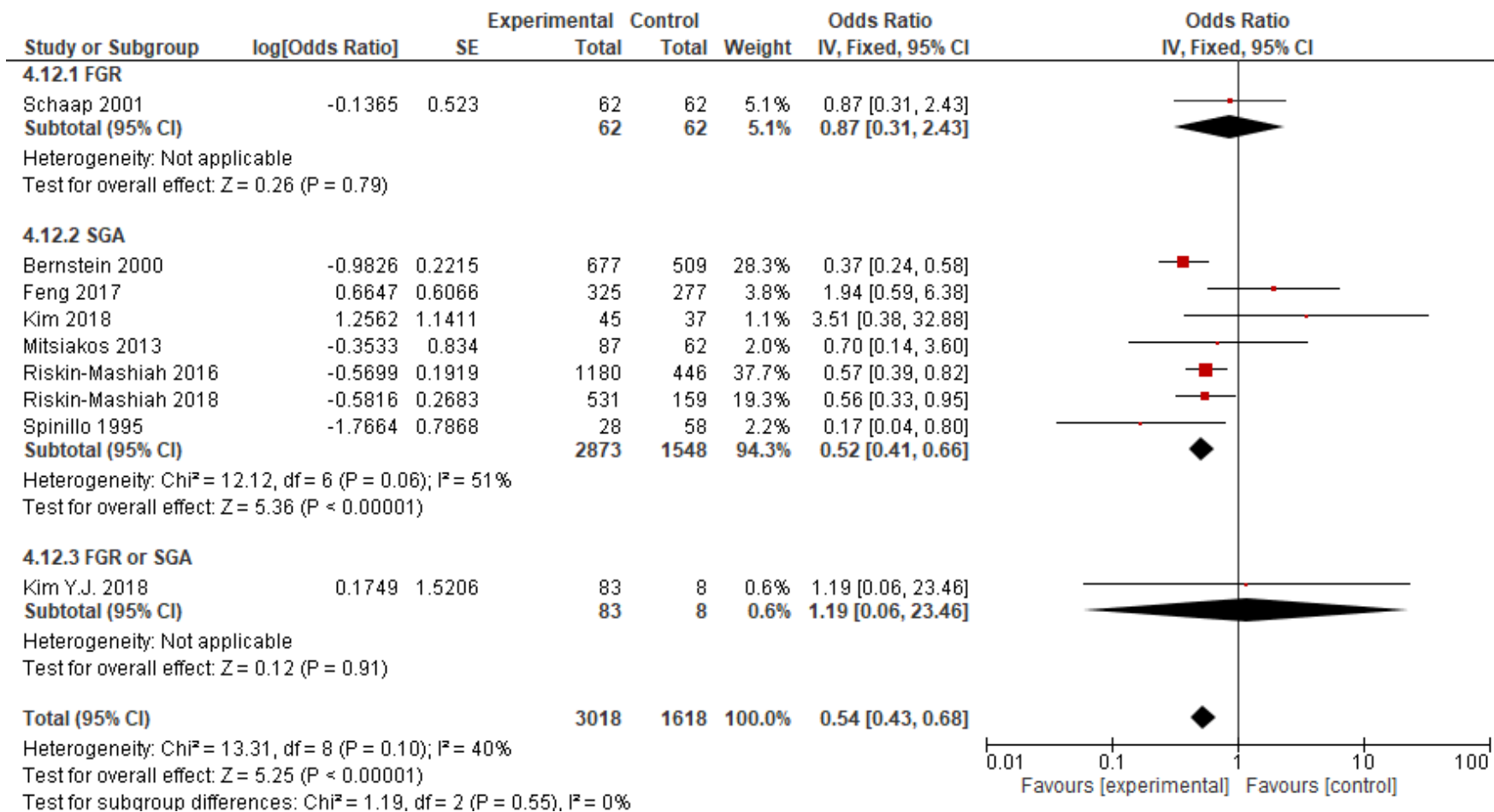
1) Neonatal death

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

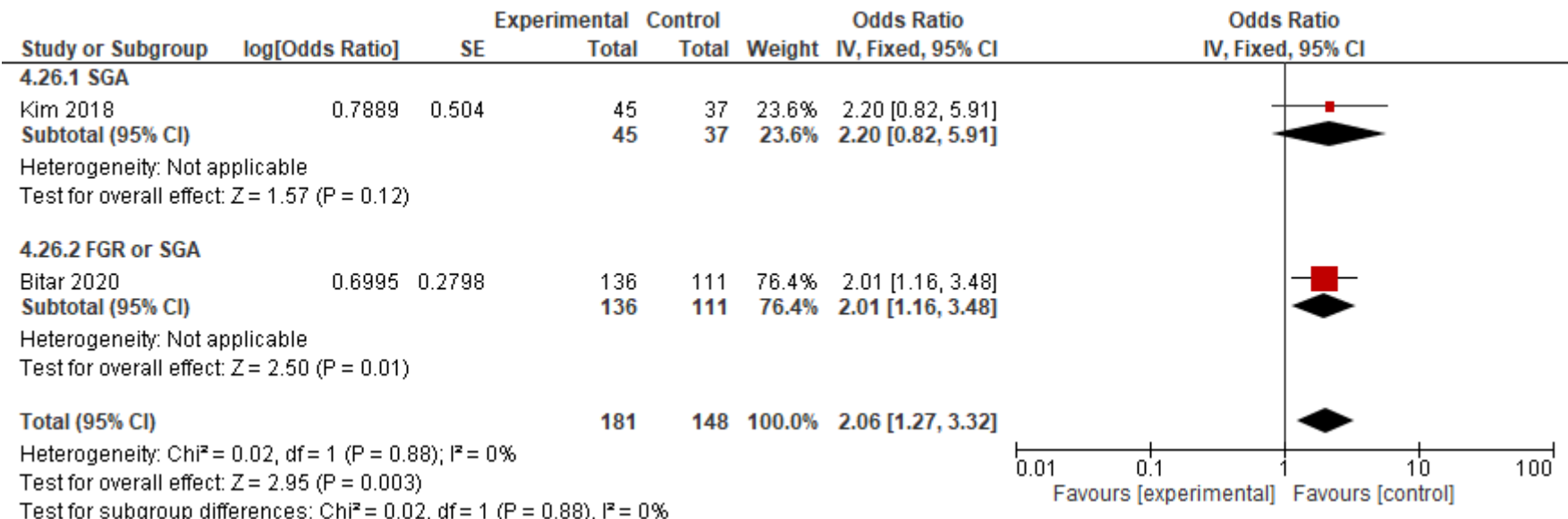
2) Severe intraventricular hemorrhage (IVH)



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

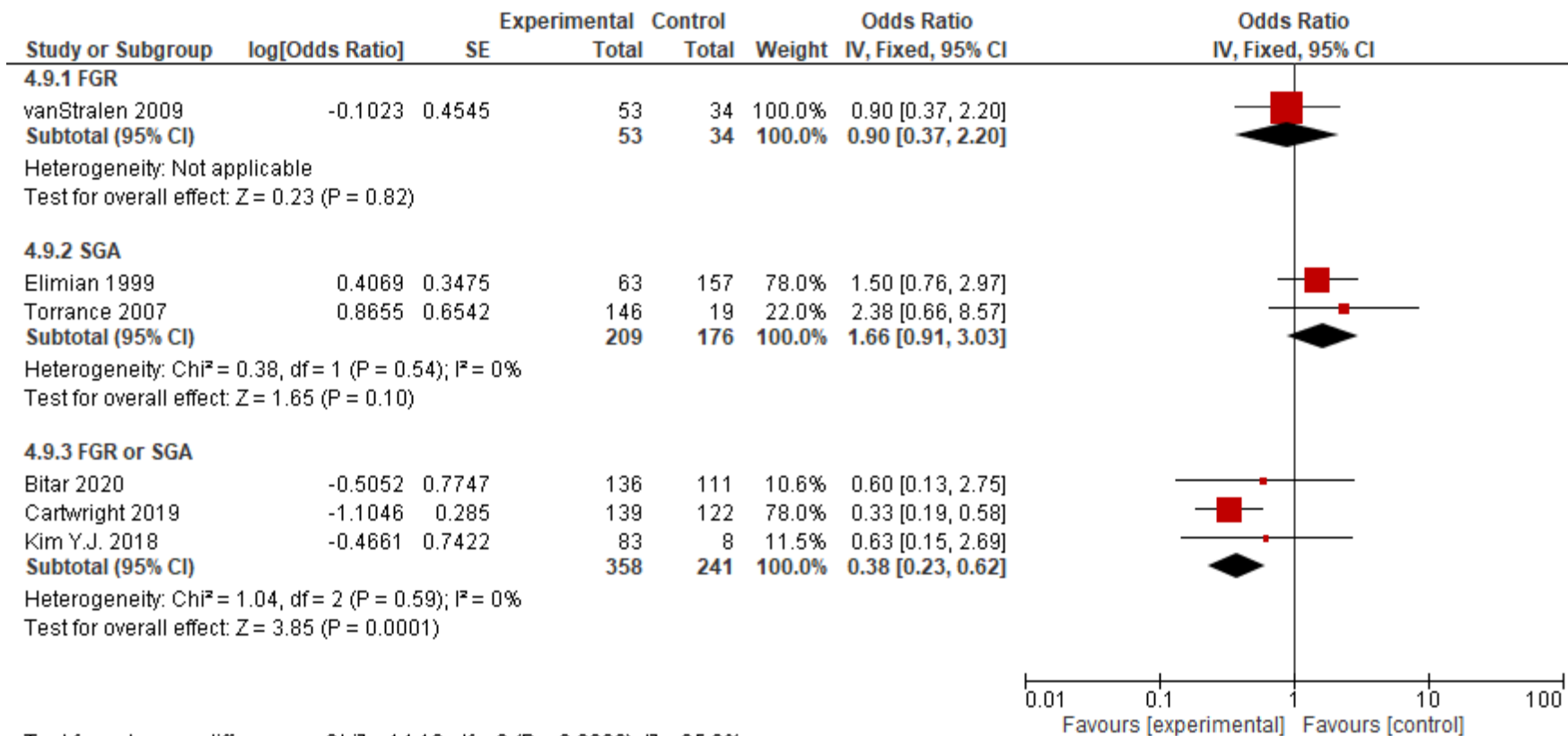
3) Neonatal hypoglycemia

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

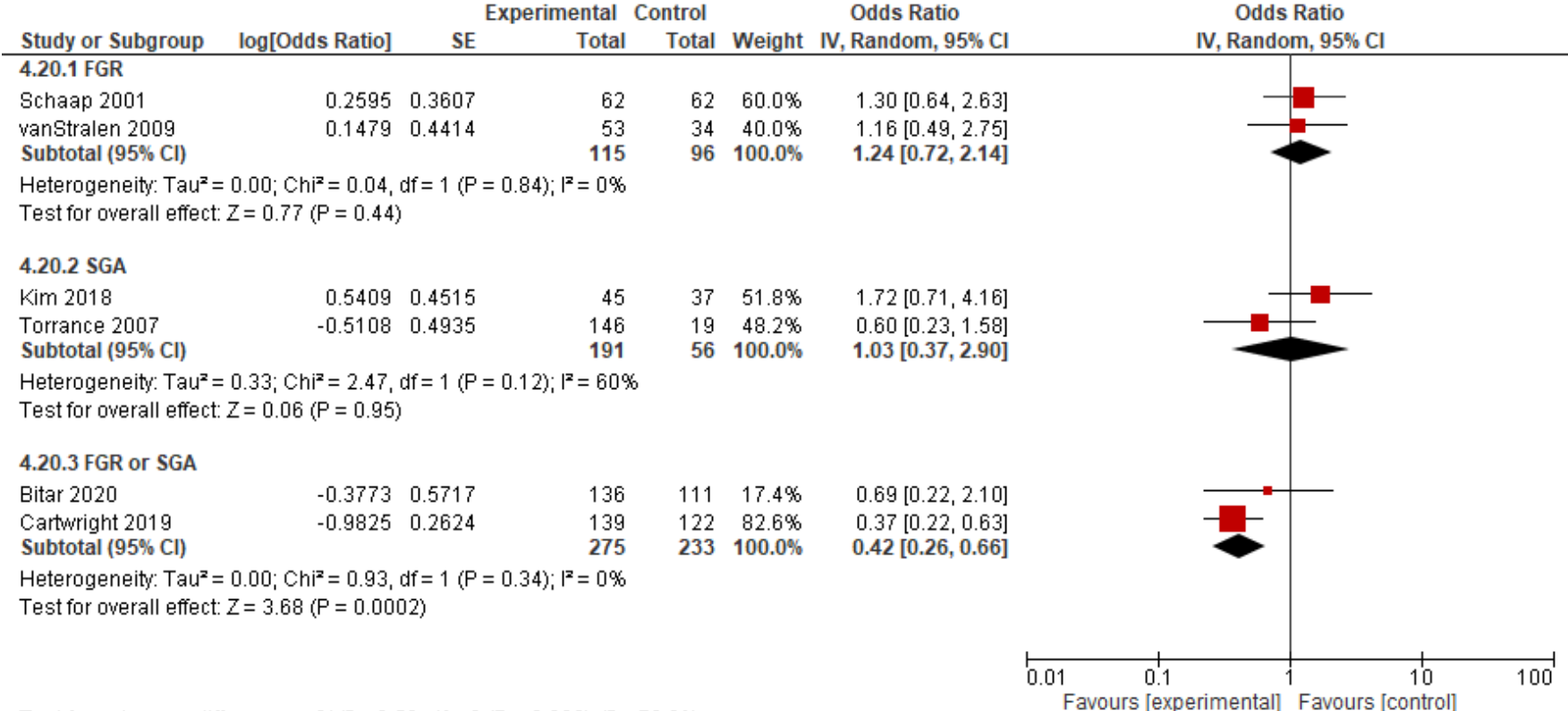
4) Surfactant use



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

5) Use of mechanical ventilation

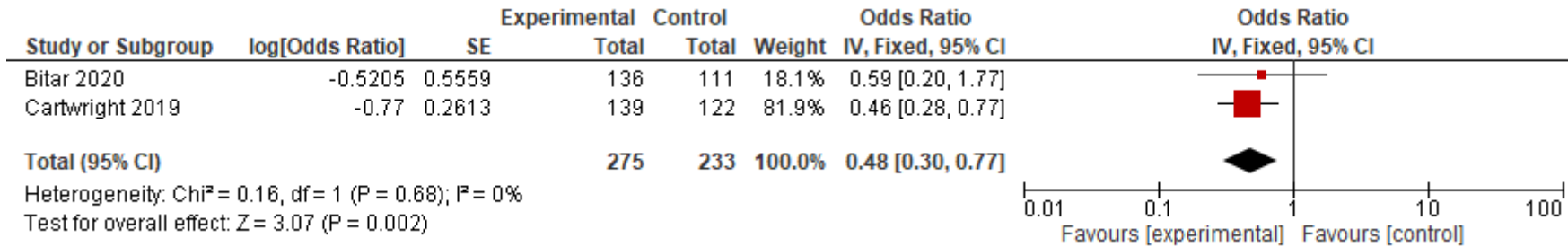
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



Test for subgroup differences: Chi² = 9.50, df = 2 (P = 0.009), I² = 78.9%

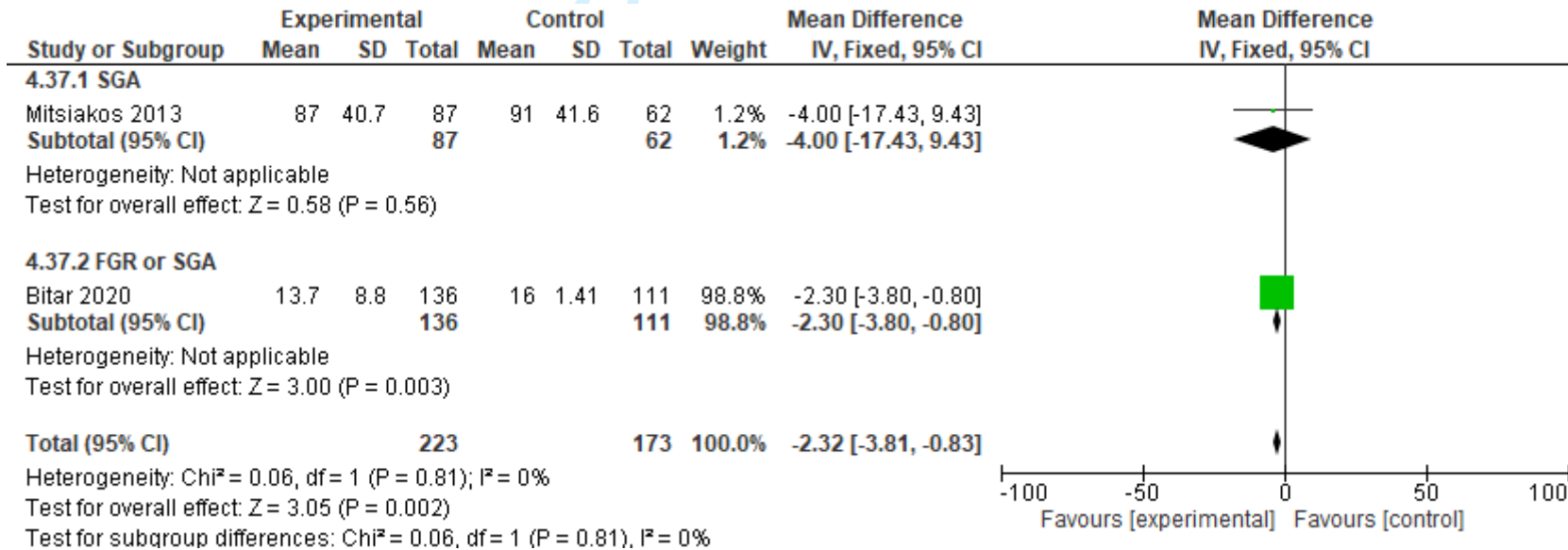
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

6) Oxygen therapy (FGR or SGA)



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

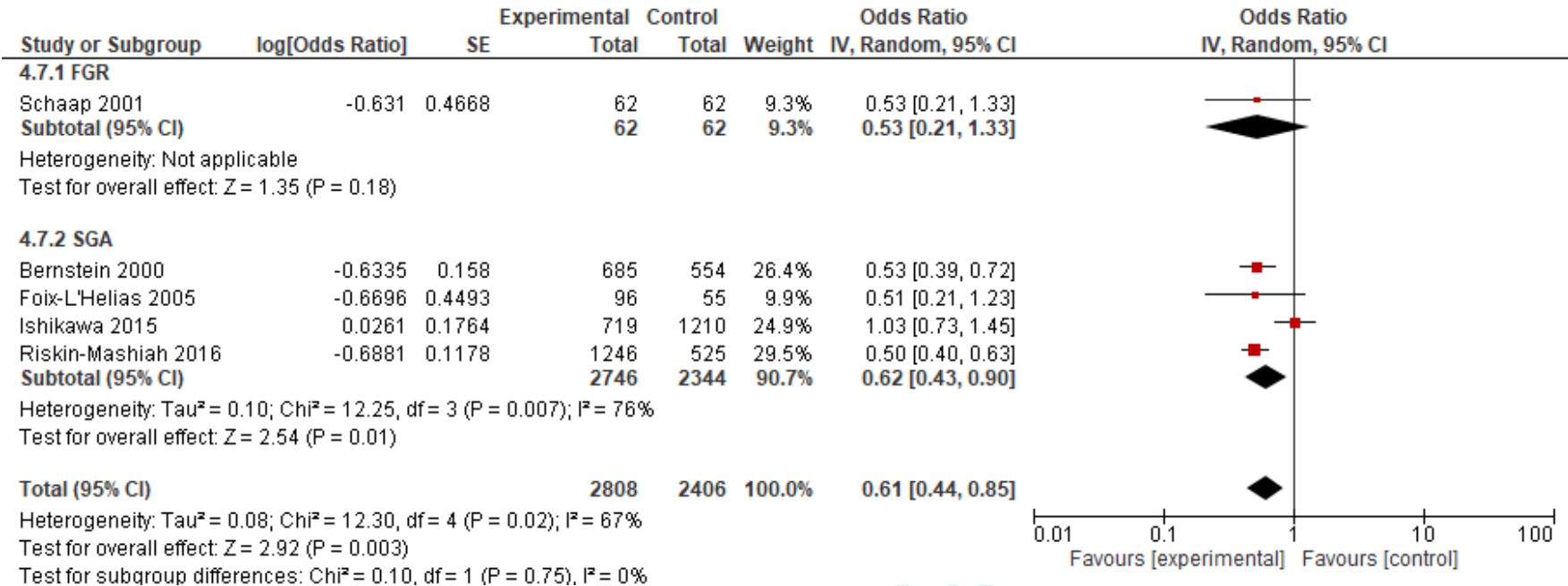
7) Duration of hospital stay (days)



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

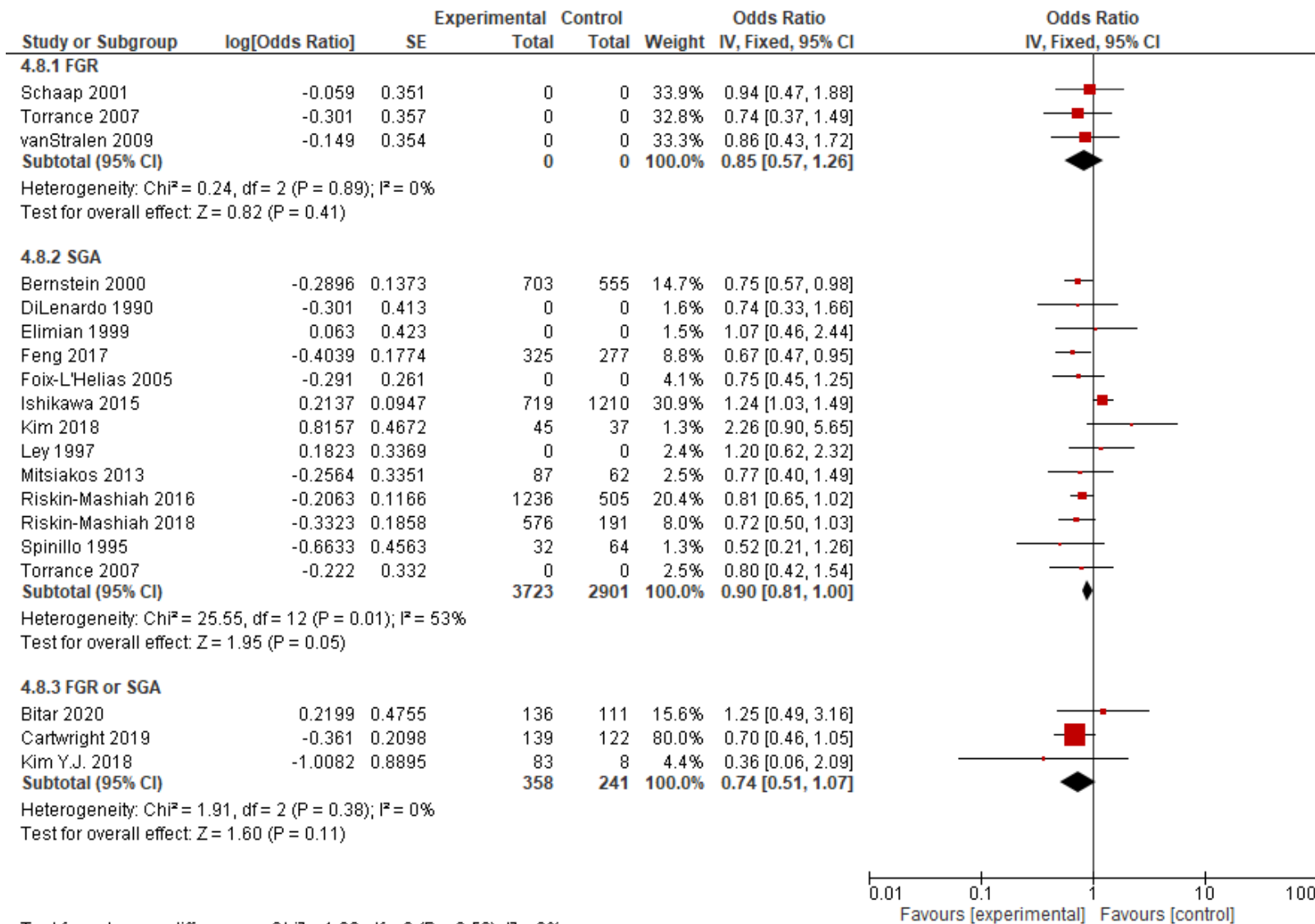
8) Death before discharge home

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

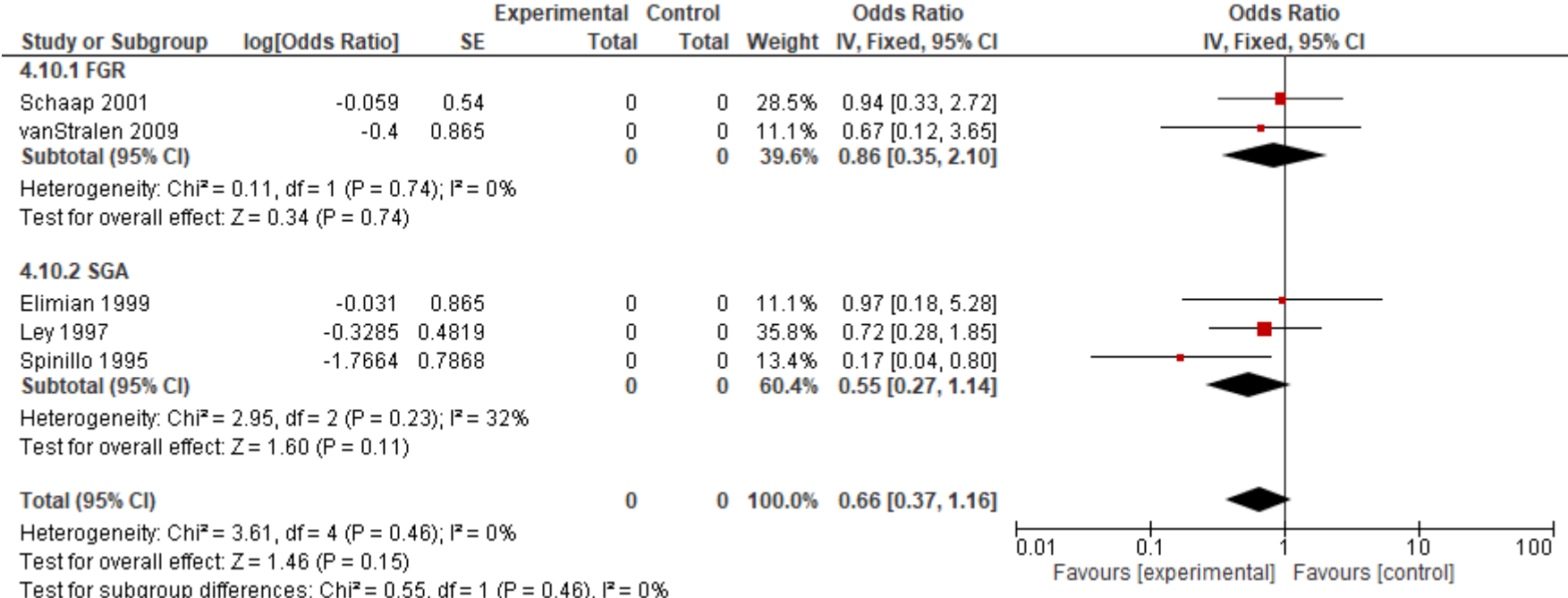
9) Respiratory distress syndrome (RDS)



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

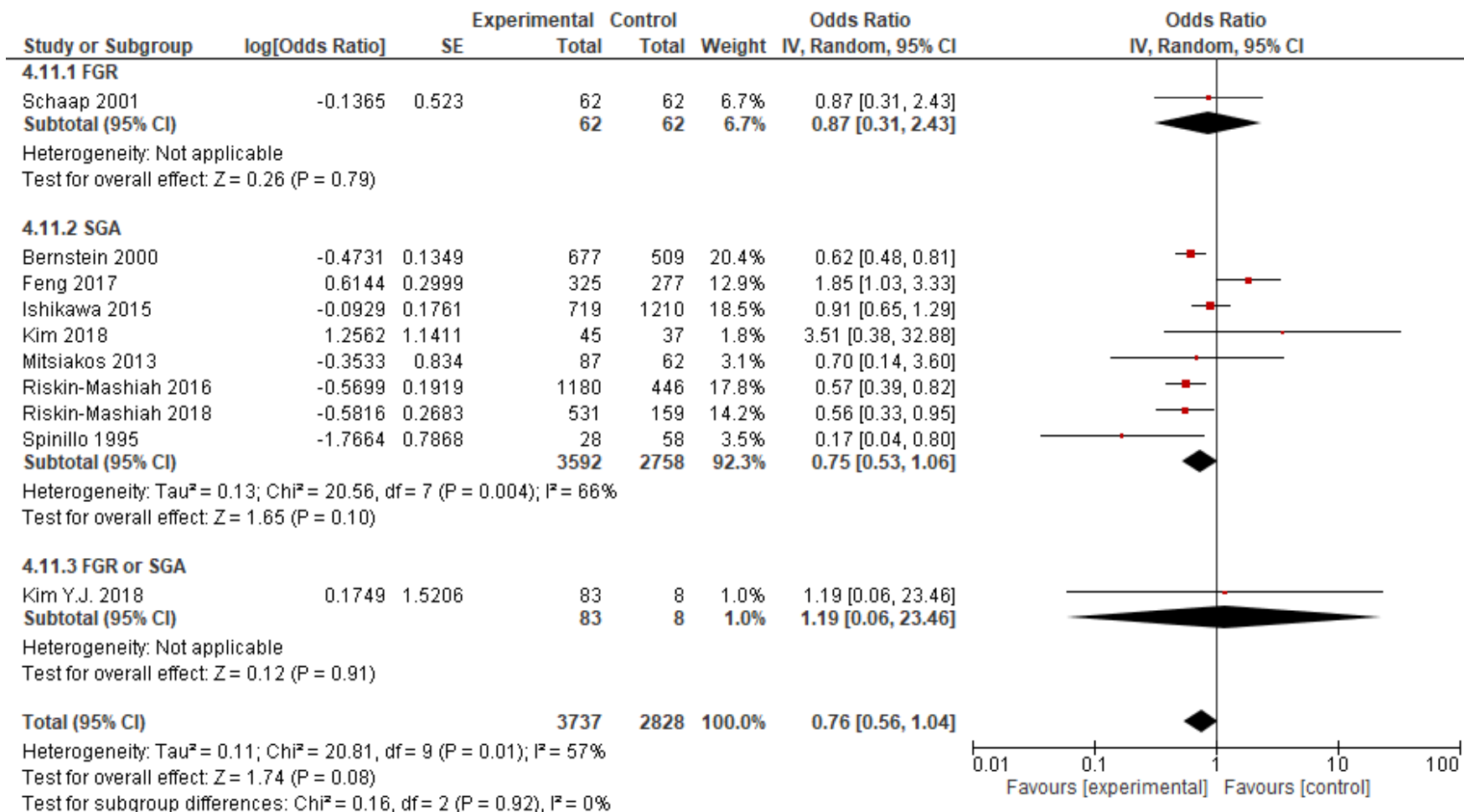
10) Major brain lesion (IVH, ICH, PVH, PVL)



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

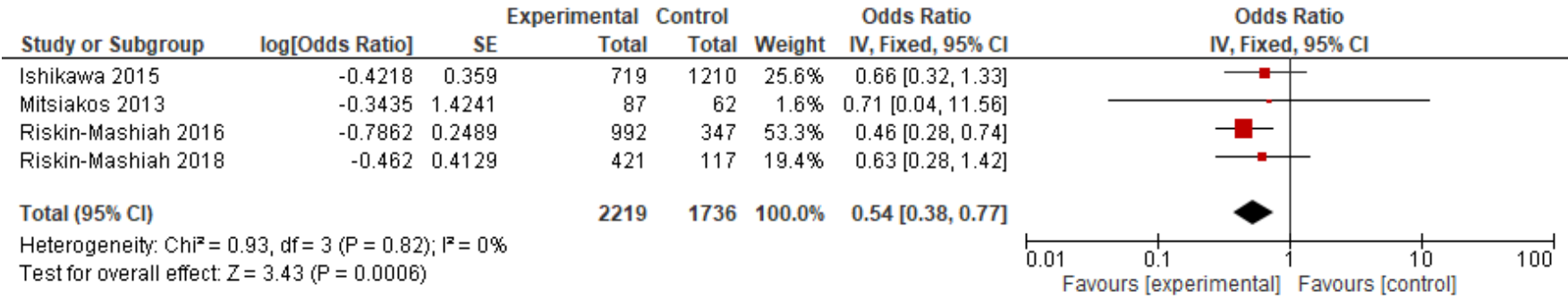
11) Intraventricular hemorrhage (IVH)



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

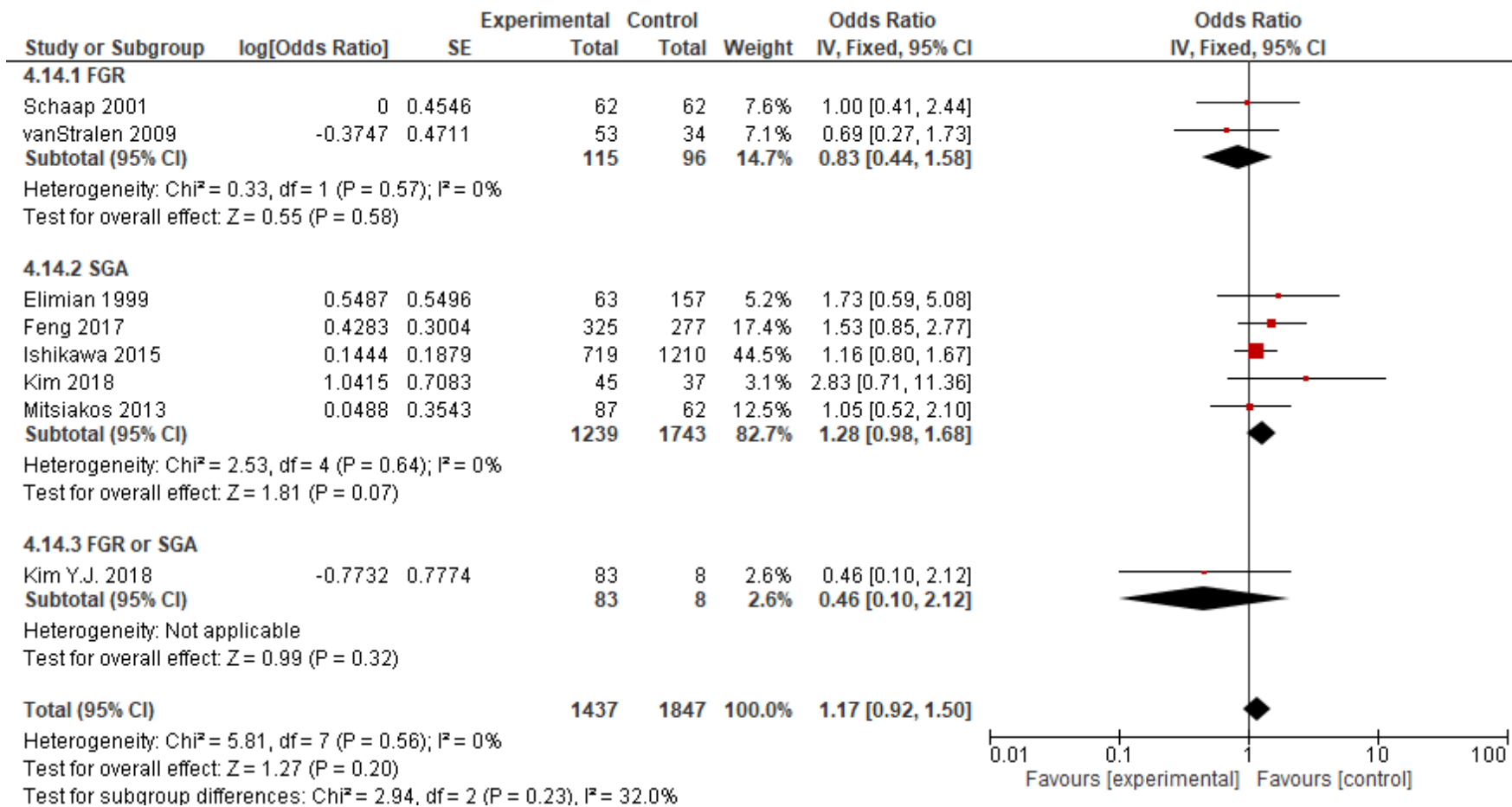
12) Periventricular leukomalacia (PVL) (SGA)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

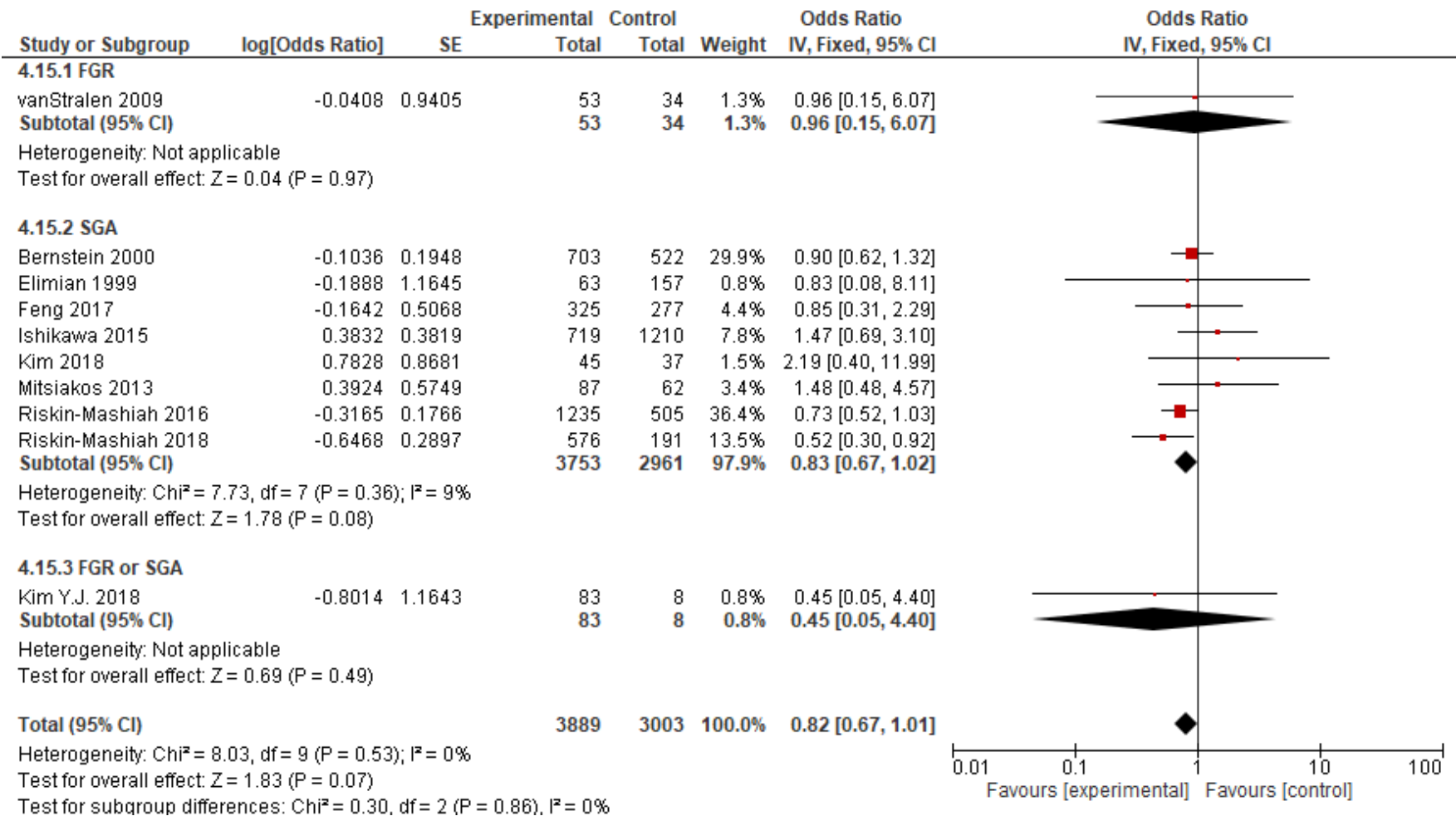
13) Neonatal sepsis



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

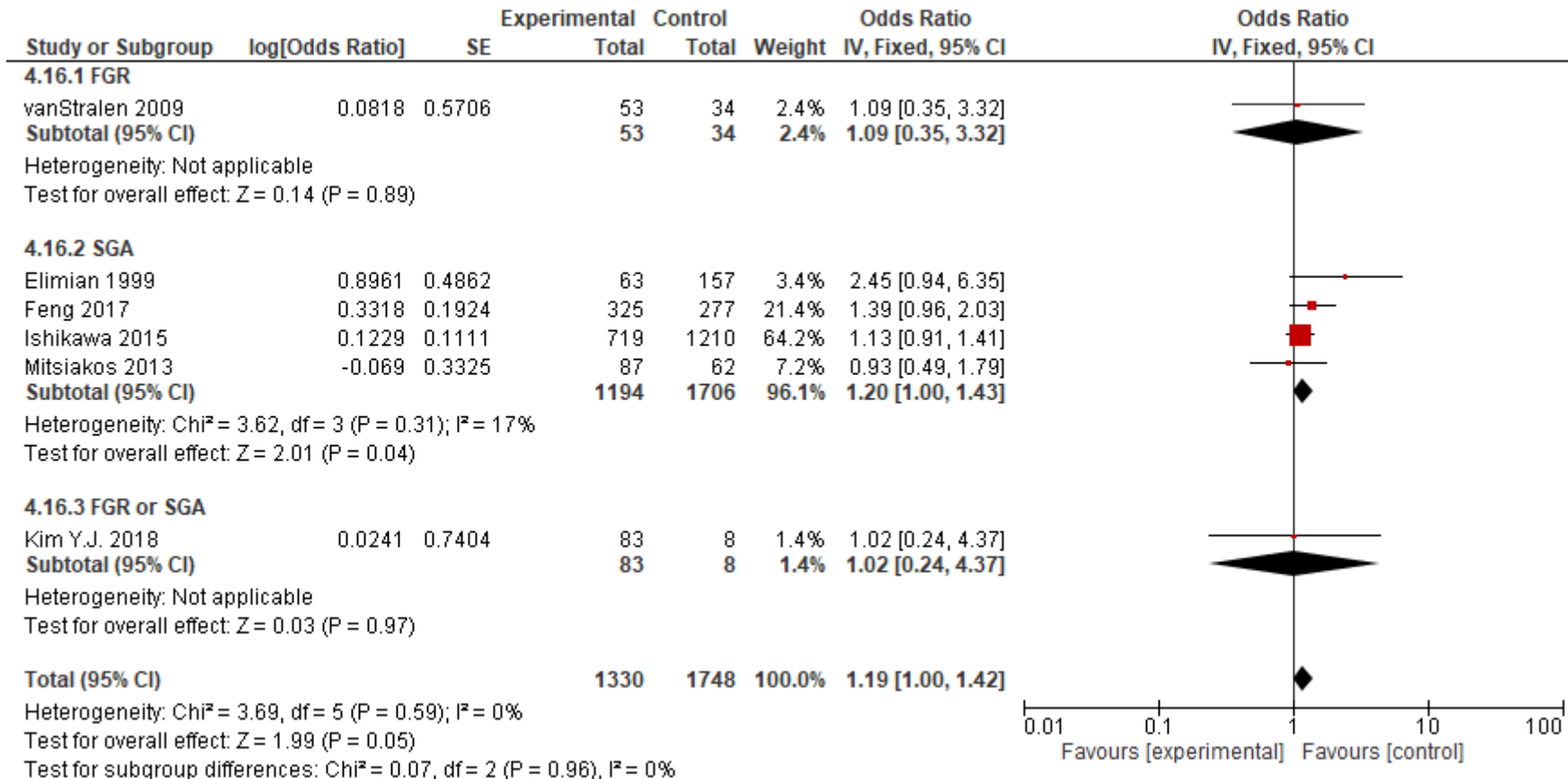
14) Necrotizing enterocolitis (NEC)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

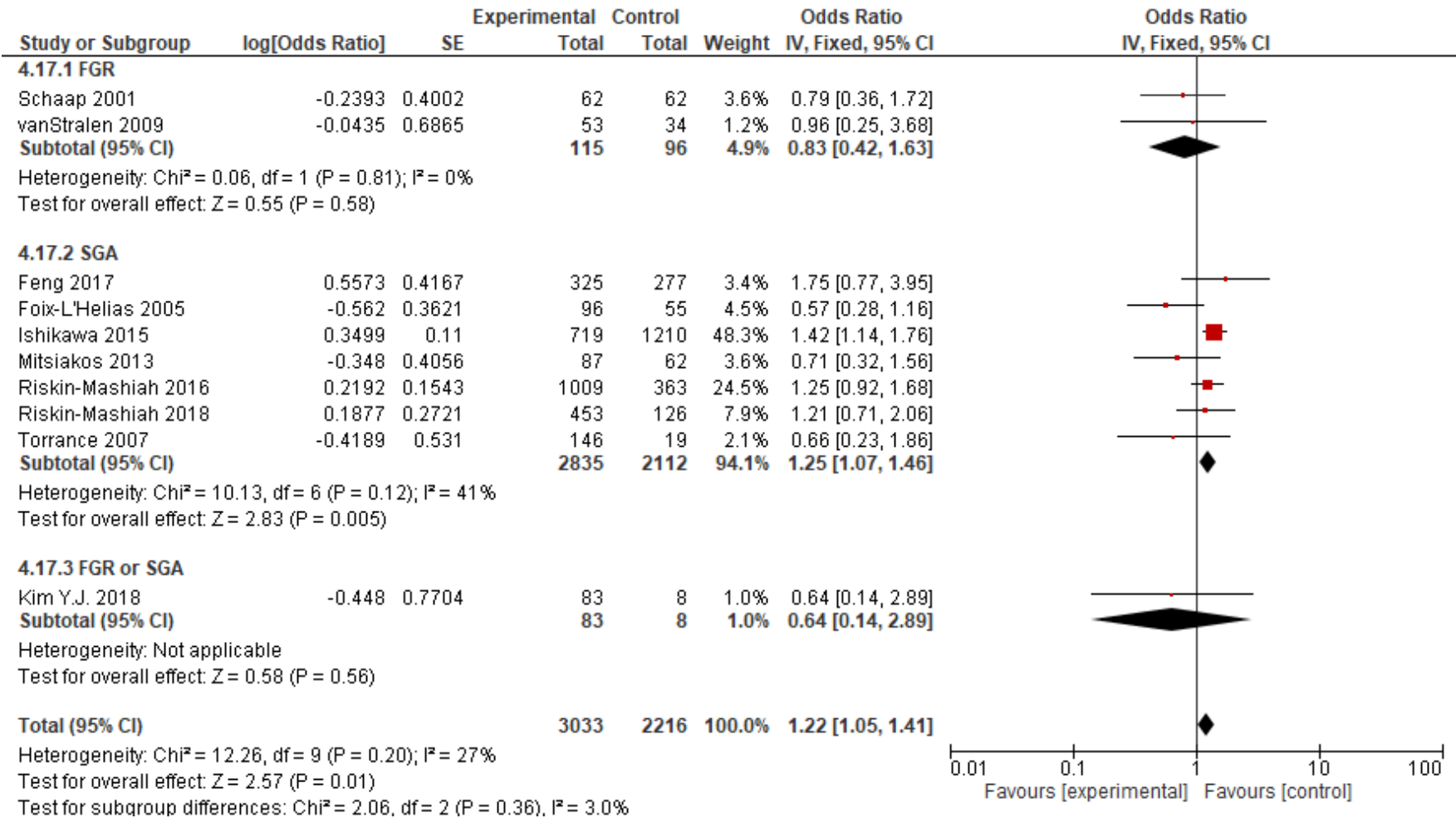
15) Patent ductus arteriosus (PDA)



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

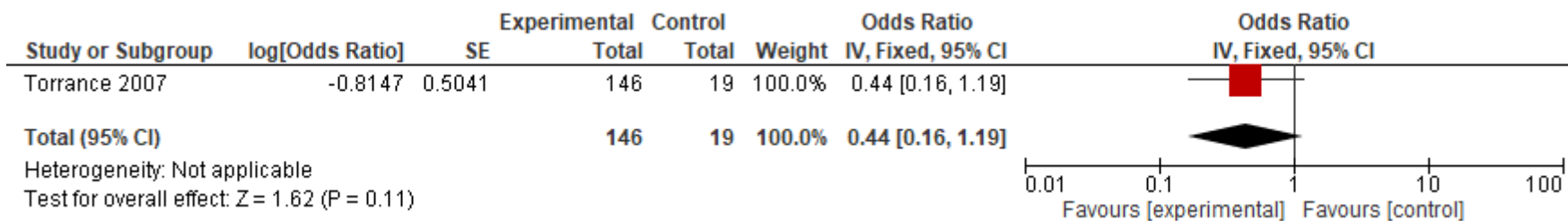
16) Bronchopulmonary dysplasia (BPD)/ Chronic lung disease (CLD)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



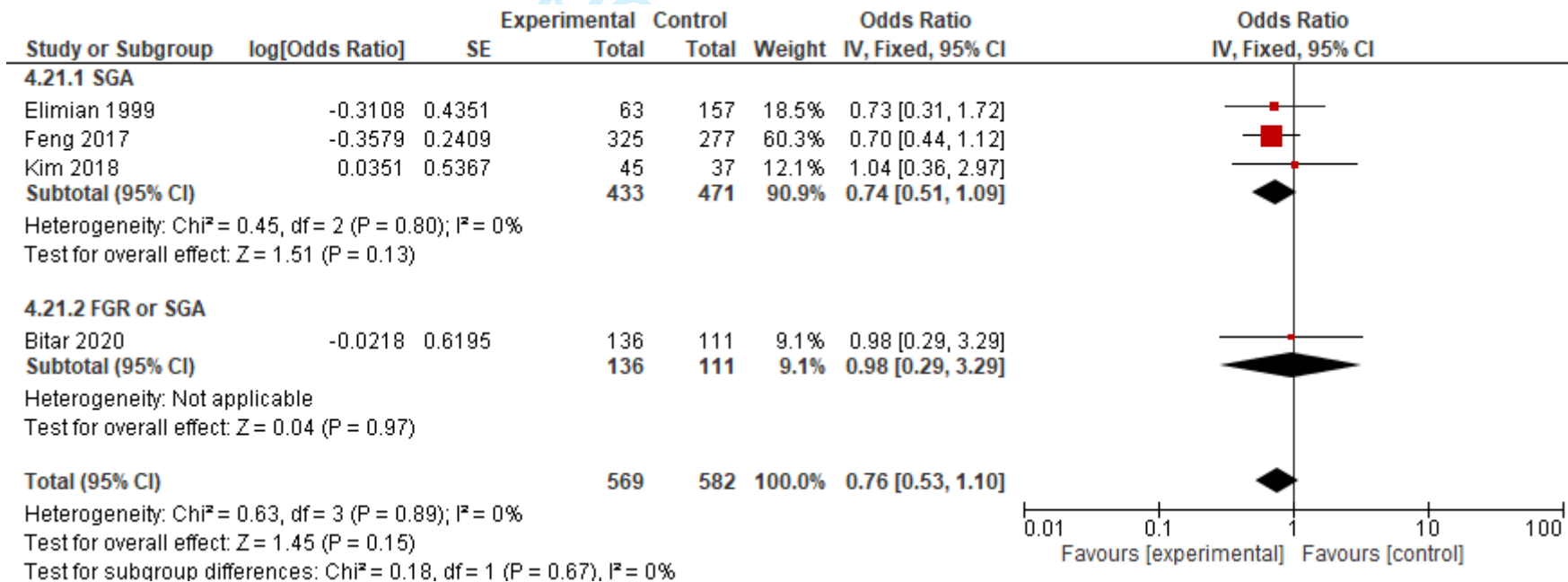
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

17) Small for Gestational age (FGR)



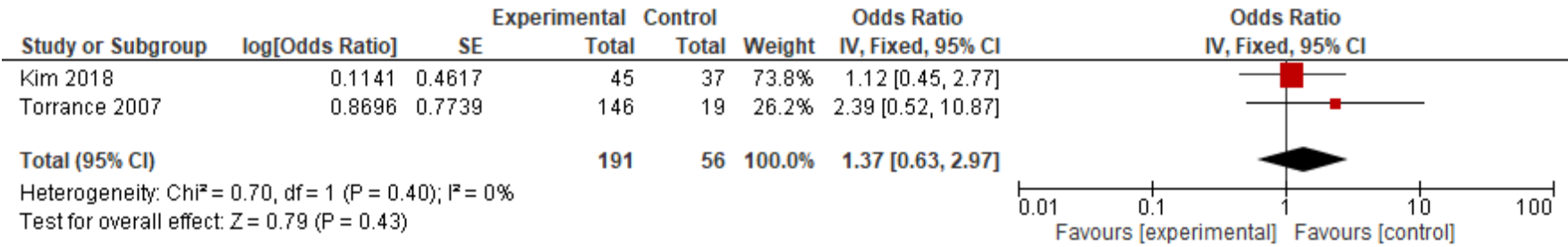
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction

18) Apgar score < 7 at 5 minutes



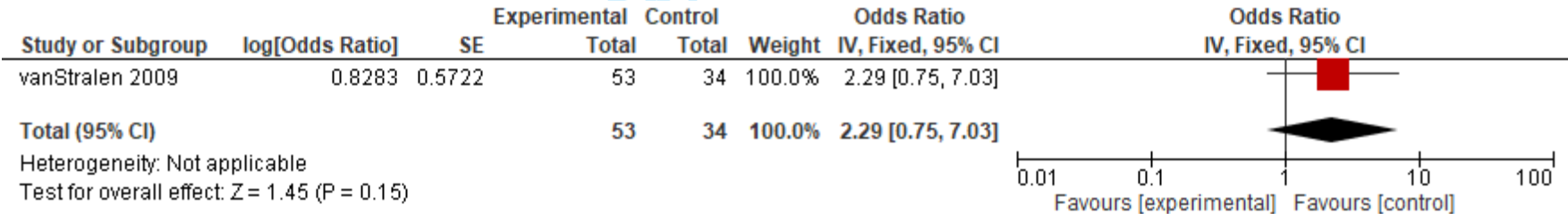
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



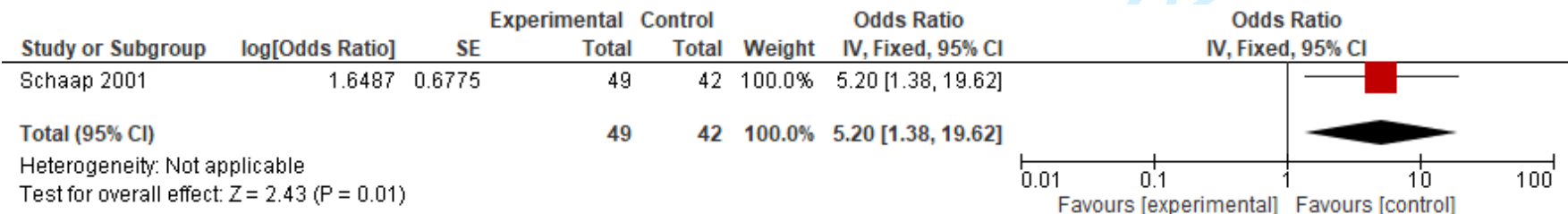
SE: Standard error; CI: Confidence interval; SGA: Small for gestational age

20) Hypotension (FGR)



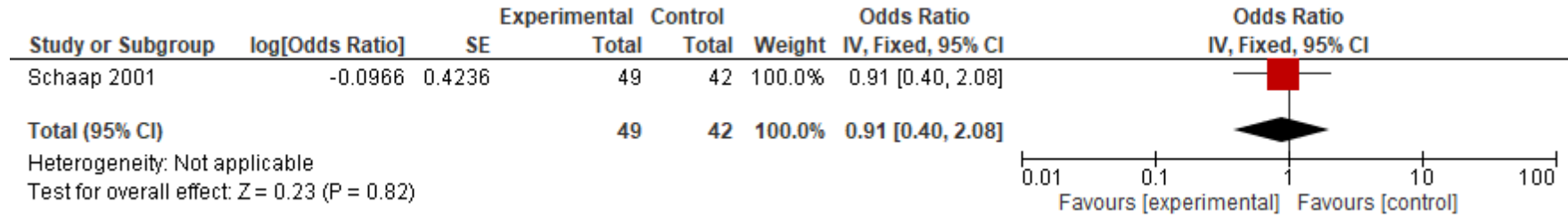
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction

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



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

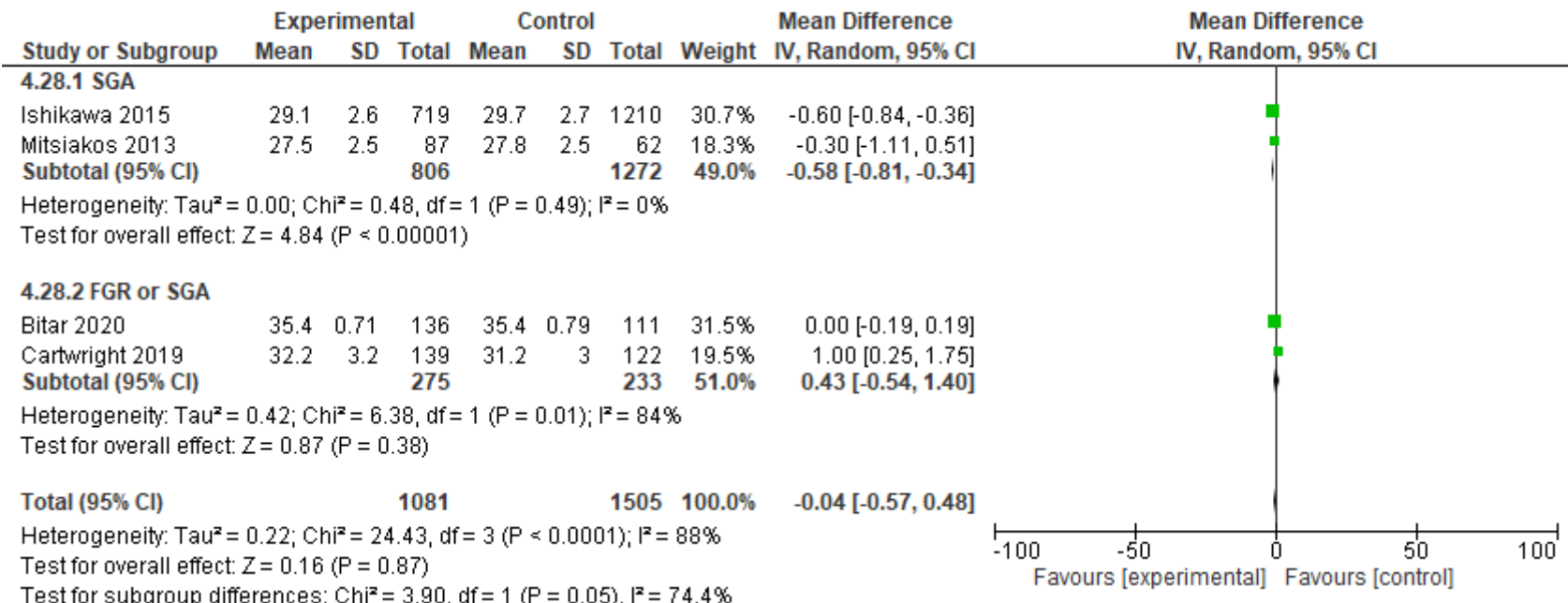
22) Abnormal behavior at long-term follow-up at school age (FGR)



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

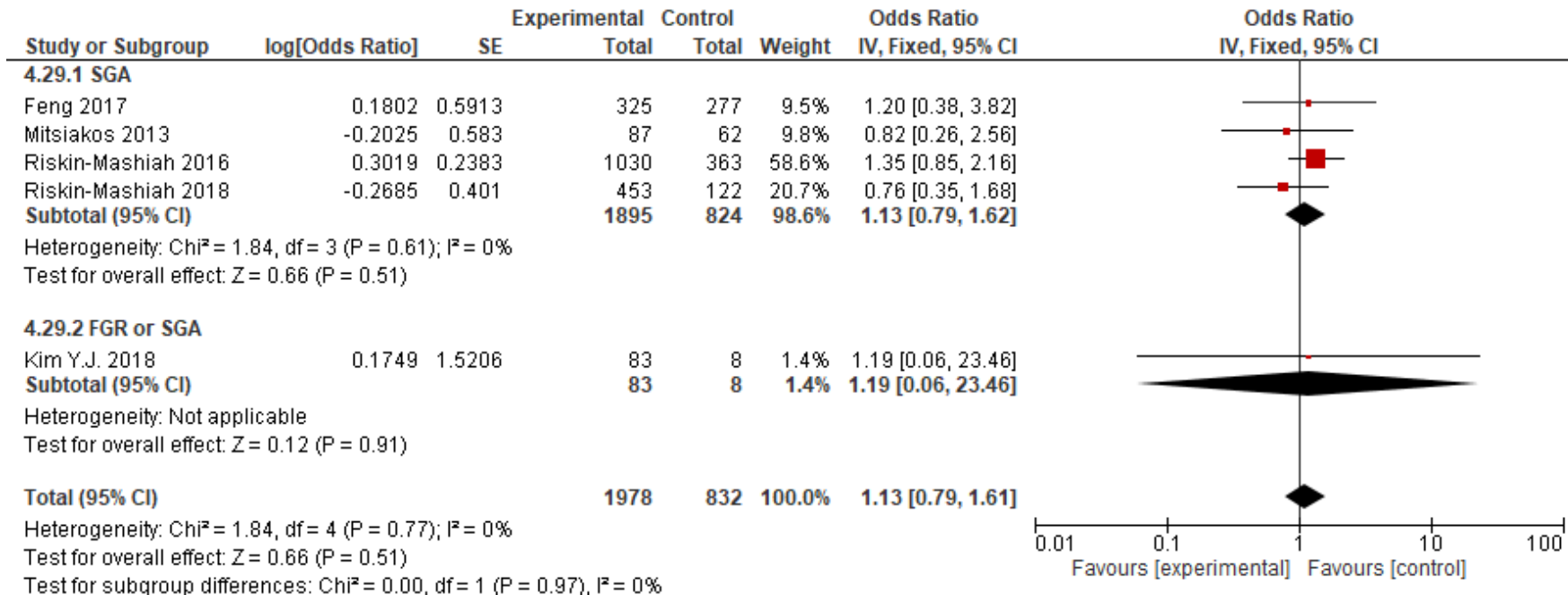
23) Gestational age at birth

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

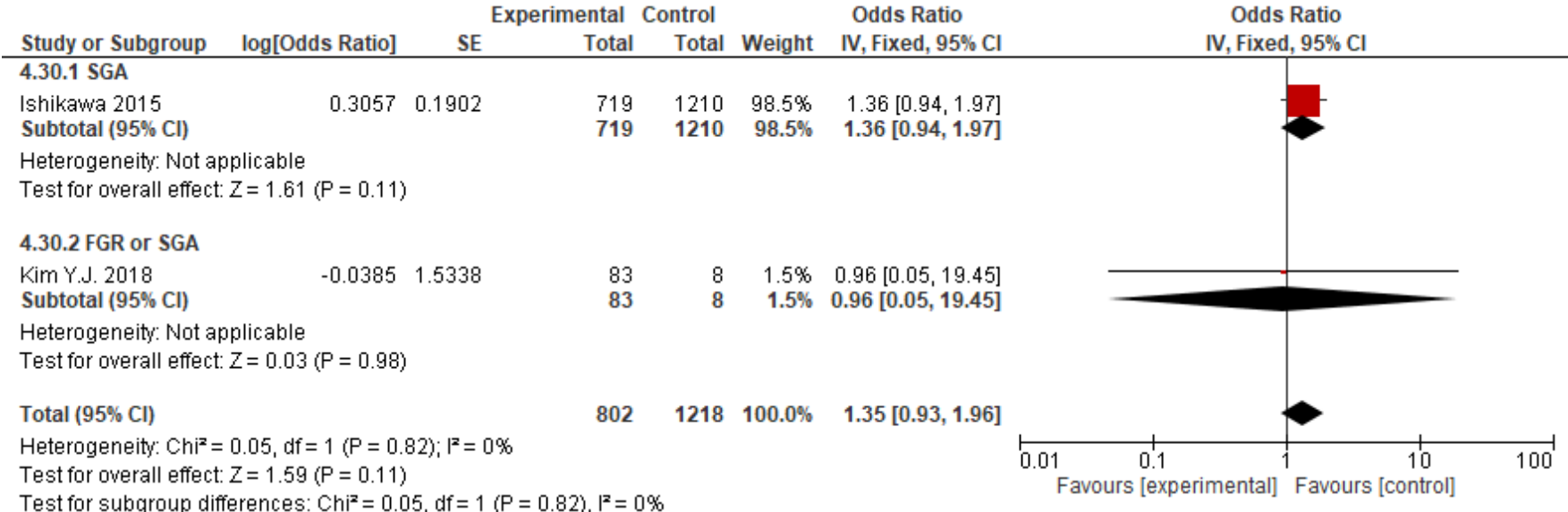
24) Retinopathy of prematurity



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

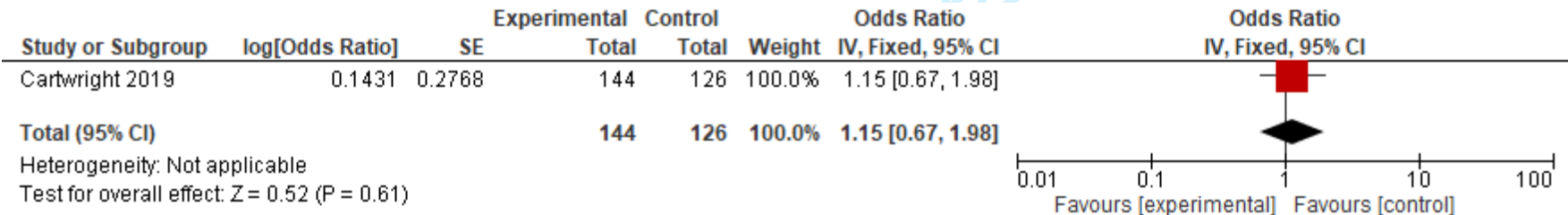
25) Neonatal adrenal insufficiency

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



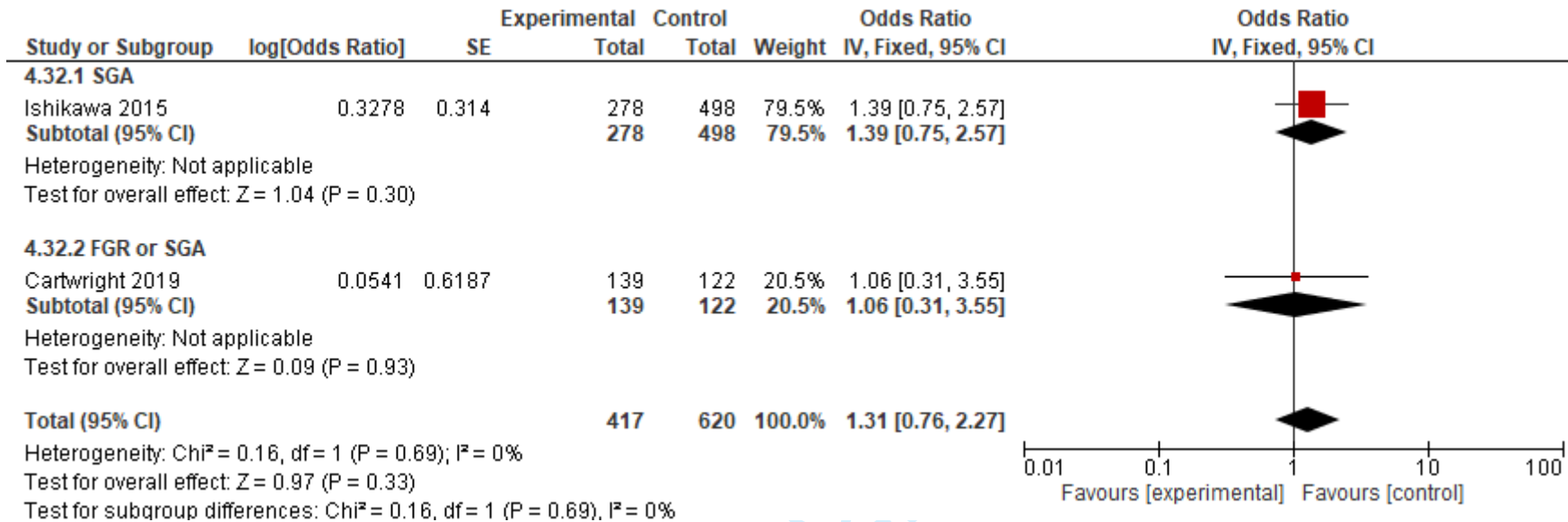
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

26) Survival free of disability (FGR or SGA)



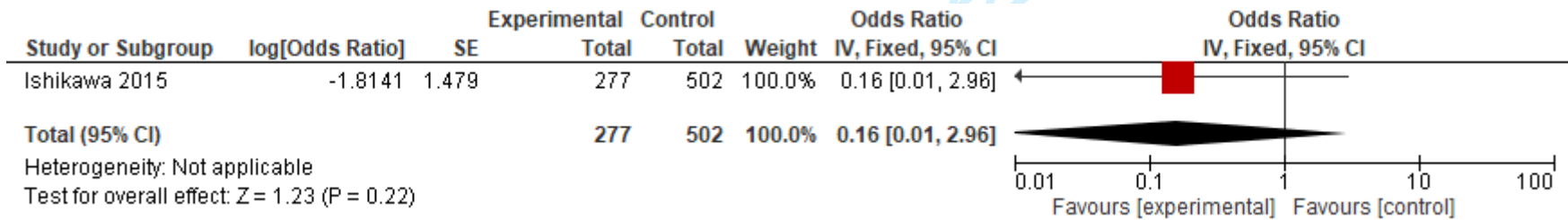
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

27) Cerebral palsy



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

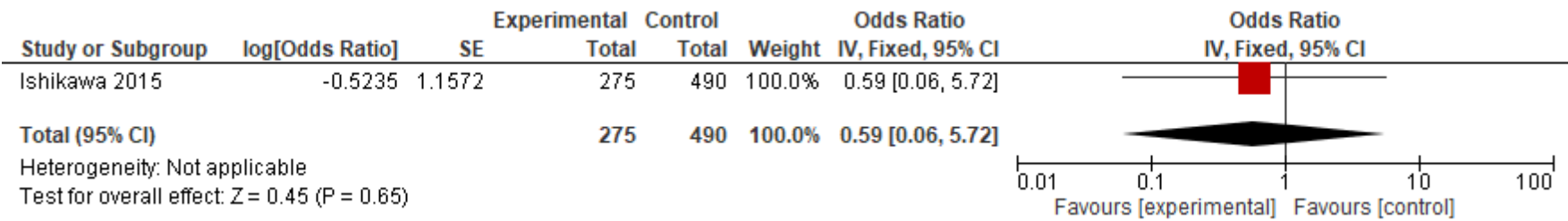
28) Severe hearing impairment (SGA)



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

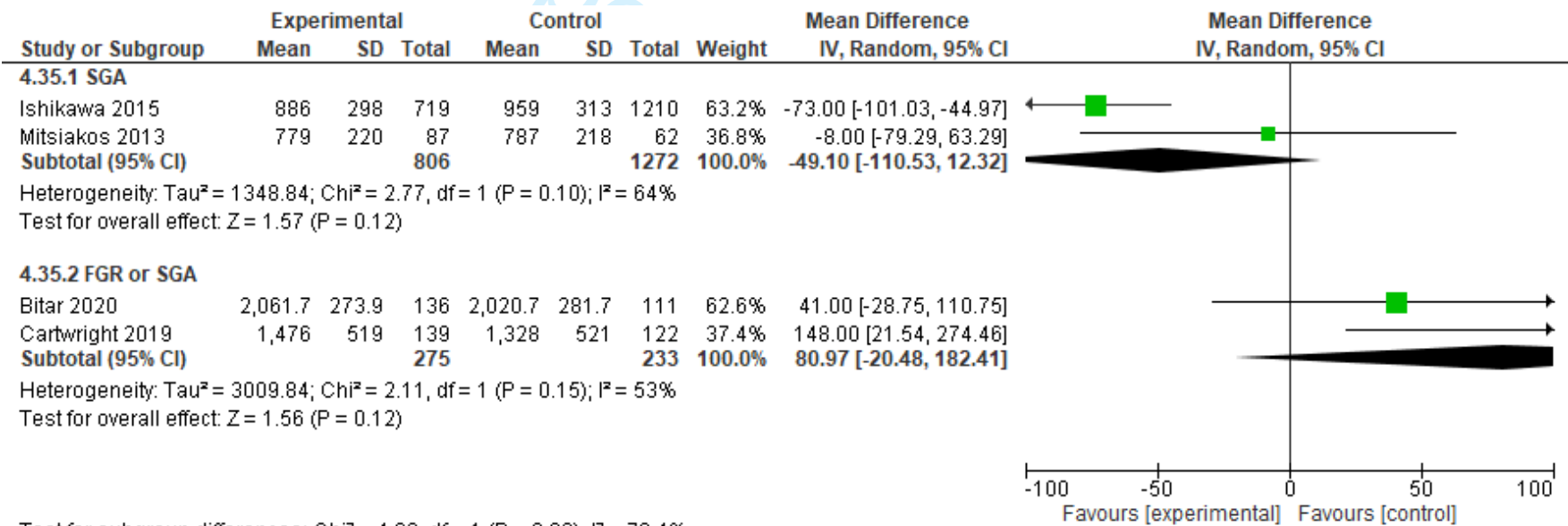
29) Visual impairment (SGA)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



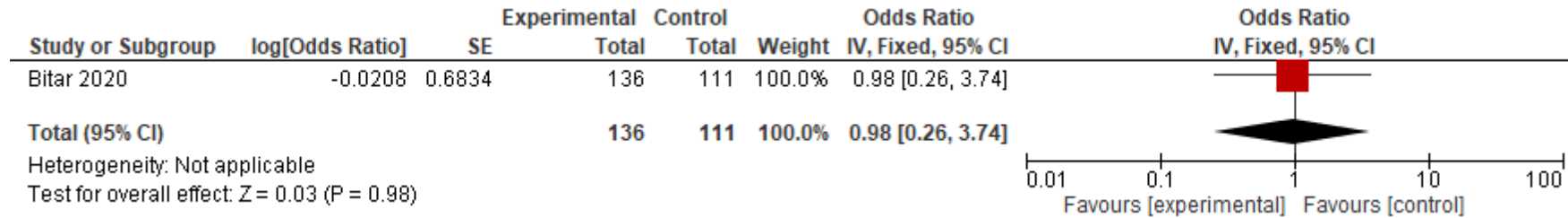
SE: Standard error; CI: Confidence interval; SGA: Small for gestational age

30) Birth weight



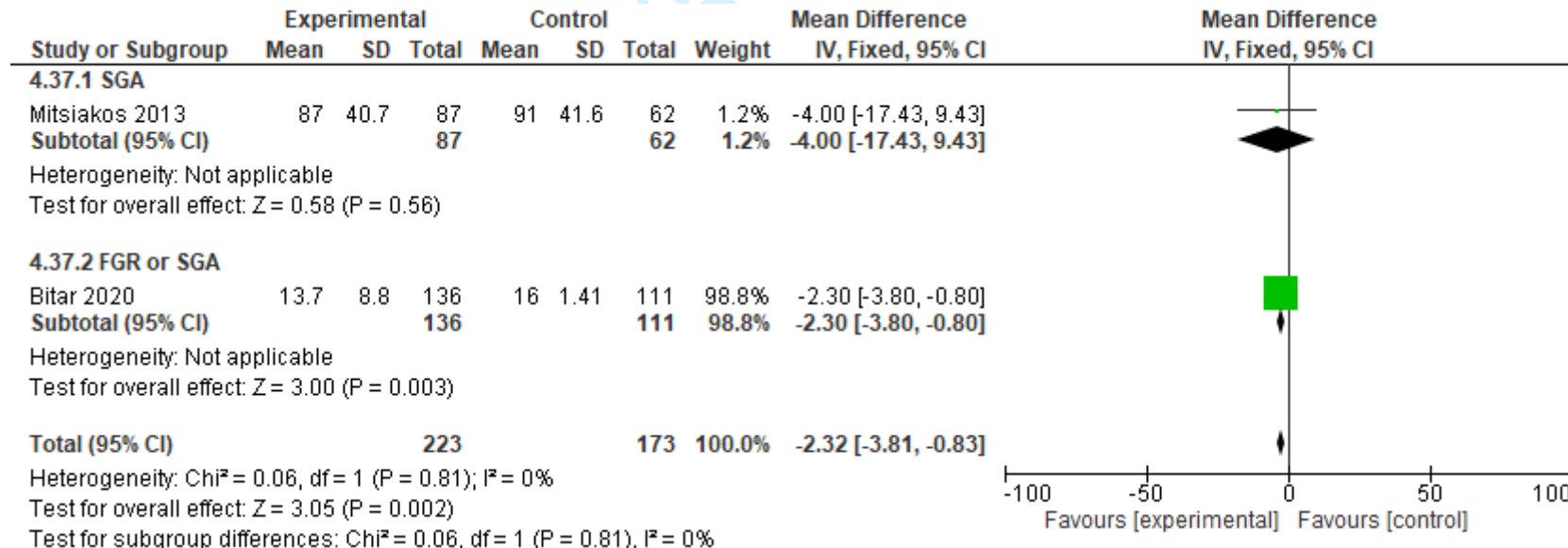
SD: Standard Deviation; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



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

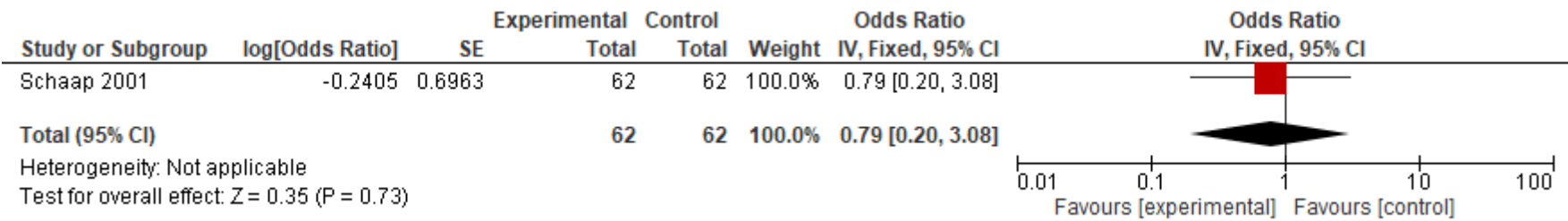
32) Duration to hospital stay, days



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

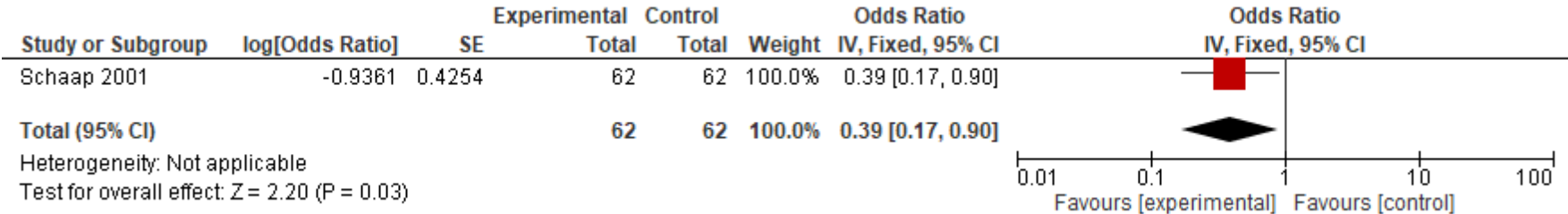
33) Death at long-term follow-up (School age) (FGR)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46



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

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



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%)	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)		
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%)	OR 0.95 (0.44 to 2.03)	9 fewer per 1,000 (from 115 fewer to 149 more)	⊕○○○○ VERY LOW	
								0.0%		0 fewer per 1,000 (from 0 fewer to 0 fewer)		

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 ^{ab}	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 ^{ab}	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%).

For peer review only

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	*	*	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	*	*	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	*	*	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 intraventricular 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							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women with growth-restricted fetuses	Placebo	Relative (95% CI)	Absolute (95% CI)		
Neonatal death (FGR)												
2	observational studies	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	*	*	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
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) (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).

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?
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	•	•	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

- 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).

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065070.R1
Article Type:	Original research
Date Submitted by the Author:	01-May-2023
Complete List of Authors:	Saito, KANA; Saitama Medical Center, Pediatrics Nishimura, Etsuko; St Luke's International University, Graduate School of Nursing Science Ota, Erika; St Luke's International University, Graduate School of Nursing Science; The Tokyo Foundation for Policy Research Namba, Fumihiko; Saitama Medical Center, Pediatrics Swa, Toshiyuki; Osaka University School of Medicine Graduate School of Medicine Ramson, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Lavin, Tina; World Health Organization, Department of Sexual and Reproductive Health and Research Cao, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Vogel, Joshua; Burnet Institute, Maternal, Child and Adolescent Health Program
Primary Subject Heading:	Paediatrics
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

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 **ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF**
5 2 **PRETERM BIRTH: A SYSTEMATIC REVIEW**
6 3

7 4 Kana Saito^a, Etsuko Nishimura^b, Erika Ota^{b,c}, Fumihiko Namba^a, Toshiyuki Swa^d,
8 5 Jenny Ramson^e, Tina Lavin^f, Jenny Cao^e, Joshua P. Vogel^e
9 6

10 7
11 7 **Affiliations**

12 8 ^a Saitama Medical Center, Saitama Medical University, Saitama, Japan

13 9 ^b St. Luke's International University, Tokyo, Japan

14 10 ^c Tokyo Foundation for Policy Research, Tokyo, Japan

15 11 ^d Osaka University, Graduate School of Medicine, Osaka, Japan

16 12 ^e Maternal, Child, and Adolescent Health Program, Burnet Institute, Melbourne,
17 13 Australia

18 14 ^f UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research,
19 15 Development and Research Training in Human Reproduction, Department of Sexual
20 16 and Reproductive Health and Research, World Health Organization, Geneva,
21 17 Switzerland.
22 18

23 19 **Correspondence to:** Kana Saito

24 20 Department of Pediatrics, Saitama Medical Center, Saitama Medical University

25 21 1981 Kamoda, Kawagoe-city, Saitama 350-8550, Japan,

26 22 Phone:81-49-228-3400

27 23 E-mail: kana988@live.jp

28 24 ORCID: 0000-0001-7781-1870
29 25

30 26 **Word count:** 4089 words
31 27

32 28 **Short title:** Systematic review: antenatal steroids in specific women
33 29
34 30
35 31
36 32
37 33
38 34
39 35
40 36
41 37
42 38
43 39
44 40
45 41
46 42
47 43
48 44
49 45
50 46
51 47
52
53
54
55
56
57
58
59
60

1
2
3
4 48 **ABSTRACT**

5 49
6 50 **Objective:** This study aimed to synthesize available evidence on the efficacy of
7 51 antenatal corticosteroid (ACS) therapy among women at risk of imminent preterm birth
8 52 with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction
9 53 (FGR), or planned cesarean section (CS) in the late preterm period.
10 54

11 55 **Methods:** A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library,
12 56 Web of Science, and Global Index Medicus was conducted for all comparative
13 57 randomized or non-randomized interventional studies in the four subpopulations. The
14 58 authors extracted data individually. Risk of Bias Assessment tool for Non-randomized
15 59 Studies (RoBANS) was used to assess the risk of bias in non-randomized studies.
16 60 Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)
17 61 tool was also used to assess the certainty of evidence.
18 62

19 63 **Results:** Thirty-one studies involving 5018 pregnant women and 10819 neonates were
20 64 included. All the included articles were observational studies in high-income countries.
21 65 Data on women with diabetes were limited, and evidence on women undergoing
22 66 planned CS was inconclusive. ACS use was associated with possibly reduced odds of
23 67 severe intraventricular hemorrhage (IVH) (pooled OR: 0.41; 95%CI: 0.19–0.87, low
24 68 certainty), and IVH (pooled OR: 0.41; 95%CI: 0.23–0.72, low certainty) in women with
25 69 histological chorioamnionitis. Among women with FGR, the rates of surfactant use
26 70 (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate certainty), mechanical ventilation
27 71 (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate certainty), and oxygen therapy (pooled
28 72 OR: 0.48; 95%CI: 0.30–0.77, moderate certainty) were probably reduced; however, the
29 73 rate of hypoglycemia probably increased (pooled OR: 2.06; 95%CI: 1.27–3.32,
30 74 moderate certainty). Definitional differences in populations and outcomes complicated
31 75 meta-analyses.
32 76

33 77 **Conclusions:** There is a paucity of evidence for women who have diabetes or are
34 78 undergoing planned CS. ACS therapy may have benefits in women with
35 79 chorioamnionitis and is probably beneficial in FGR; however, it can increase neonatal
36 80 hypoglycemia. Well-designed studies with adequate follow-up are required.
37 81

38 82 **Protocol registration:**
39 83 PROSPERO (CRD42021267816)
40 84

41 85 **Strengths and limitations of this study:**

- 42 86 -This review included a broad search strategy.
43 87 -This review applied rigorous quality assessment and GRADE methodology.
44 88 -All included studies were observational studies.
45 89 -Definitional differences between populations and outcomes complicated the meta-
46 90 analysis.
47 91 -Most studies were conducted in high-income countries.
48 92
49 93
50 94

95 INTRODUCTION

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

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

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

1
2
3
4 119 maternal glycaemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women
5
6 120 giving birth, causing 22.6–36.9% of total stillbirths [9-11]. Chorioamnionitis treatment
7
8 121 involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided
9
10 122 due to concerns that its immunosuppressive effects may worsen outcomes for women
11
12 123 and their babies. However, the relative benefits and harms of using ACS in clinical
13
14 124 settings are unclear. FGR is associated with an increased risk of morbidity and mortality
15
16 125 [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as
17
18 126 SGA neonates include constitutionally small ones [16]. In most cases, FGR fetuses are
19
20 127 delivered as SGA neonates [17]. In this study, we targeted pregnant women with both
21
22 128 FGR fetuses and SGA neonates.
23
24 129 One clinical scenario with uncertainty regarding ACS efficacy is women undergoing
25
26 130 elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37 weeks'
27
28 131 gestation). Babies born in the late preterm period have lower risks of mortality and
29
30 132 morbidity than those born before 34 weeks' gestation; however, they have higher risks
31
32 133 of adverse outcomes than those born at term [18-21]. In many countries, the rising rate
33
34 134 of provider-initiated late preterm birth has been linked to the generalized increase in the
35
36 135 CS rate [22]. Regardless of the gestational age, babies born via elective CS do not have
37
38 136 the usual physical and hormonal stimuli of passage through the birth canal; thus, they
39
40 137 tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested
41
42 138 that the risk of neonatal hypoglycemia is greater following CS; however, this may be
43
44 139 confounded by the underlying indication for CS [26].
45
46 140 In 2016, members of our team published a systematic review assessing the effectiveness
47
48 141 of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of
49
50 142 ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for
51
52
53
54
55
56
57
58
59
60

1
2
3
4 143 those undergoing elective CS in the late preterm period was found. The review could
5
6 144 not draw firm conclusions regarding the effects of ACS on women with growth-
7
8 145 restricted fetuses, although low-quality evidence suggested that ACS reduces neonatal
9
10 146 IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015
11
12 147 ACS recommendations [28]. ACS recommendations are currently being updated as part
13
14 148 of the WHO's living guidelines in maternal and perinatal health programs [29]. Our aim
15
16 149 is to update the 2016 systematic review and provide a contemporary evidence base for
17
18 150 researchers, clinicians, and maternal and newborn health stakeholders on safe, effective
19
20 151 clinical management in preterm birth.
21
22
23
24
25
26

27 153 **METHODS**

28
29 154 The specific review objectives are presented in Box 1, comprising four related questions
30
31 155 on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or
32
33 156 gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm
34
35 157 period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA
36
37 158 infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are
38
39 159 explained in Supplementary table 1. SGA infants are all neonates with birth weights
40
41 160 below the 10th percentile. In this survey, FGR fetuses were defined with each study
42
43 161 inclusion criterion (Supplementary table 1). The review protocol was registered on
44
45 162 PROSPERO (CRD42021267816) and reported per the Preferred Reporting Items for
46
47 163 Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary file 1,
48
49 164 Supplementary table 2) [30].
50
51
52
53
54

55 165
56
57 166 Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a
58
59
60

167 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

168

169 **Study eligibility criteria**

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

1
2
3
4 179 diabetes, women undergoing elective CS in the late preterm period, women with
5
6 180 chorioamnionitis, and women with FGR fetuses or SGA infants.
7
8
9 181 Articles in any language and from any country were eligible for inclusion if they
10
11 182 reported on one or more of WHO's priority outcomes for preterm birth guideline
12
13 183 development [28]. Maternal outcomes were death, maternal morbidity, and therapy side
14
15 184 effects. Newborn and child outcomes of interest were perinatal mortality, fetal
16
17 185 mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric
18
19 186 status, and therapy side effects (Supplementary table 3).
20
21
22
23
24

25 188 **Data sources and search strategy**

26
27 189 An information specialist was consulted for the development of the search strategy. A
28
29 190 systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of
30
31 191 Science, and Global Index Medicus was conducted with no date restrictions on June 6,
32
33 192 2021. Controlled vocabularies supplemented with free keywords were used to search for
34
35 193 the relevant concept areas, with duplicates removed in the process to yield a total
36
37 194 number of abstracts for each database (Supplementary table 4). Reference lists of the
38
39 195 included articles, including any recent systematic reviews, were also hand-searched for
40
41 196 further potentially relevant studies. All citations were imported into a Rayyan
42
43 197 (<http://rayyan.qcri.org>) library for eligibility assessment.
44
45
46
47
48
49

50 199 **Study selection, data extraction, and quality assessment**

51
52 200 Two reviewers (KS, EN) independently assessed the titles and abstracts of identified
53
54 201 citations for eligibility. Any disagreement resulted in automatic inclusion into the next
55
56 202 level of screening. Subsequently, full-text publications of potentially eligible studies
57
58
59
60

1
2
3
4 203 were obtained and assessed in duplicate by two reviewers working independently, with
5
6 204 disagreements resolved through discussions or by consulting a third reviewer. The two
7
8
9 205 reviewers also independently extracted baseline and outcome data and assessed the
10
11 206 quality, with these data compared and any discrepancies resolved through discussions or
12
13 207 by consulting a third reviewer. Extracted data were entered into the Review Manager
14
15 208 version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study
16
17 209 quality, observational studies were assessed using the Risk of Bias Assessment tool for
18
19 210 Non-randomized Studies (RoBANS) [31]. If we identified any randomized trials, we
20
21 211 planned to use the Cochrane Risk of Bias tool [32]. Potential publication bias was
22
23 212 inspected visually using funnel plots for asymmetry in situations where data for a single
24
25 213 outcome were available from at least ten studies.
26
27
28
29
30

31 214 32 215 **Data synthesis and analysis**

33
34 216 Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs)
35
36 217 were determined for dichotomous data using the Mantel–Haenszel analysis (fixed-
37
38 218 effects model). Where between-study clinical or methodological heterogeneity
39
40 219 undermined the compatibility of the quantitative results, or if substantial statistical
41
42 220 heterogeneity was detected, the random-effects meta-analysis was used. Data were
43
44 221 pooled using ORs when the numbers of events were available and using logarithms of
45
46 222 the ORs weighted by the inverse variance when events were not available. For
47
48 223 continuous data, mean differences (MDs) with 95% CIs were used. Statistical
49
50 224 heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics.
51
52 225 Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi^2
53
54 226 test for heterogeneity. For the analysis of women with FGR fetuses and/or SGA babies,
55
56
57
58
59
60

1
2
3
4 227 we reported results for three subpopulations (SGA only, FGR only, and SGA with
5
6 228 FGR). Data from the three populations were combined, and pooled ORs were calculated
7
8
9 229 if the heterogeneity for that outcome was less than 60%.

10
11 230 All statistical analyses were performed using RevMan5. The threshold for statistical
12
13 231 significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were
14
15 232 prepared for each research question using GRADEpro (<https://grade.pro.org/>). Grading
16
17 233 of Recommendations Assessment, Development, and Evaluation (GRADE), an
18
19 234 approach for grading the certainty of evidence in systematic reviews and clinical
20
21 235 practice guidelines, was used in this review.
22
23
24
25

26 27 237 **Patients and public involvement**

28
29 238 Since this is a systematic review of previously published data, there was no direct
30
31 239 involvement of patients or the public.
32
33

34 240

35 36 241 **RESULTS**

37 38 242 **Effects of ACS therapy on women with pregestational and/or gestational diabetes** 39 40 243 **mellitus**

41
42 244 The search identified 179 citations: 11 potentially eligible studies were evaluated, and
43
44 245 three studies met the eligibility criteria, providing data on 725 pregnant women and 830
45
46 246 neonates (Supplementary file 2) [33-35]. All studies were conducted in high-income
47
48 247 countries and data collection was performed between 2008 and 2017 (Supplementary
49
50 248 table 1). One study involved women with pregestational diabetes only, one study
51
52 249 involved women with gestational diabetes only, and one study involved women with
53
54 250 either pregestational or gestational diabetes. All included studies were judged as having
55
56
57
58
59
60

251 a low risk of bias across all domains (Supplementary file 3, Supplementary table 5).
 252 Data were available for six outcomes (Table 1). One retrospective cohort study found
 253 that in women with gestational diabetes, the likelihood of neonatal intensive care unit
 254 (NICU) admission is possibly increased (one study, 162 infants; OR: 7.41; 95%CI:
 255 5.04–10.89, *low-certainty evidence*); however, the effect of ACS therapy on neonatal
 256 hypoglycemia was uncertain (two studies, 215 infants; pooled OR: 1.44; 95%CI:
 257 0.702.97, *very-low-certainty evidence*) [33]. The certainty of evidence was also very
 258 low for other outcomes; hence, no meaningful conclusions could be drawn.

259

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

Neonatal outcomes	No of studies	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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 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 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

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

263

264 **Effects of ACS therapy on women undergoing elective CS in the late preterm** 265 **period**

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

273
274

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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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 \leq 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

275

276

277

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

279 The search identified 418 citations: 12 potentially eligible studies were evaluated, and
 280 eight were found to be eligible (Supplementary file 2) [38-45]. Two were prospective
 281 cohort studies and six were retrospective, providing data on 1372 pregnant women and
 282 1460 neonates (Supplementary table 1). Four studies included pregnant women with
 283 clinical chorioamnionitis, and there were variations in the diagnostic criteria
 284 (Supplementary table 1). All studies were conducted in high-income countries between
 285 1989 and 2014. Additional unpublished crude data from the four included studies were
 286 extracted from a previous meta-analysis identified through the search process [38,41-
 287 43,46]. All included studies were judged as having a low risk of bias overall, although
 288 six studies were judged as having a high risk of bias regarding confounding variables as
 289 adjusted analyses were not reported (Supplementary file 3, Supplementary table 5).
 290 Data for 27 outcomes were available, with data reported separately for women with
 291 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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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)	131 fewer 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 (47.4%)	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-

1
2
3
4 310 **gestational-age infants**
5

6 311 The search identified 261 citations: 36 potentially eligible studies were assessed, and 18
7
8 312 studies were included (Supplementary file 2) [41,47-63]. Of these, twelve studies
9
10 313 included women with SGA infants only, four studies included women with FGR or
11
12 314 SGA infants, and two studies included women with FGR infants only (Supplementary
13
14 315 table 1). Among the studies that included FGR fetuses, the definitions of FGR varied
15
16 316 widely (Supplementary table 1). Since SGA status is insufficient to determine FGR, we
17
18 317 separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three
19
20 318 populations were combined, and the pooled OR in total was calculated. Data were
21
22 319 available from 2714 pregnant women and 8324 neonates enrolled between 1984 and
23
24 320 2019. We excluded three studies on maternal outcomes for omitting the number of
25
26 321 pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017
27
28 322 [50,53,58]. These studies included multiple gestations; hence, there was the risk of
29
30 323 double, triple, or more counts to one maternal outcome event. All were observational
31
32 324 studies conducted in high-income countries. Additional unpublished data from the study
33
34 325 by Torrance et al. (2007) were extracted from a review paper published in 2009
35
36 326 identified through the search strategy [53,64]. Most included studies were judged as
37
38 327 having a low risk of bias across all domains. Seven studies had a high risk of bias for
39
40 328 the domain regarding confounding variables. Three studies had a high risk of bias
41
42 329 regarding incomplete outcome data (Supplementary file 3, Supplementary table 5). For
43
44 330 SGA infants only, 12 studies provided data on 30 outcomes (Supplementary file 4,
45
46 331 Supplementary table 6). The administration of ACS for women with SGA was
47
48 332 associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies,
49
50 333 684 women; pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the
51
52
53
54
55
56
57
58
59
60

1
2
3
4 334 odds of neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–
5
6 335 0.97, *low-certainty evidence*) were possibly reduced (Table 4). Two studies involving
7
8 336 FGR infants only provided data for 18 review outcomes; the odds of death or
9
10 337 disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39;
11
12 338 95%CI: 0.17–0.90, *low-certainty evidence*) were possibly reduced (Table 4). Four
13
14 339 studies involved SGA or FGR infants, providing data for 25 outcomes (Supplementary
15
16 340 file 4, Supplementary table 6). The administration of ACS for women with SGA or
17
18 341 FGR was associated with a possible reduction in the odds of surfactant use (three
19
20 342 studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62, *moderate-certainty evidence*),
21
22 343 mechanical ventilation use (two studies, 508 infants; pooled OR: 0.42; 95%CI: 0.26–
23
24 344 0.66, *moderate-certainty evidence*), oxygen use (two studies, 508 infants; pooled OR:
25
26 345 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*) although the odds of
27
28 346 hypoglycemia increased (one study, 247 infants; pooled OR: 2.01; 95%CI: 1.16–3.48,
29
30 347 *low-certainty evidence*) (Table 4). Pooled ORs involving women and newborns from all
31
32 348 three populations (i.e., FGR only, SGA only, and FGR or SGA combined into SGA
33
34 349 and/or FGR) could be determined for 20 outcomes (Supplementary file 4,
35
36 350 Supplementary table 6). ACS administration for women with SGA and/or FGR was
37
38 351 associated with a possible reduction in severe IVH (nine studies, 4636 infants; pooled
39
40 352 OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital stay (two
41
42 353 studies, 396 infants; MD –2.23 days; 95%CI: –3.81––0.83, *low-certainty evidence*).
43
44 354 However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–
45
46 355 2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329 infants;
47
48 356 pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were possibly
49
50 357 increased (Table 4).
51
52
53
54
55
56
57
58
59
60

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

Maternal outcomes	No of study	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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

360
361 *The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in
362 total and calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH:
363 Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, SGA:
364 Small for gestational age. ^{a)} We calculated the numerators using the crude OR in the study by Ley et al. (1997).

1
2
3
4
5
6 365 **DISCUSSION**
7
8

9 366 This systematic review identified 31 observational studies on the benefits and
10
11
12 367 drawbacks of using ACS in subgroups of women with specific pregnancy
13
14
15 368 complications. In women with diabetes and those undergoing elective late preterm CS,
16
17
18 369 the available evidence on the effects of ACS therapy was largely very-low-certainty;
19
20
21 370 thus, conclusions could not be drawn. In women with histological and clinical
22
23
24 371 chorioamnionitis, ACS therapy was associated with the benefit of IVH reduction. In
25
26
27 372 women with FGR and/or SGA babies, ACS therapy possibly has benefits regarding
28
29
30 373 neonatal morbidity and mortality, as well as the reduced use of respiratory support
31
32
33 374 interventions for the newborn; however, neonatal hypoglycemia might be increased.
34
35

36 375

37
38
39 376 **Effects of ACS therapy on women with pregestational and/or gestational diabetes**
40

41
42 377 A clinical concern regarding ACS use in women with diabetes is the possibility of
43
44
45 378 steroid-induced insulin resistance and consequent hyperglycemia, which causes
46
47
48 379 avoidable harm to the neonate. For example, in women with insulin-dependent diabetes,
49
50
51 380 ketoacidosis may occur if insulin dosing is not increased following steroid
52
53
54 381 administration [65]. A 2002 Danish study conducted on 24 pregnant women with
55
56
57 382 diabetes who received steroids suggested that insulin dose adjustment may be required
58
59
60

1
2
3
4
5
6 383 for up to five days after ACS administration [66]. However, in the current review, there
7
8
9 384 was insufficient evidence to determine whether ACS increased neonatal hypoglycemia,
10
11
12 385 respiratory morbidity, or mortality. One retrospective study suggested that ACS use in
13
14
15 386 women with gestational diabetes increases the risk of NICU admission; however, the
16
17
18 387 authors noted that the birthweight in the ACS group was significantly lower than that in
19
20
21 388 the unexposed group, which may explain this finding [33]. Well-designed studies are
22
23
24 389 needed that describe adjustments to maternal diabetic regimens at the time of ACS
25
26
27 390 therapy and from the time of ACS administration to birth and report on important
28
29
30 391 newborn health outcomes.
31
32

33 392

36 393 **Effects of ACS therapy on women undergoing elective CS in the late preterm**
37
38
39 394 **period**
40
41

42 395 The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup
43
44
45 396 analysis on gestational age at trial entry reported findings from seven trials recruiting
46
47
48 397 women in the late preterm period [2]. This subgroup analysis suggested that ACS
49
50
51 398 reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh M
52
53
54 399 et al. reported that ACS reduced the need for respiratory support and increased the risk
55
56
57 400 of hypoglycemia with moderate certainty in late preterm [67]. However, no subgroup
58
59
60

1
2
3
4
5
6 401 analyses were conducted on CS [67]. Hence, these findings cannot be generalized to all
7
8
9 402 women undergoing CS in the late preterm period. The RCT by Gyamfi-Bannerman
10
11
12 403 CEA et al. reported that ACS in the late preterm period reduced the risk of transient
13
14
15 404 tachypnea of the newborn, surfactant use, and BPD [68]. Their subgroup analysis of
16
17
18 405 planned CS showed ACS resulted in no significant difference in their primary outcome
19
20
21 406 and severe respiratory complication [68]. Their primary outcome was defined as any of
22
23
24 407 the following occurrences within 72 hours after birth: continuous positive airway
25
26
27 408 pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours,
28
29
30 409 supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four
31
32
33 410 continuous hours, mechanical ventilation, stillbirth, neonatal death, or the need for
34
35
36 411 extracorporeal membrane oxygenation (ECMO) [68]. Their severe respiratory
37
38
39 412 complications were defined as any of the following occurrences within 72 hours after
40
41
42 413 birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired
43
44
45 414 oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal
46
47
48 415 death, or the need for ECMO [68]. Their outcomes did not adequately fit our outcomes,
49
50
51 416 and the study was not included in this review. Our review demonstrates that there is
52
53
54 417 currently insufficient evidence to draw conclusions on the benefits and possible harms
55
56
57 418 of ACS when used in this subpopulation, although an ongoing randomized trial in New
58
59
60

1
2
3
4
5
6 419 Zealand is assessing the effects of ACS therapy on women with CS planned between 35
7
8
9 420 weeks 0 days and 39 weeks 6 days [69].
10

11
12 421

13
14
15 422 **Effects of ACS on women with chorioamnionitis**

16
17
18 423 Women with chorioamnionitis are typically excluded from ACS efficacy trials due to
19
20
21 424 concerns that the prolongation of pregnancy and/or immunosuppression may worsen
22
23
24 425 outcomes for these women and their newborns. Although ACS appears to be associated
25
26
27 426 with reduced IVH and severe IVH rates in women with histological chorioamnionitis,
28
29
30 427 there was insufficient evidence of other important infection-related maternal and
31
32
33 428 neonatal outcomes in this review. While these conclusions are similar to those of a 2011
34
35
36 429 review by Been et al., we do not consider that the available evidence supports the
37
38
39 430 routine use of ACS therapy in women with chorioamnionitis, as clinical trials
40
41
42 431 comparing ACS therapy to no ACS therapy in this population and reliable evidence
43
44
45 432 regarding infection-related outcomes are still lacking [46]. Significant overlap exists
46
47
48 433 between clinical and histological chorioamnionitis [70]. Histological chorioamnionitis
49
50
51 434 reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis
52
53
54 435 [71]. However, since physicians must decide the indications for ACS therapy when
55
56
57 436 clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant
58
59
60

1
2
3
4
5
6 437 women with clinical chorioamnionitis should be encouraged.
7
8

9 438

10
11
12 439 **Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-**
13
14
15 440 **gestational-age infants**

16
17
18 441 The totality of the evidence identified in this review suggests that ACS therapy should
19
20
21 442 be used in the fetal growth restriction setting. Although the evidence was mainly of low
22
23
24 443 or very low certainty, benefits were observed for several outcomes, and no harm was
25
26
27 444 reported. The current review identified more substantial evidence than that identified in
28
29
30 445 our 2016 systematic review, which was unable to draw solid conclusions about the
31
32
33 446 effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest
34
35
36 447 trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled
37
38
39 448 2852 women and reported preterm newborn mortality and morbidity benefits, recruited
40
41
42 449 189 women with known or suspected fetal growth restriction [72]. The current review
43
44
45 450 did not identify the benefits regarding the outcome RDS, which might be attributable to
46
47
48 451 a single retrospective cohort study in Japan in which neonates in the ACS group were
49
50
51 452 delivered significantly earlier than those in the control group [56]. A sensitivity analysis
52
53
54 453 in which we excluded this study suggested that RDS is significantly lower for SGA
55
56
57 454 babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal
58
59
60

1
2
3
4
5
6 455 hypoglycemia in this subpopulation, which warrants further exploration in future
7
8
9 456 research. In this meta-analysis, only two studies targeted pregnant women with FGR.
10
11
12 457 Since the SGA status does not accurately represent FGR, studies evaluating the effects
13
14
15 458 of ACS therapy on pregnant women with FGR fetuses should be encouraged.
16
17

18 459

21 460 **Strengths and limitations**

22
23
24 461 The strengths of this review were its broad search strategy, which included studies
25
26
27 462 published in languages other than English, rigorous quality assessments, and the use of
28
29
30 463 the GRADE methodology to assess the reliability of the review's findings. Thus, we
31
32
33 464 consider the risk of missing potentially eligible studies to be low, although we
34
35
36 465 acknowledge that publication bias may affect these results. One limitation of the present
37
38
39 466 review is the difference in how studies defined, identified, or diagnosed the subgroup
40
41
42 467 conditions and outcomes of interest. These differences might have created a bias in the
43
44
45 468 review conclusions. However, we explored and reported heterogeneity for meta-
46
47
48 469 analyses. Another limitation is that most of the included studies were conducted in high-
49
50
51 470 income countries, although over 60% of all preterm births globally occur in African and
52
53
54 471 South Asian countries [73]. This review did not lead to any evidence of high certainty,
55
56
57 472 and one reason for this observation is that all studies were observational. In 1990,
58
59
60

1
2
3
4
5
6 473 Crowley P et al. reported a structured review of ACS for preterm birth [74]. The review
7
8
9 474 revealed that ACS significantly reduced the risk of IVH and respiratory morbidity [74].
10
11
12 475 In 1995, the National Institutes of Health developed a consensus on recommending
13
14
15 476 ACS treatment for preterm birth [75]. In our review, only one study targeting women
16
17
18 477 with chorioamnionitis and two studies targeting women with FGR started before 1990
19
20
21 478 [40,49,52]. It would be challenging to conduct the RCTs on ACS efficacy even in these
22
23
24 479 special populations after the review by Crowley P et al. [74]. The latest Cochrane
25
26
27 480 review on ACS treatment for preterm birth involved a subgroup analysis in the seven
28
29
30 481 special conditions [2]. However, the review did not conduct a subgroup analysis
31
32
33 482 regarding women with diabetes, chorioamnionitis, and FGR [2]. Furthermore, the latest
34
35
36 483 review on ACS for later preterm birth did not perform any subgroup analysis due to the
37
38
39 484 lack of stratified data based on the mode of delivery [67]. Considering the
40
41
42 485 circumstances, guidelines on ACS therapy by international bodies are yet to develop
43
44
45 486 solid recommendations for these special populations. Hence, we consider this review
46
47
48 487 valid. Prospective cohort studies on ACS efficacy for these four special populations
49
50
51 488 should be encouraged. The studies should include precise data on the time sequence
52
53
54 489 between ACS admission and the onset of maternal outcomes to determine the effect of
55
56
57 490 ACS therapy on maternal outcomes.
58
59
60

1
2
3
4
5
6
7 491

8
9 492 **CONCLUSION**

10
11
12 493 ACS has possible benefits in the setting of FGR and/or SGA; however, direct evidence
13
14
15 494 of its efficacy and safety for pregnant women with pregestational and/or gestational
16
17
18 495 diabetes mellitus and those undergoing elective CS in the late preterm period is still
19
20
21 496 lacking. Although ACS may have some benefits in the context of histological
22
23
24 497 chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with
25
26
27 498 adequate follow-up for long-term child outcomes are needed to confirm the upsides and
28
29
30 499 downsides of ACS use in these subpopulations.
31

32
33 500

34
35
36 501 **AUTHOR CONTRIBUTIONS**

37
38
39 502 Dr. Saito participated in the conceptualization and design of the study, conducted title,
40
41
42 503 abstract, and full-text screening, performed data extraction, analysis, and interpretation,
43
44
45 504 assessed the risk of bias, drafted the initial manuscript, and critically reviewed the
46
47
48 505 manuscript. Ms. Nishimura conducted the title abstract and full-text screening,
49
50
51 506 performed data extraction, analysis, and interpretation, assessed the risk of bias, and
52
53
54 507 critically reviewed the manuscript. Dr. Swa conceptualized and designed the search
55
56
57 508 strategy, conducted a systematic search, and critically reviewed the manuscript for
58
59
60

1
2
3
4
5
6 509 important intellectual content. Dr. Ramson assisted in the interpretation of data and the
7
8
9 510 assessment of the risk of bias and critically reviewed the manuscript for important
10
11
12 511 intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and
13
14
15 512 manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel
16
17
18 513 designed and planned the study, assisted with developing the literature search strategy
19
20
21 514 and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the
22
23
24 515 execution of the study. All authors approved the final manuscript as submitted and
25
26
27 516 agreed to be accountable for all aspects of the work.
28
29

30 517

31 32 33 518 **DATA SHARING STATEMENT**

34
35
36 519 Data were obtained from the published journal article, and extracts are available from
37
38
39 520 the corresponding author upon reasonable request.
40
41

42 521

43 44 45 522 **FUNDING**

46
47
48 523 This work was supported by UNDP/UNFPA/ UNICEF/WHO/World Bank Special
49
50
51 524 Program of Research, Development and Research Training in Human Reproduction,
52
53
54 525 WHO (Grand Number: not applicable) and Research Program on Rare and Intractable
55
56
57 526 Diseases co-sponsored program supported with grants from the Japanese Ministry of
58
59
60

1
2
3
4
5
6 527 Health, Labour and Welfare Science (Grant Number: JPMH22FC117) and the grant
7
8
9 528 from the Japanese Ministry of Education, Culture, Sports, Science and Technology
10
11
12 529 (Grant Number: 22K20865).

13
14
15 530

16
17
18 531 **COMPETING INTERESTS**

19
20
21 532 None declared.

22
23
24 533

25
26
27 534 **SUPPLEMENTARY FILES**

28
29
30 535 Supplementary table 1: Characteristic tables

31
32
33 536 Supplementary table 2: PRISMA 2020 Checklist

34
35
36 537 Supplementary table 3: Review outcomes

37
38
39 538 Supplementary table 4: Database-specific search terms and strategies

40
41
42 539 Supplementary table 5: Risk of bias tables

43
44
45 540 Supplementary table 6: GRADE tables

46
47
48 541 Supplementary file 1: PROSPERO

49
50
51 542 Supplementary file 2: PRISMA flow diagrams

52
53
54 543 Supplementary file 3: Risk of bias figures

55
56
57 544 Supplementary file 4: Forest plots
58
59
60

1
2
3
4
5
6 5457
8
9 546 **ETHICS APPROVAL**10
11
12 547 As this study is a systematic review of published studies; thus, ethical approval was not
13
14
15 548 required.
1617
18 54919
20
21 550 **REFERENCES**22
23 551 [1] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for
24 552 prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.
25 553 1972;50(4):5155-25. <https://doi.org/10.1542/peds.50.4.515>.26
27 554 [2] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating
28 555 fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*.
29 556 2020;12:CD004454. <https://doi:10.1002/14651858.CD004454.pub.4>.30
31 557 [3] Committee on Obstetric Practice. Committee opinion no. 713 summary: antenatal
32 558 corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):493-494.
33 559 <https://doi:10.1097/AOG.0000000000002231>.34
35 560 [4] World Health Organization. Managing complications in pregnancy and childbirth: a
36 561 guide for midwives and doctors, 2nd ed. 2017.
37 562 <https://apps.who.int/iris/handle/10665/255760>. (accessed 24 Mar 2022).38
39 563 [5] Skoll A, Boutin A, Bujold E, et al. No. 364-antenatal corticosteroid therapy for
40 564 improving neonatal outcomes. *J Obstet Gynaecol Can*. 2018;40(9):1219-1239.
41 565 <https://doi:10.1016/j.jogc.2018.04018>.42
43 566 [6] Japan Society of Obstetrics and Gynecology. Obstetrics and Gynecology clinical
44 567 guideline 2020. https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf (accessed 24 Mar
45 568 2022).46
47 569 [7] McGillick EV, Morrison JL, McMillen IC, et al. Intrafetal glucose infusion alters
48 570 glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of
49 571 the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol*.
50 572 2014;307(5):R538-R545. <https://doi:10.1152/ajpregu.00053.2014>.51
52 573 [8] Kawakita T, Bowers K, Hazrati S, et al. Increased Neonatal Respiratory Morbidity
53 574 Associated with Gestational and Pregestational Diabetes: A Retrospective Study. *Am J*
54
55
56
57
58
59
60

- 1
2
3
4
5
6 575 *Perinatol.* 2017;34(11):1160-1168. <https://doi:10.1055/s-0037-1604414>.
- 7 576 [9] Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth.
8 577 *Am J Obstet Gynecol.* 2007;196(3):229 e1-4. [https://doi: 10.1016/j.ajog.2006.10.900](https://doi:10.1016/j.ajog.2006.10.900).
- 9 578 [10] Gordon A, Lahra M, Raynes-Greenow C, et al. Histological chorioamnionitis is
10 579 increased at extremes of gestation in stillbirth: a population-based study. *Infect Dis Obstet*
11 580 *Gynecol.* 2011;2011:456728. [https://doi: 10.1155/2011/456728](https://doi:10.1155/2011/456728).
- 12 581 [11] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection:
13 582 A systematic review and meta-analysis. *PLoS Med.* 2019;16(12):e1002984. [https:// doi:](https://doi:10.1371/journal.pmed.1002984)
14 583 [10.1371/journal.pmed.1002984](https://doi:10.1371/journal.pmed.1002984).
- 15 584 [12] Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and
16 585 neonatal encephalopathy. *Am J Obstet Gynecol.* 2003;188(4):1011-1015. [https://doi:](https://doi:10.1067/mob.2003.233)
17 586 [10.1067/mob.2003.233](https://doi:10.1067/mob.2003.233).
- 18 587 [13] Pasupathy D, Wood AM, Pell JP, et al. Rates of and factors associated with delivery-
19 588 related perinatal death among term infants in Scotland. *JAMA.* 2009;302(6):660-668.
20 589 [https:// doi: 10.1001/jama.2009.1111](https://doi:10.1001/jama.2009.1111).
- 21 590 [14] McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal
22 591 death in term and late preterm singletons. *Obstet Gynecol.* 2013;122(4):869-877. [https://](https://doi:10.1097/AOG.0b013e3182a265ab)
23 592 [doi: 10.1097/AOG.0b013e3182a265ab](https://doi:10.1097/AOG.0b013e3182a265ab).
- 24 593 [15] MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special
25 594 educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med.*
26 595 2010;7(6):e1000289. [https:// doi: 10.1371/journal.pmed.1000289](https://doi:10.1371/journal.pmed.1000289).
- 27 596 [16] Nardozza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current
28 597 knowledge. *Arch Gynecol Obstet.* 2017;295(5):1061-1077. [https:// doi: 10.1007/s00404-](https://doi:10.1007/s00404-017-4341-9)
29 598 [017-4341-9](https://doi:10.1007/s00404-017-4341-9).
- 30 599 [17] Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight
31 600 and gestational age. *J Pediatr.* 1967;71(2):159-163. [https://doi: 10.1016/s0022-](https://doi:10.1016/s0022-3476(67)80066-0)
32 601 [3476\(67\)80066-0](https://doi:10.1016/s0022-3476(67)80066-0).
- 33 602 [18] Wang ML, Dorer DJ, Fleming MP, et al. Clinical outcomes of near-term infants.
34 603 *Pediatrics.* 2004;114(2):372-6. [https:// doi: 10.1542/peds.114.2.372](https://doi:10.1542/peds.114.2.372).
- 35 604 [19] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm
36 605 birth and maternal medical conditions on newborn morbidity risk. *Pediatrics.*
37 606 2008;121(2):e223-232. [https:// doi: 10.1542/peds.2006-3629](https://doi:10.1542/peds.2006-3629).
- 38 607 [20] Leone A, Ersfeld P, Adams M, et al. Neonatal morbidity in singleton late preterm
39 608 infants compared with full-term infants. *Acta Paediatr.* 2012;101(1):e6-10. [https:// doi:](https://doi:10.1111/j.1651-2227.2011.02459.x)
40 609 [10.1111/j.1651-2227.2011.02459.x](https://doi:10.1111/j.1651-2227.2011.02459.x).
- 41 610 [21] Mitha A, Chen R, Altman M, et al. Neonatal Morbidities in Infants Born Late

- 1
2
3
4
5
6 611 Preterm at 35-36 Weeks of Gestation: A Swedish Nationwide Population-based Study. *J*
7 612 *Pediatr.* 2021;233:43-50 e5. [https:// doi: 10.1016/j.jpeds.2021.02.066](https://doi.org/10.1016/j.jpeds.2021.02.066).
- 8
9 613 [22] Richards JL, Kramer MS, Deb-Rinker P, et al. Temporal Trends in Late Preterm and
10 614 Early Term Birth Rates in 6 High-Income Countries in North America and Europe and
11 615 Association With Clinician-Initiated Obstetric Interventions. *JAMA.* 2016;316(4):410-
12 616 419. [https:// doi: 10.1001/jama.2016.9635](https://doi.org/10.1001/jama.2016.9635).
- 13
14 617 [23] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of
15 618 delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol.*
16 619 1995;102(2):101-106. [https:// doi: 10.1111/j.1471-0528.1995.tb09060.x](https://doi.org/10.1111/j.1471-0528.1995.tb09060.x).
- 17
18 620 [24] Zanardo V, Simbi AK, Franzoi M, et al. Neonatal respiratory morbidity risk and
19 621 mode of delivery at term: influence of timing of elective caesarean delivery. *Acta*
20 622 *Paediatr.* 2004;93(5):643-647. [https:// doi: 10.1111/j.1651-2227.2004.tb02990.x](https://doi.org/10.1111/j.1651-2227.2004.tb02990.x).
- 21
22 623 [25] Hansen AK, Wisborg K, Uldbjerg N, et al. Risk of respiratory morbidity in term
23 624 infants delivered by elective caesarean section: cohort study. *BMJ.* 2008;336(7635):85-
24 625 87. [https:// doi: 10.1136/bmj.39405.539282.BE](https://doi.org/10.1136/bmj.39405.539282.BE).
- 25
26 626 [26] Groom KM. Antenatal corticosteroids after 34weeks' gestation: Do we have the
27 627 evidence? *Semin Fetal Neonatal Med.* 2019;24(3):189-196. [https:// doi:](https://doi.org/10.1016/j.siny.2019.03.001)
28 628 [10.1016/j.siny.2019.03.001](https://doi.org/10.1016/j.siny.2019.03.001).
- 29
30 629 [27] Amiya RM, Mlunde LB, Ota E, et al. Antenatal Corticosteroids for Reducing
31 630 Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of
32 631 Imminent Preterm Birth: A Systematic Review and Meta-Analysis. *PLoS One.*
33 632 2016;11(2):e0147604. [https:// doi: 10.1371/journal.pone.0147604](https://doi.org/10.1371/journal.pone.0147604).
- 34
35 633 [28] World Health Organization. WHO recommendations on intervention to improve
36 634 preterm birth outcomes. World Health Organizaiton; 2015.
37 635 <https://www.who.int/publications/i/item/9789241508988> (accessed 24 Mar 2022).
- 38
39 636 [29] Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines'
40 637 approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health.*
41 638 2019;4(4):e001683. [https:// doi: 10.1136/bmjgh-2019-001683](https://doi.org/10.1136/bmjgh-2019-001683).
- 42
43 639 [30] PRISMA. PRISMA Checklist. 2020. [http://presma-](http://presma-statement.org/PRISMAStatement/Checklist)
44 640 [statement.org/PRISMAStatement/Checklist](http://presma-statement.org/PRISMAStatement/Checklist) (accessed 24 Mar 2022).
- 45
46 641 [31] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for
47 642 nonrandomized studies showed moderate reliability and promising validity. *J Clin*
48 643 *Epidemiol.* 2013;66(4):408-414. [https:// doi: 10.1016/j.jclinepi.2012.09.016](https://doi.org/10.1016/j.jclinepi.2012.09.016).
- 49
50 644 [32] Cochrane Methods. Risk of Bias 2 (ROB2) tool. 2020.
51 645 <https://methods.cochrane.org/risk-bias-2>. (accessed 24 Mar 2022).
- 52
53 646 [33] Krispin E, Hochberg A, Chen R, et al. Neonatal outcome in gestational-diabetic
54
55
56
57
58
59
60

- 1
2
3
4
5
6 647 mothers treated with antenatal corticosteroids delivering at the late preterm and term.
7 648 *Arch Gynecol Obstet.* 2018;298(4):689-695. [https:// doi: 10.1007/s00404-018-4848-8](https://doi.org/10.1007/s00404-018-4848-8).
- 8
9 649 [34] Battarbee AN, Sandoval G, Grobman WA, et al. Antenatal corticosteroids and preterm
10 650 neonatal morbidity and mortality among women with and without diabetes in pregnancy.
11 651 *Am J Perinatol.* 2022;39:67-74. [https:// doi: 10.1055/s-0040-1714391](https://doi.org/10.1055/s-0040-1714391).
- 12
13 652 [35] Cassimatis IR, Battarbee AN, Allshouse AA, et al. Neonatal outcomes associated
14 653 with late preterm betamethasone administration in women with pregestational diabetes.
15 654 *Pediatr Neonatol.* 2020;61(6):645-646. [https:// doi: 10.1016/j.pedneo.2020.07.002](https://doi.org/10.1016/j.pedneo.2020.07.002).
- 16
17 655 [36] Kirshenbaum M, Mazaki-Tovi S, Amikam U, et al. Does antenatal steroids treatment
18 656 prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal morbidity?
19 657 Evidence from a case control study. *Arch Gynecol Obstet.* 2018;297(1):101-107. [http://](http://doi.org/10.1007/s00404-017-4557-8)
20 658 [doi: 10.1007/s00404-017-4557-8](http://doi.org/10.1007/s00404-017-4557-8).
- 21
22 659 [37] de la Huerza Lopez A, Sendarrubias Alonso M, Jimenez Jimenez AP, et al.
23 660 [Antenatal corticosteroids and incidence of neonatal respiratory distress after elective
24 661 caesarean section in late preterm and term neonates]. *An Pediatr (Engl Ed).*
25 662 2019;91(6):371-377. Corticoides antenatales e incidencia de distrés respiratorio del recién
26 663 nacido en las cesáreas programadas del pretérmino tardío y término precoz. [https:// doi:](https://doi.org/10.1016/j.anpedi.2018.12.004)
27 664 [10.1016/j.anpedi.2018.12.004](https://doi.org/10.1016/j.anpedi.2018.12.004).
- 28
29 665 [38] Baud O, Zupan V, Lacaze-Masmonteil T, et al. The relationships between antenatal
30 666 management, the cause of delivery and neonatal outcome in a large cohort of very preterm
31 667 singleton infants. *BJOG.* 2000;107(7):877-884. [https:// doi: 10.1111/j.1471-](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x)
32 668 [0528.2000.tb11086.x](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x).
- 33
34 669 [39] Elimian A, Verma U, Beneck D, et al. Histologic chorioamnionitis, antenatal steroids,
35 670 and perinatal outcomes. *Obstet Gynecol.* 2000;96(3):333-6. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(00)00928-5)
36 671 [7844\(00\)00928-5](https://doi.org/10.1016/s0029-7844(00)00928-5).
- 37
38 672 [40] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30 weeks
39 673 gestation with histologic chorioamnionitis. *Am J Perinatol.* 2005;22(3):155-159. [https://](https://doi.org/10.1055/s-2005-865020)
40 674 [doi: 10.1055/s-2005-865020](https://doi.org/10.1055/s-2005-865020).
- 41
42 675 [41] Foix-L'heliass L, Baud O, Lenclen R, et al. Benefit of antenatal glucocorticoids
43 676 according to the cause of very premature birth. *Arch Dis Child Fetal Neonatal Ed.*
44 677 2005;90(1):F46-48. [https:// doi: 10.1136/adc.2003.042747](https://doi.org/10.1136/adc.2003.042747).
- 45
46 678 [42] Goldenberg RL, Andrews WW, Faye-Petersen OM, et al. The Alabama preterm birth
47 679 study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various
48 680 markers of intrauterine infection. *Am J Obstet Gynecol.* 2006;195(4):1020-1024. [https://](https://doi.org/10.1016/j.ajog.2006.06.033)
49 681 [doi: 10.1016/j.ajog.2006.06.033](https://doi.org/10.1016/j.ajog.2006.06.033).
- 50
51 682 [43] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 683 involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am*
7 684 *J Obstet Gynecol.* 2009;201(6):587 e1-8. [https:// doi: 10.1016/j.ajog.2009.06.025](https://doi.org/10.1016/j.ajog.2009.06.025).
- 8
9 685 [44] Ahn HM, Park EA, Cho SJ, et al. The association of histological chorioamnionitis
10 686 and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four
11 687 weeks' gestation. *Neonatology.* 2012;102(4):259-64. [https:// doi: 10.1159/000339577](https://doi.org/10.1159/000339577).
- 12
13 688 [45] Ryu YH, Oh S, Sohn J, Lee J. The Associations between Antenatal Corticosteroids
14 689 and In-Hospital Outcomes of Preterm Singleton Appropriate for Gestational Age
15 690 Neonates according to the Presence of Maternal Histologic Chorioamnionitis.
16 691 *Neonatology.* 2019;116(4):369-375. [https:// doi: 10.1159/000502650](https://doi.org/10.1159/000502650).
- 17
18 692 [46] Been JV, Degraeuwe PL, Kramer BW, et al. Antenatal steroids and neonatal outcome
19 693 after chorioamnionitis: a meta-analysis. *BJOG.* 2011;118(2):113-122. [https://doi:](https://doi.org/10.1111/j.1471-0528.2010.02751.x)
20 694 [10.1111/j.1471-0528.2010.02751.x](https://doi.org/10.1111/j.1471-0528.2010.02751.x).
- 21
22 695 [47] Di Lenardo D, Piermarocchi P, Cazzaro L, et al. Betamethasone and theophylline in
23 696 the prevention of the Respiratory Distress Syndrome (RDS) : Trend up-date. *JFOET Med.*
24 697 1990; 10 (1-4):27-31. Retrieved from [https://pascal-](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
25 698 [francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
- 26
27 699 [48] Spinillo A, Capuzzo E, Ometto A, et al. Value of antenatal corticosteroid therapy in
28 700 preterm birth. *Early Hum Dev.* 1995;42(1):37-47. [https:// doi: 10.1016/0378-](https://doi.org/10.1016/0378-3782(95)01638-j)
29 701 [3782\(95\)01638-j](https://doi.org/10.1016/0378-3782(95)01638-j).
- 30
31 702 [49] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in
32 703 infants with impaired intrauterine growth. *Acta Paediatr.* 1997;86(10):1090-1096. [https://](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x)
33 704 [doi: 10.1111/j.1651-2227.1997.tb14814.x](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x).
- 34
35 705 [50] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids in
36 706 obstetric subgroups. *Obstet Gynecol.* 1999;93(2):174-179. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(98)00400-1)
37 707 [7844\(98\)00400-1](https://doi.org/10.1016/s0029-7844(98)00400-1).
- 38
39 708 [51] Bernstein IM, Horbar JD, Badger GJ, et al. Morbidity and mortality among very-
40 709 low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford
41 710 Network. *Am J Obstet Gynecol.* 2000;182:198-206. [https:// doi: 10.1016/s0002-](https://doi.org/10.1016/s0002-9378(00)70513-8)
42 711 [9378\(00\)70513-8](https://doi.org/10.1016/s0002-9378(00)70513-8).
- 43
44 712 [52] Schaap AH, Wolf H, Bruinse HW, et al. Effects of antenatal corticosteroid
45 713 administration on mortality and long-term morbidity in early preterm, growth-restricted
46 714 infants. *Obstet Gynecol.* 2001;97(6):954-960. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(01)01343-6)
47 715 [7844\(01\)01343-6](https://doi.org/10.1016/s0029-7844(01)01343-6).
- 48
49 716 [53] Torrance HL, Mulder EJ, Brouwers HA, et al. Respiratory outcome in preterm small
50 717 for gestational age fetuses with or without abnormal umbilical artery Doppler and/or
51 718 maternal hypertension. *J Matern Fetal Neonatal Med.* 2007;20(8):613-621. [https:// doi:](https://doi.org/10.1016/j.jmfm.2007.08.001)
- 52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 719 10.1080/14767050701463662.
7 720 [54] van Stralen G, van der Bos J, Lopriore E, et al. No short-term benefits of antenatal
8 721 corticosteroid treatment in severely preterm growth restricted fetuses: a case-control
9 722 study. *Early Hum Dev.* 2009;85(4):253-257.https:// doi:
10 723 10.1016/j.earlhumdev.2008.10.010.
11
12 724 [55] Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial to
13 725 severely growth restricted fetuses? *J Matern Fetal Neonatal Med.* 2013;26(15):1496-
14 726 1499. https:// doi: 10.3109/14767058.2013.789852.
15
16 727 [56] Ishikawa H, Miyazaki K, Ikeda T, et al. The Effects of Antenatal Corticosteroids on
17 728 Short- and Long-Term Outcomes in Small-for-Gestational-Age Infants. *Int J Med Sci.*
18 729 2015;12(4):295-300. https:// doi: 10.7150/ijms.11523.
19
20 730 [57] Riskin-Mashiah S, Riskin A, Bader D, et al. Antenatal corticosteroid treatment in
21 731 singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-
22 732 based study. *BJOG.* 2016;123(11):1779-1786. https:// doi: 10.1111/1471-0528.13723.
23
24 733 [58] Collaborative Study Group for Respiratory Distress Syndrome in Preterm I. [Effect
25 734 of antenatal corticosteroids therapy on the mortality and morbidity of small for gestational
26 735 age infants born at 24-34 completed weeks: a retrospective multicenter study]. *Zhonghua*
27 736 *Er Ke Za Zhi.* 2017;55(8):613-618. https:// doi: 10.3760/cma.j.issn.0578-
28 737 1310.2017.08.013.
29
30 738 [59] Kim WJ, Han YS, Ko HS, et al. Antenatal corticosteroids and outcomes of preterm
31 739 small-for-gestational-age neonates in a single medical center. *Obstet Gynecol Sci.*
32 740 2018;61(1):7-13. https:// doi: 10.5468/ogs.2018.61.1.7.
33
34 741 [60] Kim YJ, Choi SH, Oh S, et al. Antenatal Corticosteroids and clinical outcomes of
35 742 preterm singleton neonates with intrauterine growth restriction. *Neonatal Med.*
36 743 2018;25(4):161-169. https://doi.org/10.5385/nm.2018.25.4.161.
37
38 744 [61] Riskin-Mashiah S, Reichman B, Bader D, et al. Population-based study on antenatal
39 745 corticosteroid treatment in preterm small for gestational age and non-small for gestational
40 746 age twin infants. *J Matern Fetal Neonatal Med.* 2018;31(5):553-559. https:// doi:
41 747 10.1080/14767058.2017.1292242.
42
43 748 [62] Cartwright RD, Crowther CA, Anderson PJ, et al. Association of fetal growth
44 749 restriction with neurocognitive function after repeated antenatal betamethasone treatment
45 750 vs placebo: secondary analysis of the ACTORDS randomized clinical trial. *JAMA Netw*
46 751 *Open.* 2019;2(2):e187636. https:// doi: 10.1001/jamanetworkopen.2018.7636.
47
48 752 [63] Bitar G, Merrill SJ, Sciscione AC, et al. Antenatal corticosteroids in the late preterm
49 753 period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM.* 2020;2(3):100153.
50 754 https:// doi: 10.1016/j.ajogmf.2020.100153.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 755 [65] Torrance HL, Derks JB, Scherjon SA, et al. Is antenatal steroid treatment effective
7 756 in preterm IUGR fetuses? *Acta Obstet Gynecol Scand.* 2009;88(10):1068-1073. [https://](https://doi.org/10.1080/00016340903176784)
8 757 doi: 10.1080/00016340903176784.
- 9
10 758 [65] Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic
11 759 ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am.* 1996;23(1):87-107. [https://](https://doi.org/10.1016/s0889-8545(05)70246-1)
12 760 doi: 10.1016/s0889-8545(05)70246-1.
- 13
14 761 [66] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid
15 762 treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction
16 763 of analoritm]. *Acta Obstet Gynecol Scand.* 2002;81(9):835-839. [https://](https://doi.org/10.1034/j.1600-0412.2002.810906.x) doi:
17 764 10.1034/j.1600-0412.2002.810906.x.
- 18
19 765 [67] Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-
20 766 36+6 weeks) deliveries-A systematic review and meta-analysis of RCTs. *PLoS One.*
21 767 2021;16(3):e0248774. [https://](https://doi.org/10.1371/journal.pone.0248774) doi: 10.1371/journal.pone.0248774.
- 22
23 768 [68] Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal Betamethasone for
24 769 Women at Risk for Late Preterm Delivery. *N Engl J Med.* 2016;374(14):1311-1320.
25 770 [https://](https://doi.org/10.1056/NEJMoa1516783) doi: 10.1056/NEJMoa1516783.
- 26
27 771 [69] University of Auckland. The C*Steroid trial.
28 772 [https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html)
29 773 [studies-pregnancy/c-steroid-trial.html](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html) (accessed 24 Mar 2022).
- 30
31 774 [70] Dong Y, St Clair PJ, Ramzy I, et al. A microbiologic and clinical study of placental
32 775 inflammation at term. *Obstet Gynecol.* 1987;70(2):175-182. Retrieved from
33 776 [https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clin](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx)
34 777 [ical_Study_of_Placental.7.aspx](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx).
- 35
36 778 [71] Redline RW. Inflammatory responses in the placenta and umbilical cord. *Semin Fetal*
37 779 *Neonatal Med.* 2006;11(5):296-301. [https://](https://doi.org/10.1016/j.siny.2006.02.011) doi: 10.1016/j.siny.2006.02.011.
- 38
39 780 [72] WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, et al. Antenatal
40 781 Dexamethasone for Early Preterm Birth in Low-Resource Countries. *N Engl J Med.*
41 782 2020;383(26):2514-2525. [https://](https://doi.org/10.1056/NEJMoa2022398) doi:10.1056/NEJMoa2022398.
- 42
43 783 [73] World Health Organization. Born too soon: the global action report on preterm birth.
44 784 World Health Organization; 2012. <https://apps.who.int/iris/handle/10665/44864>
45 785 (accessed 24 Mar 2022).
- 46
47 786 [74] Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration
48 787 before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet*
49 788 *Gynaecol.* 1990;97(1):11-25. [https://](https://doi.org/10.1111/j.1471-0528.1990.tb01711.x) doi: 10.1111/j.1471-0528.1990.tb01711.x.
- 50
51 789 [75] Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus
52 790 Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal
53
54
55
56
57
58
59
60

1
2
3
4
5
6 791 Outcomes. *JAMA*. 1995;273(5):413-418. <https://>
7 792 [doi:10.1001/jama.1995.03520290065031](https://doi.org/10.1001/jama.1995.03520290065031).
8
9 793
10
11 794
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

PROSPERO
International prospective register of systematic reviews

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

PROSPERO

International prospective register of systematic reviews

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

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.

PROSPERO

International prospective register of systematic reviews

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.

Exclusion: Pregnant women with the population at 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.

PROSPERO

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 fulfil one or more of the following conditions:

1. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
2. having intrauterine inflammation, infection, or both; or
3. 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.

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)

PROSPERO

International prospective register of systematic reviews

- 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.

PROSPERO International prospective register of systematic reviews

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

PROSPERO

International prospective register of systematic reviews

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 T^2 , I^2 , and τ^2 statistics.

Heterogeneity will be deemed substantial if T^2 will be greater than zero and either I^2 will be greater than 50% or $p < 0.10$ in the τ^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 $p < 0.10$ 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

PROSPERO

International prospective register of systematic reviews

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

PROSPERO**International prospective register of systematic reviews**1
2
3
4 No

5 Education

6 No

7
8 Endocrine and metabolic disorders

9 No

10
11 Eye disorders

12 No

13
14 General interest

15 No

16
17 Genetics

18 No

19
20 Health inequalities/health equity

21 No

22
23 Infections and infestations

24 No

25
26 International development

27 No

28
29 Mental health and behavioural conditions

30 No

31
32 Musculoskeletal

33 No

34
35 Neurological

36 No

37
38 Nursing

39 No

40
41 Obstetrics and gynaecology

42 No

43
44 Oral health

45 No

46
47 Palliative care

48 No

49
50 Perioperative care

51 No

52
53 Physiotherapy

54 No

55
56 Pregnancy and childbirth

57 Yes

58
59 Public health (including social determinants of health)

60 No

Rehabilitation

No

Respiratory disorders

No

PROSPERO

International prospective register of systematic reviews

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?

PROSPERO**International prospective register of systematic reviews**

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

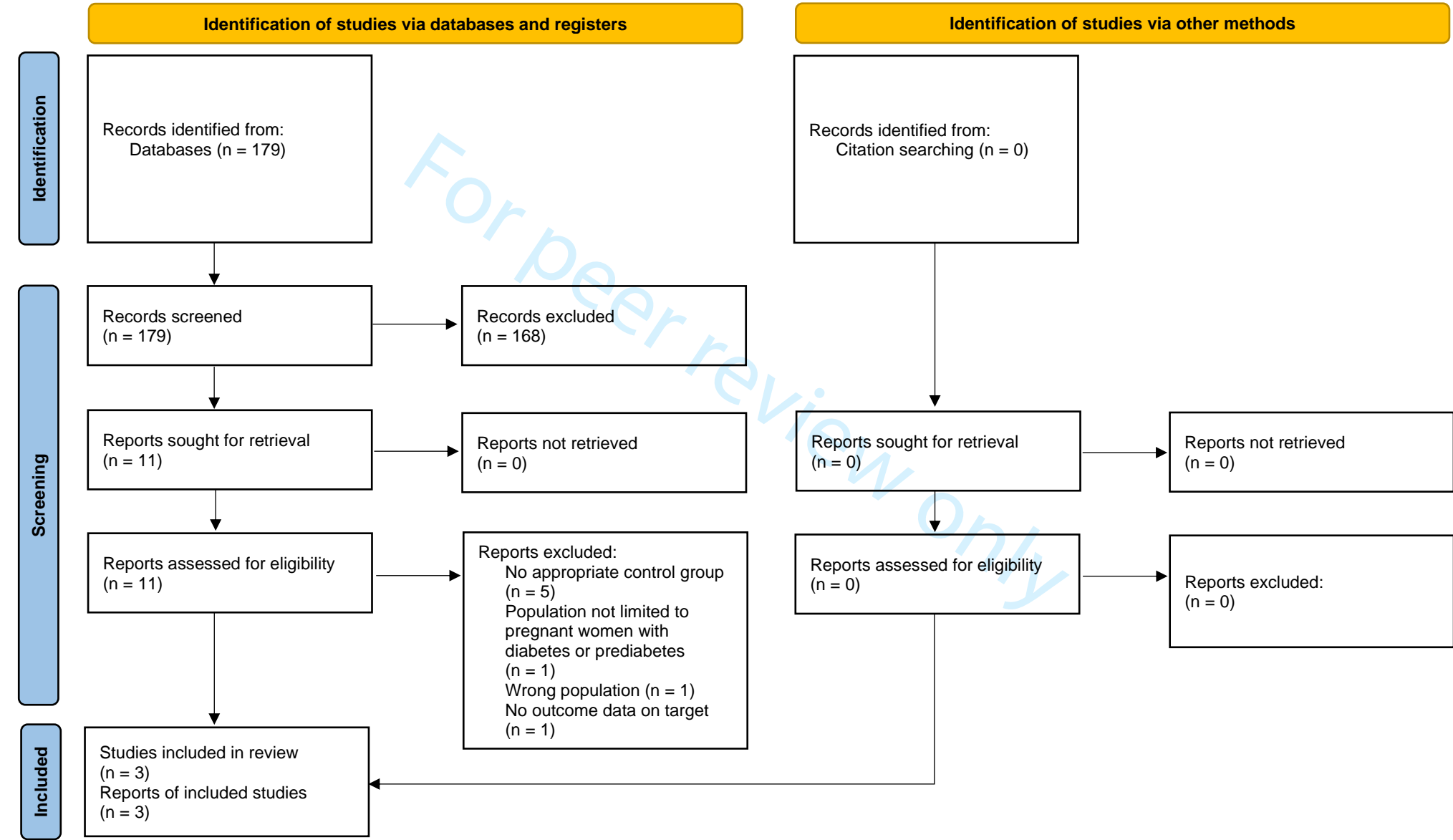


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

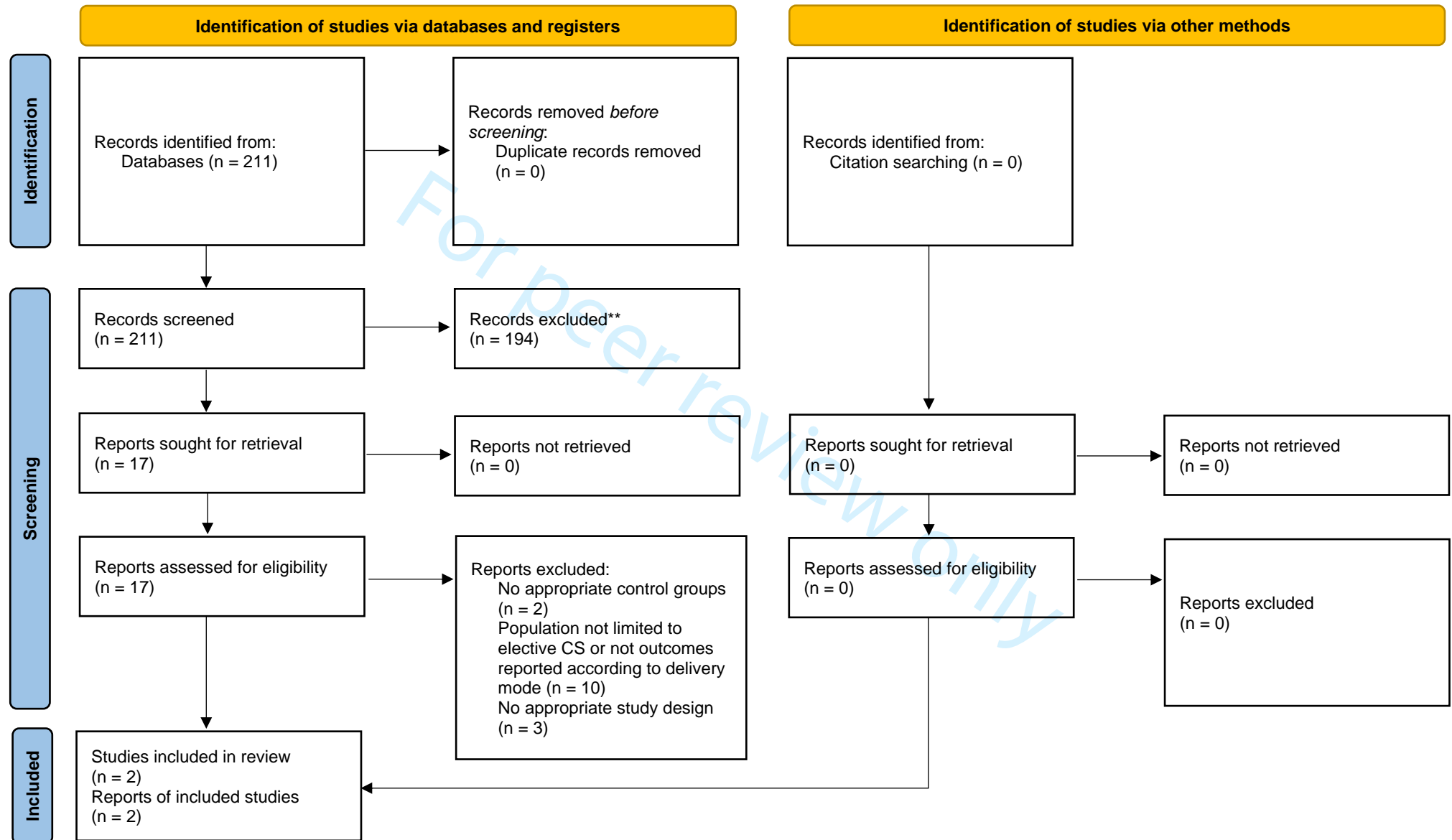


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

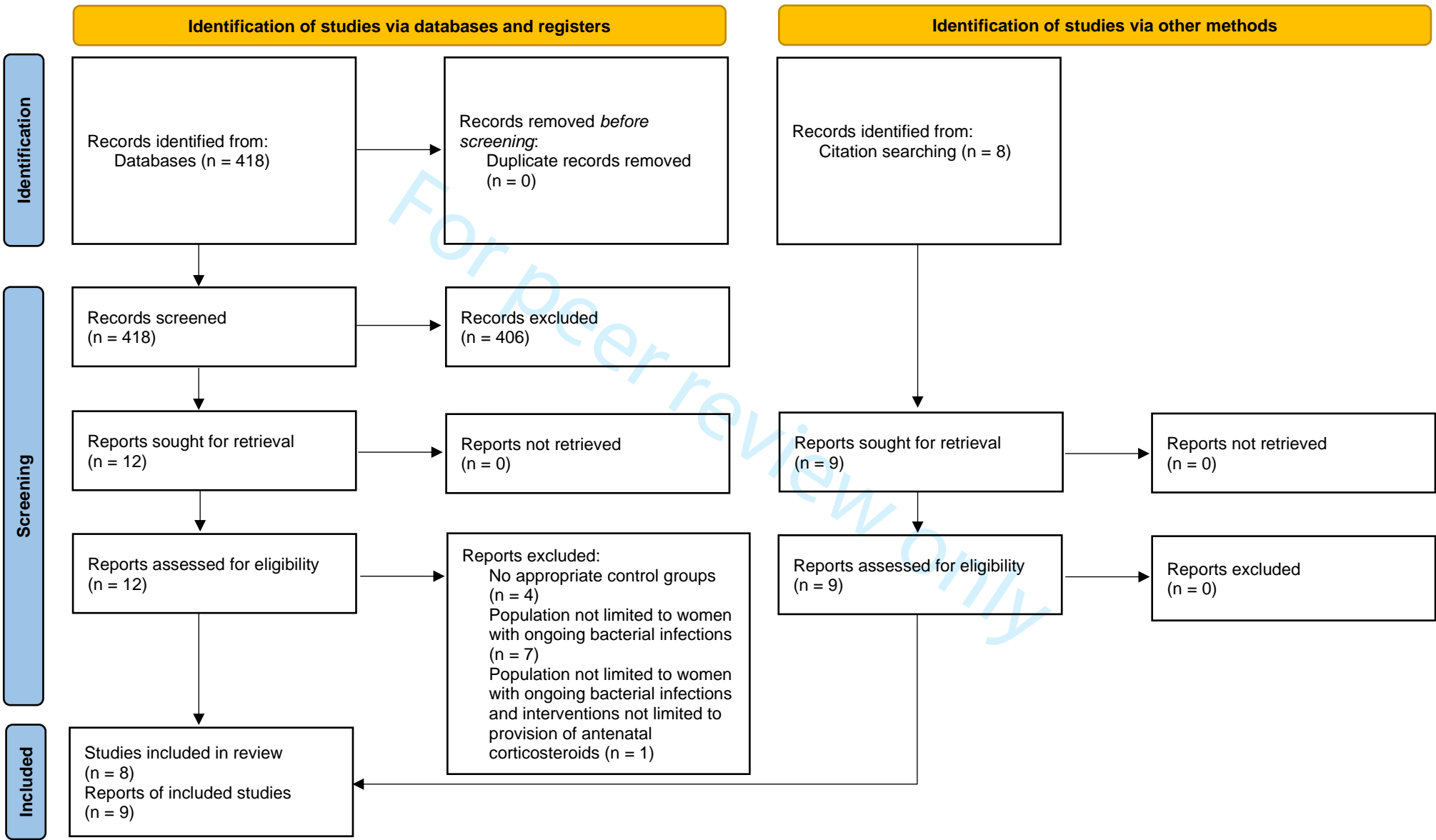
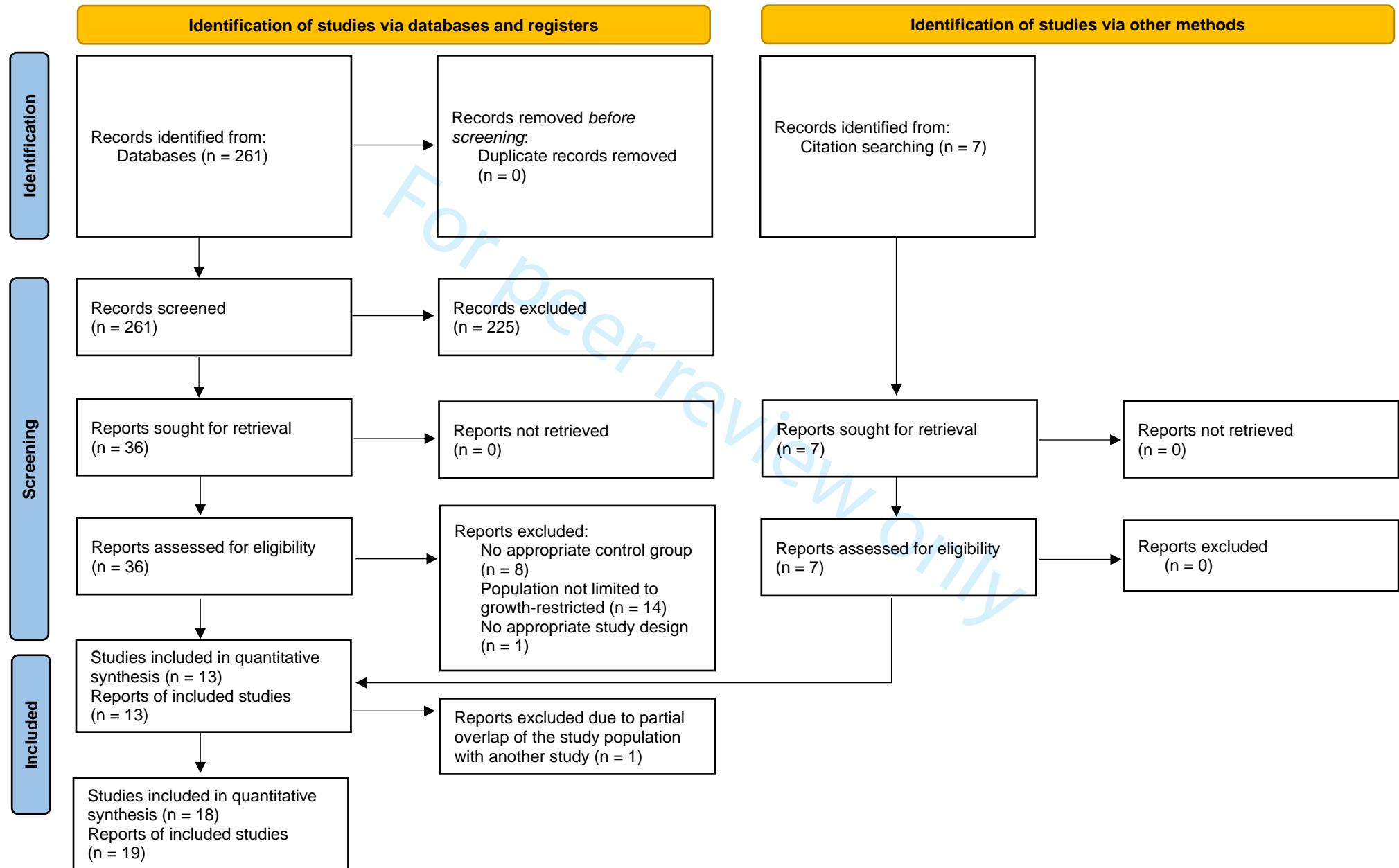


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure 1: 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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Battarbee 2020	+	+	+	+	+	+
Cassimatis 2020	+	?	+	+	+	+
Krispin 2018	+	+	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
de la Huerga Lopez 2019	+	-	+	+	+	+
Kirshenbaum 2018	+	-	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Ahn 2012	+	-	+	+	+	+
Baud 2000	+	+	+	+	+	+
Been 2009	+	-	+	+	+	+
Dempsey 2005	+	-	+	+	+	+
Elimian 2000	+	-	+	+	+	+
Foix-L'Helias 2005	?	-	+	+	+	+
Goldenberg 2006	+	-	+	+	+	+
Ryu 2019	+	+	+	+	+	+

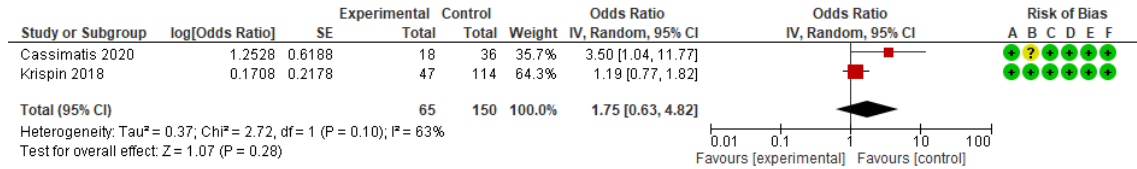
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
 Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Bernstein 2000	+	-	+	+	+	+
Bitar 2020	+	+	+	+	+	+
Cartwright 2019	+	+	+	+	-	+
DiLenardo 1990	?	-	+	+	+	+
Elimian 1999	+	-	+	+	+	+
Feng 2017	+	?	+	+	+	+
Foix-L'Helias 2005	?	-	+	+	+	+
Ishikawa 2015	+	+	+	+	-	+
Kim 2018	+	+	+	+	+	+
Kim Y.J. 2018	+	-	+	+	+	+
Ley 1997	+	?	+	+	+	+
Mitsiakos 2013	+	-	+	+	-	+
Riskin-Mashiah 2016	+	+	+	+	+	+
Riskin-Mashiah 2018	+	+	+	+	+	+
Schaap 2001	?	+	+	+	+	+
Spinillo 1995	+	+	+	+	+	+
Torrance 2007	+	+	+	+	+	+
vanStralen 2009	+	-	+	+	+	+

Supplementary file 4: Forest plots

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

1) Caesarean section



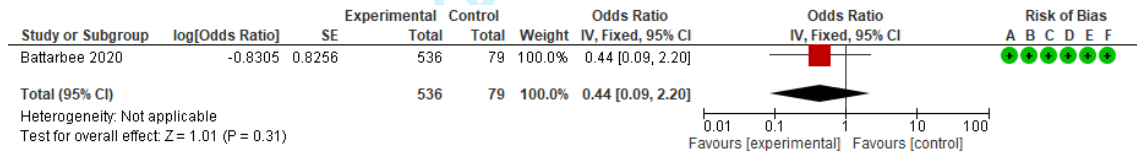
Risk of bias legend

- (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

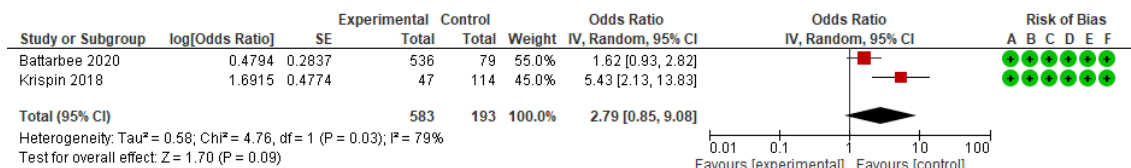


Risk of bias legend

- (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)

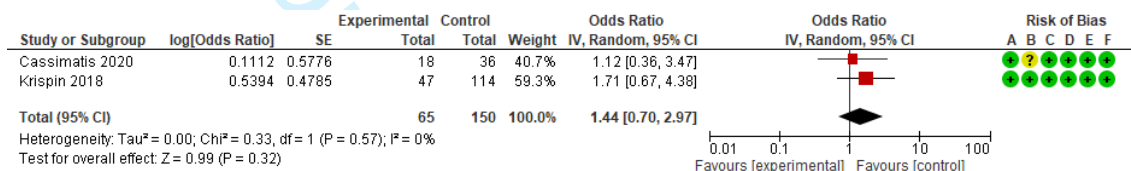


Risk of bias legend

- (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)
- (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) Admission to neonatal intensive care unit (NICU)



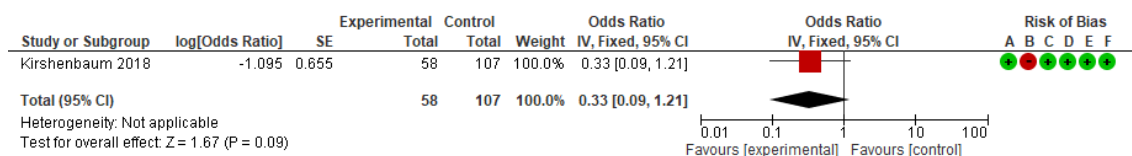
Risk of bias legend

- (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 undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders

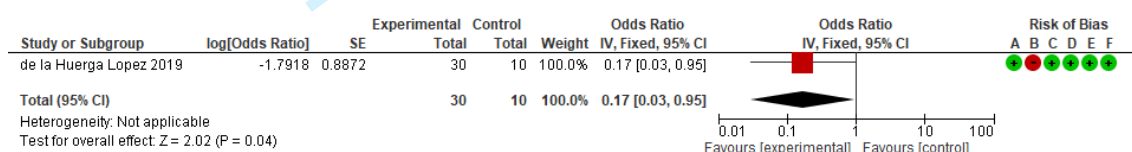


Risk of bias legend

- (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) Gestational diabetes mellitus



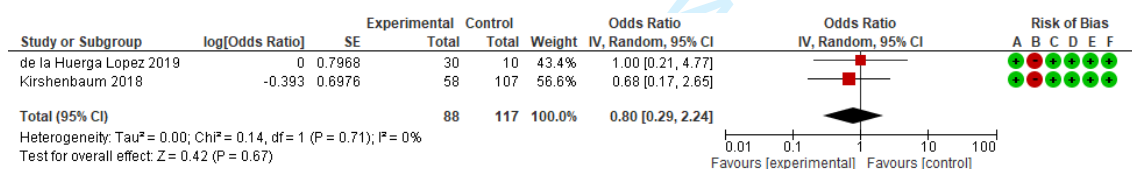
Risk of bias legend

- (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)

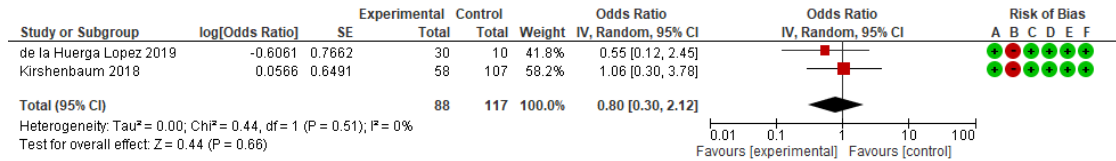


Risk of bias legend

- (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

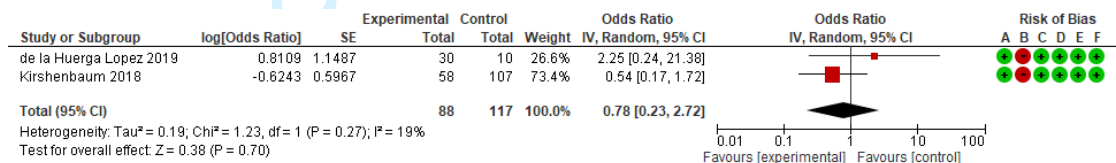


Risk of bias legend

- (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) Admission to neonatal intensive care unit (NICU)

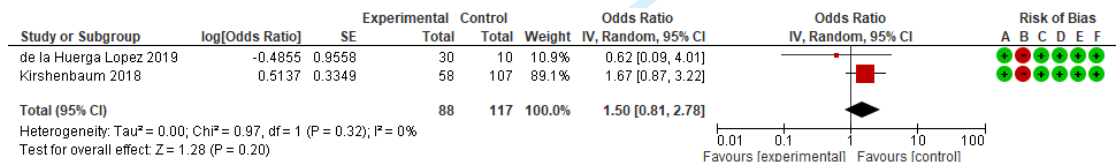


Risk of bias legend

- (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

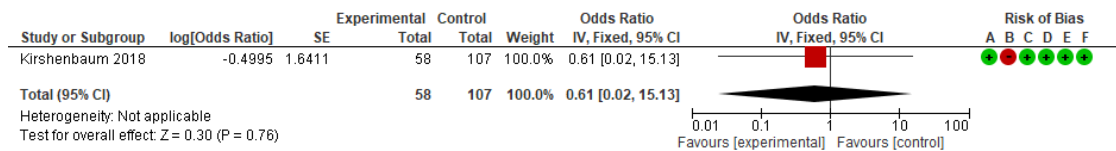


Risk of bias legend

- (A) Selection of participants (selection bias)
- (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

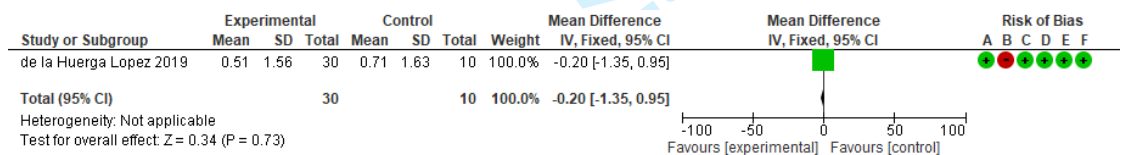


Risk of bias legend

- (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

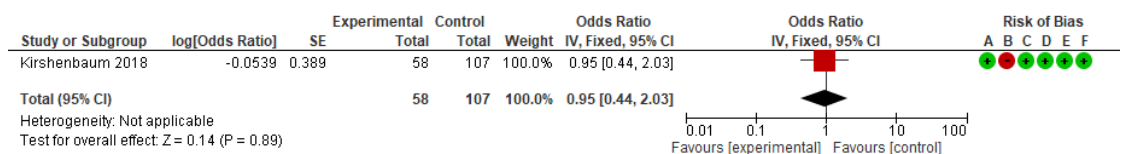


Risk of bias legend

- (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

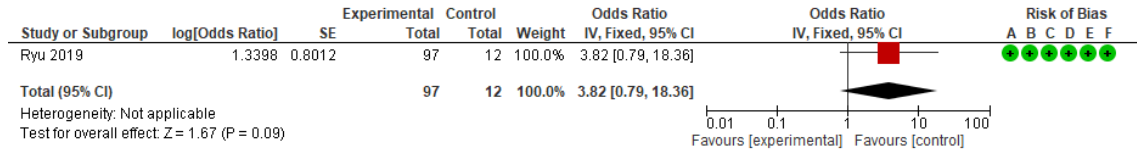
- (A) Selection of participants (selection bias)
- (B) Confounding variables (selection bias)
- (C) Measurement of exposure (performance bias)
- (D) Blinding of outcomes assessment (Detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective outcome reporting (reporting bias)

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)



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

2) Gestational diabetes mellitus (HC)

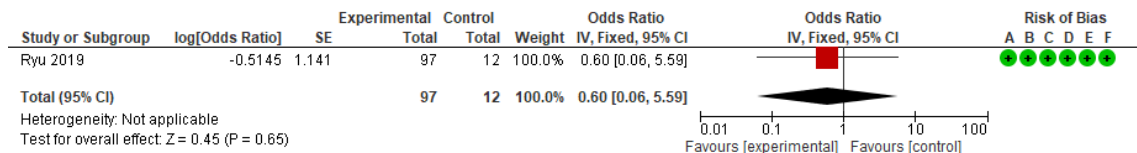


Risk of bias legend

- (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

3) Preeclampsia or eclampsia (HC)



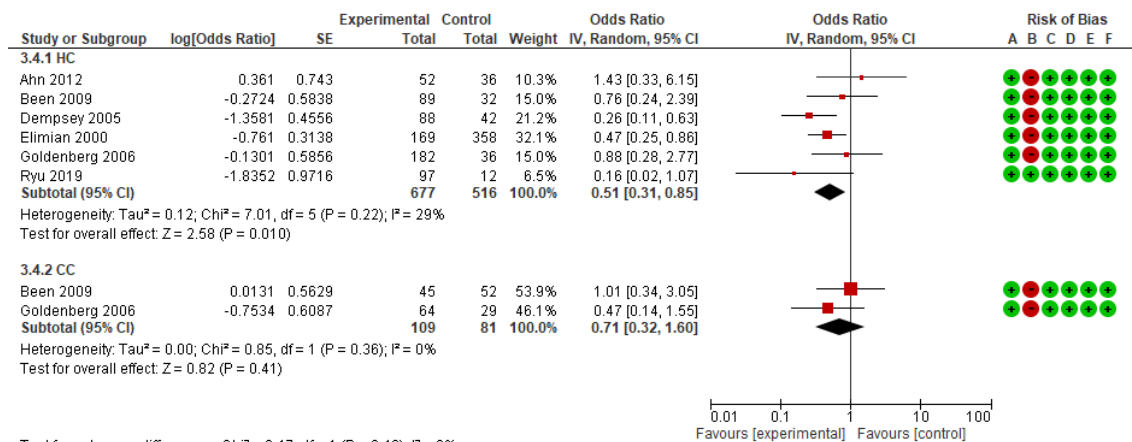
Risk of bias legend

- (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

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

1) Neonatal death



Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%

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; CC: Clinical chorioamnionitis

2) Death before discharge home (CC)

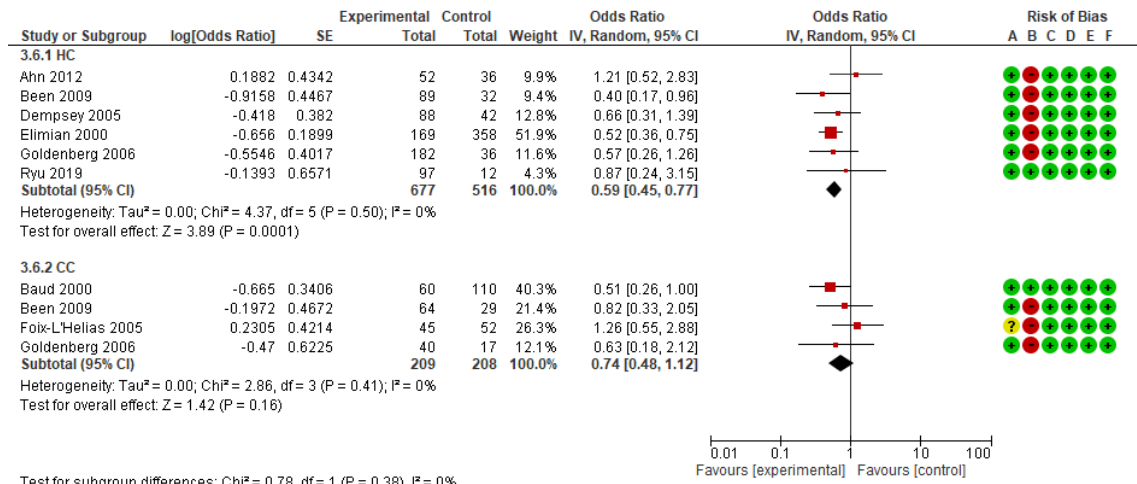


Risk of bias legend

- (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)

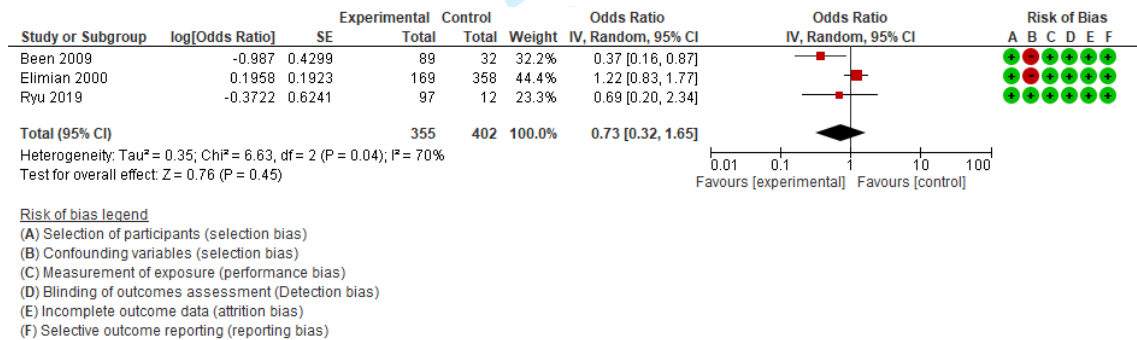
SE: Standard error; CI: Confidence interval; CC: Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



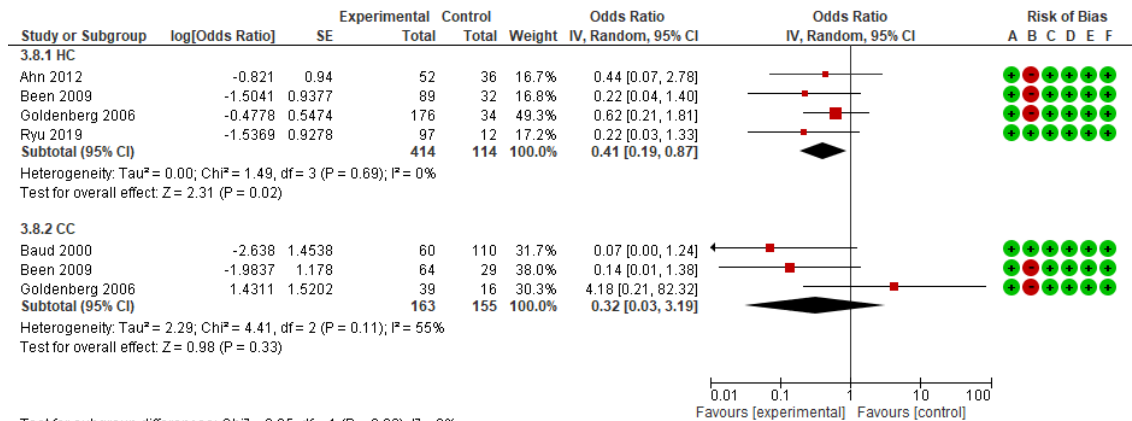
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

4) Surfactant use (HC)



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

5) Severe intraventricular hemorrhage (IVH)



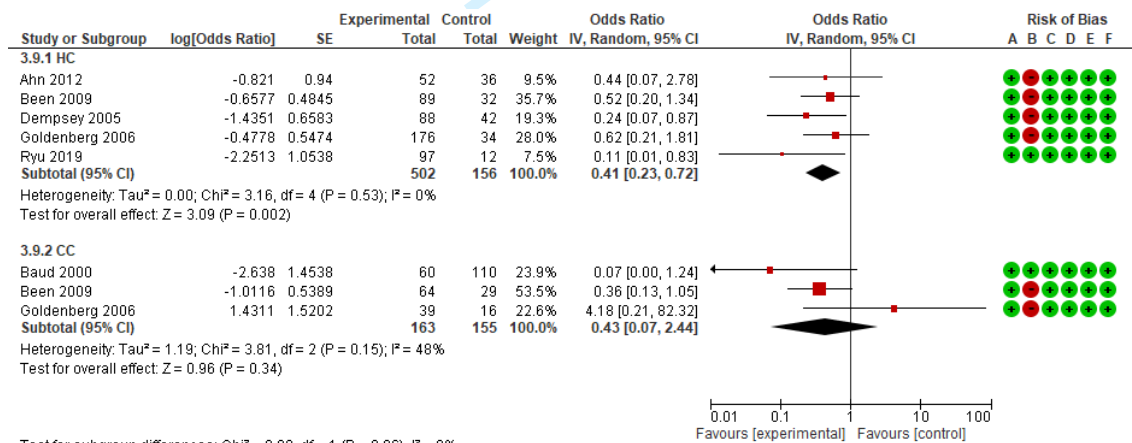
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%

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; CC: Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



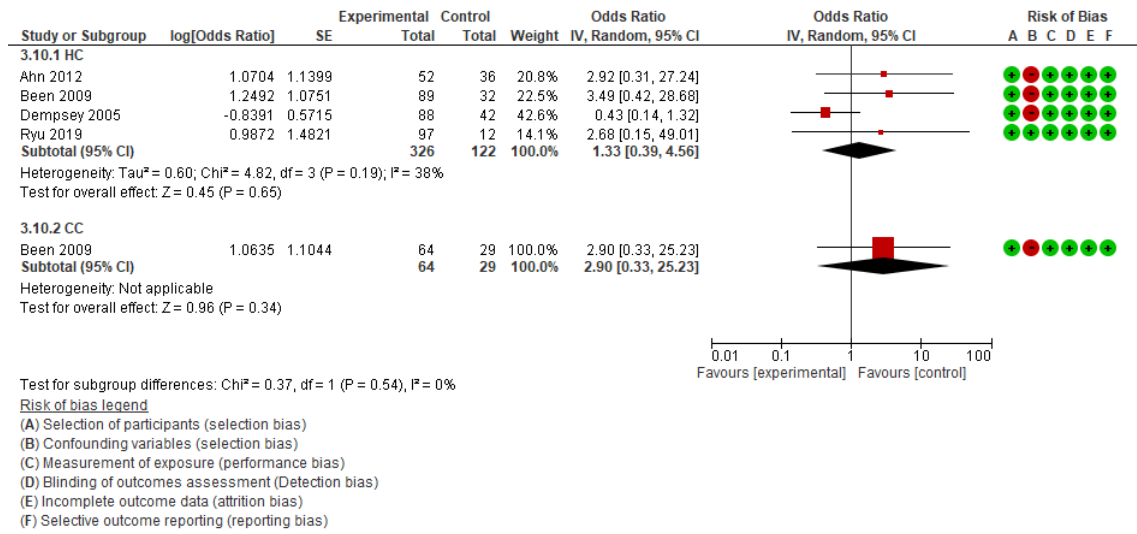
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

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)

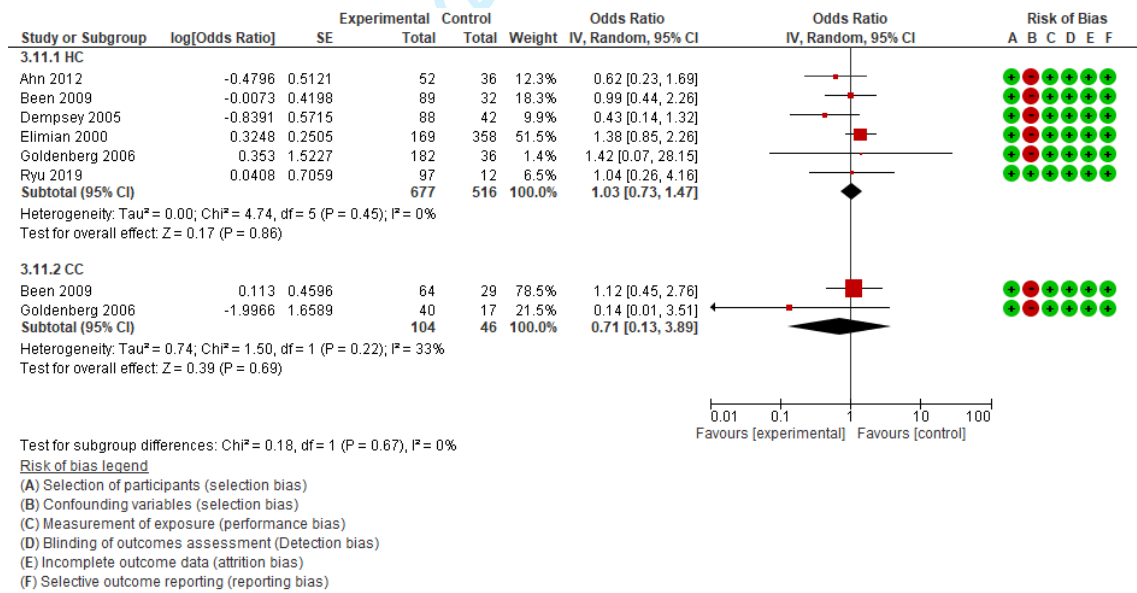
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

7) Early-onset sepsis



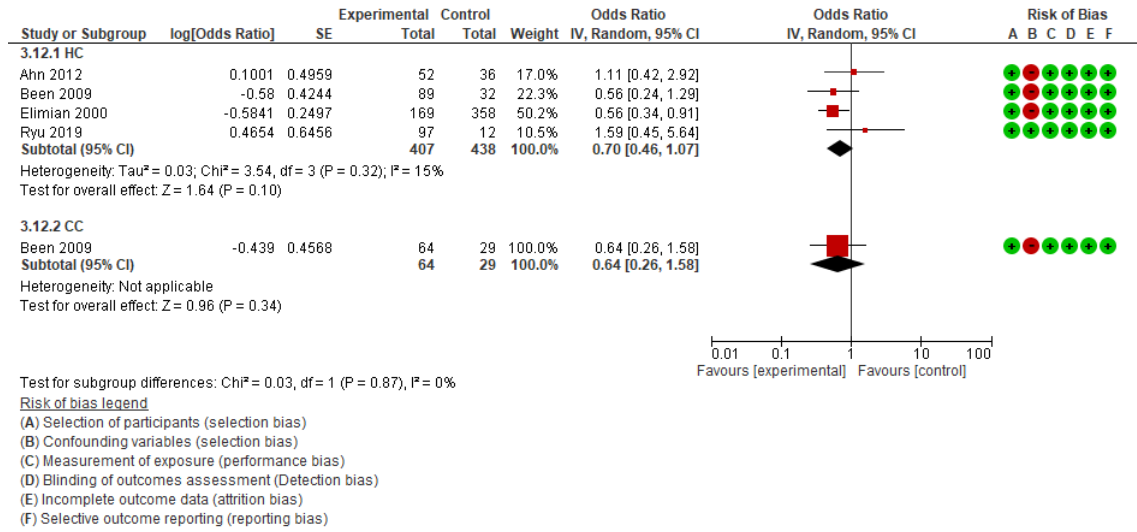
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

8) Sepsis



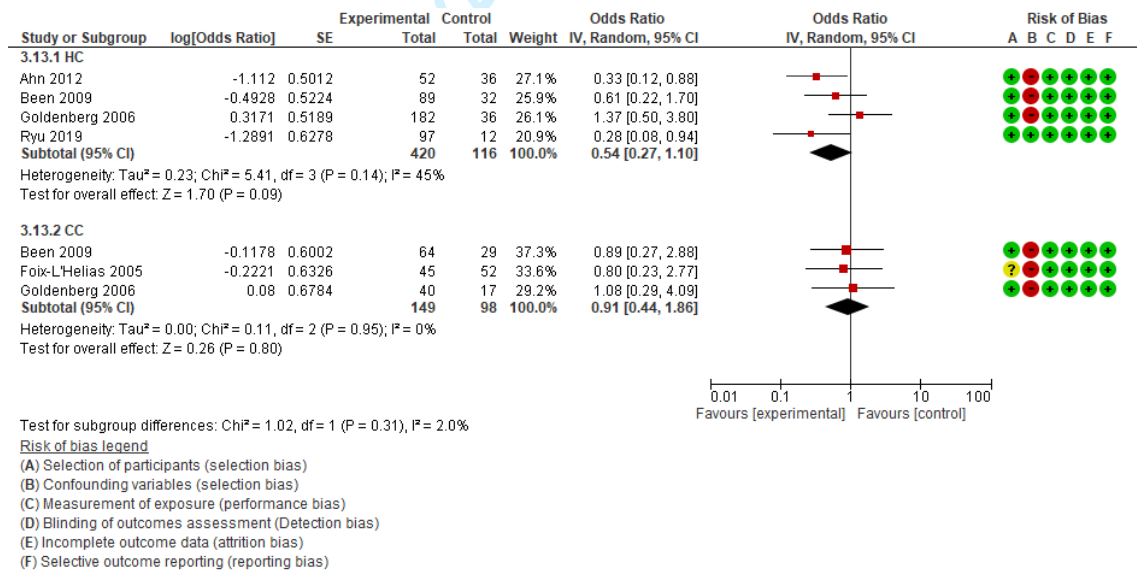
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



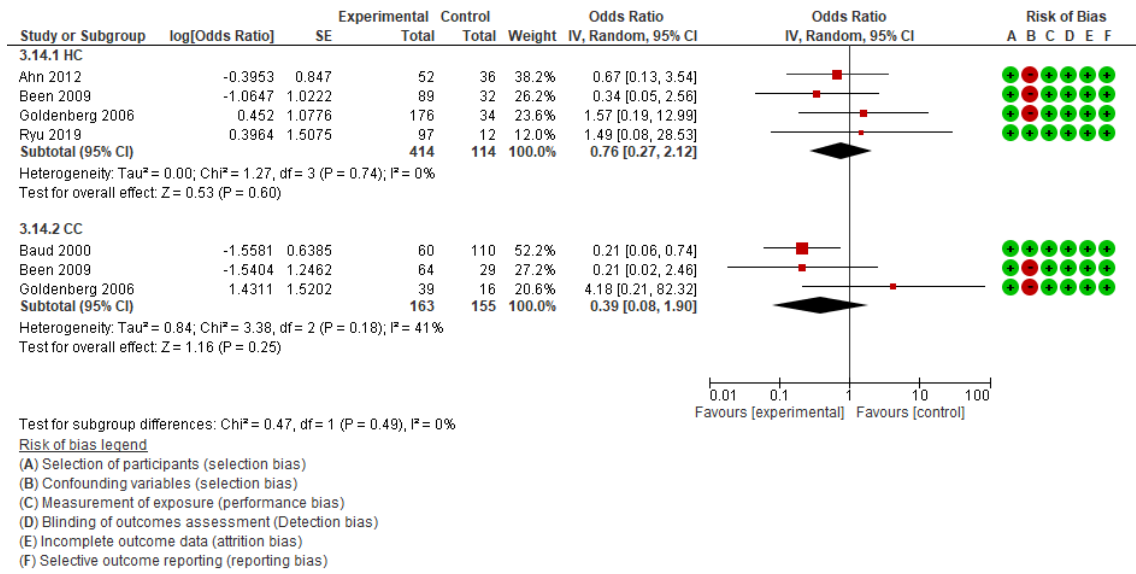
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



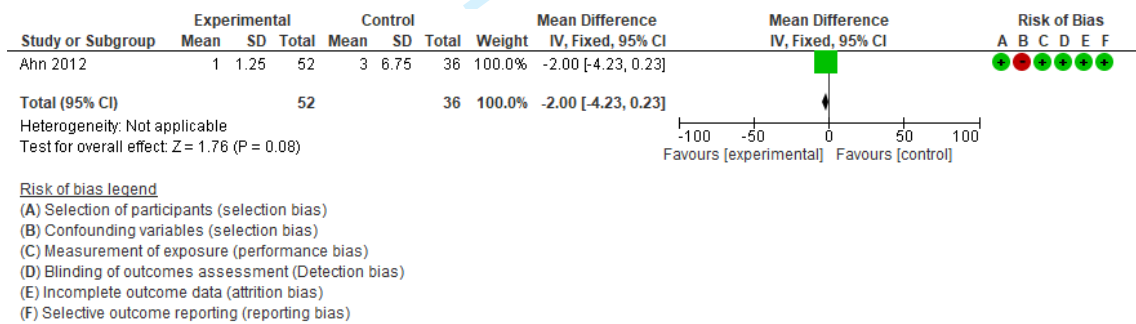
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

11) Periventricular leukomalacia (PVL)



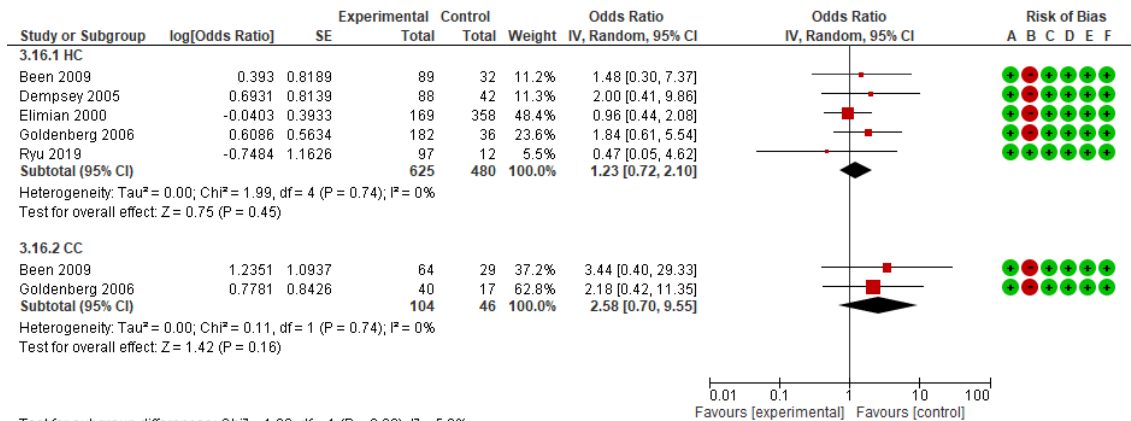
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



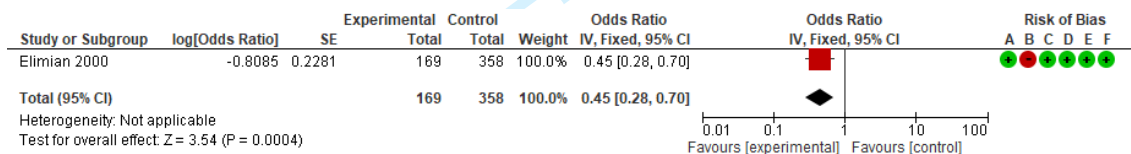
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

13) Necrotizing enterocolitis (NEC)



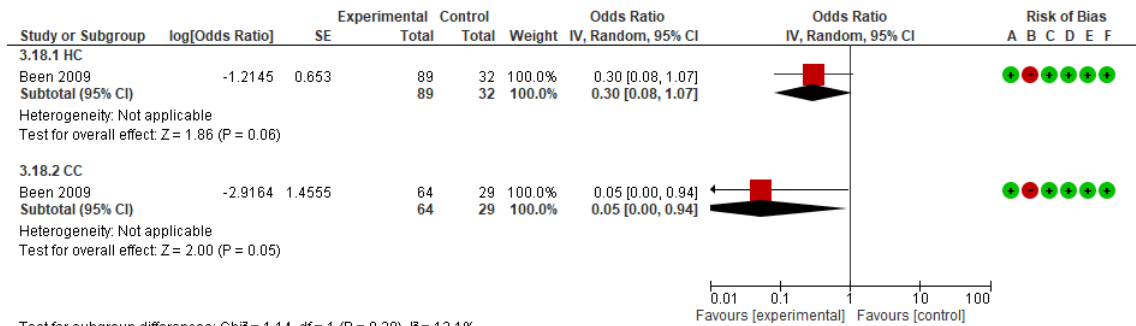
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



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

15) Use of mechanical ventilation



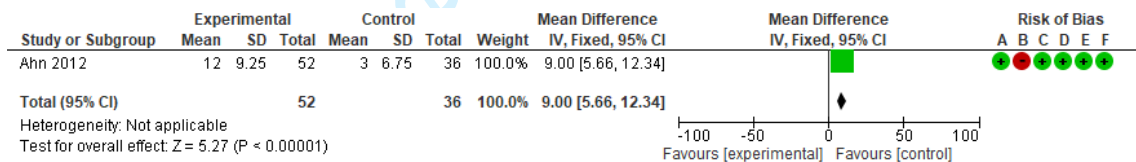
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.1%

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; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)

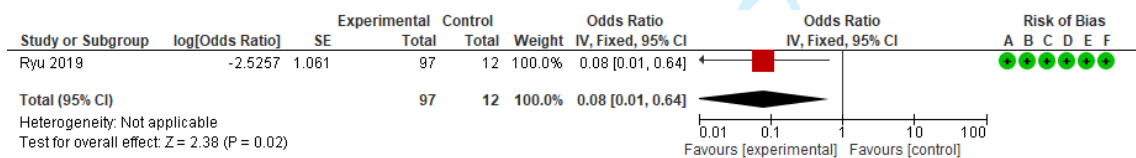


Risk of bias legend

- (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

17) Hypotension within 7 postnatal days (HC)

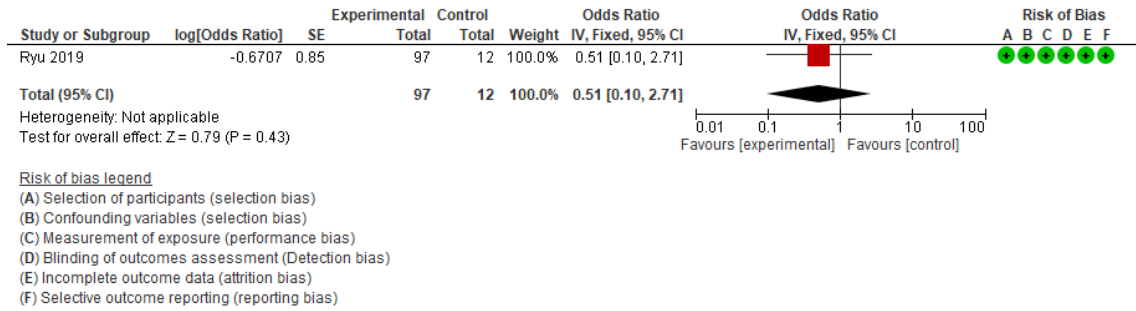


Risk of bias legend

- (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)

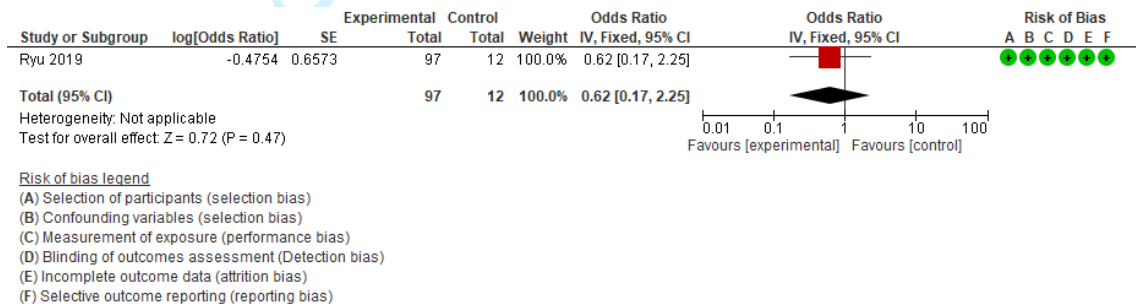
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Retinopathy of prematurity requiring treatment (HC)



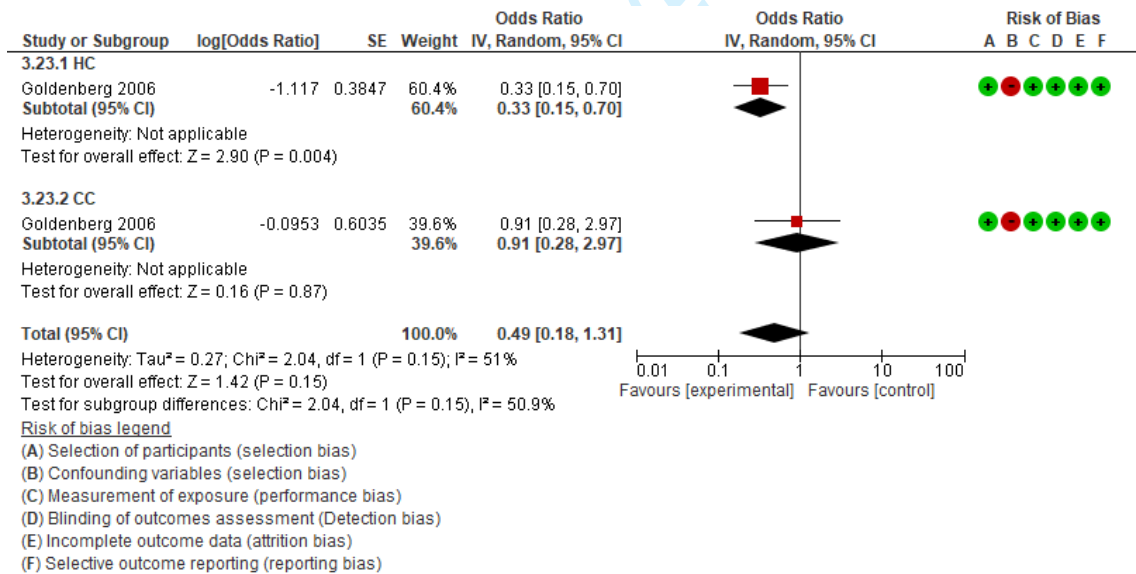
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

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)

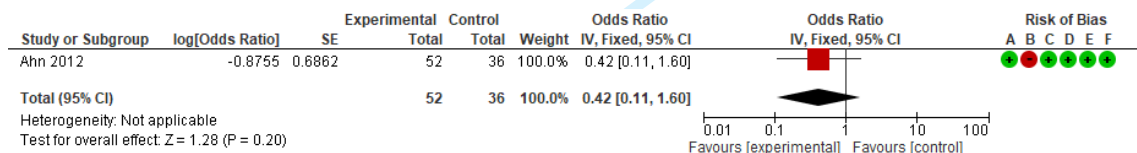


Risk of bias legend

- (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)



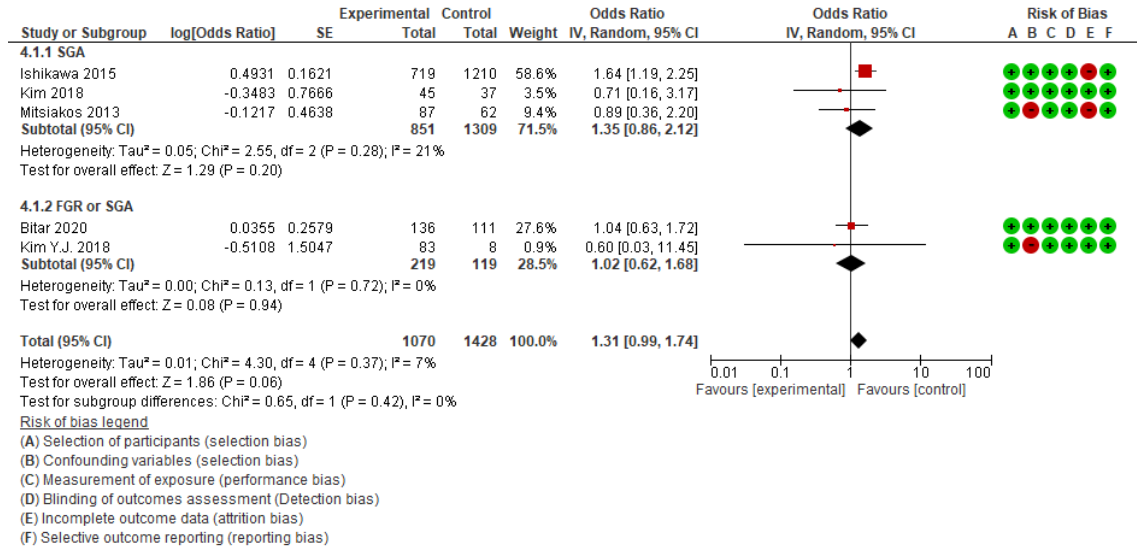
Risk of bias legend

- (A) Selection of participants (selection bias)
- (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

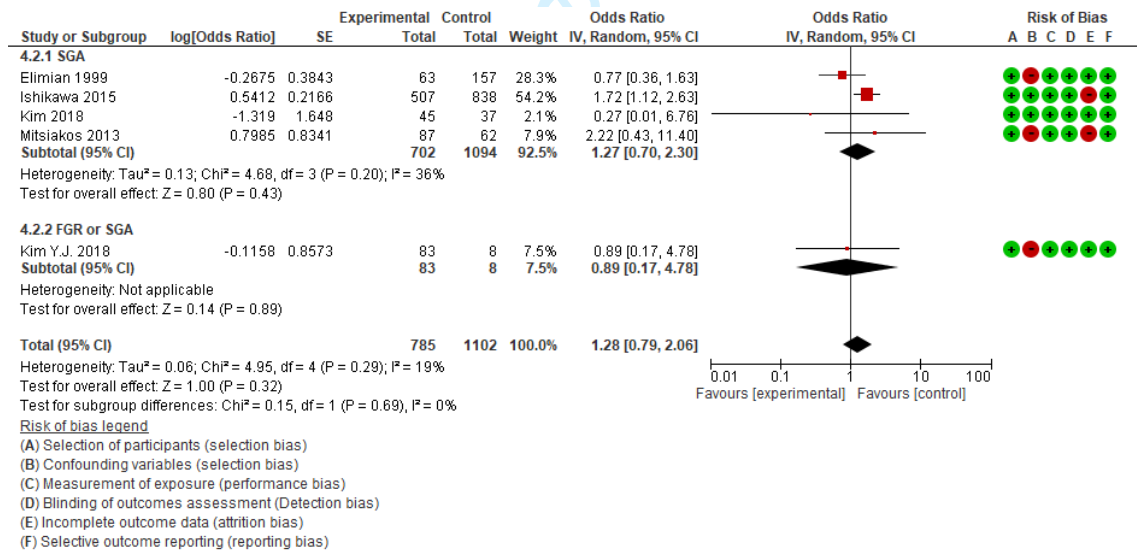
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



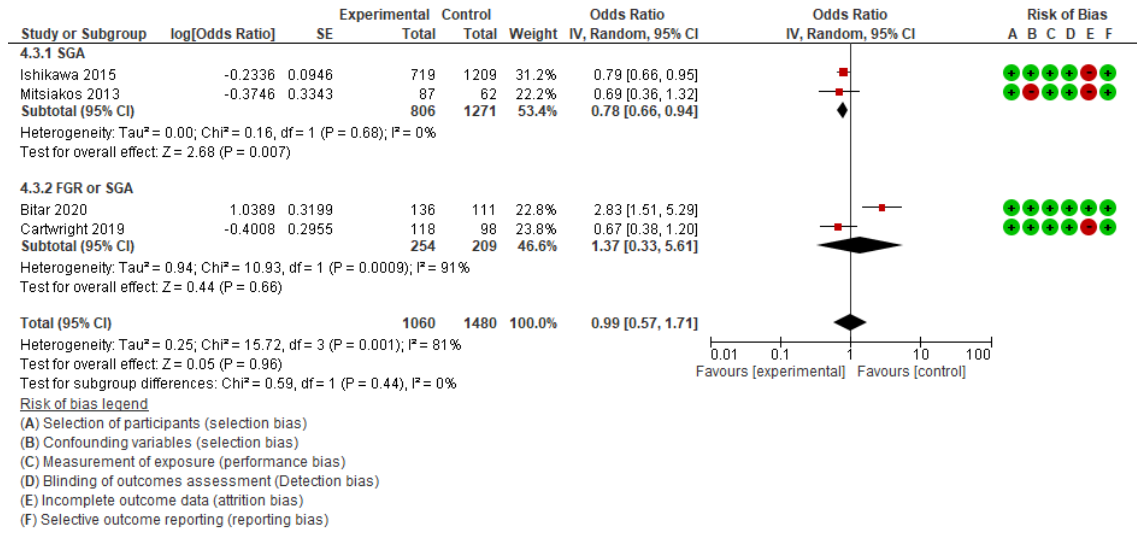
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

2) Chorioamnionitis (histologic and /or clinical)



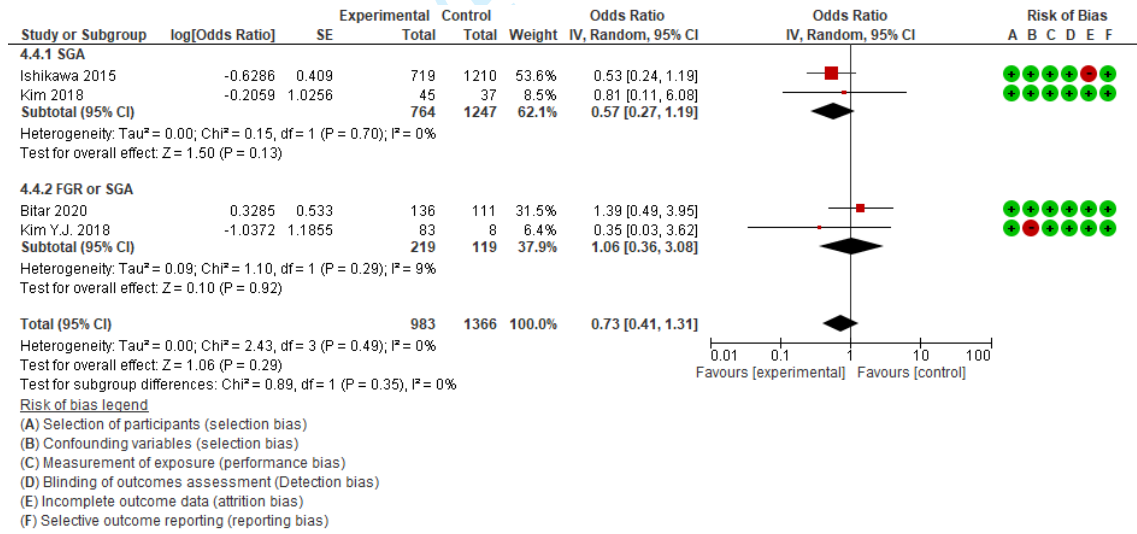
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

3) Preeclampsia.



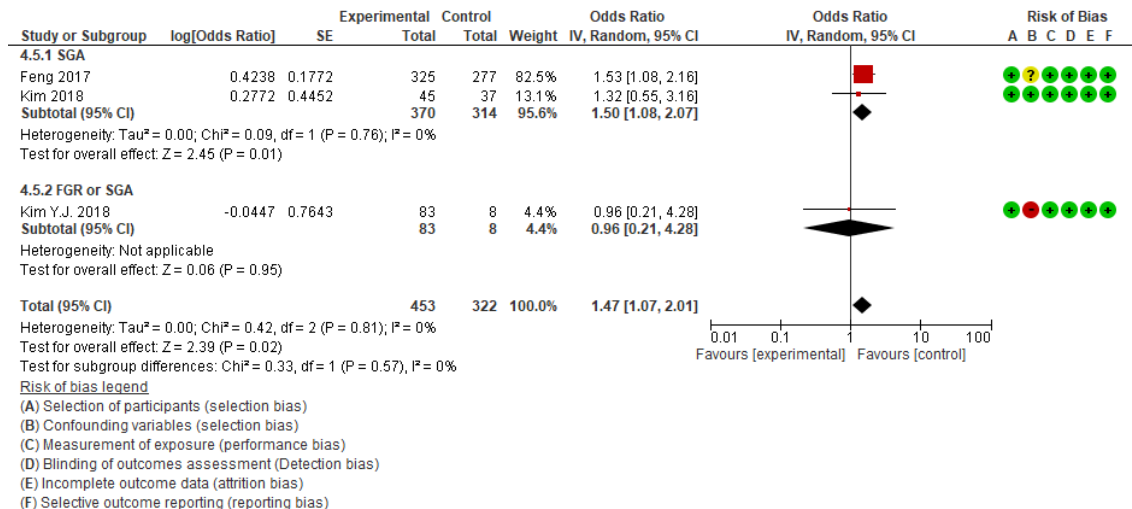
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Gestational diabetes mellitus.



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

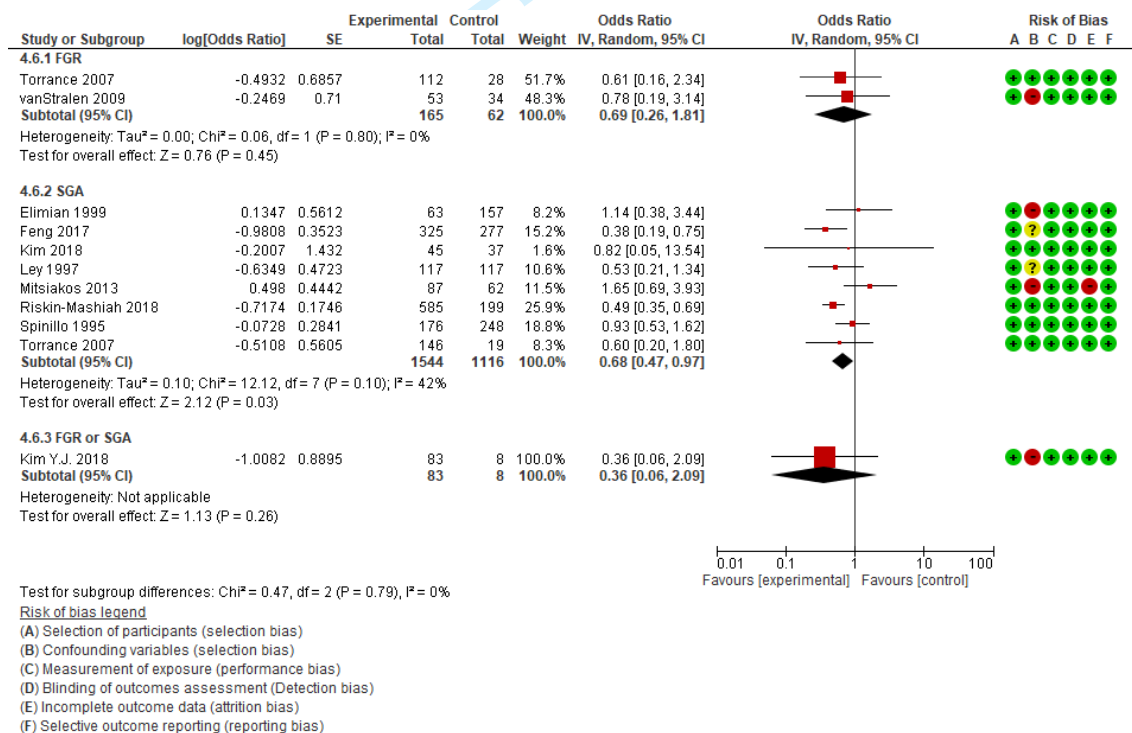
5) Pregnancy induced hypertension.



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

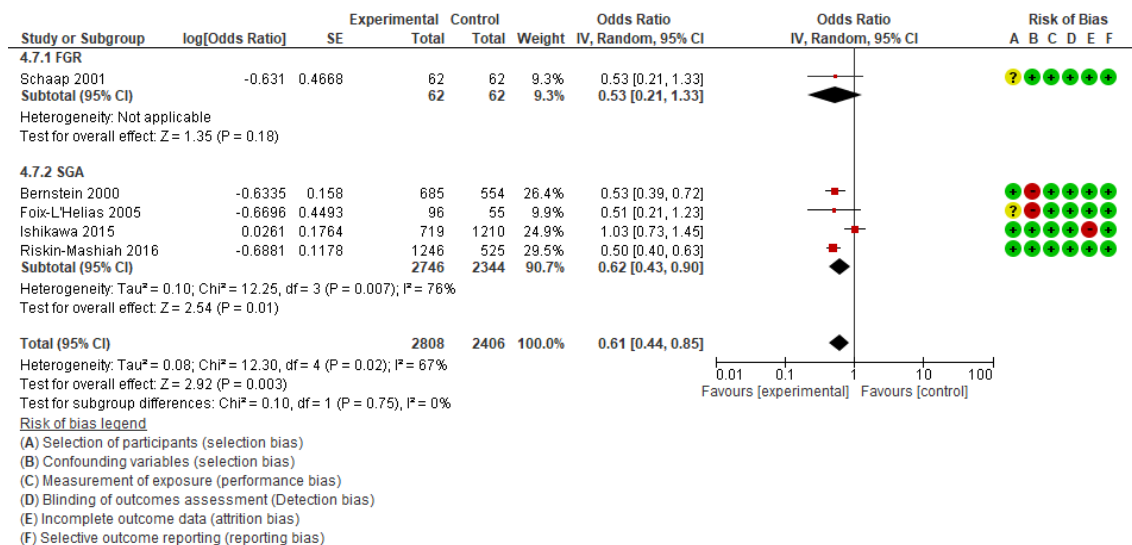
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



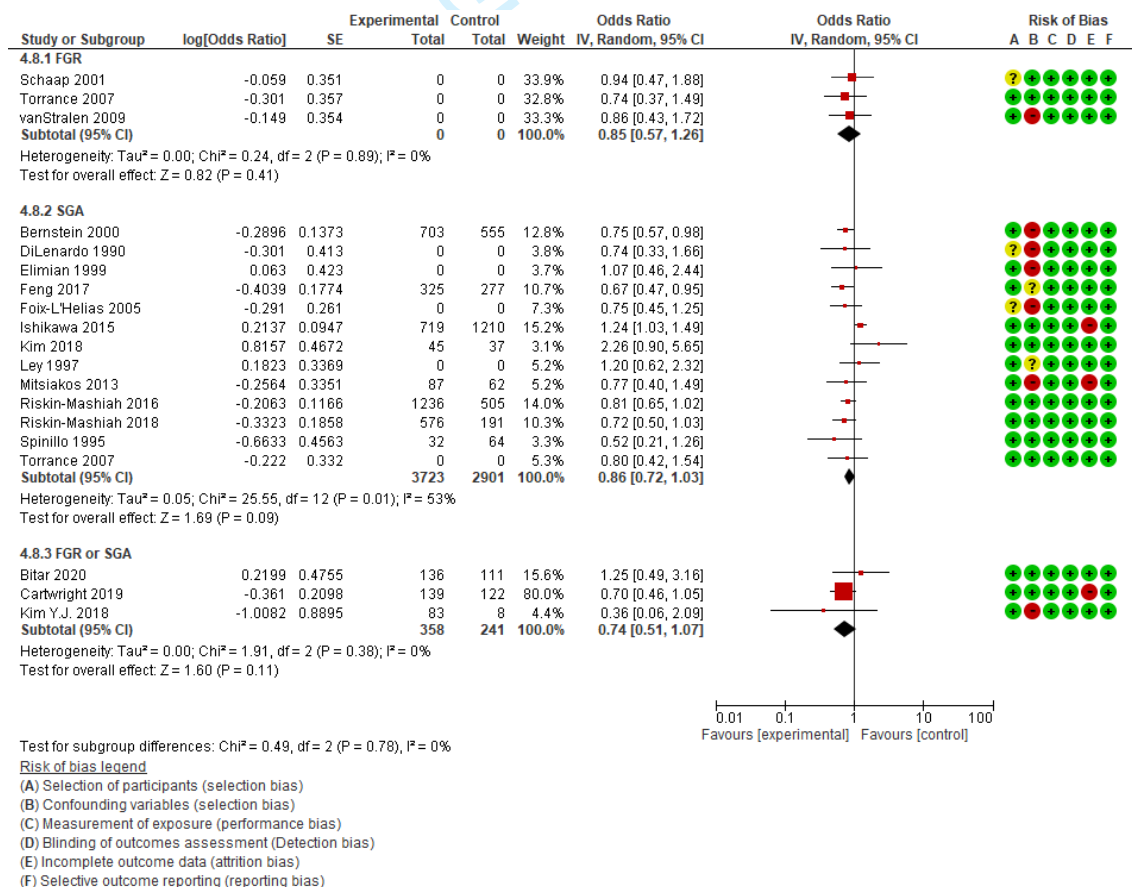
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

2) Death before discharge home



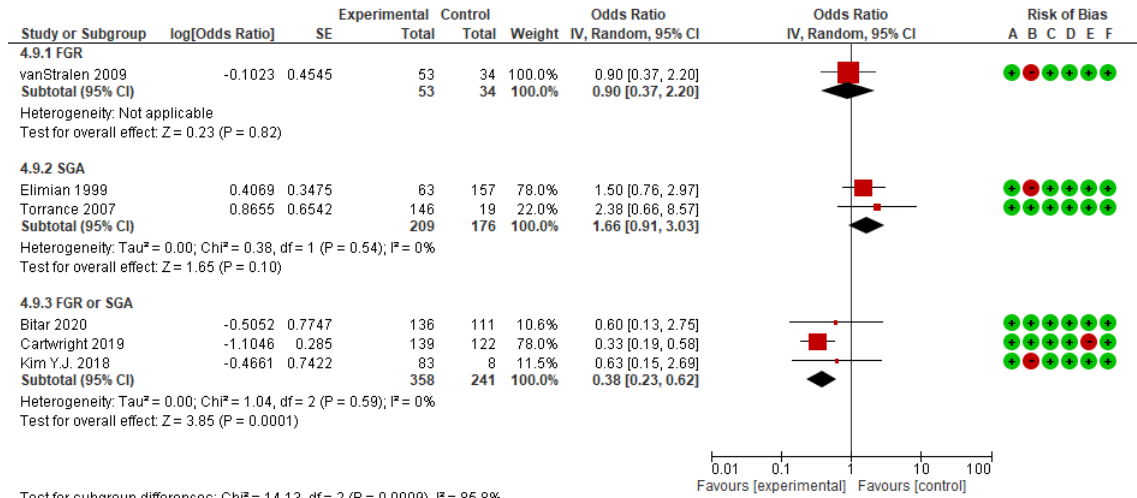
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



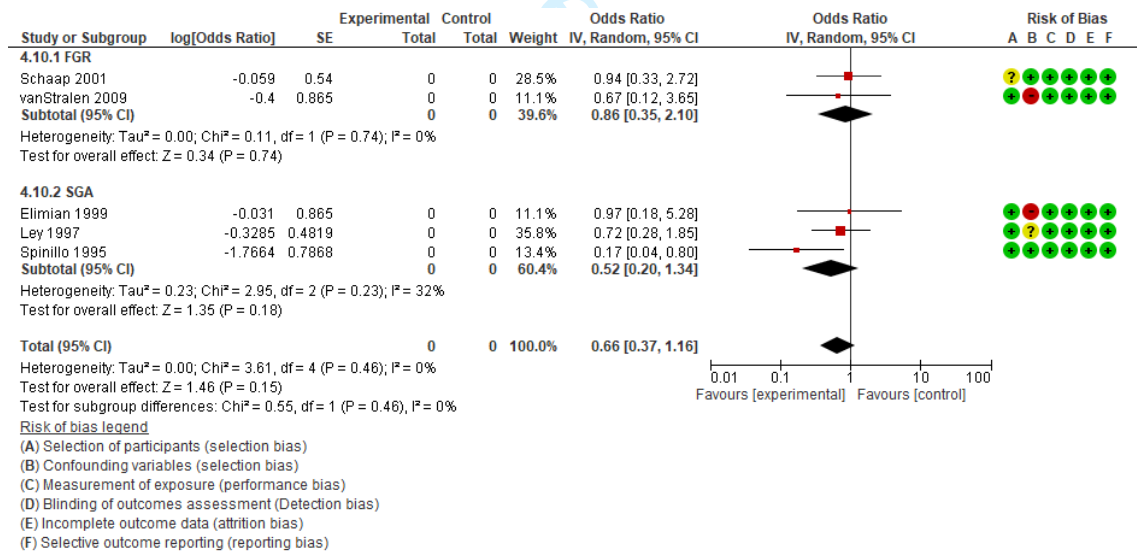
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Surfactant use



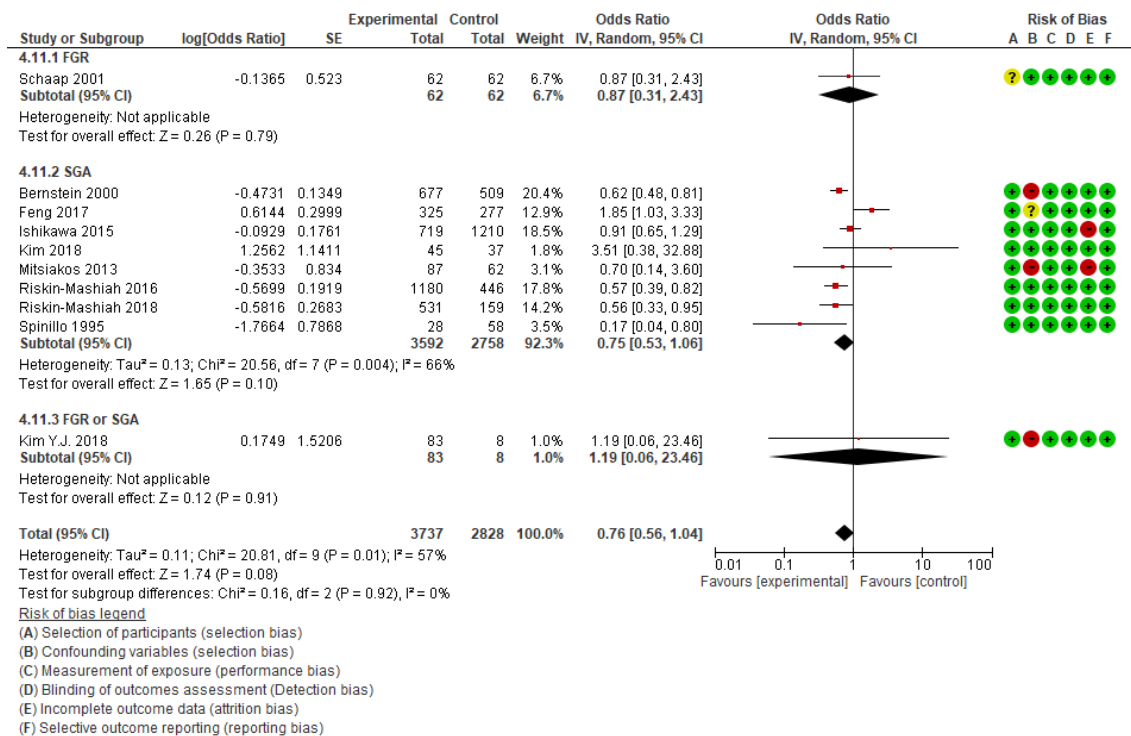
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



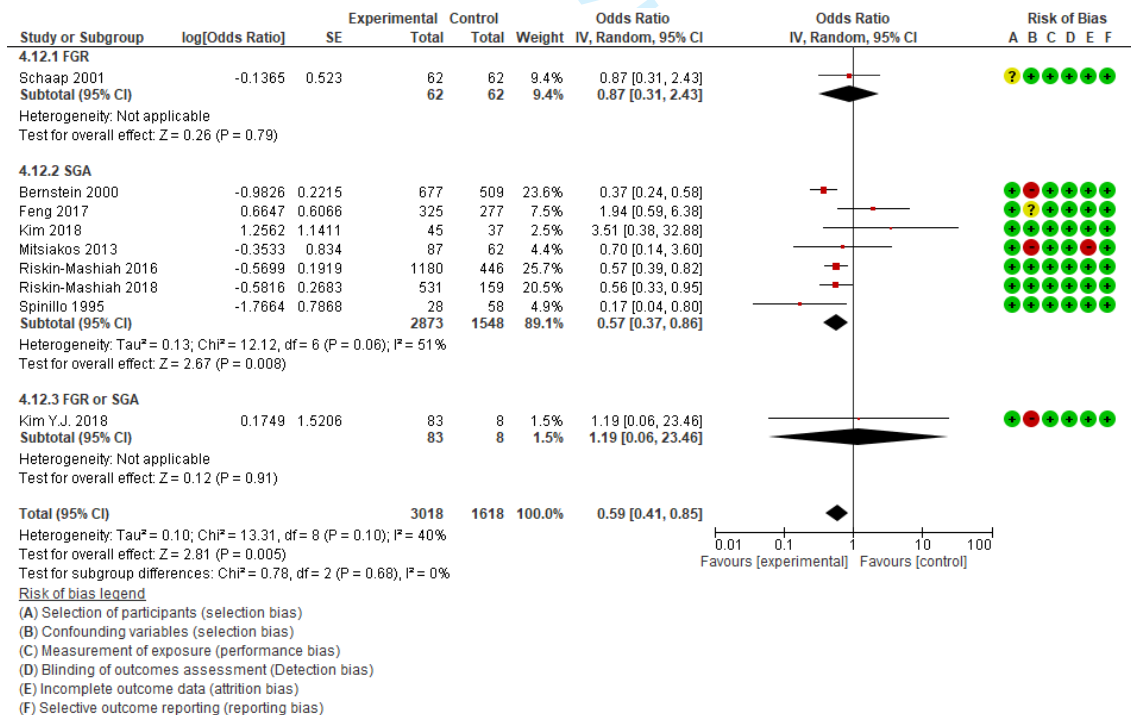
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

6) Interventricular haemorrhage



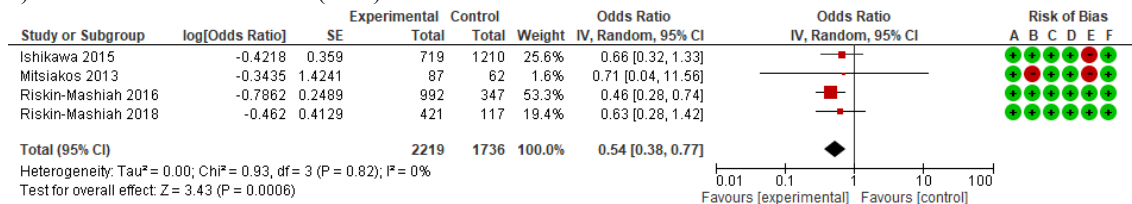
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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)

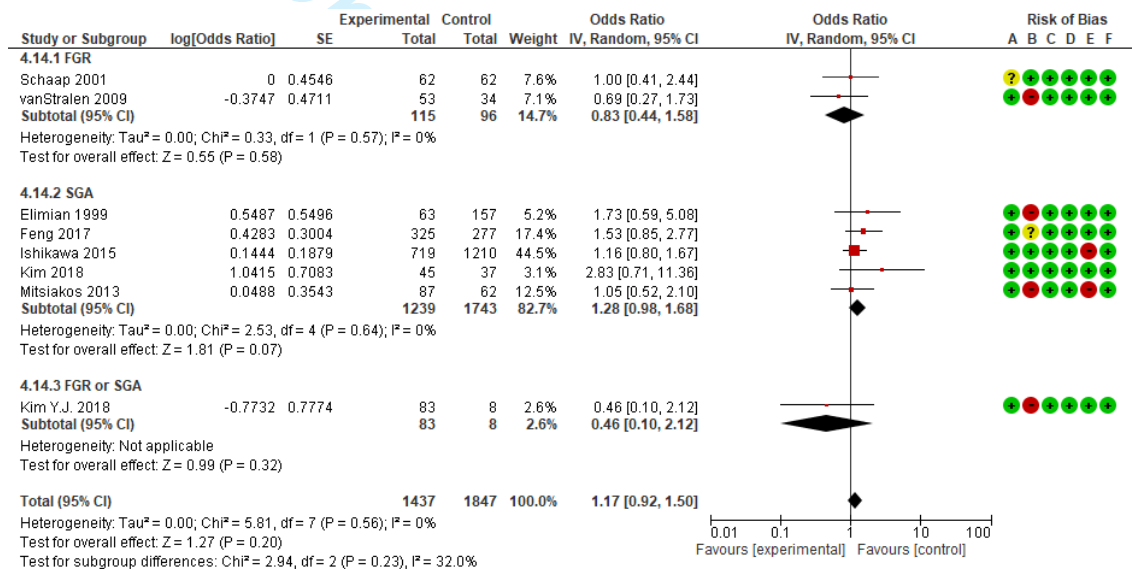


Risk of bias legend

- (A) Selection of participants (selection bias)
- (B) Confounding variables (selection bias)
- (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

9) Neonatal sepsis

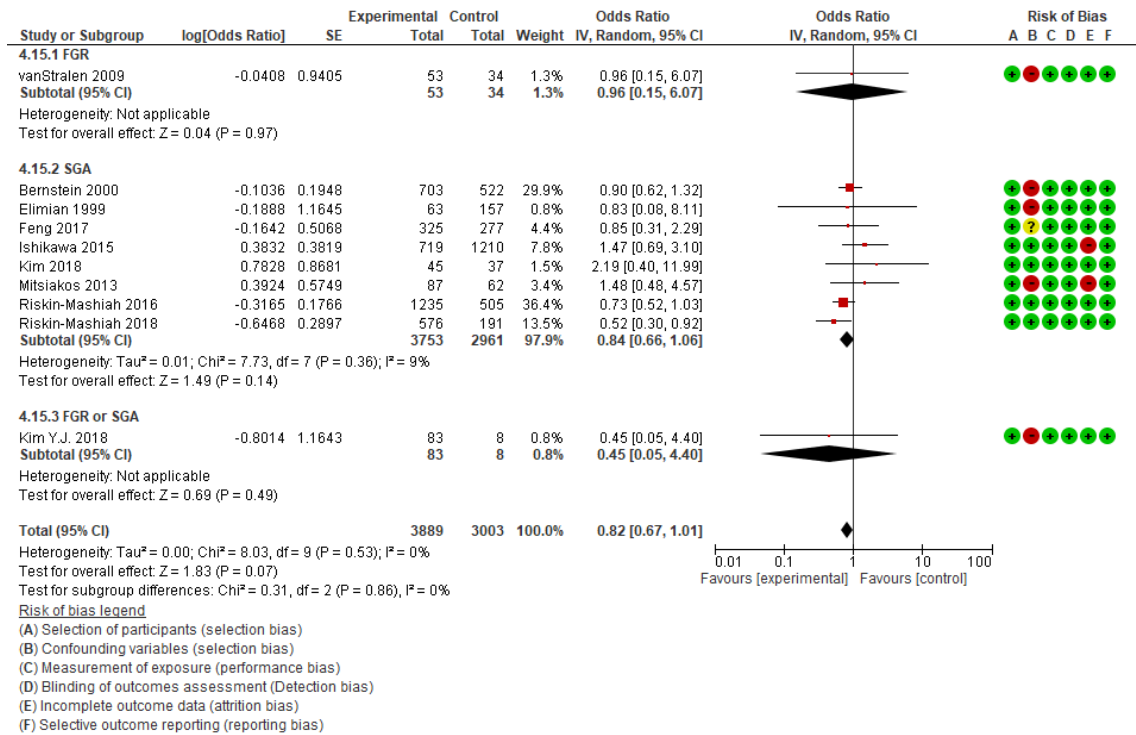


Risk of bias legend

- (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)

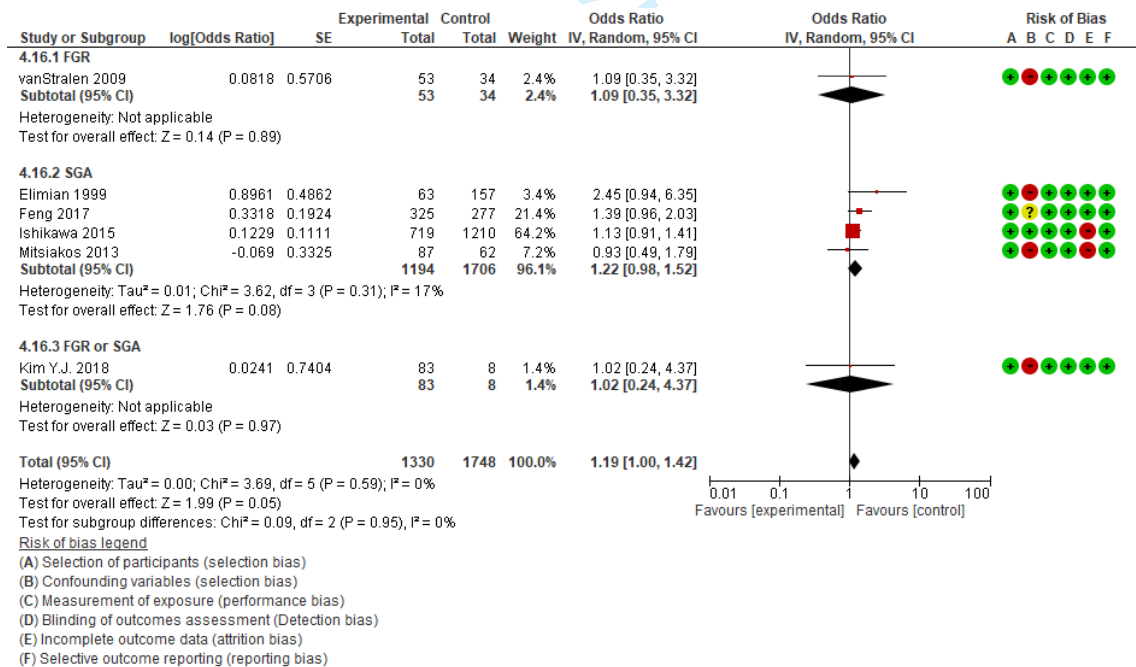
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

10) Necrotizing enterocolitis



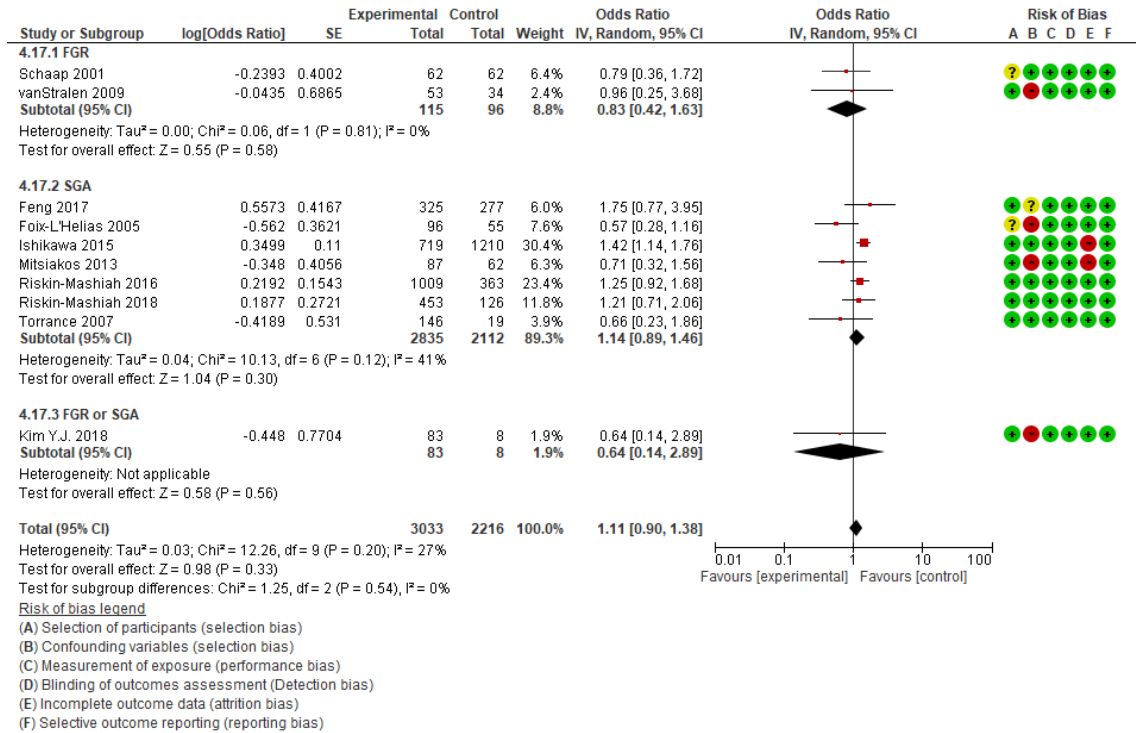
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

11) Patent ductus arteriosus



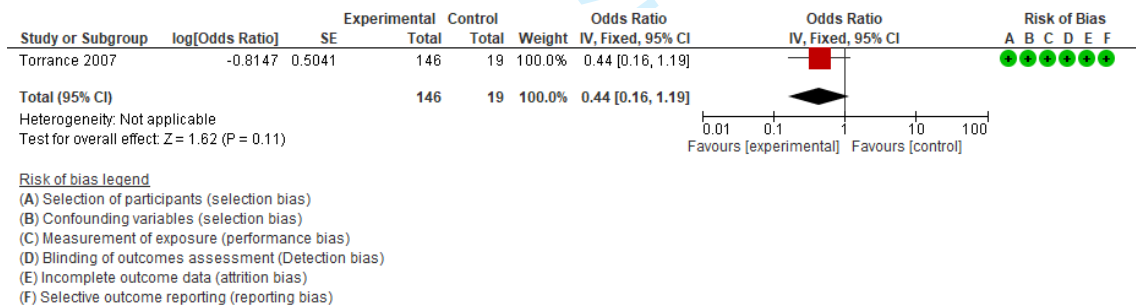
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



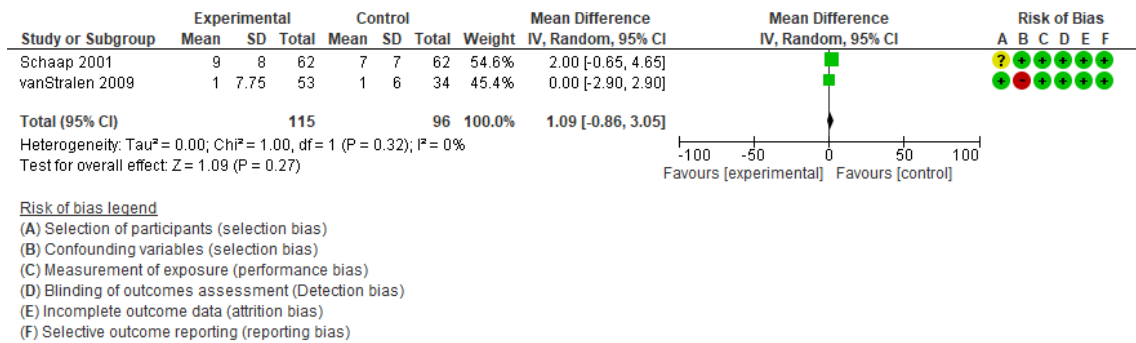
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



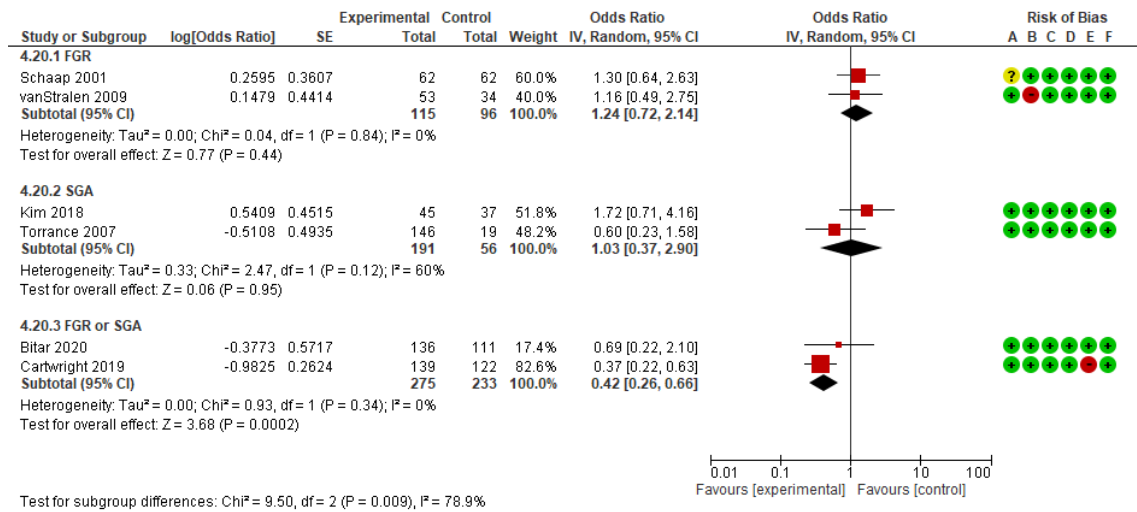
SE: Standard error; CI: Confidence interval

14) Duration of mechanical ventilation (FGR)



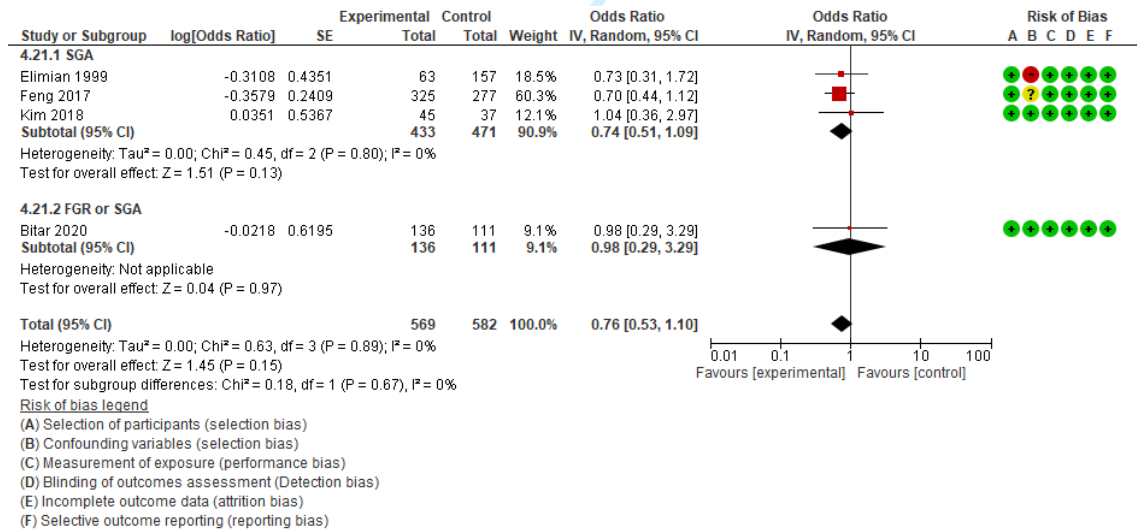
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction

15) Use of mechanical ventilation



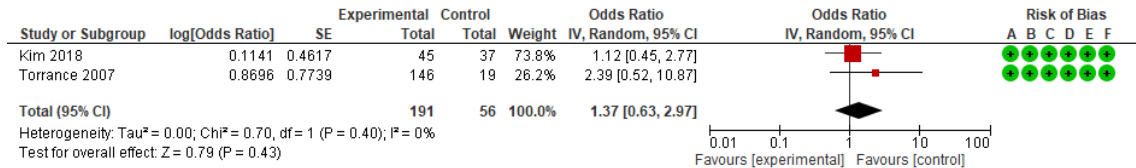
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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)

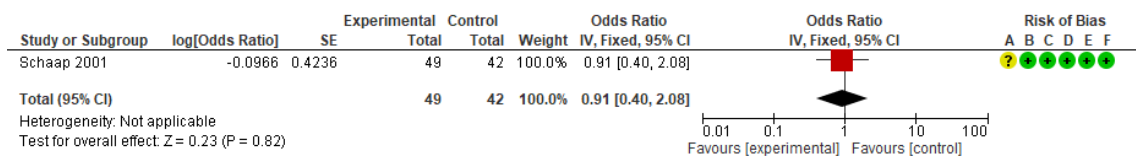


Risk of bias legend

- (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)

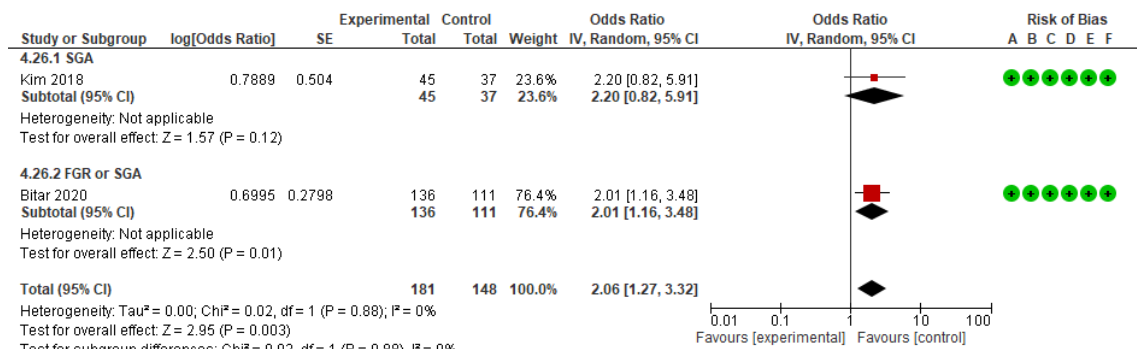


Risk of bias legend

- (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

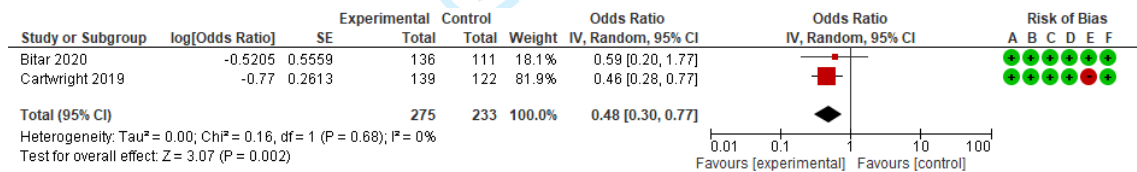
21) Neonatal hypoglycemia



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

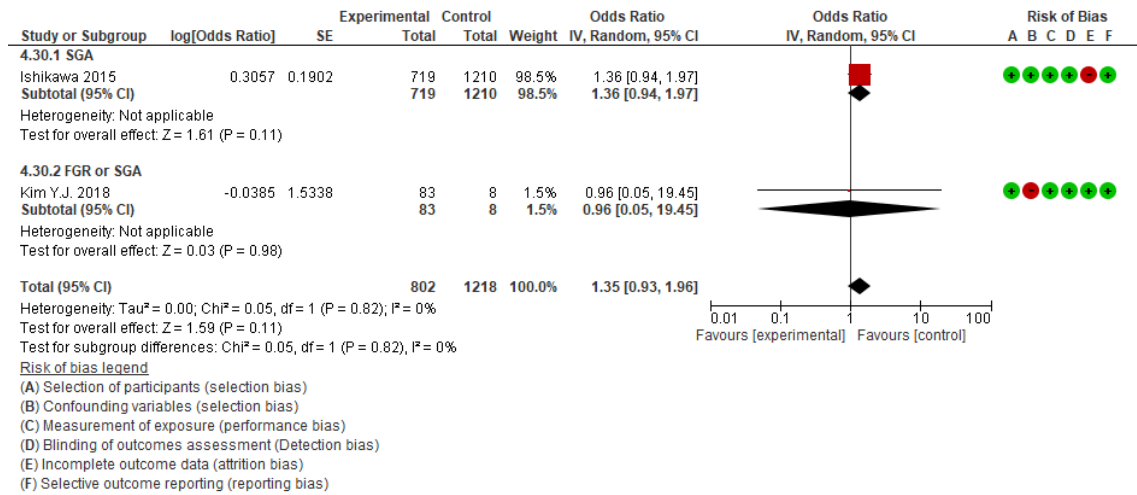
22) Oxygen therapy (FGR or SGA)



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)

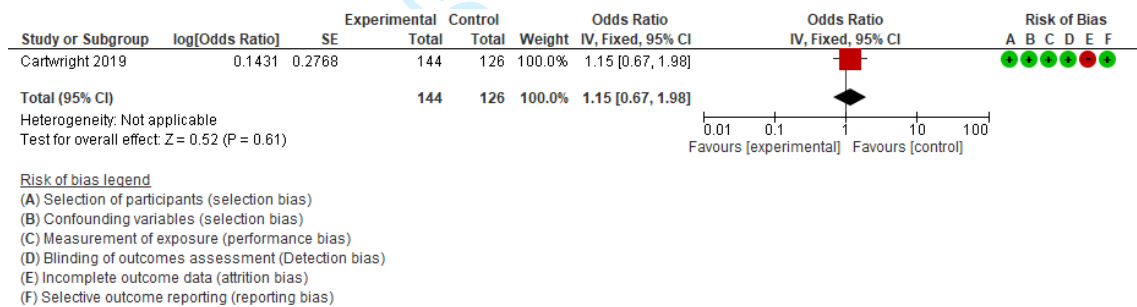
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

25) Neonatal adrenal insufficiency



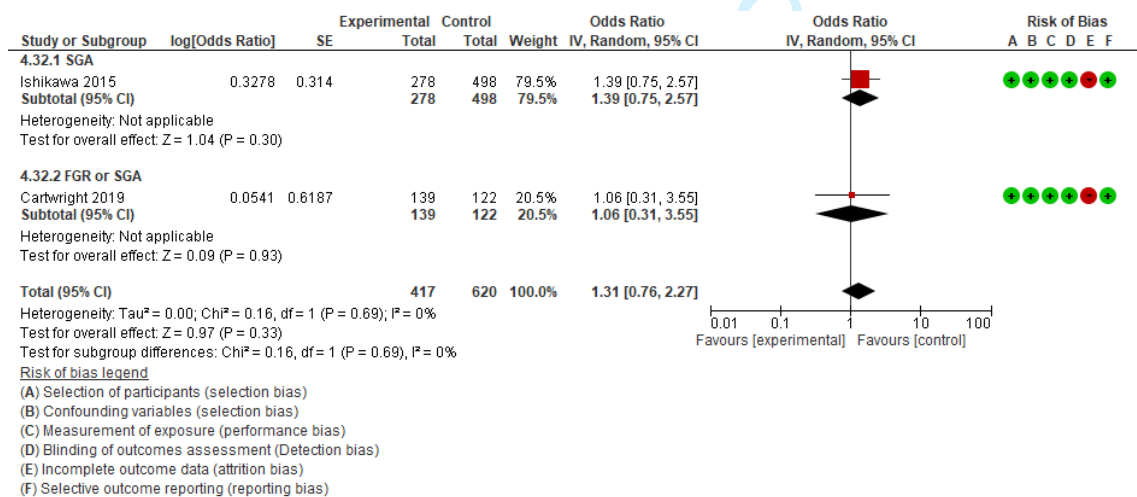
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

26) Survival free of disability (FGR or SGA)



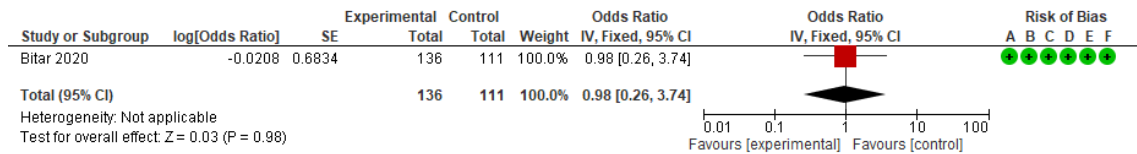
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

27) Cerebral palsy



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

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

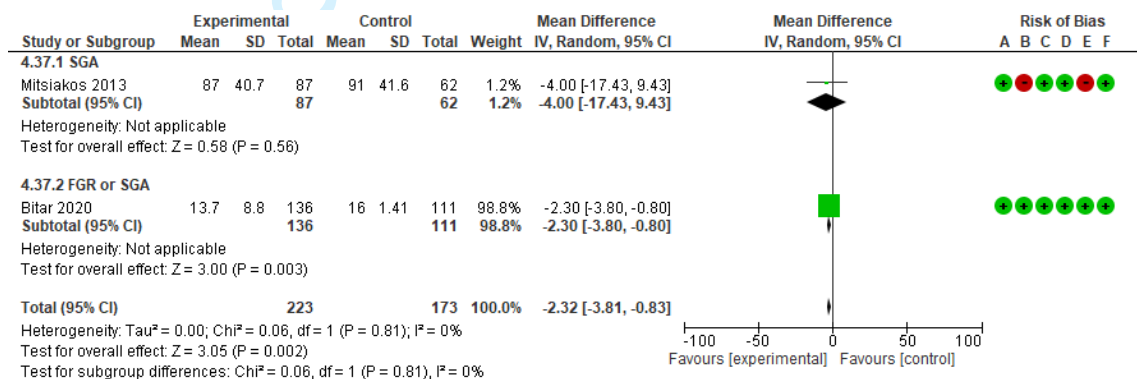


Risk of bias legend

- (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; FGR: Fetus growth restriction; SGA: Small for gestational age

32) Duration of hospital stay

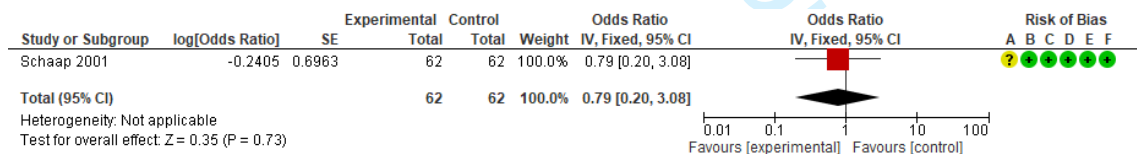


Risk of bias legend

- (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

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

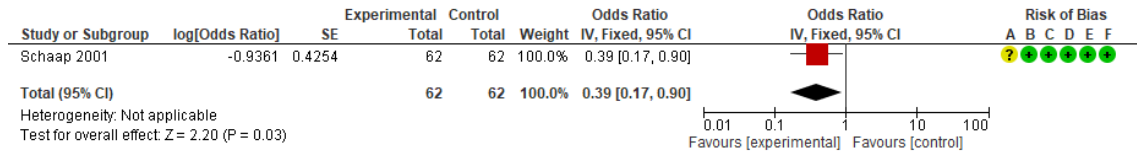


Risk of bias legend

- (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

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

For peer review only

Supplementary table 1: Characteristic 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

Goldenberg 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
Eliimian 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

4			HC: Redline et al. *3
5	Been et al., 2009	HC/ CC	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)
8	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
10	Dempsey et al., 2005	HC	HC: the presence of abundant polymorphonuclear leukocytes in the chorion and amnion
12	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
15	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 amniotic fluid obtained by amniocentesis
17	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

1													
2													
3													
4													
5													
6													
7	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	
8													
9													
10													
11													
12													
13	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	
14													
15													
16													
17													
18	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	
19													
20													
21													
22	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	
23													
24													
25													
26	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	
27													
28													
29													
30													
31	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	
32													
33													
34													
35	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	
36													
37													
38													
39													
40													
41													
42													
43													
44													
45													
46													

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 percetile based on the growth curve of Olsen et al. *1with 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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/>

For peer review only

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

1
2
3
4 Periventricular leukomalacia (PVL)
5
6 Major brain lesion damage
7
8 Necrotizing enterocolitis (NEC)
9
10 Sepsis
11
12 Early onset sepsis
13
14 Systemic inflammatory response syndrome
15
16 Meningitis
17
18 Neonatal hypoglycemia
19
20 Neonatal adrenal insufficiency
21
22 Intrahepatic cholestasis
23
24 Retinopathy of prematurity (ROP)
25
26 Gestational age at birth
27
28 Birth weight
29
30 Neonatal intensive care unit (NICU) admission
31
32 Duration of hospital stay
33
34 Survival free from disability
35
36 Death at long-term follow up
37
38 Death or disability/handicap at 2 years
39
40 Cerebral palsy
41
42 Severe hearing impairment
43
44 Visual impairment
45
46

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 \geq 90mmHg measured at least twice and proteinuria \geq 0.3g/24g.
Hypertensive disorders	P2 Kirshenbaum 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.

	<u>P4</u>
	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	<u>P1</u> Battarbee et al. (2020): Death within 48h after birth.
---------------------------------------	--

Death before discharge home	<u>P3</u> Foix-L’Helias et al. (2005): Death before discharge home.
	<u>P4</u> 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	<u>P2</u> Kishenbaum et al. (2018): Apgar score ≤7 at 5 min after birth.
-------------------------------------	--

Apgar score <7 at 5min after birth	<u>P1</u> Krispin et al. (2018): Apgar score <7 at 5 min after birth.
	<u>P3</u> Elimian et al. (2000): Apgar score <7 at 5 min after birth.
	<u>P4</u> 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	<u>P4</u> 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)	<u>P1</u> Battarbee et al. (2020). Defined as a clinical diagnosis of respiratory distress syndrome, hyaline
-------------------------------------	--

membrane disease, or respiratory insufficiency requiring oxygen therapy with $FiO_2 \geq 0.40$ 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 as 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'Heliass 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 findings.

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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

1
2
3 $\geq 30\%$.

4 van Stralen et al. (2009): Based on radiological criteria (poor lung expansion) and clinical criterial (need
5 for supplemental oxygen, sternal retraction, intercostal and subcostal recession, grunting and tachypnea).

6 Torrance et al. (2007): Defined as clinical signs of RDS with oxygen requirement and typical findings
7 on a chest X-ray.

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

9 Schaap et al. (2001): Defined as tachypnea, chest wall retractions, and oxygen requirement in the
10 presence of a chest X-ray classified as RDS.

11 Bernstein et al. (2000): Required both a PaO₂ <50mmHg in room air plus central cyanosis in room air or
12 a requirement for supplemental oxygen to maintain a PaO₂ >50mmHg.

13 Elimian et al. (1999): Diagnosed clinically and by the need for mechanical ventilation and oxygen for a
14 least 48 hors and the presence of radiologic chest findings.

15 Ley et al. (1997): No data.

16 Spinillo et al. (1995): Diagnosed with physical signs of respiratory distress (grunting, chest retraction,
17 tachypnea) and required ventilatory support for >48hr and radiologic chest findings.

18 Di Lenardo et al. (1990): Based on the basis of radiological indications and worsening of the symptoms
19 from a clinical point of view.

20
21
22 **Bronchopulmonary dysplasia (BPD)/**
23 **Chronic lung disease (CLD)**

24 **P3**

25 Ryu et al. (2019): Listed in the online supplementary Table1.*¹

26 Ahn et al. (2012): Based on National Institute of Child and Human Development criteria.*⁴

27 Been et al. (2009): Diagnosed with a dependency on oxygen supplementation at a postmenstrual age of
28 36 weeks.

29 Goldenberg et al. (2006): Defined as infant oxygen requirement at 28 days or oxygen requirement at 36
30 weeks of life.

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

32 **P4**

33 Kim YJ et al. (2018): No data.

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

35 Feng et al. (2017): No data.

36 Riskin-Mashiah et al. (2016): Diagnosed according to the criteria of Bancalari et al.*⁵ including clinical
37 and radiologic features. Together with the requirement for oxygen supplementation at 36 weeks post
38 menstrual age.

39 Ishikawa et al. (2015): Defined when an infant continued to receive supplemental oxygen on the 28th day
40 after birth and at the 36th week based on postmenstrual age.

41 Mitsiakos et al. (2013): Based on oxygen supplementation at 36 weeks postmenstrual age.

42 van Stralen et al. (2009): No data.
43 For peer review only: <http://www.bmj.com/site/about/guidelines.xhtml>

44
45
46

	<p>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.</p> <p>Foix-L'Helias et al. (2005): No data.</p> <p>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.</p>
Pneumonia	<p>P3</p> <p>Dempsey et al. (2005): Defined by a combination of X-ray changes, endotracheal tube aspirates, and positive inflammatory markers.</p>
Use of mechanical ventilation	<p>P3</p> <p>Been et al. (2009): No data.</p> <p>P4</p> <p>Bitar et al. (2020): No data.</p> <p>Cartwright et al. (2019): No data.</p> <p>Kim et al. (2018): Mechanical ventilation within 48 hours after birth.</p> <p>van Stralen et al. (2009): No data.</p> <p>Torrance et al. (2007): No data.</p> <p>Schaap et al. (2001): No data.</p>
Surfactant use	<p>P3</p> <p>Ryu et al. (2019): Listed in the online supplementary Table1.*1</p> <p>Been et al. (2009): No data.</p> <p>Elimian et al. (2000): No data.</p> <p>P4</p> <p>Bitar et al. (2020): No data.</p> <p>Cartwright et al. (2019): No data.</p> <p>Kim YJ et al. (2018): Defined as the administration of any prophylactic or rescue surfactant.</p> <p>van Stralen et al. (2009): No data.</p> <p>Torrance et al. (2007): No data.</p> <p>Elimian et al. (1999): No data.</p>
Oxygen therapy	<p>P4</p> <p>Bitar et al. (2020): No data.</p> <p>Cartwright et al. (2019): No data.</p>
Oxygen requirement for at least 4 h	<p>P2</p> <p>Kishenbaum et al. (2018): Oxygen requirement for at least 4 hours.</p>

1		
2		
3	Mean duration of mechanical ventilations	P2
4		de la Huerga Lopez et al. (2019): No data.
5		P3
6		Ahn et al. (2012): No data.
7		
8	Duration of oxygen use	P3
9		Ahn et al. (2012): No data.
10		
11	Patent ductus arteriosus (PDA)	P3
12		Ryu et al. (2019): Listed in the online supplementary Table1.*1
13		Ahn et al. (2012): Diagnosed by echocardiography and medical treatment or surgical ligation were performed when necessary.
14		Been et al. (2009): Persistence of the open ductus arteriosus postnatally, as demonstrated by ultrasonographic examination.
15		Elimian et al. (2000): Required medical or surgical intervention.
16		P4
17		Kim YJ et al. (2018): No data.
18		Feng et al. (2019): No data.
19		Ishikawa et al. (2015): Diagnosed based on both echocardiographic findings and clinical evidence of a volume overload due to a left-to-right shunt.
20		Mitsiakos et al. (2013): No data.
21		van Stralen et al. (2009): No data.
22		Elimian et al. (1999): No data.
23		
24	Hypotension within 7 postnatal days	P3
25		Ryu et al. (2019): Listed in the online supplementary Table1.*1
26		
27	Hypotension	P4
28		van Stralen et al. (2009): Defined as a mean arterial pressure ≤ 30 mmHg requiring treatment with volume expanders and/or inotropic support.
29		
30		
31	Intraventricular hemorrhage (IVH)	P2
32		Kishenbaum et al. (2018): No data.
33		P3
34		Ryu et al. (2019): Defined as grade ≥ 3 and listed in the online supplementary Table1.*1
35		Ahn et al. (2012): Defined according to the IVH grading by Papile et al.*6
36		Been et al. (2009): Defined according to Volpe.*7
37		Goldenberg et al. (2006): Defined as grade 3 or 4 by ultrasound criteria.*7
38		For Dempsey (2005): Graded according to the Papile classification.*6
39		Baud et al. (2000): Defined as grade 3 or 4 of Papile classification.*6
40		
41		
42		
43		
44		
45		
46		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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.
For more review (2000): <http://bmjopen.bmj.com/lookup/abstract/guidelines.xhtml>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 \geq 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 \geq 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 \(SDG 3.2.2\) \(who.int\)](https://www.who.int/indicators/mortality-rates/neonatal-mortality-rate).

*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.

- 1
2
3 *7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
4 *8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg.
5 1978;187(1):1-7. doi:10.1097/0000658-197801000-00001.
6 *9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol.
7 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
8 *10. Frederiks AM, Nederlandse groeidoagrammen 1997 in historisch perspectief. In: Wit JM, ed. De Vierde Landelijke Groeistudie 1997. Presentatie
9 nieuwe groeidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
10 *11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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	(MH "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

1 **Supplementary table 5: Risk of bias**

2
3 **Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes**

4
5
6 ***Risk of bias assessments (RoBANS)***

7
8

Study ID	Seque nce genera tion	Allocat ion concea lment	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	-

9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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	<p>Low</p> <p>All participants from a single, university-affiliated, tertiary medical center had GDM and delivered after 34 weeks of gestation between 2012 and 2016.</p>	<p>Low</p> <p>No differences in maternal age, gravidity, body mass index, and hypertensive disorders were confirmed between the exposed and unexposed groups.</p> <p>Women treated with corticosteroids had higher rates of nulliparity than women who were not treated (55% vs. 34%, respectively, p = 0.001).</p> <p>Multivariate analysis adjusting for gravity, parity, primiparity, hypertensive disorders, BMI, birth weight and gestational age at delivery was conducted in adverse composite neonatal outcome.</p>	<p>Low</p> <p>Data obtained from a comprehensive computerized perinatal database</p>	<p>Low</p> <p>No statement to indicate that blinding was performed, but unlikely to affect outcome measurements</p>	<p>Low</p> <p>No missing data</p>	<p>Low</p> <p>All predefined outcomes reported</p>	-

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	Seque nce genera tion	Allocat ion concea lment	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	<p>Low</p> <p>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).</p> <p>Cases and controls were selected from same pool (e.g., same gestational age, same birth weight).</p>	<p>Low</p> <p>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.</p>	<p>Low</p> <p>Data was obtained from an electronic database.</p>	<p>Low</p> <p>No statement to indicate that blinding was performed, but unlikely to affect outcome measurements.</p>	<p>Low</p> <p>No loss to follow-up</p>	<p>Low</p> <p>All predefined outcomes reported.</p>	-

Study ID	Sequencing 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 (\geq 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

Table with columns: Certainty assessment (No of studies, Study design, Risk of bias, Inconsistency, Indirectness, Imprecision, Other considerations), No of patients (women with PGDM, placebo), Effect (Relative (95% CI), Absolute (95% CI)), Certainty, Importance. Rows include: Caesarean section, Neonatal death within 48 hours of birth, Apgar score <seven at 5 minutes, Respiratory distress syndrome (RDS) and moderate/severe RDS, Neonatal hypoglycemia, Admission to neonatal intensive care unit.

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.

For peer review only

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 ^{ab}	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 ^{ab}	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 ^{ab}	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 ^{ab}	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 ^{ab}	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 ^{ab}	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 ^{ab}	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 \geq 60%).

For peer review only

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 ^a	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 intraventricular 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)		
Appgar 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

- 1
- 2
- 3 a. Evidence based on high missing data,
- 4 b. Estimate based on wide confidence interval crossing the line of no effect.
- 5 c. Estimate based on small sample size.
- 6 d. Heterogeneity is high (I-square=>60%).
- 7 e. Evidence based on studies with design limitations, including lack of adjustment for potential confounding factors.
- 8 f. Raw data unavailable for one of the included studies (only ORs and 95% CIs reported).
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

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).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

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 intraventricular 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	

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).

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

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

3 **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).

For peer review only

1
2
3
4
5
6 1 **ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF**
7 2 **PRETERM BIRTH: A SYSTEMATIC REVIEW**
8
9 3

10 4 Kana Saito^a, Etsuko Nishimura^b, Erika Ota^{b,c}, Fumihiko Namba^a, Toshiyuki Swa^d,
11 5 Jenny Ramson^e, Tina Lavin^f, Jenny Cao^e, Joshua P. Vogel^e
12 6

13 7
14 7 **Affiliations**

15 8 ^a Saitama Medical Center, Saitama Medical University, Saitama, Japan

16 9 ^b St. Luke's International University, Tokyo, Japan

17 10 ^c Tokyo Foundation for Policy Research, Tokyo, Japan

18 11 ^d Osaka University, Graduate School of Medicine, Osaka, Japan

19 12 ^e Maternal, Child, and Adolescent Health Program, Burnet Institute, Melbourne,
20 13 Australia

21 14 ^f UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research,
22 15 Development and Research Training in Human Reproduction, Department of Sexual
23 16 and Reproductive Health and Research, World Health Organization, Geneva,
24 17 Switzerland.
25 18

26 19 **Correspondence to:** Kana Saito

27 20 Department of Pediatrics, Saitama Medical Center, Saitama Medical University

28 21 1981 Kamoda, Kawagoe-city, Saitama 350-8550, Japan,

29 22 Phone: 81-49-228-3400

30 23 E-mail: kana988@live.jp

31 24 ORCID: 0000-0001-7781-1870
32 25

33 26 **Word count:** ~~3796~~ **4089** words
34 27

35 28 **Short title:** Systematic review: antenatal steroids in specific women
36 29
37 30
38 31
39 32
40 33
41 34
42 35
43 36
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

37 **ABSTRACT**

38
39 **Objective:** ~~Synthesize~~ **This study aimed to synthesize** available evidence on **the**
40 **efficacy of antenatal corticosteroid** (ACS ~~effectiveness~~) **therapy** among women at
41 risk of imminent preterm birth with pregestational/gestational diabetes,
42 chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in
43 the late preterm period.

44
45 **Methods:** A **systematic** search of MEDLINE, EMBASE, CINAHL, Cochrane Library,
46 Web of Science, **and** Global Index Medicus was conducted for all comparative
47 randomized or non-randomized interventional studies in the four subpopulations. ~~Data~~
48 **The authors** extracted ~~independently by authors~~ **data individually**. Risk of Bias
49 Assessment tool for Non-randomized Studies (RoBANS) was used to assess **the risk of**
50 **bias** in non-randomized studies. Grading of Recommendations, Assessment,
51 Development, and Evaluations (GRADE) tool was used to assess the certainty of
52 evidence.

53
54 **Results:** ~~Twenty-three~~ **Thirty-one studies involving 5018 pregnant women and**
55 **10819 neonates** ~~18003 pregnant women/neonates~~ were included. All **the** included
56 articles were observational studies **in high-income countries**. Data on women with
57 diabetes were limited, and evidence on women undergoing planned CS was
58 inconclusive. ACS **use** was associated with possibly reduced odds of ~~neonatal mortality~~
59 ~~(pooled OR: 0.49; 95%CI: 0.33–0.74, low certainty)~~, severe intraventricular
60 hemorrhage (IVH) (pooled OR: 0.41; 95%CI: **0.190.23–0.870.72**, low **certainty**), and
61 IVH (pooled OR: 0.41; 95%CI: **0.230.19–0.720.87**, low **certainty**) in women with
62 histological chorioamnionitis. Among women with FGR, **the rates of** surfactant use
63 (pooled OR: 0.38; 95%CI: 0.23–0.62, moderate **certainty**), mechanical ventilation
64 (pooled OR: 0.42; 95%CI: 0.26–0.66, moderate **certainty**), and oxygen therapy (pooled
65 OR: 0.48; 95%CI: 0.30–0.77, moderate **certainty**) were probably reduced, ~~but~~
66 **however, the rate of** hypoglycemia probably increased (pooled OR: 2.06; 95%CI:
67 1.27–3.32, moderate **certainty**). Definitional differences for **in** populations and
68 outcomes complicated meta-analyses. ~~Most studies were conducted in high-income~~
69 ~~countries.~~

70
71 **Conclusions:** Evidence ~~There is lacking~~ **a paucity of evidence** for women with **who**
72 **have** diabetes or **are** undergoing planned CS. ACS ~~might~~ **therapy may** have benefits in

1
2
3
4
5
6 73 women with chorioamnionitis. ~~ACS~~ **and** is probably beneficial in FGR ~~but;~~ **however,**
7 74 **it** can increase neonatal hypoglycemia. Well-designed studies with adequate follow-up
8
9 75 are required.

10 76

11 77 **Protocol registration:**

12
13 78 PROSPERO (CRD42021267816; Supplementary File S1)

14
15 79

16 80 **Strengths and limitations of this study:**

17 81 -This review included a broad search strategy.

18 82 -This review applied rigorous quality assessment and GRADE methodology.

19 83 **-All included studies were observational studies.**

20 84 -Definitional differences for population **between populations** and outcomes
21 85 complicated **the** meta-analysis.

22 86 -Most studies were conducted in high-income countries.

23
24 87

25
26 88

27
28
29
30 89 **INTRODUCTION**

31
32
33 90 Antenatal **Previous studies demonstrated that antenatal** corticosteroids (ACS), such

34
35
36 91 as intramuscular dexamethasone or betamethasone, ~~have been shown to cross the~~

37
38
39 92 placenta and can induce fetal lung maturation (1). When ACS is administered to women

40
41
42 93 at risk of imminent preterm birth ~~prior to~~ **before** 34 weeks' gestation, the risk of

43
44
45 94 perinatal death, neonatal death, and respiratory distress syndrome (RDS) is significantly

46
47
48 95 reduced (2). ACS **therapy** also probably decreases the risk of intraventricular

49
50
51 96 hemorrhage (IVH) and reduces **the rate of** developmental delay in childhood (2).

52
53
54 97 **Therefore,** As a result, the World Health Organization (WHO) and several

55
56
57 98 **international** obstetric and gynecological societies ~~internationally~~ recommend ACS

1
2
3
4
5
6 99 therapy in women **before or** up to 34 weeks' gestation for improving preterm
7
8
9 100 **newborns'** outcomes (3-6). Some national organizations have recommended the **ACS**
10
11
12 101 use of ACS in women at risk of preterm birth up to 36 weeks' gestation **based** on the
13
14
15 102 ~~basis of the evidence that there may be some~~ **of the existence of possible** respiratory-
16
17
18 103 related benefits for the newborn (3,5).
19
20
21 104 However, the **current** evidence regarding **the** benefits and possible harms of ACS use
22
23
24 105 in subpopulations of women with specific complications of pregnancy, such as women
25
26
27 106 with diabetes, chorioamnionitis, or babies fetal growth restriction (FGR), is more
28
29
30 107 controversial. Women with diabetes, chorioamnionitis, or babies with FGR are at **a**
31
32
33 108 higher risk of adverse perinatal outcomes, ~~but;~~ **however,** they are generally excluded
34
35
36 109 from ACS efficacy trials (2). Consequently, any subgroup **analysis** to explore the
37
38
39 110 effects of ACS ~~in~~ **on** women with these complications is unlikely to provide direct **yield**
40
41
42 111 **concrete** evidence from which conclusions can be drawn.
43
44
45 112 While pregnant women with diabetes are at a higher risk of spontaneous preterm birth
46
47
48 113 and may require ACS, glucocorticoids have hyperglycemic effects, **and** respiratory
49
50
51 114 morbidities that affect preterm infants may be exacerbated in the setting of poor
52
53
54 115 maternal **glycemic** control (7) (8) . Chorioamnionitis **is** ~~(acute inflammation of the~~
55
56
57 116 ~~membranes and chorion of the placenta)~~ is estimated to affect 3.9% of women giving
58
59
60

1
2
3
4
5
6 117 birth, ~~and causing 22.6–36.9% of total stillbirths (9-11)~~. Chorioamnionitis treatment
7
8
9 118 involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided
10
11
12 119 due to concerns that its immunosuppressive effects may worsen outcomes for ~~the~~
13
14
15 120 ~~woman~~ women and ~~her baby~~ their babies. However, the relative benefits and harms of
16
17
18 121 using ACS in ~~this clinical~~ settings are unclear. FGR is associated with an increased
19
20
21 122 risk of morbidity and mortality (12-15). Small for gestational age (SGA) status
22
23
24 123 does not accurately represent FGR as SGA neonates include constitutionally small
25
26
27 124 ones (16). In most cases, FGR fetuses are delivered as SGA neonates (17). In this
28
29
30 125 study, we targeted pregnant women with both FGR fetuses and SGA neonates. ~~In~~
31
32
33 126 many high-income countries, small for gestational age (SGA) neonates account for
34
35
36 127 approximately 10% of all babies; this proportion is generally higher in low-to-middle-
37
38
39 128 income countries.¹¹⁻¹³ SGA is associated with an increased risk of neonatal morbidity-
40
41
42 129 and mortality than those babies born appropriate for gestational age (AGA).^{14,15} The
43
44
45 130 term SGA is often used as a proxy measure for FGR because most cases of SGA are
46
47
48 131 caused by FGR.¹⁶ Clarifying ACS effects in women at risk of imminent preterm birth-
49
50
51 132 with growth-restricted fetuses is necessary.
52
53
54 133 One additional clinical scenario with where there is uncertainty regarding ACS efficacy
55
56
57 134 is ~~in~~ women undergoing elective Caesarean section (CS) in the late preterm period (i.e.,
58
59
60

1
2
3
4
5
6 135 34 to <37 weeks' gestation). Babies born in **the** late preterm **period** have lower risks of
7
8
9 136 mortality and morbidity ~~compared with~~ **than** those born ~~prior to~~ **before** 34 weeks'
10
11
12 137 gestation; however, they have higher risks of adverse outcomes than ~~babies~~ **those** born
13
14
15 138 at term (18-21). In many countries, the **rising** rate of provider-initiated late preterm
16
17
18 139 birth is ~~rising, which has been linked to the more generalised~~ **generalized** increase in
19
20
21 140 **the** CS use **rate (22)**. Regardless of **the** gestational age, babies born via elective CS do
22
23
24 141 not have the usual physical and hormonal stimuli of passage through the birth canal;
25
26
27 142 thus, they tend to have higher rates of respiratory morbidity (23-25). Some studies have
28
29
30 143 suggested that the risk of neonatal **hypoglycemia** is greater following CS ~~although~~;
31
32
33 144 **however**, this may be confounded by the underlying indication for CS (26).
34
35
36 145 In 2016, members of our team published a systematic review ~~to~~ **assessing** the
37
38
39 146 effectiveness of ACS **therapy** in these four clinical situations (27). ~~No~~ ~~The review did~~
40
41
42 147 ~~not find any~~ direct evidence ~~on~~ **of** the effects of ACS ~~in~~ **therapy on** pregnant women
43
44
45 148 with diabetes **who were** at risk of preterm birth or for those undergoing elective CS in
46
47
48 149 the late preterm period **was found**. The review could not draw firm conclusions
49
50
51 150 regarding the effects of ACS ~~in~~ **on** women with growth-restricted fetuses, although low-
52
53
54 151 quality evidence suggested that ACS reduces neonatal IVH in women with
55
56
57 152 chorioamnionitis (27). **The review's findings** ~~of the previous review~~ informed WHO's
58
59
60

1
2
3
4
5
6 153 2015 ACS recommendations (28). ACS recommendation are currently being
7
8
9 154 updated as part of the WHO's living guidelines in maternal and perinatal health
10
11
12 155 programs, the ACS recommendations are currently being updated-(29). Hence, Our
13
14
15 156 aim is to update the 2016 systematic review and provide a contemporary evidence base
16
17
18 157 for researchers, clinicians, and maternal and newborn health stakeholders on safe, ~~and~~
19
20
21 158 effective clinical management in preterm birth.
22
23

159

160 **METHODS**

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

1
2
3
4
5
6
7 171 Analyses (PRISMA) checklist (**Supplementary file 1, Supplementary table 2**) (30).
8

9
10 172

11 173 Box 1. Four Participant, Intervention, Comparison, **and** Outcome (PICO) questions for
12
13 174 **the a** systematic review

14 **P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes**

15 P: Women at risk of imminent preterm birth **less than 37 weeks** with pregestational diabetes mellitus
16 and/or gestational diabetes mellitus

17 I: ACS administration

18 C: Placebo or no treatment

19 O: World Health Organization (WHO) priority outcomes for preterm birth

20
21
22 **P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period**

23 P: Women undergoing elective CS in the late preterm period **between 34 weeks and 0 days and 36 weeks and 6 days**

24 I: ACS administration

25 C: Placebo or no treatment

26 O: WHO priority outcomes for preterm birth

27
28
29 **P3: Effects of ACS therapy on women with chorioamnionitis**

30 P: Women at risk of imminent preterm birth **less than 37 weeks** with chorioamnionitis

31 I: ACS administration

32 C: Placebo or no treatment

33 O: WHO priority outcomes for preterm birth

34
35 **P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants**

36 P: Women at risk of imminent preterm birth **less than 37 weeks** with growth-restricted fetuses and/or
37 small-for-gestational-age infants

38 I: ACS administration

39 C: Placebo or no treatment

40 O: WHO priority outcomes for preterm birth
41

42
43 175

44
45 176 **Study eligibility criteria**

46
47
48 177 Eligible studies were randomized or **non-randomized** primary research studies that

49
50
51 178 reported on the effects of ACS **therapy** in the four subpopulations. This included

52
53
54 179 published, unpublished, and ongoing randomized or quasi-randomized controlled trials,

55
56
57 180 controlled before-after studies, interrupted-time-series studies, historically controlled
58
59
60

1
2
3
4
5
6 181 studies, cohort studies, and cross-sectional studies comparing any ACS ~~administration~~
7
8
9 182 (betamethasone, dexamethasone, or hydrocortisone) ~~given~~ **administered** either
10
11
12 183 parentally or enterally with placebo or no treatment. Study populations of interest were
13
14
15 184 women at risk of imminent preterm birth or provider-initiated preterm birth and where
16
17
18 185 the study population fulfilled one or more of the following conditions: women with
19
20
21 186 pregestational and/or gestational diabetes, women undergoing elective CS in the late
22
23
24 187 preterm period, women with chorioamnionitis, and women with a FGR **fetuses** or SGA
25
26
27 188 **infants**.

28
29
30 189 Articles in any language and from any country were eligible for inclusion if they
31
32
33 190 reported on one or more of ~~the review outcomes of interest that reflected~~ WHO's
34
35
36 191 priority outcomes for preterm birth guideline development (28). Maternal outcomes
37
38
39 192 were death, maternal morbidity, and ~~side effects of therapy~~ **side effects**. Newborn and
40
41
42 193 child outcomes of interest were perinatal mortality, fetal mortality, neonatal mortality,
43
44
45 194 neonatal morbidity, neurodevelopment, anthropometric status, and ~~side effects of~~
46
47
48 195 therapy **side effects (Supplementary table 3)**.

49
50
51 196

52 53 54 197 **Data sources and search strategy**

55
56
57 198 An information specialist was consulted for developing **the development of** the search
58
59
60

1
2
3
4
5
6 199 strategy. A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library,
7
8
9 200 Web of Science, and Global Index Medicus was conducted with no date restrictions on
10
11
12 201 June 6, 2021. Controlled vocabularies supplemented with free keywords were used to
13
14
15 202 search for the relevant concept areas, with duplicates removed in the process to yield a
16
17
18 203 total number of abstracts for each database . Reference lists of the included articles,
19
20
21 204 including any recent systematic reviews, were also hand-searched for further potentially
22
23
24 205 relevant studies. All citations were imported into a Rayyan (<http://rayyan.qcri.org>)
25
26
27 206 library for eligibility assessment.
28
29

30
31 207

32 33 208 **Study selection, data extraction, and quality assessment**

34
35
36 209 Two reviewers (KS, EN) independently assessed the titles and abstracts of identified
37
38
39 210 citations for eligibility. Any disagreement resulted in automatic inclusion into the next
40
41
42 211 level of screening. Subsequently, full-text publications of potentially eligible studies
43
44
45 212 were obtained and assessed in duplicate by two reviewers working independently, with
46
47
48 213 disagreements resolved through discussions or by consulting a third reviewer. The two
49
50
51 214 reviewers also independently extracted baseline and outcome data and assessed the
52
53
54 215 quality, with these data compared and any discrepancies resolved through discussions
55
56
57 216 or by consulting a third reviewer. Extracted data were entered into the Review Manager
58
59
60

1
2
3
4
5
6 217 version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study
7
8
9 218 quality, observational studies were assessed using the Risk of Bias Assessment tool for
10
11
12 219 Non-randomized Studies (RoBANS) (31). If we identified any randomized trials, we
13
14
15 220 planned to use the Cochrane Risk of Bias tool (32). ~~We planned to assess for~~ Potential
16
17
18 221 publication bias ~~was through visual inspection~~ inspected visually using of funnel plots
19
20
21 222 for asymmetry in situations where data for a single outcome were available from ~~10 or~~
22
23
24 223 ~~more~~ at least ten studies.
25
26

27
28
29
30 224

31 **Data synthesis and analysis**

32
33 226 Aggregate odds ratios (ORs) and relative risks (~~RRs~~) with 95% confidence intervals
34
35
36 227 (CIs) were determined for dichotomous data using the Mantel–Haenszel analysis
37
38
39 228 (fixed-effects model). Where between-study clinical or methodological heterogeneity
40
41
42 229 undermined the compatibility of the quantitative results, or if substantial statistical
43
44
45 230 heterogeneity was detected, the random-effects meta-analysis was used. Data were
46
47
48 231 pooled using ORs when the numbers of events were available and using logarithms of
49
50
51 232 the ORs weighted by the inverse variance when events were not available. For
52
53
54 233 continuous data, mean differences (MDs) with 95% CIs were used. Statistical
55
56
57 234 heterogeneity was determined for each meta-analysis using I^2 and Chi^2 statistics.
58
59
60

1
2
3
4
5
6 235 Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$ in the Chi²
7
8
9 236 test for heterogeneity. For the analysis ~~on~~ **of** women with FGR fetuses and/or SGA
10
11
12 237 babies, we reported results for three subpopulations (SGA only, FGR only, **and** SGA **or**
13
14
15 238 FGR). Data from the three populations were combined, and pooled ORs were calculated
16
17
18 239 if the heterogeneity for that outcome was less than 60%.

20
21 240 All statistical analyses were performed using RevMan5. ~~Statistical~~ **The threshold for**
22
23
24 241 **statistical** significance was set at an alpha level of 0.05 for all analyses. Evidence
25
26
27 242 profiles were prepared for each research question using GRADEpro
28
29
30 243 (<https://gradepr.org/>). Grading of Recommendations Assessment, Development, and
31
32
33 244 Evaluation (GRADE) ~~is~~, an approach for grading the certainty of evidence in
34
35
36 245 systematic reviews and clinical practice guidelines ~~and~~, was used in this review.
37
38

39 246

42 247 **Patients and public involvement**

43
44
45 248 As **Since** this ~~paper~~ is a systematic review of previously published data, there was no
46
47
48 249 direct involvement ~~from~~ **of** patients or the public.
49

50
51 250

54 251 **RESULTS**

55
56
57 252 **Effects of ACS in therapy on women with pregestational and/or gestational**
58
59
60

253 **diabetes mellitus**

254 The search identified 179 citations; ~~from which~~ 11 potentially eligible studies were
255 evaluated, and **three** ~~five~~ studies met the eligibility criteria, providing data for **on 725**
256 ~~8,067~~ pregnant women **and 830** neonates (**Supplementary file 2** Figure 1) (33) (34)
257 (35). All studies were conducted in high-income countries and ~~collected data~~ **collection**
258 **was performed** between 2006~~8~~ and 2017(**Supplementary table 1**). One study involved
259 women with pregestational diabetes only, ~~two~~ **one study** involved women with
260 gestational diabetes only, and ~~two~~ **one study** involved women with either pregestational
261 or gestational diabetes. ~~Three~~ **Two** studies used betamethasone only, ~~one study used~~
262 dexamethasone or betamethasone, and in one study, the corticosteroid used was not
263 specified. All included studies were judged as **having a** low risk of bias across all
264 domains, ~~except for~~ ~~the two studies~~ ~~that were~~ judged as **having a** high risk of selection-
265 bias (**Supplementary file 3, Supplementary table 5** Figure 2; Supplementary File S6).
266 Data were available for ~~5~~ **six** outcomes (Table 1; Supplementary File S7). One
267 retrospective cohort study found that in women with gestational diabetes, the likelihood
268 of neonatal intensive care unit (NICU) admission is possibly increased (~~1~~ **one** study,
269 **161**~~2262~~ infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty evidence*) (33); however,
270 the effect of ACS **therapy** on neonatal hypoglycemia was uncertain (~~3~~ **two** studies,

271 **2152376** infants; pooled OR: **1.44**; 95%CI: **0.70–2.97**, *very-low-certainty evidence*)

272 **(33)**. **The certainty** of evidence was also very low for other outcomes; hence, no

273 meaningful conclusions could be drawn (Supplementary File S8).

274

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

Neonatal outcomes	No of studies	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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)	207 more 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

276 *ACS: Antenatal corticosteroid, CI: Confidence interval, NICU: Neonatal intensive care unit, OR: Odds ratio, RDS:

277 Respiratory distress syndrome. *There was no maternal outcome.

278

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

280 **period**

281 The search identified 211 citations; ~~from which~~ 17 potentially eligible studies were

282 evaluated, and two studies were included (**Supplementary file 2** ~~Figure 23~~) (36,37).

283 **The two studies** were observational studies (~~one case-control, one retrospective cohort~~)

284 conducted in high-income countries between 2011 and 2017, providing data for **on** 205

285 pregnant women/neonates (**Supplementary table 1**). ~~In both studies, betamethasone~~

286 ~~was used. The case-control study was judged as having a low risk of bias for all~~

287 domains (Figure 4; Supplementary File S6). The two studies were retrospective cohort
 288 study was judged as **having a** high risk of bias for the selection of participants and
 289 confounding variables (**Supplementary file 3, Supplementary table 5**). Data for ~~10~~ **on**
 290 **eleven** outcomes were available; however, **but** all had very low certainty; so, no
 291 meaningful conclusions could be drawn (Table 2; Supplementary Files S7 **and** S8).

292

293 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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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

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

296

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

298 The search identified 418 citations; ~~from which~~ 12 potentially eligible studies were
 299 evaluated, and eight studies met the eligibility criteria **were found to be eligible**

300 (**Supplementary file 2 Figure 35**) (38) (39) (40) (41) (42) (43) (44) (45). Two were

1
2
3
4
5
6
7 301 prospective cohort studies and six were retrospective cohorts, providing data on 1460
8
9 302 1372 pregnant women/ and 1460 neonates (Supplementary table 1) (~~Supplementary~~
10
11
12 303 table 1 File S5). Four studies included pregnant women with clinical
13
14
15 304 chorioamnionitis, and variation there were variations in the diagnostic criteria
16
17
18 305 (Supplementary table 1). All studies were conducted in high-income countries, ~~and~~
19
20
21 306 women were enrolled women between 1989 and 2014. One study evaluated
22
23
24 307 dexamethasone, four studies evaluated betamethasone, and three studies evaluated
25
26
27 308 either betamethasone or dexamethasone. Additional unpublished crude data from the
28
29
30 309 four included studies were extracted from a previous meta-analysis identified through
31
32
33 310 the search process (38) (41) (42) (43) (46). All included studies were judged as having
34
35
36 311 a low risk of bias overall, although six studies were judged as having a high risk of bias
37
38
39 312 for the domain regarding confounding variables as adjusted analyses were not reported
40
41
42 313 (Supplementary file 3, Supplementary table 5 Figure 6; Supplementary File S6). Data
43
44
45 314 for ~~25~~ 27 outcomes were available, with data reported separately for women with
46
47
48 315 histological chorioamnionitis and women with clinical chorioamnionitis (Table 3;
49
50
51 316 Supplementary file 4 File S7). Amongst women with histological chorioamnionitis, ACS
52
53
54 317 administration was associated with a possible reduction in the odds of severe
55
56
57 318 intraventricular hemorrhage neonatal mortality (six four studies, 528 1193 infants;
58
59
60

319 pooled OR: **0.41** 0.49; 95%CI: **0.19** 0.33–**0.87** 0.74, *low-certainty evidence*), **IVH (five**
 320 **studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, low-certainty evidence)**–
 321 ~~IVH (five studies, 658 infants; pooled OR: 0.41; 95%CI: 0.23–0.72, low-certainty~~
 322 ~~evidence), and severe IVH (four studies, 528 infants; pooled OR: 0.41; 95%CI: 0.19–~~
 323 ~~0.87, low-certainty evidence)~~. ACS might result in no difference in neonatal sepsis;
 324 however, **the** evidence was uncertain (**six** studies, 1193 infants: pooled OR: 1.03;
 325 95%CI: 0.73–1.47, *very-low-certainty evidence*). The certainty of evidence was very
 326 low for other outcomes – (Supplementary **table S9** File S8). In women with clinical
 327 chorioamnionitis, ACS administration was associated with a possible reduction in the
 328 odds of IVH (three studies, 318 infants, pooled OR: 0.39; 95%CI: 0.15–0.99, *low-*
 329 *certainty evidence*), and periventricular leukomalacia (three studies, 318 infants, pooled
 330 OR: 0.30; 95%CI: 0.11–0.86, *low-certainty evidence*)– neonatal sepsis, only very-low-
 331 certainty evidence was available **for neonatal sepsis (two** studies, 150 infants, pooled
 332 OR: **0.71** 0.96; 95%CI: **0.13** 0.40–**2.29** **3.89**). The certainty of evidence was very low for
 333 all other outcomes (**Supplementary table 6**)–(Supplementary **table 6** File S8).

334

335 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		
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)	131 fewer 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

336 *There was no maternal outcome in clinical chorioamnionitis.

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

340

341 **Effects of ACS in therapy on women with growth-restricted fetuses and/or small-**

342 **for-gestational-age infants**

343 The search identified 261 citations; ~~from which~~ 36 potentially eligible studies were

344 assessed, and 18 studies were included (**Supplementary file 2** Figure 47) (41,47-63).

345 Of these, ~~12~~**twelve** studies included women with SGA infants only, ~~4~~**four** studies

346 included women with FGR or SGA infants, and ~~2~~**two** studies included women with

1
2
3
4
5
6 347 FGR infants only (Supplementary table 1)-(Supplementary ~~table 1~~File S5). The five
7
8
9 348 Among the studies that included FGR fetuses, and the definitions of FGR showed a
10
11
12 349 wide variety varied widely. Since SGA status is insufficient to determine FGR, we
13
14
15 350 separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three
16
17
18 351 populations were combined, and the pooled OR in total were was calculated. Data
19
20
21 352 were available from 2714 pregnant women and 8324 neonates enrolled between
22
23
24 353 1984 and 2019. We excluded three studies on maternal outcomes for omitting the
25
26
27 354 number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng
28
29
30 355 et al., 2017 (50,53,58). These studies included multiple gestations; hence, there was
31
32
33 356 the risk of double, triple, or more counts to one maternal outcome event. All were
34
35
36 357 observational studies conducted in high-income countries. Data were available from
37
38
39 358 ~~8271 pregnant women/neonates enrolled between 1984 and 2019.~~ Additional
40
41
42 359 unpublished data from the study by Torrance et al. (2007) were extracted from a review
43
44
45 360 paper published in 2009, which was identified through the search strategy (53,64). Most
46
47
48 361 ~~of the included studies (17 of 18 studies)~~ were judged as having a low risk of bias
49
50
51 362 across all domains. ~~Seven~~ Five studies had were judged as having a high risk of bias
52
53
54 363 for the domain regarding confounding variables. Three ~~Four~~ studies were judged as
55
56
57 364 having a high risk of bias regarding incomplete outcome data (Supplementary file 3,
58
59
60

1
2
3
4
5
6
7 365 **Supplementary table 5** Figure 8; Supplementary File S6). For SGA infants only, 12
8
9 366 studies provided data on ~~3027~~ outcomes (**Supplementary file 4, Supplementary table**
10
11
12 367 **6** Files S7 and S8). **The administration of ACS for women with SGA was associated**
13
14
15 368 **with increasing odds of pregnancy induced hypertension (PIH) chorioamnionitis (2**
16
17
18 369 **studies, 684 women; pooled OR 1.50, 95%CI:1.08–2.07, low-certainty evidence)**The
19
20
21 370 administration of ACS for women with SGA was associated with the increasing odds of
22
23
24 371 pregnancy-induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI:
25
26
27 372 1.08 to 2.07, *low-certainty evidence*) although the odds of neonatal mortality (**eight**
28
29
30 373 studies, ~~2660~~2710 infants; pooled OR: ~~0.68~~0.61; 95%CI: ~~0.47~~0.49–~~0.97~~0.78, *low-*
31
32
33 374 *certainty evidence*) and severe IVH (six studies, 3235 infants; pooled OR: 0.60; 95%CI:
34
35
36 375 0.45–0.80, *low-certainty evidence*) were possibly reduced (Table 4; Supplementary
37
38
39 376 **Files S7 and S8**). Two studies involving FGR infants only provided data for ~~18~~19
40
41
42 377 review outcomes; **the odds of death or disability/handicap at 2 years' corrected age**
43
44
45 378 **(one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17-0.98, low-certainty**
46
47
48 379 **evidence) were possibly reduced (Table 4).** however, all outcomes were assessed as
49
50
51 380 very low-certainty evidence (Supplementary Files S7 and S8). Four studies involved
52
53
54 381 SGA or FGR infants, providing data for ~~25~~24 outcomes (**Supplementary file 4,**
55
56
57 382 **Supplementary table 6**). The administration of ACS for women with SGA or FGR was
58
59
60

1
2
3
4
5
6 383 associated with a possible reduction in the odds of surfactant use (~~3~~**three** studies, 599
7
8
9 384 infants; pooled OR: 0.38; 95%CI: 0.23–0.62, *moderate-certainty evidence*), ~~use of~~
10
11
12 385 mechanical ventilation **use** (~~2~~**two** studies, 508 infants; pooled OR: 0.42; 95%CI: 0.26–
13
14
15 386 0.66, *moderate-certainty evidence*), **and** oxygen use (~~2~~**two** studies, 508 infants; pooled
16
17
18 387 OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*) **although the odds of**
19
20
21 388 **hypoglycemia increased (one study, 247 infants; pooled OR: 2.01; 95%CI: 1.16–**
22
23
24 389 **3.48, low-certainty evidence**), ~~and duration of hospital stay (one study, 247 infants; MD~~
25
26
27 390 ~~=2.3 days, 95%CI: –3.8 –0.8, *low-certainty evidence*) (Table 4; Supplementary **Files**~~
28
29
30 391 **S7 and S8**). Pooled ORs involving women and newborns from all three populations
31
32
33 392 (i.e., FGR only, SGA only, and FGR or SGA combined into SGA and/or FGR) could be
34
35
36 393 determined for ~~20~~**18** outcomes (**Supplementary file 4, Supplementary table 6**). The
37
38
39 394 ~~administration of ACS~~ **administration** for women with SGA and/or FGR was
40
41
42 395 associated with a possible reduction in severe IVH (~~8~~**nine** studies, ~~46363450~~**46363450** infants;
43
44
45 396 pooled OR: ~~0.59~~**0.62**, 95%CI: ~~0.41~~**0.47–0.85**~~0.82~~, *low-certainty evidence*) and in
46
47
48 397 duration of hospital stay (~~2~~**two** studies, 396 infants; MD –2.23 days; 95%CI: –3.81–
49
50
51 398 ~~–0.83, *low-certainty evidence*~~). **However, the odds of PIH (three studies, 775 women;**
52
53
54 399 **pooled OR 1.47, 95%CI: 1.07–2.01, low-certainty evidence**) and neonatal
55
56
57 400 **hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32,**
58
59
60

401 **moderate-certainty evidence** were possibly increased (Table 4, **Supplementary Files**
 402 **S7 and S8**). However, the odds of PIH (3 studies, 775 women; pooled OR 1.47; 95%CI:
 403 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies, 329
 404 infants; pooled OR: 2.06; 95%CI: 1.27–3.32, *moderate-certainty evidence*) were
 405 possibly increased (Table 4; Supplementary Files S7 and S8).

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

Maternal outcomes	No of study	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
Pregnancy induced hypertension						
Total	3	<u>195/453</u> (43.0%)	<u>99/322 (30.7%)</u>	<u>1.47</u> (1.07–2.01)	<u>87 more per 1000 (from 15 more to 164 more)</u>	<u>Low</u>
SGA	2	<u>144/370</u> (38.9%)	<u>94/314 (29.9%)</u>	<u>1.50</u> (1.08–2.07)	<u>91 more per 1000 (from 16 more to 170 more)</u>	<u>Low</u>
Neonatal outcomes						
Neonatal death						
SGA	8	<u>242/1544</u> (15.7%)	<u>196/1116</u> (17.6%)	<u>0.680, 0.61</u> (0.47–0.97) <u>0.49–0.78</u>	<u>490 fewer per 1000 (from 850 fewer to 40 fewer)</u>	Low
Severe IVH						
Total	9	<u>190/3018</u> (6.3%)	<u>171/1618</u> (10.6%)	<u>0.59 (0.41–0.85)</u> 0.62 (0.47–0.82)	<u>4135 fewer per 1000 (from 5949 fewer to 1416 fewer)</u>	Low
SGA	6	<u>143/2196</u> (6.5%)	<u>99/1039 (9.5%)</u>	<u>0.60</u> (0.45–0.80)	<u>36 fewer per 1000 (from 50 fewer to 18 fewer)</u>	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	4	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

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

1
2
3
4
5
6 412 **DISCUSSION**

7
8
9 413 **This systematic review identified 31 observational studies on the benefits and**

10
11
12 414 **drawbacks of using ACS in subgroups of women with specific pregnancy**

13
14
15 415 **complications.** This systematic review identified 33 observational studies pertaining to

16
17
18 416 the benefits and possible harms of using ACS in subgroups of women with specific

19
20
21 417 complications of pregnancy. In women with diabetes and those undergoing elective late

22
23
24 418 preterm CS, the available evidence on **the** effects of ACS **therapy** was largely **very-**

25
26
27 419 **low-certainty; thus,** conclusions could not be drawn. In women with histological and

28
29
30 420 clinical chorioamnionitis, ACS **therapy** was associated with **the** benefits of **IVH**

31
32
33 421 **reduction.** In women with FGR and/or SGA babies, ACS **therapy** possibly has benefits

34
35
36 422 **regarding** neonatal morbidity and mortality, as well as **the** reduced use of respiratory

37
38
39 423 support interventions for the newborn; **however,** neonatal hypoglycemia might be

40
41
42 424 increased.

43
44
45 425

46
47
48 426 **Effects of ACS therapy on women with pregestational and/or gestational diabetes**

49
50
51 427 A clinical concern regarding the ACS use of ACS in women with diabetes is the

52
53
54 428 possibility of steroid-induced insulin resistance and consequent hyperglycemia causing,

55
56
57 429 **which causes** avoidable harm to the neonate. For example, in women with insulin-

1
2
3
4
5
6 430 dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following
7
8
9 431 steroid administration (65). A 2002 Danish study **conducted** on 24 pregnant women
10
11
12 432 with diabetes who received steroids suggested that insulin dose adjustment may be
13
14
15 433 required for up to **five** days after ACS administration (66). However, in the current
16
17
18 434 review, there was insufficient evidence to **assess determine** whether ACS increased
19
20
21 435 neonatal hypoglycemia, respiratory morbidity, or mortality. One retrospective study
22
23
24 436 suggested that ACS use in women with gestational diabetes increases the risk of NICU
25
26
27 437 **admission;** however, the authors noted that **the neonatal** birthweight in the ACS group
28
29
30 438 was significantly lower than that in the unexposed group, which may explain this
31
32
33 439 finding (33). ~~Further~~ **Well**-designed studies are needed **that** ~~on this clinical question and~~
34
35
36 440 ~~would ideally describe any~~ adjustments to maternal diabetic regimens at the time of
37
38
39 441 ACS therapy and **from** the time ~~of from~~ ACS administration to birth and report on
40
41
42 442 important newborn health outcomes.

443

444 **Effects of ACS in therapy on women undergoing elective CS in the late preterm**445 **period**446 **The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a**447 **subgroup analysis on gestational age at trial entry reported findings from seven**

1
2
3
4
5
6 448 trials recruiting women in the late preterm period (2). This subgroup analysis
7
8
9 449 suggested that ACS reduces the rates of neonatal death and RDS in the late
10
11
12 450 preterm period (2). Deshmukh M et al. reported that ACS reduced the need for
13
14
15 451 respiratory support and increased the risk of hypoglycemia with moderate
16
17
18 452 certainty in late preterm (67). However, no subgroup analyses were conducted on
19
20
21 453 CS (67). Hence, these findings cannot be generalized to all women undergoing CS
22
23
24 454 in the late preterm period. The RCT by Gyamfi-Bannerman CEA et al. reported
25
26
27 455 that ACS in the late preterm period reduced the risk of transient tachypnea of the
28
29
30 456 newborn, surfactant use, and BPD (68). Their subgroup analysis of planned CS
31
32
33 457 showed ACS resulted in no significant difference in their primary outcome and
34
35
36 458 severe respiratory complication (68). Their primary outcome was defined as any of
37
38
39 459 the following occurrences within 72 hours after birth: continuous positive airway
40
41
42 460 pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous
43
44
45 461 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for
46
47
48 462 at least four continuous hours, mechanical ventilation, stillbirth, neonatal death, or
49
50
51 463 the need for extracorporeal membrane oxygenation (ECMO) (68). Their severe
52
53
54 464 respiratory complications were defined as any of the following occurrences within
55
56
57 465 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a
58
59
60

1
2
3
4
5
6 466 **fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical**
7
8
9 467 **ventilation, stillbirth, neonatal death, or the need for ECMO (68). Their outcomes**
10
11
12 468 **did not adequately fit our outcomes, and the study was not included in this review.**
13
14

15 469 The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup-
16
17
18 470 analysis on gestational age at trial entry reported on findings from seven trials (4142-
19
20
21 471 women) recruiting women at ≥ 34 weeks 0 days gestation.² This subgroup analysis-
22
23
24 472 suggested that ACS reduces RDS and increases neonatal hypoglycemia when used in-
25
26
27 473 the late preterm period. Two systematic reviews (2018 and 2021) on trials of ACS in the
28
29
30 474 late preterm period drew similar conclusions.^{68,69} However, the CS rate (only reported-
31
32
33 475 in five trials) was less than 30% in four of these trials⁷⁰⁻⁷³; hence, these findings cannot
34
35
36 476 be generalized to all women undergoing CS in the late preterm period. Our review
37
38
39 477 demonstrates **that** there is currently insufficient evidence to draw conclusions on the
40
41
42 478 benefits and possible harms of ACS when used in this subpopulation, although an
43
44
45 479 ongoing randomized trial in New Zealand is assessing the effects of ACS ~~in~~ **therapy on**
46
47
48 480 women with CS planned between 35 weeks 0 days and 39 weeks 6 days (69).
49
50

51 481

52 53 54 482 **Effects of ACS ~~in-on~~ women with chorioamnionitis**

55
56
57 483 Women with chorioamnionitis are typically excluded from ACS efficacy trials due to
58
59
60

1
2
3
4
5
6 484 concerns that **the** prolongation of pregnancy and/or immunosuppression may worsen
7
8
9 485 outcomes for **these** women and **their** newborns. While **Although** ACS appears to be
10
11
12 486 associated with reduced ~~neonatal mortality~~, IVH, and severe IVH **rates** in women with
13
14
15 487 histological chorioamnionitis, there was insufficient evidence ~~for~~ **of** other important
16
17
18 488 infection-related maternal and newborn **neonatal** outcomes **in this review**. While these
19
20
21 489 conclusions are broadly similar to **those of** a 2011 review by Been et al., we do not
22
23
24 490 consider that the available evidence supports the routine use of ACS **therapy** in women
25
26
27 491 with chorioamnionitis, as clinical trials comparing ACS therapy ~~with~~ **to** no ACS
28
29
30 492 **therapy** in this population and reliable evidence ~~for~~ **regarding** infection-related
31
32
33 493 outcomes are still lacking (46). **Significant overlap exists between clinical and**
34
35
36 494 **histological chorioamnionitis (70). Histological chorioamnionitis reflects antenatal**
37
38
39 495 **inflammatory exposure more accurately than clinical chorioamnionitis (71).**
40
41
42 496 **However, since physicians must decide the indications for ACS therapy when**
43
44
45 497 **clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant**
46
47
48 498 **women with clinical chorioamnionitis should be encouraged.** It is unlikely that such
49
50
51 499 trials will be performed, although well-conducted observational studies could provide
52
53
54 500 useful additional evidence.
55
56
57 501

1
2
3
4
5
6 502 **Effects of ACS in therapy on women with growth-restricted fetuses and/or small-**
7
8
9 503 **for-gestational-age infants**
10
11
12 504 The totality of **the** evidence identified in this review suggests that ACS **therapy** should
13
14
15 505 be used in the setting of fetal growth restriction **setting. Although the evidence was**
16
17
18 506 **mainly of low or very low certainty, benefits were observed for several outcomes,**
19
20
21 507 **and no harm was reported.** While the evidence was largely low or very low certainty,
22
23
24 508 ~~benefits were observed for several outcomes (including neonatal death, severe IVH, and~~
25
26
27 509 ~~use of respiratory support interventions) and an absence of harms. The current review~~
28
29
30 510 identified more **substantial** evidence (18 studies) than that identified in our 2016
31
32
33 511 systematic review, ~~(8 **eight** studies) that **which** was unable to draw **solid** conclusions of~~
34
35
36 512 **about** the effects of ACS **therapy** in this subpopulation (27). It is also noteworthy that
37
38
39 513 the largest trial of **on** ACS **therapy** in low-resource countries, the WHO ACTION-I
40
41
42 514 Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity
43
44
45 515 benefits, recruited 189 women with known or suspected fetal growth restriction (72).
46
47
48 516 The current review did not identify **the** benefits for **regarding** the outcome RDS, which
49
50
51 517 might be attributable to a single retrospective cohort study in Japan in which neonates in
52
53
54 518 the ACS group were delivered significantly earlier than those in the control group (56).
55
56
57 519 A sensitivity analysis in which we excluded this study **suggested** that RDS is
58
59
60

1
2
3
4
5
6 520 significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS
7
8
9 521 increases **the rate of** neonatal hypoglycemia in this subpopulation, which warrants
10
11
12 522 further exploration in future research. **In this meta-analysis, only two studies targeted**
13
14
15 523 **pregnant women with FGR. Since the SGA status does not accurately represent**
16
17
18 524 **FGR, studies evaluating the effects of ACS therapy on pregnant women with FGR**
19
20
21 525 **fetuses should be encouraged.**
22
23

24 526

27 527 **Strengths and limitations**

28
29
30 528 ~~Strengths~~ **The strengths** of this review ~~were its~~ included a broad search strategy, which
31
32
33 529 included studies published in languages other than English, rigorous quality
34
35
36 530 **assessments**, and **the** use of **the** GRADE methodology to assess the reliability of the
37
38
39 531 **review's** findings. ~~We thus~~ **Thus, we** consider the risk of missing potentially eligible
40
41
42 532 studies to be low, although we acknowledge that publication bias may affect these
43
44
45 533 results. One limitation of the present review is the difference in how studies defined,
46
47
48 534 identified, or diagnosed the subgroup conditions and outcomes ~~and~~ **of** interest. These
49
50
51 535 differences might have created **a** bias in the review conclusions. However, we explored
52
53
54 536 and reported heterogeneity for meta-analyses, ~~as well as downgrading for imprecision.~~
55
56
57 537 Another limitation is that most **of the** included studies were conducted in high-income
58
59
60

1
2
3
4
5
6 538 countries, although over 60% of all preterm births globally occur in African and South
7
8
9 539 Asian countries (73). This review did not lead to any evidence of high certainty, and
10
11
12 540 one reason for this observation is that all 31 studies were observational. In 1990,
13
14
15 541 Crowley P et al. reported a structured review of ACS for preterm birth (74). The
16
17
18 542 review revealed that ACS significantly reduced the risk of IVH and respiratory
19
20
21 543 morbidity (74). In 1995, the National Institutes of Health developed a consensus on
22
23
24 544 recommending ACS treatment for preterm birth (75). In our review, only one
25
26
27 545 study targeting women with chorioamnionitis and two studies targeting women
28
29
30 546 with FGR started before 1990 (49) (52) (40). It would be challenging to conduct the
31
32
33 547 RCTs on ACS efficacy even in these special populations after the review by
34
35
36 548 Crowley P et al. (74). The latest Cochrane review on ACS treatment for preterm
37
38
39 549 birth involved a subgroup analysis in the seven special conditions (2). However, the
40
41
42 550 review did not conduct a subgroup analysis regarding women with diabetes,
43
44
45 551 chorioamnionitis, and FGR (2). Furthermore, the latest review on ACS for later
46
47
48 552 preterm birth did not perform any subgroup analysis due to the lack of stratified
49
50
51 553 data based on the mode of delivery (67). Considering the circumstances, guidelines
52
53
54 554 on ACS therapy by international bodies are yet to develop solid recommendations
55
56
57 555 for these special populations. Hence, we consider this review valid. Prospective
58
59
60

1
2
3
4
5
6 556 **cohort studies on ACS efficacy for these four special populations should be**
7
8
9 557 **encouraged. The studies should include precise data on the time sequence between**
10
11
12 558 **ACS admission and the onset of maternal outcomes to determine the effect of ACS**
13
14
15 559 **therapy on maternal outcomes.**
16
17

18 560

21 561 CONCLUSION

23
24 562 ACS **has** possible benefits in the setting of FGR and/or SGA; however, direct evidence
25
26
27 563 ~~on~~ **of** its effectiveness **efficacy** and safety for pregnant women with pregestational
28
29
30 564 and/or gestational diabetes mellitus and those undergoing elective CS in **the** late
31
32
33 565 preterm **period** is **still** lacking. While **Although** ACS might **may** have some benefits in
34
35
36 566 the context of histological chorioamnionitis, more evidence is required. Well-designed
37
38
39 567 studies **(ideally trials)** with adequate follow-up for long-term child outcomes are
40
41
42 568 needed to confirm the effects **upsides** and harms **downsides** of ACS use in these
43
44
45 569 subpopulations.
46
47

48 570

51 571 AUTHOR CONTRIBUTIONS

53
54 572 Dr. Saito participated in the conceptualization and design of the study,₂ conducted title,
55
56
57 573 abstract, and full-text screening,₃ performed data extraction, analysis, and interpretation,
58
59
60

1
2
3
4
5
6 574 assessed the risk of bias,² drafted the initial manuscript,² and critically **reviewed** the
7
8
9 575 manuscript. Ms. Nishimura conducted **the** title abstract and full-text screening,
10
11
12 576 performed data extraction, analysis, and interpretation,² assessed the risk of bias,² and
13
14
15 577 critically **reviewed** the manuscript. Dr. Swa conceptualized and designed the search
16
17
18 578 strategy, conducted a systematic search, and critically reviewed the manuscript for
19
20
21 579 important intellectual content. Dr. Ramson assisted in the interpretation of data and the
22
23
24 580 assessment of **the** risk of bias and critically reviewed the manuscript for important
25
26
27 581 intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and
28
29
30 582 manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel
31
32
33 583 designed and planned the study, assisted with developing the literature search strategy
34
35
36 584 and resolving inclusion conflicts, critically **reviewed** the manuscript, and supervised the
37
38
39 585 execution of the study. All authors approved the final manuscript as submitted and
40
41
42 586 **agreed** to be accountable for all aspects of the work.
43
44

45 587

48 588 **DATA SHARING STATEMENT**

49
50
51 589 Data were obtained from **the** published journal **article, and** extracts are available **from**
52
53
54 590 **the corresponding author** upon reasonable request.
55

56
57 591
58
59
60

1
2
3
4
5
6 592 **FUNDING**
7

8
9 593 This work was supported by UNDP/UNFPA/ UNICEF/WHO/World Bank Special
10
11
12 594 Program of Research (WBSPR), Development and Research Training in Human
13
14
15 595 Reproduction (HRP), WHO (Grand Number: not applicable) , the Research Program on
16
17
18 596 Rare and Intractable Diseases co-sponsored program supported with grants from the
19
20
21 597 Japanese Ministry of Health, Labour and Welfare Science (JMōH)-(Grant Number:
22
23
24 598 JPMH22FC117) and the grant from the Japanese Ministry of Education, Culture,
25
26
27 599 Sports, Science and Technology (Grant Number: 22K20865)
28
29

30 600

31
32
33 601 **COMPETING INTERESTS**
34

35
36 602 None declared.
37

38
39 603
40

41
42 604 **SUPPLEMENTARY FILES**
43

44
45 605 Supplementary table 1: Characteristic tables
46

47
48 606 Supplementary table 2: PRISMA 2020 Checklist
49

50
51 607 Supplementary table 3: Review outcomes
52

53
54 608 Supplementary table 4: Database-specific search terms and strategies
55

56
57 609 Supplementary table 5: Risk of bias tables
58
59
60

1
2
3
4
5
6 610 **Supplementary table 6**: GRADE tables

7
8
9 611 **Supplementary file 1**: PROSPERO

10
11
12 612 **Supplementary file 2: PRISMA flow diagrams**

13
14
15 613 **Supplementary file 3: Risk of bias figures**

16
17
18 614 **Supplementary file 4**: Forest plots

19
20
21 615

22
23
24 616 **ETHICS APPROVAL**

25
26
27 617 As this study is a systematic review of published studies; **thus**, ethical approval was not
28
29
30 618 required.

31
32
33 619

34
35 620 **REFERENCES**

36
37 621 [1] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for
38 622 prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.
39 623 1972;50(4):5155-25. <https://doi.org/10.1542/peds.50.4.515>.

40
41 624 [2] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating
42 625 fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*.
43 626 2020;12:CD004454. <https://doi:10.1002/14651858.CD004454.pub.4>.

44
45 627 [3] Committee on Obstetric Practice. Committee opinion no. 713 summary: antenatal
46 628 corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):493-494.
47 629 <https://doi:10.1097/AOG.0000000000002231>.

48
49 630 [4] World Health Organization. Managing complications in pregnancy and childbirth: a
50 631 guide for midwives and doctors, 2nd ed. 2017.
51 632 <https://apps.who.int/iris/handle/10665/255760>. (accessed 24 Mar 2022).

52
53 633 [5] Skoll A, Boutin A, Bujold E, et al. No. 364-antenatal corticosteroid therapy for
54 634 improving neonatal outcomes. *J Obstet Gynaecol Can*. 2018;40(9):1219-1239.
55 635 <https://doi:10.1016/j.jogc.2018.04018>.

- 1
2
3
4
5
6 636 [6] Japan Society of Obstetrics and Gynecology. Obstetrics and Gynecology clinical
7 637 guideline 2020. https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf (accessed 24 Mar
8 638 2022).
- 9
10 639 [7] McGillick EV, Morrison JL, McMillen IC, et al. Intrafetal glucose infusion alters
11 640 glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of
12 641 the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol*.
13 642 2014;307(5):R538-R545. <https://doi:10.1152/ajpregu.00053.2014>.
- 14
15 643 [8] Kawakita T, Bowers K, Hazrati S, et al. Increased Neonatal Respiratory Morbidity
16 644 Associated with Gestational and Pregestational Diabetes: A Retrospective Study. *Am J*
17 645 *Perinatol*. 2017;34(11):1160-1168. <https://doi:10.1055/s-0037-1604414>.
- 18
19 646 [9] Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth.
20 647 *Am J Obstet Gynecol*. 2007;196(3):229 e1-4. <https://doi:10.1016/j.ajog.2006.10.900>.
- 21
22 648 [10] Gordon A, Lahra M, Raynes-Greenow C, et al. Histological chorioamnionitis is
23 649 increased at extremes of gestation in stillbirth: a population-based study. *Infect Dis Obstet*
24 650 *Gynecol*. 2011;2011:456728. <https://doi:10.1155/2011/456728>.
- 25
26 651 [11] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection:
27 652 A systematic review and meta-analysis. *PLoS Med*. 2019;16(12):e1002984. [https://doi:](https://doi:10.1371/journal.pmed.1002984)
28 653 [10.1371/journal.pmed.1002984](https://doi:10.1371/journal.pmed.1002984).
- 29
30 654 [12] Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and
31 655 neonatal encephalopathy. *Am J Obstet Gynecol*. 2003;188(4):1011-1015. [https://doi:](https://doi:10.1067/mob.2003.233)
32 656 [10.1067/mob.2003.233](https://doi:10.1067/mob.2003.233).
- 33
34 657 [13] Pasupathy D, Wood AM, Pell JP, et al. Rates of and factors associated with delivery-
35 658 related perinatal death among term infants in Scotland. *JAMA*. 2009;302(6):660-668.
36 659 <https://doi:10.1001/jama.2009.1111>.
- 37
38 660 [14] McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal
39 661 death in term and late preterm singletons. *Obstet Gynecol*. 2013;122(4):869-877. [https://](https://doi:10.1097/AOG.0b013e3182a265ab)
40 662 doi:10.1097/AOG.0b013e3182a265ab.
- 41
42 663 [15] MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special
43 664 educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med*.
44 665 2010;7(6):e1000289. <https://doi:10.1371/journal.pmed.1000289>.
- 45
46 666 [16] Nardoza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current
47 667 knowledge. *Arch Gynecol Obstet*. 2017;295(5):1061-1077. [https://doi:10.1007/s00404-](https://doi:10.1007/s00404-017-4341-9)
48 668 [017-4341-9](https://doi:10.1007/s00404-017-4341-9).
- 49
50 669 [17] Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight
51 670 and gestational age. *J Pediatr*. 1967;71(2):159-163. [https://doi:10.1016/s0022-](https://doi:10.1016/s0022-3476(67)80066-0)
52 671 [3476\(67\)80066-0](https://doi:10.1016/s0022-3476(67)80066-0).
- 53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 672 [18] Wang ML, Dorer DJ, Fleming MP, et al. Clinical outcomes of near-term infants.
7 673 *Pediatrics*. 2004;114(2):372-6. [https:// doi: 10.1542/peds.114.2.372](https://doi.org/10.1542/peds.114.2.372).
- 8
9 674 [19] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm
10 675 birth and maternal medical conditions on newborn morbidity risk. *Pediatrics*.
11 676 2008;121(2):e223-232. [https:// doi: 10.1542/peds.2006-3629](https://doi.org/10.1542/peds.2006-3629).
- 12
13 677 [20] Leone A, Ersfeld P, Adams M, et al. Neonatal morbidity in singleton late preterm
14 678 infants compared with full-term infants. *Acta Paediatr*. 2012;101(1):e6-10. [https:// doi:](https://doi.org/10.1111/j.1651-2227.2011.02459.x)
15 679 [10.1111/j.1651-2227.2011.02459.x](https://doi.org/10.1111/j.1651-2227.2011.02459.x).
- 16
17 680 [21] Mitha A, Chen R, Altman M, et al. Neonatal Morbidities in Infants Born Late
18 681 Preterm at 35-36 Weeks of Gestation: A Swedish Nationwide Population-based Study. *J*
19 682 *Pediatr*. 2021;233:43-50 e5. [https:// doi: 10.1016/j.jpeds.2021.02.066](https://doi.org/10.1016/j.jpeds.2021.02.066).
- 20
21 683 [22] Richards JL, Kramer MS, Deb-Rinker P, et al. Temporal Trends in Late Preterm and
22 684 Early Term Birth Rates in 6 High-Income Countries in North America and Europe and
23 685 Association With Clinician-Initiated Obstetric Interventions. *JAMA*. 2016;316(4):410-
24 686 419. [https:// doi: 10.1001/jama.2016.9635](https://doi.org/10.1001/jama.2016.9635).
- 25
26 687 [23] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of
27 688 delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol*.
28 689 1995;102(2):101-106. [https:// doi: 10.1111/j.1471-0528.1995.tb09060.x](https://doi.org/10.1111/j.1471-0528.1995.tb09060.x).
- 29
30 690 [24] Zanardo V, Simbi AK, Franzoi M, et al. Neonatal respiratory morbidity risk and
31 691 mode of delivery at term: influence of timing of elective caesarean delivery. *Acta*
32 692 *Paediatr*. 2004;93(5):643-647. [https:// doi: 10.1111/j.1651-2227.2004.tb02990.x](https://doi.org/10.1111/j.1651-2227.2004.tb02990.x).
- 33
34 693 [25] Hansen AK, Wisborg K, Uldbjerg N, et al. Risk of respiratory morbidity in term
35 694 infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336(7635):85-
36 695 87. [https:// doi: 10.1136/bmj.39405.539282.BE](https://doi.org/10.1136/bmj.39405.539282.BE).
- 37
38 696 [26] Groom KM. Antenatal corticosteroids after 34weeks' gestation: Do we have the
39 697 evidence? *Semin Fetal Neonatal Med*. 2019;24(3):189-196. [https:// doi:](https://doi.org/10.1016/j.siny.2019.03.001)
40 698 [10.1016/j.siny.2019.03.001](https://doi.org/10.1016/j.siny.2019.03.001).
- 41
42 699 [27] Amiya RM, Mlunde LB, Ota E, et al. Antenatal Corticosteroids for Reducing
43 700 Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of
44 701 Imminent Preterm Birth: A Systematic Review and Meta-Analysis. *PLoS One*.
45 702 2016;11(2):e0147604. [https:// doi: 10.1371/journal.pone.0147604](https://doi.org/10.1371/journal.pone.0147604).
- 46
47 703 [28] World Health Organization. WHO recommendations on intervention to improve
48 704 preterm birth outcomes. World Health Organizaiton; 2015.
49 705 <https://www.who.int/publications/i/item/9789241508988> (accessed 24 Mar 2022).
- 50
51 706 [29] Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines'
52 707 approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health*.
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 708 2019;4(4):e001683. [https:// doi: 10.1136/bmjgh-2019-001683](https://doi.org/10.1136/bmjgh-2019-001683).
- 7 709 [30] PRISMA. PRISMA Checklist. 2020. [http://presma-](http://presma-statement.org/PRISMAStatement/Checklist)
8 [statement.org/PRISMAStatement/Checklist](http://presma-statement.org/PRISMAStatement/Checklist) (accessed 24 Mar 2022).
- 9
10 710
11 711 [31] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for
12 712 nonrandomized studies showed moderate reliability and promising validity. *J Clin*
13 713 *Epidemiol*. 2013;66(4):408-414. [https:// doi: 10.1016/j.jclinepi.2012.09.016](https://doi.org/10.1016/j.jclinepi.2012.09.016).
- 14 714 [32] Cochrane Methods. Risk of Bias 2 (ROB2) tool. 2020.
15 715 <https://methods.cochrane.org/risk-bias-2>. (accessed 24 Mar 2022).
- 16 716 [33] Krispin E, Hochberg A, Chen R, et al. Neonatal outcome in gestational-diabetic
17 717 mothers treated with antenatal corticosteroids delivering at the late preterm and term.
18 718 *Arch Gynecol Obstet*. 2018;298(4):689-695. [https:// doi: 10.1007/s00404-018-4848-8](https://doi.org/10.1007/s00404-018-4848-8).
- 19 719 [34] Battarbee AN, Sandoval G, Grobman WA, et al. Antenatal corticosteroids and preterm
20 720 neonatal morbidity and mortality among women with and without diabetes in pregnancy.
21 721 *Am J Perinatol*. 2022;39:67-74. [https:// doi: 10.1055/s-0040-1714391](https://doi.org/10.1055/s-0040-1714391).
- 22 722 [35] Cassimatis IR, Battarbee AN, Allshouse AA, et al. Neonatal outcomes associated
23 723 with late preterm betamethasone administration in women with pregestational diabetes.
24 724 *Pediatr Neonatol*. 2020;61(6):645-646. [https:// doi: 10.1016/j.pedneo.2020.07.002](https://doi.org/10.1016/j.pedneo.2020.07.002).
- 25 725 [36] Kirshenbaum M, Mazaki-Tovi S, Amikam U, et al. Does antenatal steroids treatment
26 726 prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal morbidity?
27 727 Evidence from a case control study. *Arch Gynecol Obstet*. 2018;297(1):101-107. [http://](http://doi.org/10.1007/s00404-017-4557-8)
28 728 [doi: 10.1007/s00404-017-4557-8](http://doi.org/10.1007/s00404-017-4557-8).
- 29 729 [37] de la Huerza Lopez A, Sendarrubias Alonso M, Jimenez Jimenez AP, et al.
30 730 [Antenatal corticosteroids and incidence of neonatal respiratory distress after elective
31 731 caesarean section in late preterm and term neonates]. *An Pediatr (Engl Ed)*.
32 732 2019;91(6):371-377. Corticoides antenatales e incidencia de distrés respiratorio del recién
33 733 nacido en las cesáreas programadas del pretérmino tardío y término precoz. [https:// doi:](https://doi.org/10.1016/j.anpedi.2018.12.004)
34 734 [10.1016/j.anpedi.2018.12.004](https://doi.org/10.1016/j.anpedi.2018.12.004).
- 35 735 [38] Baud O, Zupan V, Lacaze-Masmonteil T, et al. The relationships between antenatal
36 736 management, the cause of delivery and neonatal outcome in a large cohort of very preterm
37 737 singleton infants. *BJOG*. 2000;107(7):877-884. [https:// doi: 10.1111/j.1471-](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x)
38 738 [0528.2000.tb11086.x](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x).
- 39 739 [39] Elimian A, Verma U, Beneck D, et al. Histologic chorioamnionitis, antenatal steroids,
40 740 and perinatal outcomes. *Obstet Gynecol*. 2000;96(3):333-6. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(00)00928-5)
41 741 [7844\(00\)00928-5](https://doi.org/10.1016/s0029-7844(00)00928-5).
- 42 742 [40] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30 weeks
43 743 gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22(3):155-159. [https://](https://doi.org/10.1016/j.ajper.2005.02.004)

- 1
2
3
4
5
6 744 doi: 10.1055/s-2005-865020.
- 7 745 [41] Foix-L'helias L, Baud O, Lenclen R, et al. Benefit of antenatal glucocorticoids
8 746 according to the cause of very premature birth. *Arch Dis Child Fetal Neonatal Ed.*
9 747 2005;90(1):F46-48. [https:// doi: 10.1136/adc.2003.042747](https://doi.org/10.1136/adc.2003.042747).
- 10 748 [42] Goldenberg RL, Andrews WW, Faye-Petersen OM, et al. The Alabama preterm birth
11 749 study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various
12 750 markers of intrauterine infection. *Am J Obstet Gynecol.* 2006;195(4):1020-1024. [https://](https://doi.org/10.1016/j.ajog.2006.06.033)
13 751 [doi: 10.1016/j.ajog.2006.06.033](https://doi.org/10.1016/j.ajog.2006.06.033).
- 14 752 [43] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal
15 753 involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am*
16 754 *J Obstet Gynecol.* 2009;201(6):587 e1-8. [https:// doi: 10.1016/j.ajog.2009.06.025](https://doi.org/10.1016/j.ajog.2009.06.025).
- 17 755 [44] Ahn HM, Park EA, Cho SJ, et al. The association of histological chorioamnionitis
18 756 and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four
19 757 weeks' gestation. *Neonatology.* 2012;102(4):259-64. [https:// doi: 10.1159/000339577](https://doi.org/10.1159/000339577).
- 20 758 [45] Ryu YH, Oh S, Sohn J, Lee J. The Associations between Antenatal Corticosteroids
21 759 and In-Hospital Outcomes of Preterm Singleton Appropriate for Gestational Age
22 760 Neonates according to the Presence of Maternal Histologic Chorioamnionitis.
23 761 *Neonatology.* 2019;116(4):369-375. [https:// doi: 10.1159/000502650](https://doi.org/10.1159/000502650).
- 24 762 [46] Been JV, Degraeuwe PL, Kramer BW, et al. Antenatal steroids and neonatal outcome
25 763 after chorioamnionitis: a meta-analysis. *BJOG.* 2011;118(2):113-122. [https://doi:](https://doi.org/10.1111/j.1471-0528.2010.02751.x)
26 764 [10.1111/j.1471-0528.2010.02751.x](https://doi.org/10.1111/j.1471-0528.2010.02751.x).
- 27 765 [47] Di Lenardo D, Piermarocchi P, Cazzaro L, et al. Betamethasone and theophylline in
28 766 the prevention of the Respiratory Distress Syndrome (RDS): Trend up-date. *J FOET Med.*
29 767 1990; 10 (1-4):27-31. Retrieved from [https://pascal-](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
30 768 [francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
- 31 769 [48] Spinillo A, Capuzzo E, Ometto A, et al. Value of antenatal corticosteroid therapy in
32 770 preterm birth. *Early Hum Dev.* 1995;42(1):37-47. [https:// doi: 10.1016/0378-](https://doi.org/10.1016/0378-3782(95)01638-j)
33 771 [3782\(95\)01638-j](https://doi.org/10.1016/0378-3782(95)01638-j).
- 34 772 [49] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in
35 773 infants with impaired intrauterine growth. *Acta Paediatr.* 1997;86(10):1090-1096. [https://](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x)
36 774 [doi: 10.1111/j.1651-2227.1997.tb14814.x](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x).
- 37 775 [50] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids in
38 776 obstetric subgroups. *Obstet Gynecol.* 1999;93(2):174-179. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(98)00400-1)
39 777 [7844\(98\)00400-1](https://doi.org/10.1016/s0029-7844(98)00400-1).
- 40 778 [51] Bernstein IM, Horbar JD, Badger GJ, et al. Morbidity and mortality among very-
41 779 low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 780 Network. *Am J Obstet Gynecol*. 2000;182:198-206. [https:// doi: 10.1016/s0002-9378\(00\)70513-8](https://doi.org/10.1016/s0002-9378(00)70513-8).
- 7
8 781
9 782 [52] Schaap AH, Wolf H, Bruinse HW, et al. Effects of antenatal corticosteroid
10 783 administration on mortality and long-term morbidity in early preterm, growth-restricted
11 784 infants. *Obstet Gynecol*. 2001;97(6):954-960. [https:// doi: 10.1016/s0029-7844\(01\)01343-6](https://doi.org/10.1016/s0029-7844(01)01343-6).
- 12
13 785
14 786 [53] Torrance HL, Mulder EJ, Brouwers HA, et al. Respiratory outcome in preterm small
15 787 for gestational age fetuses with or without abnormal umbilical artery Doppler and/or
16 788 maternal hypertension. *J Matern Fetal Neonatal Med*. 2007;20(8):613-621. [https:// doi: 10.1080/14767050701463662](https://doi.org/10.1080/14767050701463662).
- 17
18 789
19 790 [54] van Stralen G, van der Bos J, Lopriore E, et al. No short-term benefits of antenatal
20 791 corticosteroid treatment in severely preterm growth restricted fetuses: a case-control
21 792 study. *Early Hum Dev*. 2009;85(4):253-257. [https:// doi: 10.1016/j.earlhumdev.2008.10.010](https://doi.org/10.1016/j.earlhumdev.2008.10.010).
- 22
23 793
24 794 [55] Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial to
25 795 severely growth restricted fetuses? *J Matern Fetal Neonatal Med*. 2013;26(15):1496-
26 796 1499. [https:// doi: 10.3109/14767058.2013.789852](https://doi.org/10.3109/14767058.2013.789852).
- 27
28 797
29 798 [56] Ishikawa H, Miyazaki K, Ikeda T, et al. The Effects of Antenatal Corticosteroids on
30 799 Short- and Long-Term Outcomes in Small-for-Gestational-Age Infants. *Int J Med Sci*.
31 800 2015;12(4):295-300. [https:// doi: 10.7150/ijms.11523](https://doi.org/10.7150/ijms.11523).
- 32
33 801
34 802 [57] Riskin-Mashiah S, Riskin A, Bader D, et al. Antenatal corticosteroid treatment in
35 803 singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-
36 804 based study. *BJOG*. 2016;123(11):1779-1786. [https:// doi: 10.1111/1471-0528.13723](https://doi.org/10.1111/1471-0528.13723).
- 37
38 805
39 806 [58] Collaborative Study Group for Respiratory Distress Syndrome in Preterm I. [Effect
40 807 of antenatal corticosteroids therapy on the mortality and morbidity of small for gestational
41 808 age infants born at 24-34 completed weeks: a retrospective multicenter study]. *Zhonghua*
42 809 *Er Ke Za Zhi*. 2017;55(8):613-618. [https:// doi: 10.3760/cma.j.issn.0578-1310.2017.08.013](https://doi.org/10.3760/cma.j.issn.0578-1310.2017.08.013).
- 43
44 810
45 811 [59] Kim WJ, Han YS, Ko HS, et al. Antenatal corticosteroids and outcomes of preterm
46 812 small-for-gestational-age neonates in a single medical center. *Obstet Gynecol Sci*.
47 813 2018;61(1):7-13. [https:// doi: 10.5468/ogs.2018.61.1.7](https://doi.org/10.5468/ogs.2018.61.1.7).
- 48
49 814
50 815 [60] Kim YJ, Choi SH, Oh S, et al. Antenatal Corticosteroids and clinical outcomes of
51 816 preterm singleton neonates with intrauterine growth restriction. *Neonatal Med*.
52 817 2018;25(4):161-169. <https://doi.org/10.5385/nm.2018.25.4.161>.
- 53
54 818
55 819 [61] Riskin-Mashiah S, Reichman B, Bader D, et al. Population-based study on antenatal
56 820 corticosteroid treatment in preterm small for gestational age and non-small for gestational
57 821
58 822
59 823
60 824

- 1
2
3
4
5
6 816 age twin infants. *J Matern Fetal Neonatal Med.* 2018;31(5):553-559. [https:// doi:](https://doi.org/10.1080/14767058.2017.1292242)
7 817 10.1080/14767058.2017.1292242.
- 8
9 818 [62] Cartwright RD, Crowther CA, Anderson PJ, et al. Association of fetal growth
10 819 restriction with neurocognitive function after repeated antenatal betamethasone treatment
11 820 vs placebo: secondary analysis of the ACTORDS randomized clinical trial. *JAMA Netw*
12 821 *Open.* 2019;2(2):e187636. [https:// doi:](https://doi.org/10.1001/jamanetworkopen.2018.7636) 10.1001/jamanetworkopen.2018.7636.
- 13
14 822 [63] Bitar G, Merrill SJ, Sciscione AC, et al. Antenatal corticosteroids in the late preterm
15 823 period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM.* 2020;2(3):100153.
16 824 [https:// doi:](https://doi.org/10.1016/j.ajogmf.2020.100153) 10.1016/j.ajogmf.2020.100153.
- 17
18 825 [65] Torrance HL, Derks JB, Scherjon SA, et al. Is antenatal steroid treatment effective
19 826 in preterm IUGR fetuses? *Acta Obstet Gynecol Scand.* 2009;88(10):1068-1073. [https://](https://doi.org/10.1080/00016340903176784)
20 827 [doi:](https://doi.org/10.1080/00016340903176784) 10.1080/00016340903176784.
- 21
22 828 [65] Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic
23 829 ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am.* 1996;23(1):87-107. [https://](https://doi.org/10.1016/s0889-8545(05)70246-1)
24 830 [doi:](https://doi.org/10.1016/s0889-8545(05)70246-1) 10.1016/s0889-8545(05)70246-1.
- 25
26 831 [66] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid
27 832 treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction
28 833 of analoritm]. *Acta Obstet Gynecol Scand.* 2002;81(9):835-839. [https:// doi:](https://doi.org/10.1034/j.1600-0412.2002.810906.x)
29 834 10.1034/j.1600-0412.2002.810906.x.
- 30
31 835 [67] Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-
32 836 36+6 weeks) deliveries-A systematic review and meta-analysis of RCTs. *PLoS One.*
33 837 2021;16(3):e0248774. [https:// doi:](https://doi.org/10.1371/journal.pone.0248774) 10.1371/journal.pone.0248774.
- 34
35 838 [68] Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal Betamethasone for
36 839 Women at Risk for Late Preterm Delivery. *N Engl J Med.* 2016;374(14):1311-1320.
37 840 [https:// doi:](https://doi.org/10.1056/NEJMoa1516783) 10.1056/NEJMoa1516783.
- 38
39 841 [69] University of Auckland. The C*Steroid trial.
40 842 [https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html)
41 843 [studies-pregnancy/c-steroid-trial.html](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html) (accessed 24 Mar 2022).
- 42
43 844 [70] Dong Y, St Clair PJ, Ramzy I, et al. A microbiologic and clinical study of placental
44 845 inflammation at term. *Obstet Gynecol.* 1987;70(2):175-182. Retrieved from
45 846 [https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clin](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx)
46 847 [ical_Study_of_Placental.7.aspx](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx).
- 47
48 848 [71] Redline RW. Inflammatory responses in the placenta and umbilical cord. *Semin Fetal*
49 849 *Neonatal Med.* 2006;11(5):296-301. [https:// doi:](https://doi.org/10.1016/j.siny.2006.02.011) 10.1016/j.siny.2006.02.011.
- 50
51 850 [72] WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, et al. Antenatal
52 851 Dexamethasone for Early Preterm Birth in Low-Resource Countries. *N Engl J Med.*
- 53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 852 2020;383(26):2514-2525. [https:// doi:10.1056/NEJMoa2022398](https://doi.org/10.1056/NEJMoa2022398).
- 7 853 [73] World Health Organization. Born too soon: the global action report on preterm birth.
8 854 World Health Organization; 2012. <https://apps.who.int/iris/handle/10665/44864>
9 855 (accessed 24 Mar 2022).
- 10 856 [74] Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration
11 857 before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet*
12 858 *Gynaecol.* 1990;97(1):11-25. [https:// doi: 10.1111/j.1471-0528.1990.tb01711.x](https://doi.org/10.1111/j.1471-0528.1990.tb01711.x).
- 13 859 [75] Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus
14 860 Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal
15 861 Outcomes. *JAMA.* 1995;273(5):413-418. [https://](https://doi.org/10.1001/jama.1995.03520290065031)
16 862 [doi:10.1001/jama.1995.03520290065031](https://doi.org/10.1001/jama.1995.03520290065031).

863

864 **FIGURE LEGENDS**

865 **Figure 1.** Flow diagram of search results and the study selection process for women
866 with pregestational and/or gestational diabetes

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

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

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

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

877 **Figure 6.** A summary of the risk of bias for each trial for women with chorioamnionitis
878 (histological or clinical). Green = low risk of bias; red = high risk of bias; yellow = unclear
879 risk of bias.

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

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

885

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

886

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065070.R2
Article Type:	Original research
Date Submitted by the Author:	11-Jun-2023
Complete List of Authors:	Saito, KANA; Saitama Medical Center, Pediatrics Nishimura, Etsuko; St Luke's International University, Graduate School of Nursing Science Ota, Erika; St Luke's International University, Graduate School of Nursing Science; The Tokyo Foundation for Policy Research Namba, Fumihiko; Saitama Medical Center, Pediatrics Swa, Toshiyuki; Osaka University School of Medicine Graduate School of Medicine Ramson, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Lavin, Tina; World Health Organization, Department of Sexual and Reproductive Health and Research Cao, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Vogel, Joshua; Burnet Institute, Maternal, Child and Adolescent Health Program
Primary Subject Heading:	Paediatrics
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

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF 2 PRETERM BIRTH: A SYSTEMATIC REVIEW

3
4 Kana Saito^a, Etsuko Nishimura^b, Erika Ota^{b,c}, Fumihiko Namba^a, Toshiyuki Swa^d,
5 Jenny Ramson^e, Tina Lavin^f, Jenny Cao^e, Joshua P. Vogel^e

7 Affiliations

8 ^a Saitama Medical Center, Saitama Medical University, Saitama, Japan

9 ^b St. Luke's International University, Tokyo, Japan

10 ^c Tokyo Foundation for Policy Research, Tokyo, Japan

11 ^d Osaka University, Graduate School of Medicine, Osaka, Japan

12 ^e Maternal, Child, and Adolescent Health Program, Burnet Institute, Melbourne,
13 Australia

14 ^f UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research,
15 Development and Research Training in Human Reproduction, Department of Sexual
16 and Reproductive Health and Research, World Health Organization, Geneva,
17 Switzerland.

19 Correspondence to: Kana Saito

20 Department of Pediatrics, Saitama Medical Center, Saitama Medical University

21 1981 Kamoda, Kawagoe-city, Saitama 350-8550, Japan,

22 Phone:81-49-228-3400

23 E-mail: kana988@live.jp

24 ORCID: 0000-0001-7781-1870

25
26 **Word count:** 4382 words

27
28 **Short title:** Systematic review: antenatal steroids in specific women

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.

94 INTRODUCTION

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

107 However, current evidence regarding the benefits and possible harms of ACS use in
108 subpopulations of women with specific complications of pregnancy, such as women
109 with diabetes, chorioamnionitis, or fetal growth restriction (FGR), is controversial.
110 Women with diabetes, chorioamnionitis, or FGR are at a higher risk of adverse perinatal
111 outcomes; however, they are generally excluded from ACS efficacy trials [2].

112 Consequently, any subgroup analysis to explore the effects of ACS on women with
113 these complications is unlikely to yield concrete evidence from which conclusions can
114 be drawn.

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

1
2
3
4 118 maternal glycaemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women
5
6 119 giving birth, causing 22.6–36.9% of stillbirths [9-11]. Chorioamnionitis treatment
7
8
9 120 involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided
10
11 121 due to concerns that its immunosuppressive effects may worsen outcomes for women
12
13 122 and their babies. However, the relative benefits and harms of using ACS in clinical
14
15 123 settings are unclear. FGR is associated with an increased risk of morbidity and mortality
16
17 124 [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as
18
19 125 SGA neonates are constitutionally, rather than pathologically, small [16]. In most cases,
20
21 126 FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant
22
23 127 women with both FGR fetuses and SGA neonates.

24
25
26
27 128 Another clinical scenario where there is uncertainty is around ACS efficacy in women
28
29 129 undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37
30
31 130 weeks' gestation). Babies born in the late preterm period have lower risks of mortality
32
33 131 and morbidity than those born before 34 weeks' gestation; however, they have higher
34
35 132 risks of adverse outcomes than those born at term [18-21]. In many countries, the rising
36
37 133 rate of provider-initiated late preterm birth has been linked to the generalized increase in
38
39 134 the CS rate [22]. Regardless of gestational age, babies born via elective CS do not have
40
41 135 the usual physical and hormonal stimuli of passage through the birth canal; thus, they
42
43 136 tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested
44
45 137 that the risk of neonatal hypoglycemia is greater following CS; however, this may be
46
47 138 confounded by the underlying indication for CS [26].

48
49
50
51 139 In 2016, members of our team published a systematic review assessing the effectiveness
52
53 140 of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of
54
55 141 ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for
56
57
58
59
60

1
2
3
4 142 those undergoing elective CS in the late preterm period was found. The review could
5
6 143 not draw firm conclusions regarding the effects of ACS on women with growth-
7
8 144 restricted fetuses, although low-quality evidence suggested that ACS reduced neonatal
9
10 145 IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015
11
12 146 ACS recommendations [28]. Now, WHO's ACS recommendations are being updated as
13
14 147 part of the WHO's living guidelines in maternal and perinatal health [29]. Our aim is to
15
16 148 update the 2016 systematic review and provide a contemporary evidence base for
17
18 149 researchers, clinicians, and maternal and newborn health stakeholders on safe, effective
19
20 150 clinical management in preterm birth.
21
22
23
24
25
26

27 152 **METHODS**

28
29 153 The specific review objectives are presented in Box 1, comprising four related questions
30
31 154 on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or
32
33 155 gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm
34
35 156 period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA
36
37 157 infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are
38
39 158 explained in Supplementary table 1. SGA infants are all neonates with birth weights
40
41 159 below the 10th percentile. In this study, FGR fetuses were defined using the operational
42
43 160 definition used in eligible studies (Supplementary table 1). The review protocol was
44
45 161 registered on PROSPERO (CRD42021267816) and reported per the Preferred
46
47 162 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist
48
49 163 (Supplementary file 1, Supplementary table 2) [30].
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 166 Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a
5 167 systematic review
6

7 **P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes**

8 P: Women at risk of imminent preterm birth less than 37 weeks with pregestational diabetes mellitus
9 and/or gestational diabetes mellitus

10 I: ACS administration

11 C: Placebo or no treatment

12 O: World Health Organization (WHO) priority outcomes for preterm birth
13

14 **P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period**

15 P: Women undergoing elective CS in the late preterm period between 34 weeks and 0 days and 36
16 weeks and 6 days

17 I: ACS administration

18 C: Placebo or no treatment

19 O: WHO priority outcomes for preterm birth
20
21

22 **P3: Effects of ACS therapy on women with chorioamnionitis**

23 P: Women at risk of imminent preterm birth less than 37 weeks with chorioamnionitis

24 I: ACS administration

25 C: Placebo or no treatment

26 O: WHO priority outcomes for preterm birth
27

28 **P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants**

29 P: Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or
30 small-for-gestational-age infants

31 I: ACS administration

32 C: Placebo or no treatment

33 O: WHO priority outcomes for preterm birth
34

35 168

36 169 **Study eligibility criteria**

37
38
39 170 Eligible studies were randomized or non-randomized primary studies that reported on
40
41 171 the effects of ACS therapy in the four subpopulations. This included published,
42
43 172 unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled
44
45 173 before-after studies, interrupted-time-series studies, historically controlled studies,
46
47 174 cohort studies, and cross-sectional studies comparing any ACS (betamethasone,
48
49 175 dexamethasone, or hydrocortisone) administered either parentally or enterally with
50
51 176 placebo or no treatment. Study populations of interest were women at risk of imminent
52
53 177 preterm birth or provider-initiated preterm birth and where the study population fulfilled
54
55 178 one or more of the following conditions: women with pregestational and/or gestational
56
57
58
59
60

1
2
3
4 179 diabetes, women undergoing elective CS in the late preterm period, women with
5
6 180 chorioamnionitis, and women with FGR fetuses or SGA infants.
7
8
9 181 Articles in any language and from any country were eligible for inclusion if they
10
11 182 reported on one or more of WHO's priority outcomes for preterm birth guideline
12
13 183 development [28]. Maternal outcomes were death, maternal morbidity, and therapy side
14
15 184 effects. Newborn and child outcomes of interest were perinatal mortality, fetal
16
17 185 mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric
18
19 186 status, and therapy side effects (Supplementary table 3).
20
21
22
23
24

25 188 **Data sources and search strategy**

26
27 189 An information specialist was consulted for the development of the search strategy. A
28
29 190 systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of
30
31 191 Science, and Global Index Medicus was conducted with no date restrictions on June 6,
32
33 192 2021. Controlled vocabularies supplemented with free keywords were used to search for
34
35 193 the relevant concept areas, with duplicates removed in the process to yield a total
36
37 194 number of abstracts for each database (Supplementary table 4). Reference lists of the
38
39 195 included articles, including any recent systematic reviews, were also hand-searched for
40
41 196 further potentially relevant studies. All citations were imported into a Rayyan
42
43 197 (<http://rayyan.qcri.org>) library for eligibility assessment.
44
45
46
47
48
49

50 199 **Study selection, data extraction, and quality assessment**

51
52 200 Two reviewers (KS, EN) independently assessed the titles and abstracts of identified
53
54 201 citations for eligibility. Any disagreement resulted in automatic inclusion into the next
55
56 202 level of screening. Subsequently, full-text publications of potentially eligible studies
57
58
59
60

1
2
3
4 203 were obtained and assessed in duplicate by two reviewers working independently, with
5
6 204 disagreements resolved through discussions or by consulting a third reviewer. The two
7
8
9 205 reviewers also independently extracted baseline and outcome data and assessed the
10
11 206 quality, with these data compared and any discrepancies resolved through discussions or
12
13 207 by consulting a third reviewer. Extracted data were entered into the Review Manager
14
15 208 version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study
16
17 209 quality, observational studies were assessed using the Risk of Bias Assessment tool for
18
19 210 Non-randomized Studies (RoBANS) [31]. We used the Cochrane Risk of Bias tool for
20
21 211 randomized trials [32]. Potential publication bias was inspected visually using funnel
22
23 212 plots for asymmetry in situations where data for a single outcome were available from at
24
25 213 least ten studies.
26
27
28
29
30

31 214

32 215 **Data synthesis and analysis**

33 216 Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs)
34
35 217 were determined for dichotomous data using the random-effects model. Crude data were
36
37 218 used when the numbers of events were available and crude OR were employed when
38
39 219 events were not available. For continuous data, mean differences (MDs) with 95% CIs
40
41 220 were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and
42
43 221 Chi^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p <$
44
45 222 0.05 in the Chi^2 test for heterogeneity. For the analysis of women with FGR fetuses
46
47 223 and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only,
48
49 224 and SGA or FGR). Data from the three populations were combined, and pooled ORs
50
51 225 were calculated if the heterogeneity for that outcome was less than 60%. Based on the
52
53 226 evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at
54
55
56
57
58
59
60

1
2
3
4 227 high risk of bias. All statistical analyses were performed using RevMan5. The threshold
5
6 228 for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence
7
8
9 229 profiles were prepared for each research question using GRADEpro
10
11 230 (<https://gradepro.org/>). Grading of Recommendations Assessment, Development, and
12
13 231 Evaluation (GRADE), an approach for grading the certainty of evidence in systematic
14
15 232 reviews and clinical practice guidelines, was used in this review.
16
17
18 233

20 234 **Patients and public involvement**

22 235 Since this is a systematic review of previously published data, there was no direct
23
24 236 involvement of patients or the public.
25
26
27 237

29 238 **RESULTS**

31 239 **Effects of ACS therapy on women with pregestational and/or gestational diabetes** 32 33 240 **mellitus**

34
35
36 241 The search identified 179 citations: 11 potentially eligible studies were evaluated, and
37
38 242 three studies met the eligibility criteria, providing data on 725 pregnant women and 830
39
40 243 neonates (Supplementary file 2) [33-35]. All studies were conducted in high-income
41
42 244 countries and data collection was performed between 2008 and 2017 (Supplementary
43
44 245 table 1). One study involved women with pregestational diabetes only, one study
45
46 246 involved women with gestational diabetes only, and one study involved women with
47
48 247 either pregestational or gestational diabetes. All included studies were judged as having
49
50 248 a low risk of bias across all domains except high risk of bias at confounding variables
51
52 249 (Supplementary file 3, Supplementary table 5). Data were available for six outcomes
53
54 250 (Table 1). One retrospective cohort study found that in women with gestational
55
56
57
58
59
60

251 diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly
 252 increased (one study, 162 infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty*
 253 *evidence*); however, the effect of ACS therapy on neonatal hypoglycemia was uncertain
 254 (two studies, 215 infants; pooled OR: 1.44; 95%CI: 0.702.97, *very-low-certainty*
 255 *evidence*) [33]. The certainty of evidence was also very low for other outcomes; hence,
 256 no meaningful conclusions could be drawn.

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

Neonatal outcomes	No of studies	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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 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 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

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

262 Effects of ACS therapy on women undergoing elective CS in the late preterm 263 period

264 The search identified 211 citations: 17 potentially eligible studies were evaluated, and
 265 three studies were included (Supplementary file 2) [36,37,38]. These were two
 266 observational studies and a randomized controlled trial (RCT). All studies were
 267 conducted in high-income countries between 2010 and 2017, providing data on 205
 268 pregnant women/neonates (Supplementary table 1). The two observational studies were
 269 judged as having a high risk of bias for confounding variables (Supplementary file 3,
 270 Supplementary table 5). Data on eleven outcomes were available but all had very low
 271 certainty; so, no meaningful conclusions could be drawn (Table 2).

273
274

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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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 \leq 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

275
276
277

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

279 The search identified 418 citations: 12 potentially eligible studies were evaluated, and
 280 eight were found to be eligible (Supplementary file 2) [39-46]. Two were prospective
 281 cohort studies and six were retrospective, providing data on 1372 pregnant women and
 282 1460 neonates (Supplementary table 1). Four studies included pregnant women with
 283 clinical chorioamnionitis, and there were variations in the diagnostic criteria
 284 (Supplementary table 1). All studies were conducted in high-income countries between
 285 1989 and 2014. Additional unpublished crude data from the four included studies were
 286 extracted from a previous meta-analysis identified through the search process [39,42-
 287 44,47]. All included studies were judged as having a low risk of bias overall except high
 288 risk of bias at confounding variables (Supplementary file 3, Supplementary table 5).
 289 Data for 27 outcomes were available, with data reported separately for women with
 290 histological chorioamnionitis and women with clinical chorioamnionitis (Table 3;
 291 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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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)	131 fewer 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 (47.4%)	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

1
2
3
4 3105
6 311 **Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-**
7
8
9 312 **gestational-age infants**

10
11 313 The search identified 261 citations: 36 potentially eligible studies were assessed, and 18
12
13 314 studies were included (Supplementary file 2) [42,48-64]. Of these, twelve studies
14
15 315 included women with SGA infants only, four studies included women with FGR or
16
17 316 SGA infants, and two studies included women with FGR infants only (Supplementary
18
19 317 table 1). Among the studies that included FGR fetuses, the definitions of FGR varied
20
21 318 widely (Supplementary table 1). Since SGA status is insufficient to determine FGR, we
22
23 319 separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three
24
25 320 populations were combined, and the pooled OR in total was calculated. Data were
26
27 321 available from 2714 pregnant women and 8324 neonates enrolled between 1984 and
28
29 322 2019. We excluded three studies on maternal outcomes for omitting the number of
30
31 323 pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017
32
33 324 [51,54,59]. These studies included multiple gestations; hence, there was the risk of
34
35 325 double, triple, or more counts to one maternal outcome event. All were observational
36
37 326 studies conducted in high-income countries. Additional unpublished data from the study
38
39 327 by Torrance et al. (2007) were extracted from a review paper published in 2009
40
41 328 identified through the search strategy [54,65]. We extracted crude data from the
42
43 329 included studies except Ley et al. (1997) [50]. The study by Ley et al. only provided the
44
45 330 adjusted ORs, controlled by birthweight deviation, gestational age, pre-eclampsia,
46
47 331 premature rupture of membranes, and mode of delivery [50]. Most of these studies were
48
49 332 judged as having a low risk of bias across all domains except high risk of bias at
50
51 333 confounding variables (Supplementary file 3, Supplementary table 5). For SGA infants
52
53
54
55
56
57
58
59
60

1
2
3
4 334 only, 12 studies provided data on 30 outcomes (Supplementary file 4, Supplementary
5
6 335 table 6). The administration of ACS for women with SGA was associated with
7
8
9 336 increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women;
10
11 337 pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the odds of pre-
12
13 338 eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95%CI: 0.66–0.94, *low-*
14
15 339 *certainty evidence*), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68;
16
17 340 95%CI: 0.47–0.97, *low-certainty evidence*), periventricular leukomalacia (PVL) (four
18
19 341 studies, 3955 infants; pooled OR: 0.54; 95%CI: 0.38–0.77, *low-certainty evidence*) were
20
21 342 possibly reduced (Table 4). Two studies involving FGR infants only provided data for
22
23 343 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age
24
25 344 (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17–0.90, *low-certainty evidence*)
26
27 345 were possibly reduced (Table 4). Four studies involved SGA or FGR infants, providing
28
29 346 data for 25 outcomes (Supplementary file 4, Supplementary table 6). The administration
30
31 347 of ACS for women with SGA or FGR was associated with a possible reduction in the
32
33 348 odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62,
34
35 349 *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants;
36
37 350 pooled OR: 0.42; 95%CI: 0.26–0.66, *moderate-certainty evidence*), oxygen use (two
38
39 351 studies, 508 infants; pooled OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*)
40
41 352 although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01;
42
43 353 95%CI: 1.16–3.48, *low-certainty evidence*) (Table 4). Pooled ORs involving women
44
45 354 and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA
46
47 355 combined into SGA and/or FGR) could be determined for 20 outcomes (Supplementary
48
49 356 file 4, Supplementary table 6). ACS administration for women with SGA and/or FGR
50
51 357 was associated with a possible reduction in severe IVH (nine studies, 4636 infants;
52
53
54
55
56
57
58
59
60

358 pooled OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital
 359 stay (two studies, 396 infants; MD –2.23 days; 95%CI: –3.81––0.83, *low-certainty*
 360 *evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47,
 361 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies,
 362 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were
 363 possibly increased (Table 4).

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

Maternal outcomes	No of study	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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

366 *The data from the three populations, SGA only, FGR only, and SGA or FGR, were combined and the pooled ORs in
 367 total and calculated. *ACS: Antenatal corticosteroid, CI: Confidence interval, FGR: Fetal growth restriction, IVH:
 368 Intraventricular hemorrhage, MD: Mean difference, OR: Odds ratio, PIH: Pregnancy -induced hypertension, PVL:
 369 Periventricular leukomalacia, SGA: Small for gestational age. ^{a)} We calculated the numerators using the adjusted OR
 370 in the study by Ley et al. (1997).
 371

1
2
3
4
5
6 372 **DISCUSSION**
7
8

9 373 This systematic review identified 31 observational studies and a RCT on the benefits
10
11
12 374 and harms of using ACS in subgroups of women with specific pregnancy complications.
13
14
15 375 In women with diabetes and those undergoing elective late preterm CS, the available
16
17
18 376 evidence on the effects of ACS therapy was largely very-low-certainty; thus,
19
20
21 377 conclusions could not be drawn. In women with histological and clinical
22
23
24 378 chorioamnionitis, ACS therapy was associated with the benefit of neonatal death, IVH
25
26
27 379 and RDS reduction. In women with FGR and/or SGA babies, ACS therapy possibly has
28
29
30 380 benefits regarding neonatal morbidity and mortality, as well as the reduced use of
31
32
33 381 respiratory support interventions for the newborn; however, neonatal hypoglycemia
34
35
36 382 might be increased.
37

38
39 383

40
41
42 384 **Effects of ACS therapy on women with pregestational and/or gestational diabetes**
43

44
45 385 A clinical concern regarding ACS use in women with diabetes is the possibility of
46
47
48 386 steroid-induced insulin resistance and consequent hyperglycemia, which causes
49
50
51 387 avoidable harm to the neonate. For example, in women with insulin-dependent diabetes,
52
53
54 388 ketoacidosis may occur if insulin dosing is not increased following steroid
55
56
57 389 administration [66]. A 2002 Danish study conducted on 24 pregnant women with
58
59
60

1
2
3
4
5
6 390 diabetes who received steroids suggested that insulin dose adjustment may be required
7
8
9 391 for up to five days after ACS administration [67]. However, in the current review, there
10
11
12 392 was insufficient evidence to determine whether ACS increased neonatal hypoglycemia,
13
14
15 393 respiratory morbidity, or mortality. One retrospective study suggested that ACS use in
16
17
18 394 women with gestational diabetes increases the risk of NICU admission; however, the
19
20
21 395 authors noted that average birthweight in the ACS group was significantly lower than
22
23
24 396 that in the unexposed group, which may explain this finding [33]. Well-designed studies
25
26
27 397 are needed that describe adjustments to maternal diabetic regimens at the time of ACS
28
29
30 398 therapy and from the time of ACS administration to birth and report on important
31
32
33 399 newborn health outcomes.

34
35
36 400

37
38
39 401 **Effects of ACS therapy on women undergoing elective CS in the late preterm**
40
41
42 402 **period**

43
44
45 403 The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup
46
47
48 404 analysis on gestational age at trial entry reported findings from seven trials recruiting
49
50
51 405 women in the late preterm period [2]. This subgroup analysis suggested that ACS
52
53
54 406 reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh et
55
56
57 407 al. reported that ACS reduced the need for respiratory support and increased the risk of

1
2
3
4
5
6 408 hypoglycemia with moderate certainty in late preterm [68]. However, no subgroup
7
8
9 409 analyses were conducted on CS [68]. Hence, these findings cannot be generalized to all
10
11
12 410 women undergoing CS in the late preterm period. The trial by Gyamfi-Bannerman et al.
13
14
15 411 reported that ACS in the late preterm period reduced their primary outcome and severe
16
17
18 412 newborn respiratory complications [38]. Their subgroup analysis showed that these
19
20
21 413 beneficial effects persisted among women admitted for planned CS only [38]. Their
22
23
24 414 primary outcome was defined as any of the following occurrences within 72 hours after
25
26
27 415 birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for
28
29
30 416 at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen
31
32
33 417 of at least 0.30 for at least four continuous hours, mechanical ventilation, or the need for
34
35
36 418 extracorporeal membrane oxygenation (ECMO) [38]. Severe respiratory complications
37
38
39 419 were defined as any of the following occurrences within 72 hours after birth: CPAP,
40
41
42 420 HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of
43
44
45 421 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death
46
47
48 422 within 72 hours after delivery, or the need for ECMO [38]. Their outcomes did not
49
50
51 423 adequately fit our outcomes, and the study did not provide their outcome data. Our
52
53
54 424 review suggests there is insufficient evidence to draw firm conclusions on the benefits
55
56
57 425 and possible harms of ACS when used in this subpopulation. At the same time, the
58
59
60

1
2
3
4
5
6 426 multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective
7
8
9 427 effects from ACS for neonatal respiratory morbidity amongst women with late preterm
10
11
12 428 CS [38]. An ongoing randomized trial in New Zealand will provide further information
13
14
15 429 on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and
16
17
18 430 39 weeks 6 days [69].
19
20

21 431

24 432 **Effects of ACS on women with chorioamnionitis**

26
27 433 Women with chorioamnionitis are typically excluded from ACS efficacy trials due to
28
29
30 434 concerns that the prolongation of pregnancy and/or immunosuppression may worsen
31
32
33 435 outcomes for these women and their newborns. Although ACS appears to be associated
34
35
36 436 with reduced neonatal death, IVH and RDS rates in women with histological
37
38
39 437 chorioamnionitis, there was insufficient evidence of other important infection-related
40
41
42 438 maternal and neonatal outcomes in this review. While these conclusions are similar to
43
44
45 439 those of a 2011 review by Been et al., we do not consider that the available evidence
46
47
48 440 supports the routine use of ACS therapy in women with chorioamnionitis, as clinical
49
50
51 441 trials comparing ACS therapy to no ACS therapy in this population and reliable
52
53
54 442 evidence regarding infection-related outcomes are still lacking [47]. Significant overlap
55
56
57 443 exists between clinical and histological chorioamnionitis [70]. Histological
58
59
60

1
2
3
4
5
6 444 chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical
7
8
9 445 chorioamnionitis [71]. However, since physicians must decide the indications for ACS
10
11
12 446 therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in
13
14
15 447 pregnant women with clinical chorioamnionitis should be encouraged.
16
17

18 448

21 449 **Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-**
22
23
24 450 **gestational-age infants**
25

26
27 451 The totality of the evidence identified in this review suggests that ACS therapy should
28
29
30 452 be used in the fetal growth restriction setting. Although the evidence was mainly of low
31
32
33 453 or very low certainty, benefits were observed for several outcomes, and no harm was
34
35
36 454 reported. The current review identified more substantial evidence than that identified in
37
38
39 455 our 2016 systematic review, which was unable to draw solid conclusions about the
40
41
42 456 effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest
43
44
45 457 trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled
46
47
48 458 2852 women and reported preterm newborn mortality and morbidity benefits, recruited
49
50
51 459 189 women with known or suspected fetal growth restriction [72]. The current review
52
53
54 460 did not identify the benefits regarding the outcome RDS, which might be attributable to
55
56
57 461 a single retrospective cohort study in Japan in which neonates in the ACS group were
58
59
60

1
2
3
4
5
6 462 delivered significantly earlier than those in the control group [57]. A sensitivity analysis
7
8
9 463 in which we excluded this study suggested that RDS is significantly lower for SGA
10
11
12 464 babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal
13
14
15 465 hypoglycemia in this subpopulation, which warrants further exploration in future
16
17
18 466 research. In this meta-analysis, two studies targeted pregnant women with FGR while
19
20
21 467 the other 16 included pregnant women with SGA. SGA status does not perfectly
22
23
24 468 represent FGR [16]. Since physicians must decide the indication for ACS therapy when
25
26
27 469 FGR is detected, studies evaluating the effects of ACS therapy on pregnant women with
28
29
30 470 FGR fetuses should be encouraged.
31
32

33 471

36 472 **Strengths and limitations**

38
39 473 The strengths of this review were its broad search strategy, which included studies
40
41
42 474 published in languages other than English, rigorous quality assessments, and the use of
43
44
45 475 the GRADE methodology to assess the reliability of the review's findings. Thus, we
46
47
48 476 consider the risk of missing potentially eligible studies to be low, although we
49
50
51 477 acknowledge that publication bias may affect these results. One limitation of the present
52
53
54 478 review is the difference in how studies defined, identified, or diagnosed the subgroup
55
56
57 479 conditions and outcomes of interest. These differences might have created a bias in the
58
59
60

1
2
3
4
5
6 480 review conclusions. However, we explored and reported heterogeneity for meta-
7
8
9 481 analyses. This analysis extracted all data from observational studies. Since adjusted
10
11
12 482 confounding variables showed a wide variety in each included study, crude data were
13
14
15 483 employed in our review. No included studies adequately considered their study design
16
17
18 484 to adjust the confounding bias. Therefore, confounding bias should be cautiously
19
20
21 485 considered in our results' interpretation. Another limitation is that most of the included
22
23
24 486 studies were conducted in high-income countries, although over 60% of all preterm
25
26
27 487 births globally occur in African and South Asian countries [73]. This review did not
28
29
30 488 lead to any evidence of high certainty, and one reason for this observation is that all
31
32
33 489 studies were observational. In 1990, Crowley P et al. reported a structured review of
34
35
36 490 ACS for preterm birth [74]. The review revealed that ACS significantly reduced the risk
37
38
39 491 of IVH and respiratory morbidity [74]. In 1995, the National Institutes of Health
40
41
42 492 developed a consensus on recommending ACS treatment for preterm birth [75]. In our
43
44
45 493 review, only one study targeting women with chorioamnionitis and two studies
46
47
48 494 targeting women with FGR started before 1990 [41,50,53]. It would be challenging to
49
50
51 495 conduct the RCTs on ACS efficacy even in these special populations after the review by
52
53
54 496 Crowley P et al. [74]. The latest Cochrane review on ACS treatment for preterm birth
55
56
57 497 involved a subgroup analysis in the seven special conditions [2]. However, the review
58
59
60

1
2
3
4
5
6 498 did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis,
7
8
9 499 and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not
10
11
12 500 perform any subgroup analysis due to the lack of stratified data based on the mode of
13
14
15 501 delivery [68]. Considering the circumstances, guidelines on ACS therapy by
16
17
18 502 international bodies are yet to develop solid recommendations for these special
19
20
21 503 populations. Hence, we consider this review valid. Prospective cohort studies on ACS
22
23
24 504 efficacy for these four special populations should be encouraged. The studies should
25
26
27 505 include precise data on the time sequence between ACS admission and the onset of
28
29
30 506 maternal outcomes to determine the effect of ACS therapy on maternal outcomes. Our
31
32
33 507 search was last conducted in June 2021 and required time for publication. Despite
34
35
36 508 scrutinizing additional sources between June 2021 and February 2023, we did not find
37
38
39 509 any further relevant studies.
40

41
42 510

43 44 45 511 **CONCLUSION**

46
47
48 512 ACS has possible benefits in the setting of FGR and/or SGA; however, direct trial
49
50
51 513 evidence of its efficacy and safety for pregnant women with pregestational and/or
52
53
54 514 gestational diabetes mellitus and those undergoing elective CS in the late preterm period
55
56
57 515 is still lacking. Although ACS may have some benefits in the context of histological
58
59
60

1
2
3
4
5
6 516 chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with
7
8
9 517 adequate follow-up for long-term child outcomes are needed to confirm the upsides and
10
11
12 518 downsides of ACS use in these subpopulations.
13
14

15 519

18 520 **AUTHOR CONTRIBUTIONS**

21 521 Dr. Saito participated in the conceptualization and design of the study, conducted title,
22
23
24 522 abstract, and full-text screening, performed data extraction, analysis, and interpretation,
25
26
27 523 assessed the risk of bias, drafted the initial manuscript, and critically reviewed the
28
29
30 524 manuscript. Ms. Nishimura conducted the title abstract and full-text screening,
31
32
33 525 performed data extraction, analysis, and interpretation, assessed the risk of bias, and
34
35
36 526 critically reviewed the manuscript. Dr. Swa conceptualized and designed the search
37
38
39 527 strategy, conducted a systematic search, and critically reviewed the manuscript for
40
41
42 528 important intellectual content. Dr. Ramson assisted in the interpretation of data and the
43
44
45 529 assessment of the risk of bias and critically reviewed the manuscript for important
46
47
48 530 intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and
49
50
51 531 manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel
52
53
54 532 designed and planned the study, assisted with developing the literature search strategy
55
56
57 533 and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the
58
59
60

1
2
3
4
5
6 534 execution of the study. All authors approved the final manuscript as submitted and
7
8
9 535 agreed to be accountable for all aspects of the work.
10

11
12 536

13
14
15 537 **DATA SHARING STATEMENT**

16
17
18 538 Data were obtained from the published journal article, and extracts are available from
19
20
21 539 the corresponding author upon reasonable request.
22

23
24 540

25
26
27 541 **FUNDING**

28
29
30 542 This work was supported by UNDP/UNFPA/ UNICEF/WHO/World Bank Special
31
32
33 543 Program of Research, Development and Research Training in Human Reproduction,
34
35
36 544 WHO (Grand Number: not applicable) and Research Program on Rare and Intractable
37
38
39 545 Diseases co-sponsored program supported with grants from the Japanese Ministry of
40
41
42 546 Health, Labour and Welfare Science (Grant Number: JPMH22FC117) and the grant
43
44
45 547 from the Japanese Ministry of Education, Culture, Sports, Science and Technology
46
47
48 548 (Grant Number: 22K20865).
49

50
51 549

52
53
54 550 **COMPETING INTERESTS**

55
56
57 551 None declared.
58
59
60

1
2
3
4
5
6 552
7
8

9 553 **SUPPLEMENTARY FILES**

10
11
12 554 Supplementary table 1: Characteristic tables
13
14

15 555 Supplementary table 2: PRISMA 2020 Checklist
16
17

18 556 Supplementary table 3: Review outcomes
19
20

21 557 Supplementary table 4: Database-specific search terms and strategies
22
23

24 558 Supplementary table 5: Risk of bias tables
25
26

27 559 Supplementary table 6: GRADE tables
28
29

30 560 Supplementary file 1: PROSPERO
31
32

33 561 Supplementary file 2: PRISMA flow diagrams
34
35

36 562 Supplementary file 3: Risk of bias figures
37
38

39 563 Supplementary file 4: Forest plots
40
41

42 564
43
44

45 565 **ETHICS APPROVAL**
46
47

48 566 This study is a systematic review of published studies; thus, ethical approval was not
49
50

51 567 required.
52
53

54 568
55
56

57 569
58
59
60

570 **REFERENCES**

- 571 [1] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for
572 prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.
573 1972;50(4):5155-25. <https://doi.org/10.1542/peds.50.4.515>.
- 574 [2] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating
575 fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*.
576 2020;12:CD004454. <https://doi:10.1002/14651858.CD004454.pub.4>.
- 577 [3] Committee on Obstetric Practice. Committee opinion no. 713 summary: antenatal
578 corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):493-494.
579 <https://doi:10.1097/AOG.0000000000002231>.
- 580 [4] World Health Organization. Managing complications in pregnancy and childbirth: a
581 guide for midwives and doctors, 2nd ed. 2017.
582 <https://apps.who.int/iris/handle/10665/255760>. (accessed 24 Mar 2022).
- 583 [5] Skoll A, Boutin A, Bujold E, et al. No. 364-antenatal corticosteroid therapy for
584 improving neonatal outcomes. *J Obstet Gynaecol Can*. 2018;40(9):1219-1239.
585 <https://doi:10.1016/j.jogc.2018.04018>.
- 586 [6] Japan Society of Obstetrics and Gynecology. Obstetrics and Gynecology clinical
587 guideline 2020. https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf (accessed 24 Mar
588 2022).
- 589 [7] McGillick EV, Morrison JL, McMillen IC, et al. Intrafetal glucose infusion alters
590 glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of
591 the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol*.
592 2014;307(5):R538-R545. <https://doi:10.1152/ajpregu.00053.2014>.
- 593 [8] Kawakita T, Bowers K, Hazrati S, et al. Increased Neonatal Respiratory Morbidity
594 Associated with Gestational and Pregestational Diabetes: A Retrospective Study. *Am J*
595 *Perinatol*. 2017;34(11):1160-1168. <https://doi:10.1055/s-0037-1604414>.
- 596 [9] Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth.
597 *Am J Obstet Gynecol*. 2007;196(3):229 e1-4. <https://doi:10.1016/j.ajog.2006.10.900>.
- 598 [10] Gordon A, Lahra M, Raynes-Greenow C, et al. Histological chorioamnionitis is
599 increased at extremes of gestation in stillbirth: a population-based study. *Infect Dis Obstet*
600 *Gynecol*. 2011;2011:456728. <https://doi:10.1155/2011/456728>.
- 601 [11] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection:
602 A systematic review and meta-analysis. *PLoS Med*. 2019;16(12):e1002984. <https://doi:10.1371/journal.pmed.1002984>.
- 603 [12] Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and

- 1
2
3
4
5
6 605 neonatal encephalopathy. *Am J Obstet Gynecol*. 2003;188(4):1011-1015. [https://doi:](https://doi.org/10.1067/mob.2003.233)
7 606 10.1067/mob.2003.233.
- 8
9 607 [13] Pasupathy D, Wood AM, Pell JP, et al. Rates of and factors associated with delivery-
10 608 related perinatal death among term infants in Scotland. *JAMA*. 2009;302(6):660-668.
11 609 [https:// doi: 10.1001/jama.2009.1111](https://doi.org/10.1001/jama.2009.1111).
- 12
13 610 [14] McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal
14 611 death in term and late preterm singletons. *Obstet Gynecol*. 2013;122(4):869-877. [https://](https://doi.org/10.1097/AOG.0b013e3182a265ab)
15 612 [doi: 10.1097/AOG.0b013e3182a265ab](https://doi.org/10.1097/AOG.0b013e3182a265ab).
- 16
17 613 [15] MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special
18 614 educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med*.
19 615 2010;7(6):e1000289. [https:// doi: 10.1371/journal.pmed.1000289](https://doi.org/10.1371/journal.pmed.1000289).
- 20
21 616 [16] Nardoza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current
22 617 knowledge. *Arch Gynecol Obstet*. 2017;295(5):1061-1077. [https:// doi: 10.1007/s00404-](https://doi.org/10.1007/s00404-017-4341-9)
23 618 [017-4341-9](https://doi.org/10.1007/s00404-017-4341-9).
- 24
25 619 [17] Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight
26 620 and gestational age. *J Pediatr*. 1967;71(2):159-163. [https://doi: 10.1016/s0022-](https://doi.org/10.1016/s0022-3476(67)80066-0)
27 621 [3476\(67\)80066-0](https://doi.org/10.1016/s0022-3476(67)80066-0).
- 28
29 622 [18] Wang ML, Dorer DJ, Fleming MP, et al. Clinical outcomes of near-term infants.
30 623 *Pediatrics*. 2004;114(2):372-6. [https:// doi: 10.1542/peds.114.2.372](https://doi.org/10.1542/peds.114.2.372).
- 31
32 624 [19] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm
33 625 birth and maternal medical conditions on newborn morbidity risk. *Pediatrics*.
34 626 2008;121(2):e223-232. [https:// doi: 10.1542/peds.2006-3629](https://doi.org/10.1542/peds.2006-3629).
- 35
36 627 [20] Leone A, Ersfeld P, Adams M, et al. Neonatal morbidity in singleton late preterm
37 628 infants compared with full-term infants. *Acta Paediatr*. 2012;101(1):e6-10. [https:// doi:](https://doi.org/10.1111/j.1651-2227.2011.02459.x)
38 629 [10.1111/j.1651-2227.2011.02459.x](https://doi.org/10.1111/j.1651-2227.2011.02459.x).
- 39
40 630 [21] Mitha A, Chen R, Altman M, et al. Neonatal Morbidities in Infants Born Late
41 631 Preterm at 35-36 Weeks of Gestation: A Swedish Nationwide Population-based Study. *J*
42 632 *Pediatr*. 2021;233:43-50 e5. [https:// doi: 10.1016/j.jpeds.2021.02.066](https://doi.org/10.1016/j.jpeds.2021.02.066).
- 43
44 633 [22] Richards JL, Kramer MS, Deb-Rinker P, et al. Temporal Trends in Late Preterm and
45 634 Early Term Birth Rates in 6 High-Income Countries in North America and Europe and
46 635 Association With Clinician-Initiated Obstetric Interventions. *JAMA*. 2016;316(4):410-
47 636 419. [https:// doi: 10.1001/jama.2016.9635](https://doi.org/10.1001/jama.2016.9635).
- 48
49 637 [23] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of
50 638 delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol*.
51 639 1995;102(2):101-106. [https:// doi: 10.1111/j.1471-0528.1995.tb09060.x](https://doi.org/10.1111/j.1471-0528.1995.tb09060.x).
- 52
53 640 [24] Zanardo V, Simbi AK, Franzoi M, et al. Neonatal respiratory morbidity risk and
54
55
56
57
58
59
60

- 1
2
3
4
5
6 641 mode of delivery at term: influence of timing of elective caesarean delivery. *Acta*
7 642 *Paediatr.* 2004;93(5):643-647. [https:// doi: 10.1111/j.1651-2227.2004.tb02990.x](https://doi.org/10.1111/j.1651-2227.2004.tb02990.x).
- 8
9 643 [25] Hansen AK, Wisborg K, Uldbjerg N, et al. Risk of respiratory morbidity in term
10 644 infants delivered by elective caesarean section: cohort study. *BMJ.* 2008;336(7635):85-
11 645 87. [https:// doi: 10.1136/bmj.39405.539282.BE](https://doi.org/10.1136/bmj.39405.539282.BE).
- 12
13 646 [26] Groom KM. Antenatal corticosteroids after 34weeks' gestation: Do we have the
14 647 evidence? *Semin Fetal Neonatal Med.* 2019;24(3):189-196. [https:// doi:](https://doi.org/10.1016/j.siny.2019.03.001)
15 648 [10.1016/j.siny.2019.03.001](https://doi.org/10.1016/j.siny.2019.03.001).
- 16
17 649 [27] Amiya RM, Mlunde LB, Ota E, et al. Antenatal Corticosteroids for Reducing
18 650 Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of
19 651 Imminent Preterm Birth: A Systematic Review and Meta-Analysis. *PLoS One.*
20 652 2016;11(2):e0147604. [https:// doi: 10.1371/journal.pone.0147604](https://doi.org/10.1371/journal.pone.0147604).
- 21
22 653 [28] World Health Organization. WHO recommendations on intervention to improve
23 654 preterm birth outcomes. World Health Organizaiton; 2015.
24 655 <https://www.who.int/publications/i/item/9789241508988> (accessed 24 Mar 2022).
- 25
26 656 [29] Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines'
27 657 approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health.*
28 658 2019;4(4):e001683. [https:// doi: 10.1136/bmjgh-2019-001683](https://doi.org/10.1136/bmjgh-2019-001683).
- 29
30 659 [30] PRISMA. PRISMA Checklist. 2020. [http://prisma-](http://prisma-statement.org/PRISMAStatement/Checklist)
31 660 [statement.org/PRISMAStatement/Checklist](http://prisma-statement.org/PRISMAStatement/Checklist) (accessed 24 Mar 2022).
- 32
33 661 [31] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for
34 662 nonrandomized studies showed moderate reliability and promising validity. *J Clin*
35 663 *Epidemiol.* 2013;66(4):408-414. [https:// doi: 10.1016/j.jclinepi.2012.09.016](https://doi.org/10.1016/j.jclinepi.2012.09.016).
- 36
37 664 [32] Cochrane Methods. Risk of Bias 2 (ROB2) tool. 2020.
38 665 <https://methods.cochrane.org/risk-bias-2>. (accessed 24 Mar 2022).
- 39
40 666 [dataset] [33] Krispin E, Hochberg A, Chen R, et al. Neonatal outcome in gestational-
41 667 diabetic mothers treated with antenatal corticosteroids delivering at the late preterm and
42 668 term. *Arch Gynecol Obstet.* 2018;298(4):689-695. [https:// doi: 10.1007/s00404-018-](https://doi.org/10.1007/s00404-018-4848-8)
43 669 [4848-8](https://doi.org/10.1007/s00404-018-4848-8).
- 44
45 670 [dataset] [34] Battarbee AN, Sandoval G, Grobman WA, et al. Antental corticosteroids
46 671 and preterm neonatal morbidity and mortality among women with and without diabetes
47 672 in pregnancy. *Am J Perinatol.* 2022;39:67-74. [https:// doi: 10.1055/s-0040-1714391](https://doi.org/10.1055/s-0040-1714391).
- 48
49 673 [dataset] [35] Cassimatis IR, Battarbee AN, Allshouse AA, et al. Neonatal outcomes
50 674 associated with late preterm betamethasone administration in women with pregestational
51 675 diabetes. *Pediatr Neonatol.* 2020;61(6):645-646. [https:// doi:](https://doi.org/10.1016/j.pedneo.2020.07.002)
52 676 [10.1016/j.pedneo.2020.07.002](https://doi.org/10.1016/j.pedneo.2020.07.002).
- 53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 677 [dataset] [36] Kirshenbaum M, Mazaki-Tovi S, Amikam U, et al. Does antenatal steroids
7 678 treatment prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal
8 679 morbidity? Evidence from a case control study. *Arch Gynecol Obstet*. 2018;297(1):101-
9 680 107. [http:// doi: 10.1007/s00404-017-4557-8](http://doi:10.1007/s00404-017-4557-8).
- 11 681 [dataset] [37] de la Huerza Lopez A, Sendarrubias Alonso M, Jimenez Jimenez AP, et al.
12 682 [Antenatal corticosteroids and incidence of neonatal respiratory distress after elective
13 683 caesarean section in late preterm and term neonates]. *An Pediatr (Engl Ed)*.
14 684 2019;91(6):371-377. Corticoides antenatales e incidencia de distrés respiratorio del recién
15 685 nacido en las cesáreas programadas del pretérmino tardío y término precoz. [https:// doi:](https://doi:10.1016/j.anpedi.2018.12.004)
16 686 10.1016/j.anpedi.2018.12.004.
- 17 687 [dataset] [38] Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal
18 688 Betamethasone for Women at Risk for Late Preterm Delivery. *N Engl J Med*.
19 689 2016;374(14):1311-1320. [https:// doi: 10.1056/NEJMoa1516783](https://doi:10.1056/NEJMoa1516783).
- 21 690 [dataset] [39] Baud O, Zupan V, Lacaze-Masmonteil T, et al. The relationships between
22 691 antenatal management, the cause of delivery and neonatal outcome in a large cohort of
23 692 very preterm singleton infants. *BJOG*. 2000;107(7):877-884. [https:// doi: 10.1111/j.1471-](https://doi:10.1111/j.1471-0528.2000.tb11086.x)
24 693 0528.2000.tb11086.x.
- 25 694 [dataset] [40] Elimian A, Verma U, Beneck D, et al. Histologic chorioamnionitis,
26 695 antenatal steroids, and perinatal outcomes. *Obstet Gynecol*. 2000;96(3):333-6. [https://](https://doi:10.1016/s0029-7844(00)00928-5)
27 696 doi: 10.1016/s0029-7844(00)00928-5.
- 28 697 [dataset] [41] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30
29 698 weeks gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22(3):155-159.
30 699 [https:// doi: 10.1055/s-2005-865020](https://doi:10.1055/s-2005-865020).
- 31 700 [dataset] [42] Foix-L'heliás L, Baud O, Lenclen R, et al. Benefit of antenatal
32 701 glucocorticoids according to the cause of very premature birth. *Arch Dis Child Fetal*
33 702 *Neonatal Ed*. 2005;90(1):F46-48. [https:// doi: 10.1136/adc.2003.042747](https://doi:10.1136/adc.2003.042747).
- 34 703 [dataset] [43] Goldenberg RL, Andrews WW, Faye-Petersen OM, et al. The Alabama
35 704 preterm birth study: corticosteroids and neonatal outcomes in 23- to 32-week newborns
36 705 with various markers of intrauterine infection. *Am J Obstet Gynecol*. 2006;195(4):1020-
37 706 1024. [https:// doi: 10.1016/j.ajog.2006.06.033](https://doi:10.1016/j.ajog.2006.06.033).
- 38 707 [dataset] [44] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal
39 708 involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am*
40 709 *J Obstet Gynecol*. 2009;201(6):587 e1-8. [https:// doi: 10.1016/j.ajog.2009.06.025](https://doi:10.1016/j.ajog.2009.06.025).
- 41 710 [dataset] [45] Ahn HM, Park EA, Cho SJ, et al. The association of histological
42 711 chorioamnionitis and antenatal steroids on neonatal outcome in preterm infants born at
43 712 less than thirty-four weeks' gestation. *Neonatology*. 2012;102(4):259-64. [https:// doi:](https://doi:10.1159/000323111)

- 1
2
3
4
5
6 713 10.1159/000339577.
- 7 714 [dataset] [46] Ryu YH, Oh S, Sohn J, Lee J. The Associations between Antenatal
8 715 Corticosteroids and In-Hospital Outcomes of Preterm Singleton Appropriate for
9 716 Gestational Age Neonates according to the Presence of Maternal Histologic
10 717 Chorioamnionitis. *Neonatology*. 2019;116(4):369-375. [https:// doi: 10.1159/000502650](https://doi.org/10.1159/000502650).
- 11 718 [47] Been JV, Degraeuwe PL, Kramer BW, et al. Antenatal steroids and neonatal outcome
12 719 after chorioamnionitis: a meta-analysis. *BJOG*. 2011;118(2):113-122. [https://doi:](https://doi.org/10.1111/j.1471-0528.2010.02751.x)
13 720 10.1111/j.1471-0528.2010.02751.x.
- 14 721 [dataset] [48] Di Lenardo D, Piermarocchi P, Cazzaro L, et al. Betamethasone and
15 722 theophylline in the prevention of the Respiratory Distress Syndrome (RDS) : Trend up-
16 723 date. *J FOET Med*. 1990; 10 (1-4):27-31. Retrieved from [https://pascal-](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
17 724 [francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
- 18 725 [dataset] [49] Spinillo A, Capuzzo E, Ometto A, et al. Value of antenatal corticosteroid
19 726 therapy in preterm birth. *Early Hum Dev*. 1995;42(1):37-47. [https:// doi: 10.1016/0378-](https://doi.org/10.1016/0378-3782(95)01638-j)
20 727 3782(95)01638-j.
- 21 728 [dataset] [50] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome
22 729 in infants with impaired intrauterine growth. *Acta Paediatr*. 1997;86(10):1090-1096.
23 730 [https:// doi: 10.1111/j.1651-2227.1997.tb14814.x](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x).
- 24 731 [dataset] [51] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids
25 732 in obstetric subgroups. *Obstet Gynecol*. 1999;93(2):174-179. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(98)00400-1)
26 733 7844(98)00400-1.
- 27 734 [dataset] [52] Bernstein IM, Horbar JD, Badger GJ, et al. Morbidity and mortality among
28 735 very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford
29 736 Network. *Am J Obstet Gynecol*. 2000;182:198-206. [https:// doi: 10.1016/s0002-](https://doi.org/10.1016/s0002-9378(00)70513-8)
30 737 9378(00)70513-8.
- 31 738 [dataset] [53] Schaap AH, Wolf H, Bruinse HW, et al. Effects of antenatal corticosteroid
32 739 administration on mortality and long-term morbidity in early preterm, growth-restricted
33 740 infants. *Obstet Gynecol*. 2001;97(6):954-960. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(01)01343-6)
34 741 7844(01)01343-6.
- 35 742 [dataset] [54] Torrance HL, Mulder EJ, Brouwers HA, et al. Respiratory outcome in
36 743 preterm small for gestational age fetuses with or without abnormal umbilical artery
37 744 Doppler and/or maternal hypertension. *J Matern Fetal Neonatal Med*. 2007;20(8):613-
38 745 621. [https:// doi: 10.1080/14767050701463662](https://doi.org/10.1080/14767050701463662).
- 39 746 [dataset] [55] van Stralen G, van der Bos J, Lopriore E, et al. No short-term benefits of
40 747 antenatal corticosteroid treatment in severely preterm growth restricted fetuses: a case-
41 748 control study. *Early Hum Dev*. 2009;85(4):253-257. [https:// doi:](https://doi.org/10.1016/j.earhumdev.2009.03.010)
42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

- 1
2
3
4
5
6 749 10.1016/j.earlhumdev.2008.10.010.
7 [dataset] [56] Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial
8 to severely growth restricted fetuses? *J Matern Fetal Neonatal Med.* 2013;26(15):1496-
9 751 1499. [https:// doi: 10.3109/14767058.2013.789852](https://doi.org/10.3109/14767058.2013.789852).
10 752
11 [dataset] [57] Ishikawa H, Miyazaki K, Ikeda T, et al. The Effects of Antenatal
12 753 Corticosteroids on Short- and Long-Term Outcomes in Small-for-Gestational-Age
13 754 Infants. *Int J Med Sci.* 2015;12(4):295-300. [https:// doi: 10.7150/ijms.11523](https://doi.org/10.7150/ijms.11523).
14 755
15 [dataset] [58] Riskin-Mashiah S, Riskin A, Bader D, et al. Antenatal corticosteroid
16 756 treatment in singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a
17 757 population-based study. *BJOG.* 2016;123(11):1779-1786. [https:// doi: 10.1111/1471-
18 758 0528.13723](https://doi.org/10.1111/1471-0528.13723).
19 759
20 [dataset] [59] Collaborative Study Group for Respiratory Distress Syndrome in Preterm
21 760 I. [Effect of antenatal corticosteroids therapy on the mortality and morbidity of small for
22 761 gestational age infants born at 24-34 completed weeks: a retrospective multicenter study].
23 762 *Zhonghua Er Ke Za Zhi.* 2017;55(8):613-618. [https:// doi: 10.3760/cma.j.issn.0578-
24 763 1310.2017.08.013](https://doi.org/10.3760/cma.j.issn.0578-1310.2017.08.013).
25 764
26 [dataset] [60] Kim WJ, Han YS, Ko HS, et al. Antenatal corticosteroids and outcomes of
27 765 preterm small-for-gestational-age neonates in a single medical center. *Obstet Gynecol Sci.*
28 766 2018;61(1):7-13. [https:// doi: 10.5468/ogs.2018.61.1.7](https://doi.org/10.5468/ogs.2018.61.1.7).
29 767
30 [dataset] [61] Kim YJ, Choi SH, Oh S, et al. Antenatal Corticosteroids and clinical
31 768 outcomes of preterm singleton neonates with intrauterine growth restriction. *Neonatal*
32 769 *Med.* 2018;25(4):161-169. <https://doi.org/10.5385/nm.2018.25.4.161>.
33 770
34 [dataset] [62] Riskin-Mashiah S, Reichman B, Bader D, et al. Population-based study on
35 771 antenatal corticosteroid treatment in preterm small for gestational age and non-small for
36 772 gestational age twin infants. *J Matern Fetal Neonatal Med.* 2018;31(5):553-559. [https://
37 773 doi: 10.1080/14767058.2017.1292242](https://doi.org/10.1080/14767058.2017.1292242).
38 774
39 [dataset] [63] Cartwright RD, Crowther CA, Anderson PJ, et al. Association of fetal
40 775 growth restriction with neurocognitive function after repeated antenatal betamethasone
41 776 treatment vs placebo: secondary analysis of the ACTORDS randomized clinical trial.
42 777 *JAMA Netw Open.* 2019;2(2):e187636. [https:// doi:
43 778 10.1001/jamanetworkopen.2018.7636](https://doi.org/10.1001/jamanetworkopen.2018.7636).
44 779
45 [dataset] [64] Bitar G, Merrill SJ, Sciscione AC, et al. Antenatal corticosteroids in the late
46 780 preterm period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM.*
47 781 2020;2(3):100153. [https:// doi: 10.1016/j.ajogmf.2020.100153](https://doi.org/10.1016/j.ajogmf.2020.100153).
48 782
49 [65] Torrance HL, Derks JB, Scherjon SA, et al. Is antenatal steroid treatment effective
50 783 in preterm IUGR fetuses? *Acta Obstet Gynecol Scand.* 2009;88(10):1068-1073. [https://
51 784 doi: 10.1111/j.1365-3113.2009.04311.x](https://doi.org/10.1111/j.1365-3113.2009.04311.x)

- 1
2
3
4
5
6 785 doi: 10.1080/00016340903176784.
- 7 786 [66] Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic
8 787 ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am.* 1996;23(1):87-107. [https://doi: 10.1016/s0889-8545\(05\)70246-1](https://doi.org/10.1016/s0889-8545(05)70246-1).
- 11 789 [67] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid
12 790 treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction
13 791 of analgoritm]. *Acta Obstet Gynecol Scand.* 2002;81(9):835-839. [https://doi: 10.1034/j.1600-0412.2002.810906.x](https://doi.org/10.1034/j.1600-0412.2002.810906.x).
- 17 793 [68] Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-
18 794 36+6 weeks) deliveries-A systematic review and meta-analysis of RCTs. *PLoS One.*
19 795 2021;16(3):e0248774. [https://doi: 10.1371/journal.pone.0248774](https://doi.org/10.1371/journal.pone.0248774).
- 22 796 [69] University of Auckland. The C*Steroid trial.
23 797 [https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html)
24 798 [studies-pregnancy/c-steroid-trial.html](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html) (accessed 24 Mar 2022).
- 27 799 [70] Dong Y, St Clair PJ, Ramzy I, et al. A microbiologic and clinical study of placental
28 800 inflammation at term. *Obstet Gynecol.* 1987;70(2):175-182. Retrieved from
29 801 [https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clin](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx)
30 802 [ical_Study_of_Placental.7.aspx](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx).
- 33 803 [71] Redline RW. Inflammatory responses in the placenta and umbilical cord. *Semin Fetal*
34 804 *Neonatal Med.* 2006;11(5):296-301. [https://doi: 10.1016/j.siny.2006.02.011](https://doi.org/10.1016/j.siny.2006.02.011).
- 36 805 [72] WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, et al. Antenatal
37 806 Dexamethasone for Early Preterm Birth in Low-Resource Countries. *N Engl J Med.*
38 807 2020;383(26):2514-2525. [https://doi:10.1056/NEJMoa2022398](https://doi.org/10.1056/NEJMoa2022398).
- 40 808 [73] World Health Organization. Born too soon: the global action report on preterm birth.
41 809 World Health Organization; 2012. <https://apps.who.int/iris/handle/10665/44864>
42 810 (accessed 24 Mar 2022).
- 44 811 [74] Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration
45 812 before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet*
46 813 *Gynaecol.* 1990;97(1):11-25. [https://doi: 10.1111/j.1471-0528.1990.tb01711.x](https://doi.org/10.1111/j.1471-0528.1990.tb01711.x).
- 49 814 [75] Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus
50 815 Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal
51 816 Outcomes. *JAMA.* 1995;273(5):413-418. [https://doi:10.1001/jama.1995.03520290065031](https://doi.org/10.1001/jama.1995.03520290065031).
- 55 818
56 819
57
58
59
60

Supplementary table 1: Characteristic 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

^aGyamfi-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	CC	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	CC	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
Goldenberg 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	CC	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	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	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	CC	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 amniotic 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 \geq 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 \geq 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 percetile 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/>

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

1
2
3
4
5 Periventricular leukomalacia (PVL)
6 Major brain lesion damage
7 Necrotizing enterocolitis (NEC)
8 Sepsis
9
10 Early onset sepsis
11
12 Systemic inflammatory response syndrome
13 Meningitis
14 Neonatal hypoglycemia
15 Neonatal adrenal insufficiency
16 Intrahepatic cholestasis
17 Retinopathy of prematurity (ROP)
18 Gestational age at birth
19 Birth weight
20 Neonatal intensive care unit (NICU) admission
21 Duration of hospital stay
22 Survival free from disability
23 Death at long-term follow up
24 Death or disability/handicap at 2 years
25 Cerebral palsy
26 Severe hearing impairment
27 Visual impairment
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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	<p>P3 Ryu et al. (2019): Listed in the online supplementary Table1*1.</p>
Preeclampsia	<p>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 \geq 90mmHg measured at least twice and proteinuria \geq0.3g/24g.</p>
Hypertensive disorders	<p>P2 Kirshenbaum et al. (2018): No data.</p>
Pregnancy induced hypertension (PIH)	<p>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.</p>
Chorioamnionitis	<p>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.</p>
Gestational diabetes mellitus	<p>P2 de la Hueruga et al. (2019): No data.</p>
	<p>P3 Ryu et al. (2019): Listed in the online supplementary Table1*1.</p>

	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

1
2
3 membrane disease, or respiratory insufficiency requiring oxygen therapy with $FiO_2 \geq 0.40$ started
4 within the first 24 hours after birth and continued for ≥ 24 hours or until neonatal demise.

5 Krispin et al. (2018): No data.

6
7 **P2**

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

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

12
13 **P3**

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

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

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

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

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

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

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

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

34
35 **P4**

36 Kim et al. (2018): No data.

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

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

40 Feng et al. (2017): No data.

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

42 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

43 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.
For peer review only (http://www.bmj.com/site/about/guidelines.xhtml)

	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.

1 2 3 4 5 6 7	Mean duration of mechanical ventilations	P2 de la Huerga Lopez et al. (2019): No data. P3 Ahn et al. (2012): No data.
8 9	Duration of oxygen use	P3 Ahn et al. (2012): No data.
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27	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. (2009): 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 to a left-to-right shunt. Mitsiakos et al. (2013): No data. van Stralen et al. (2009): No data. Elimian et al. (1999): No data.
28 29 30	Hypotension within 7 postnatal days	P3 Ryu et al. (2019): Listed in the online supplementary Table1.*1
31 32 33 34	Hypotension	P4 van Stralen et al. (2009): Defined as a mean arterial pressure ≤ 30 mmHg requiring treatment with volume expanders and/or inotropic support.
35 36 37 38 39 40 41 42 43 44 45 46	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.
For more review (2000): <http://bmjopen.bmj.com/lookup/lookup/guidelines.xhtml>

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

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 \(SDG 3.2.2\) \(who.int\)](https://www.who.int/indicators/mortality-rates/neonatal-mortality-rate).

*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.

- 1
2
3 *7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
4 *8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg.
5 1978;187(1):1-7. doi:10.1097/0000658-197801000-00001.
6 *9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol.
7 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
8 *10. Frederiks AM, Nederlandse groeidoagrammen 1997 in historisch perspectief. In: Wit JM, ed. De Vierde Landelijke Groeistudie 1997. Presentatie
9 nieuwe groeidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
10 *11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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	(MH "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	Sequencing 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 (\geq 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							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with PGDM	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section												
2	observational studies	not serious	serious ^a	not serious	serious ^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.

For peer review only

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

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

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

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

1	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	
2	Chronic lung disease / bronchopulmonary dysplasia (CC)												
3	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	
4	Periventricular leukomalacia (HC)												
5	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	
6	Periventricular leukomalacia (CC)												
7	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	
8	Mean duration of mechanical ventilation, days (HC)												
9	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	
10	Necrotizing enterocolitis (HC)												
11	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	
12	Necrotizing enterocolitis (CC)												
13	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	
14	Apgar score <7 at 5 minutes (HC)												
15	1	observational studies	not serious	not serious	not serious	serious ^{b,a}	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	
16	Use of mechanical ventilation (HC)												
17	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	
18	Use of mechanical ventilation (CC)												
19	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	
20	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

- 1
- 2
- 3 a. Estimate based on wide confidence interval crossing the line of no effect.
- 4 b. Estimate based on small sample size.
- 5 c. Heterogeneity is high (I-square \geq 60%).
- 6 d. Wide difference of denominators between ACS and control group.
- 7 e. The data were extracted from one study.
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

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 ^s	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	none	386/3592 (10.7%)	378/2758 (13.7%)	OR 0.75 (0.53 to 1.06)	31 fewer per 1,000 (from 59 fewer to 7 more)	⊕○○○ Very low
Severe interventricular haemorrhage (grade3-4) (SGA)											
7	observational studies	not serious	serious ^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

Appgar score < 5 at 1 minute (SGA)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	49/191 (25.7%)	15/56 (26.8%)	OR 1.37 (0.63 to 2.97)	66 more per 1,000 (from 81 fewer to 253 more)	⊕○○○ Very low
Neonatal hypoglycemia (SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	17/45 (37.8%)	8/37 (21.6%)	OR 2.20 (0.82 to 5.91)	161 more per 1,000 (from 32 fewer to 404 more)	⊕○○○ Very low
Gestational age at birth (SGA)											
2	observational studies	not serious	not serious	not serious	serious ^d	none	806	1272	-	MD 0.58 lower (0.81 lower to 0.34 lower)	⊕○○○ Very low
Small for gestational age (< 2.3rd percentile for gestational age) (SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	63/146 (43.2%)	12/19 (63.2%)	OR 0.44 (0.16 to 1.19)	202 fewer per 1,000 (from 416 fewer to 39 more)	⊕○○○ Very low
Neonatal adrenal insufficiency (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	53/719 (7.4%)	67/1210 (5.5%)	OR 1.36 (0.94 to 1.97)	18 more per 1,000 (from 3 fewer to 48 more)	⊕○○○ Very low
Cerebral palsy (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	19/278 (6.8%)	25/498 (5.0%)	OR 1.39 (0.75 to 2.57)	18 more per 1,000 (from 12 fewer to 69 more)	⊕○○○ Very low
Severe hearing impairment (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	0/277 (0.0%)	5/502 (1.0%)	OR 0.16 (0.01 to 2.96)	8 fewer per 1,000 (from 10 fewer to 19 more)	⊕○○○ Very low
Visual impairment (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	1/275 (0.4%)	3/490 (0.6%)	OR 0.59 (0.06 to 5.72)	3 fewer per 1,000 (from 6 fewer to 28 more)	⊕○○○ Very low
Birth weight (SGA)											
2	observational studies	not serious	serious ^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 ^{ab}	none	87	62	-	MD 4 lower (17.43 lower to 9.43 higher)	⊕○○○ Very low

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

Explanations

- 1
- 2
- 3 a. Estimate based on wide confidence interval crossing the line of no effect.
- 4 b. Estimate based on small sample size.
- 5 c. Heterogeneity is high (I-square=>60%).
- 6 d. Estimate based on the risk of selection bias.
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

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 ^{ab}	none	20/165 (12.1%)	6/62 (9.7%)	OR 0.69 (0.26 to 1.81)	28 fewer per 1,000 (from 70 fewer to 66 more)	⊕○○○ Very low	
Death before discharge home (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	9/62 (14.5%)	15/62 (24.2%)	OR 0.53 (0.21 to 1.33)	97 fewer per 1,000 (from 179 fewer to 56 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR)												
3	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	-	-	OR 0.85 (0.57 to 1.26)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ Very low	
Surfactant use (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	19/53 (35.8%)	13/34 (38.2%)	OR 0.90 (0.37 to 2.20)	25 fewer per 1,000 (from 196 fewer to 194 more)	⊕○○○ Very low	
Major brain lesion (IVH, ICH, PVH, PVL) (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	12/116 (10.3%)	10/96 (10.4%)	OR 0.86 (0.35 to 2.10)	13 fewer per 1,000 (from 65 fewer to 92 fewer)	⊕○○○ Very low	
Interventricular haemorrhage (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Severe interventricular haemorrhage (grade3-4) (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Neonatal sepsis (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	45/115 (39.1%)	36/96 (37.5%)	OR 0.83 (0.44 to 1.58)	43 fewer per 1,000 (from 166 fewer to 112 more)	⊕○○○ Very low	
Necrotizing enterocolitis (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	3/53 (5.7%)	2/34 (5.9%)	OR 0.96 (0.15 to 6.07)	2 fewer per 1,000 (from 50 fewer to 216 more)	⊕○○○ Very low	
Patent ductus arteriosus (FGR)												

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	10/53 (18.9%)	6/34 (17.6%)	OR 1.09 (0.35 to 3.32)	13 more per 1,000 (from 107 fewer to 239 more)	⊕○○○ Very low
Chronic lung disease / bronchopulmonary dysplasia (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	22/115 (19.1%)	23/96 (24.0%)	OR 0.83 (0.42 to 1.63)	32 fewer per 1,000 (from 123 fewer to 100 more)	⊕○○○ Very low
Duration of mechanical ventilation (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	115	96	-	MD 1.09 higher (0.86 lower to 3.05 higher)	⊕○○○ Very low
Use of mechanical ventilation (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	61/115 (53.0%)	45/96 (46.9%)	OR 1.24 (0.72 to 2.14)	54 more per 1,000 (from 80 fewer to 185 more)	⊕○○○ Very low
Hypotension (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	15/53 (28.3%)	5/34 (14.7%)	OR 2.29 (0.75 to 7.03)	136 more per 1,000 (from 33 fewer to 401 more)	⊕○○○ Very low
Growth <10th percentile in early childhood (FGR)											
1	observational studies	not serious	not serious	not serious	serious ^b	none	14/49 (28.6%)	3/42 (7.1%)	OR 5.20 (1.38 to 19.62)	214 more per 1,000 (from 25 more to 530 more)	⊕○○○ Very low
Abnormal behavior at long-term follow-up at school age (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	21/49 (42.9%)	19/42 (45.2%)	OR 0.91 (0.40 to 2.08)	23 fewer per 1,000 (from 204 fewer to 180 more)	⊕○○○ Very low
Death at long-term follow-up (school age) (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	4/62 (6.5%)	5/62 (8.1%)	OR 0.79 (0.20 to 3.08)	16 fewer per 1,000 (from 63 fewer to 132 more)	⊕○○○ Very low
Death or disability/handicap at 2yrs' corrected age (FGR)											
1	observational studies	not serious	not serious	not serious	serious ^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							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	136/219 (62.1%)	56/119 (47.1%)	OR 1.02 (0.62 to 1.68)	5 more per 1,000 (from 115 fewer to 128 more)	⊕○○○	Very low
Chorioamnionitis (histologic and /or clinical) (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	19/83 (22.9%)	2/8 (25.0%)	OR 0.89 (0.17 to 4.78)	21 fewer per 1,000 (from 196 fewer to 364 more)	⊕○○○	Very low
Preeclampsia (FGR or SGA)												
2	observational studies	<u>not serious</u>	serious ^c	not serious	serious ^a	none	78/254 (30.7%)	52/209 (24.9%)	OR 1.37 (0.33 to 5.61)	63 more per 1,000 (from 150 fewer to 401 more)	⊕○○○	Very low
Gestational diabetes mellitus (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	14/219 (6.4%)	7/119 (5.9%)	OR 1.06 (0.36 to 3.08)	3 more per 1,000 (from 37 fewer to 103 more)	⊕○○○	Very low
Pregnancy induced hypertension (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	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 ^{ab}	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 ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○	Very low
Severe interventricular haemorrhage (grade3-4) (FGR or SGA)												

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low
Neonatal sepsis (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	18/83 (21.7%)	3/8 (37.5%)	OR 0.46 (0.10 to 2.12)	159 fewer per 1,000 (from 318 fewer to 185 more)	⊕○○○ Very low
Necrotizing enterocolitis (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	1/8 (12.5%)	OR 0.45 (0.05 to 4.40)	65 fewer per 1,000 (from 118 fewer to 261 more)	⊕○○○ Very low
Patent ductus arteriosus (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	42/83 (50.6%)	4/8 (50.0%)	OR 1.02 (0.24 to 4.37)	5 more per 1,000 (from 306 fewer to 314 more)	⊕○○○ Very low
Chronic lung disease / bronchopulmonary dysplasia (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	23/83 (27.7%)	3/8 (37.5%)	OR 0.64 (0.14 to 2.89)	98 fewer per 1,000 (from 298 fewer to 259 more)	⊕○○○ Very low
Use of mechanical ventilation (FGR or SGA)											
2	observational studies	not serious	not serious	not serious	not serious	strong association	73/275 (26.5%)	94/233 (40.3%)	OR 0.42 (0.26 to 0.66)	182 fewer per 1,000 (from 254 fewer to 95 fewer)	⊕⊕⊕○ Moderate
Apgar score < 7 at 5 minutes (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	6/136 (4.4%)	5/111 (4.5%)	OR 0.98 (0.29 to 3.29)	1 fewer per 1,000 (from 32 fewer to 89 more)	⊕○○○ Very low
Neonatal hypoglycemia (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	strong association	55/136 (40.4%)	28/111 (25.2%)	OR 2.01 (1.16 to 3.48)	152 more per 1,000 (from 29 more to 288 more)	⊕⊕○○ Low
Oxygen therapy (FGR or SGA)											
2	observational studies	not serious	not serious	not serious	not serious	strong association	79/275 (28.7%)	94/233 (40.3%)	OR 0.48 (0.30 to 0.77)	158 fewer per 1,000 (from 235 fewer to 61 fewer)	⊕⊕⊕○ Moderate
Gestational age at birth (FGR or SGA)											
2	observational studies	not serious	serious ^s	not serious	serious ^a	none	275	233	-	MD 0.43 higher (0.54 lower to 1.4 higher)	⊕○○○ Very low
Retinopathy of prematurity (FGR or SGA)											

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

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

Explanations

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

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

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

2

3 Explanations

- 4 a. Estimate based on wide confidence interval crossing the line of no effect.
5 b. Estimate based on small sample size.
6 c. Heterogeneity is high (I-square=>60%).
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

PROSPERO
International prospective register of systematic reviews

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

PROSPERO

International prospective register of systematic reviews

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

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.

PROSPERO

International prospective register of systematic reviews

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.

Exclusion: Pregnant women with the population at 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.

PROSPERO

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 fulfil one or more of the following conditions:

1. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
2. having intrauterine inflammation, infection, or both; or
3. 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.

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)

PROSPERO

International prospective register of systematic reviews

- 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.

PROSPERO International prospective register of systematic reviews

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

PROSPERO**International prospective register of systematic reviews**

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 T^2 , I^2 , and τ^2 statistics.

Heterogeneity will be deemed substantial if T^2 will be greater than zero and either I^2 will be greater than 50% or $p < 0.10$ in the τ^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 $p < 0.10$ 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

PROSPERO**International prospective register of systematic reviews**

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

PROSPERO**International prospective register of systematic reviews**1
2
3
4 No

5 Education

6 No

7
8 Endocrine and metabolic disorders

9 No

10
11 Eye disorders

12 No

13
14 General interest

15 No

16
17 Genetics

18 No

19
20 Health inequalities/health equity

21 No

22
23 Infections and infestations

24 No

25
26 International development

27 No

28
29 Mental health and behavioural conditions

30 No

31
32 Musculoskeletal

33 No

34
35 Neurological

36 No

37
38 Nursing

39 No

40
41 Obstetrics and gynaecology

42 No

43
44 Oral health

45 No

46
47 Palliative care

48 No

49
50 Perioperative care

51 No

52
53 Physiotherapy

54 No

55
56 Pregnancy and childbirth

57 Yes

58
59 Public health (including social determinants of health)

60 No

Rehabilitation

No

Respiratory disorders

No

PROSPERO

International prospective register of systematic reviews

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?

PROSPERO**International prospective register of systematic reviews**

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

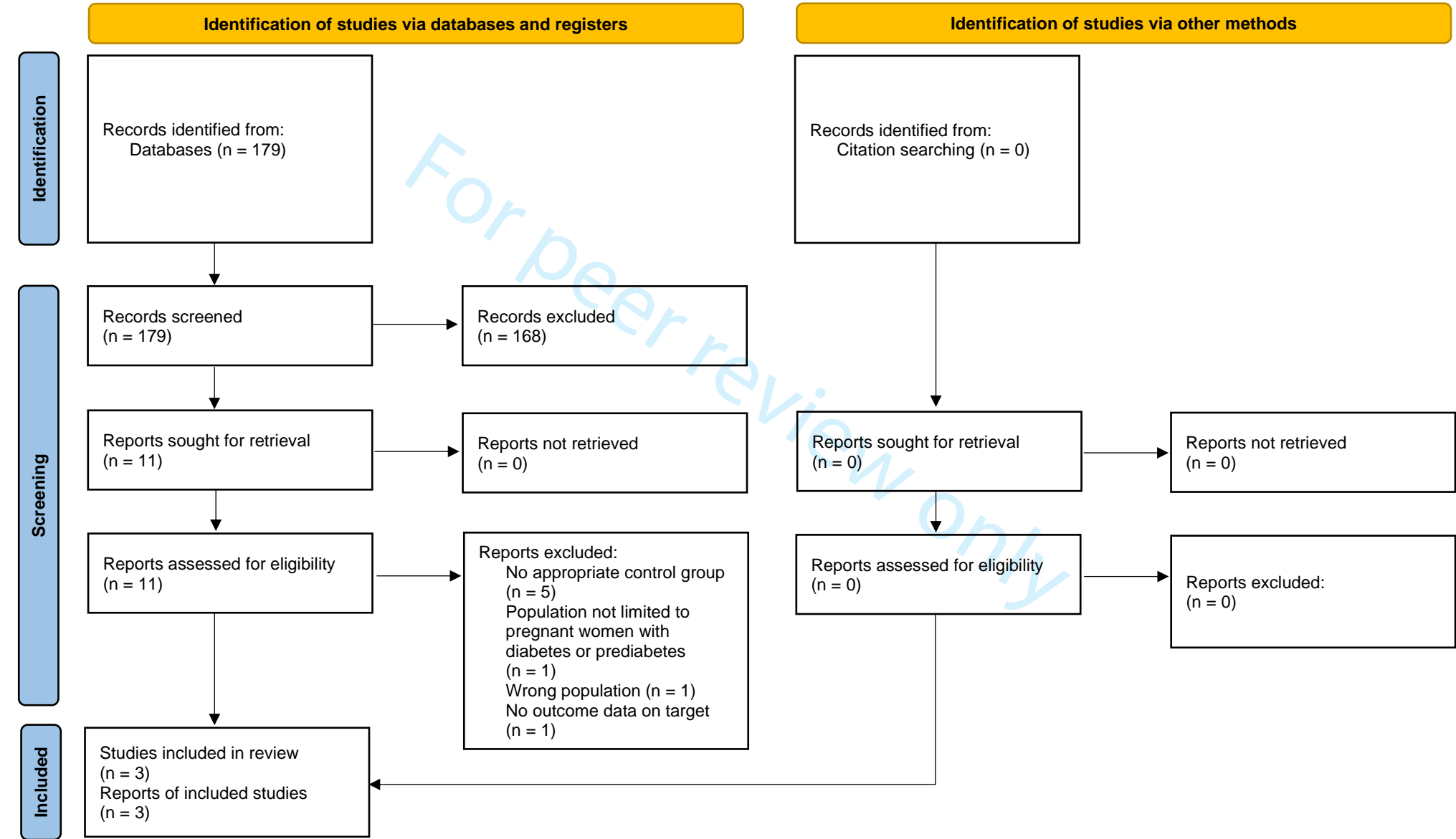


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

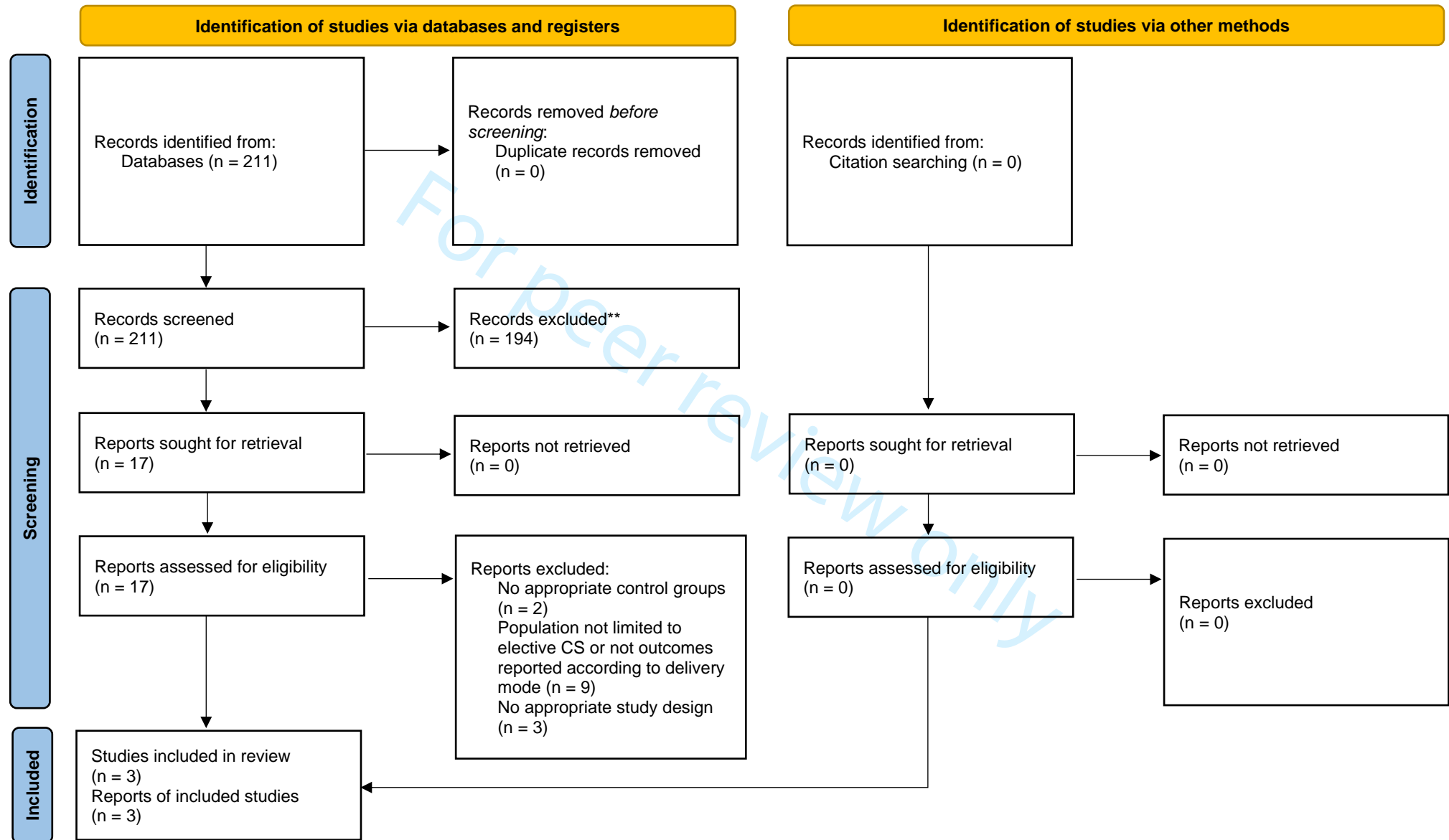


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

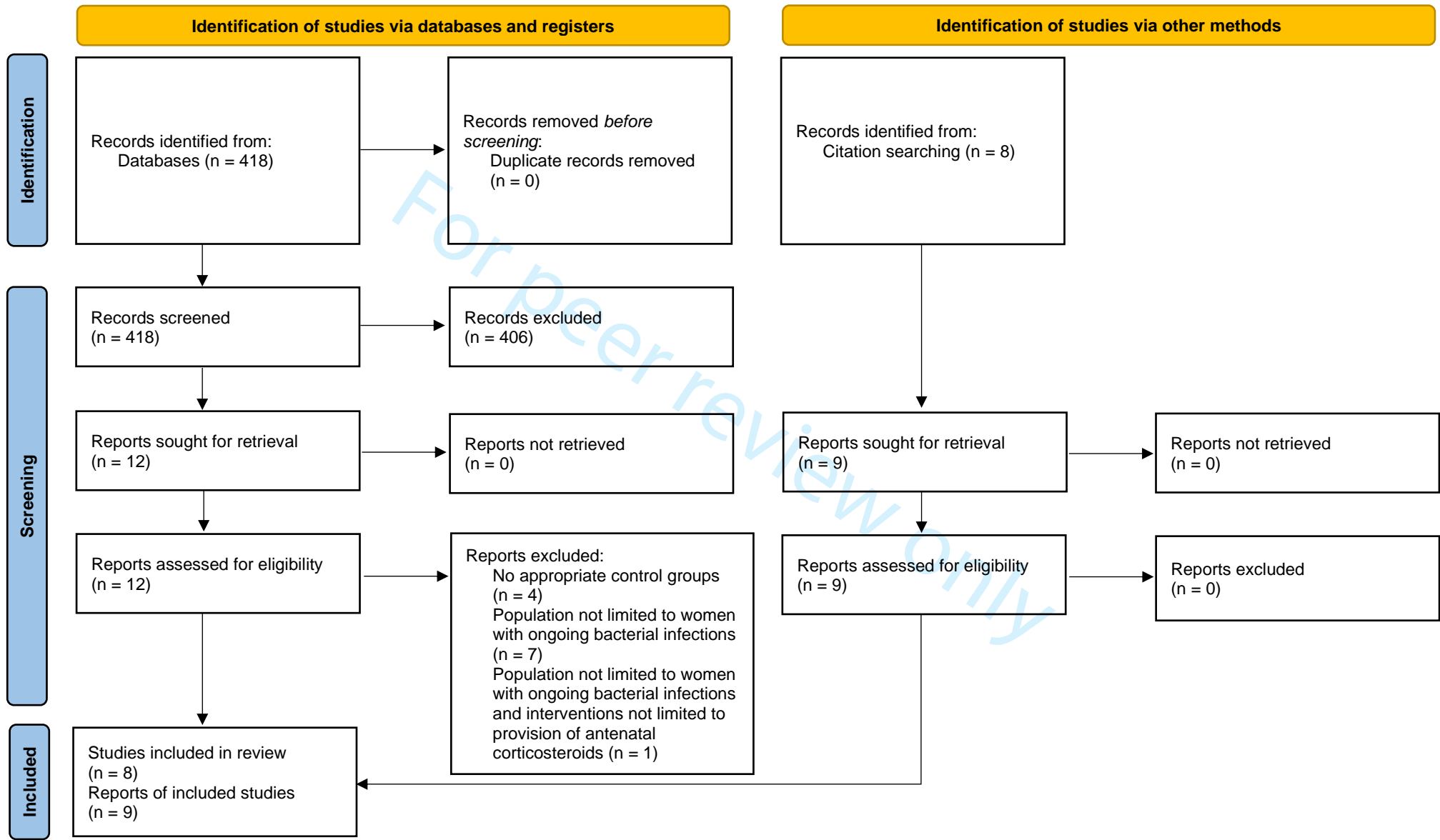
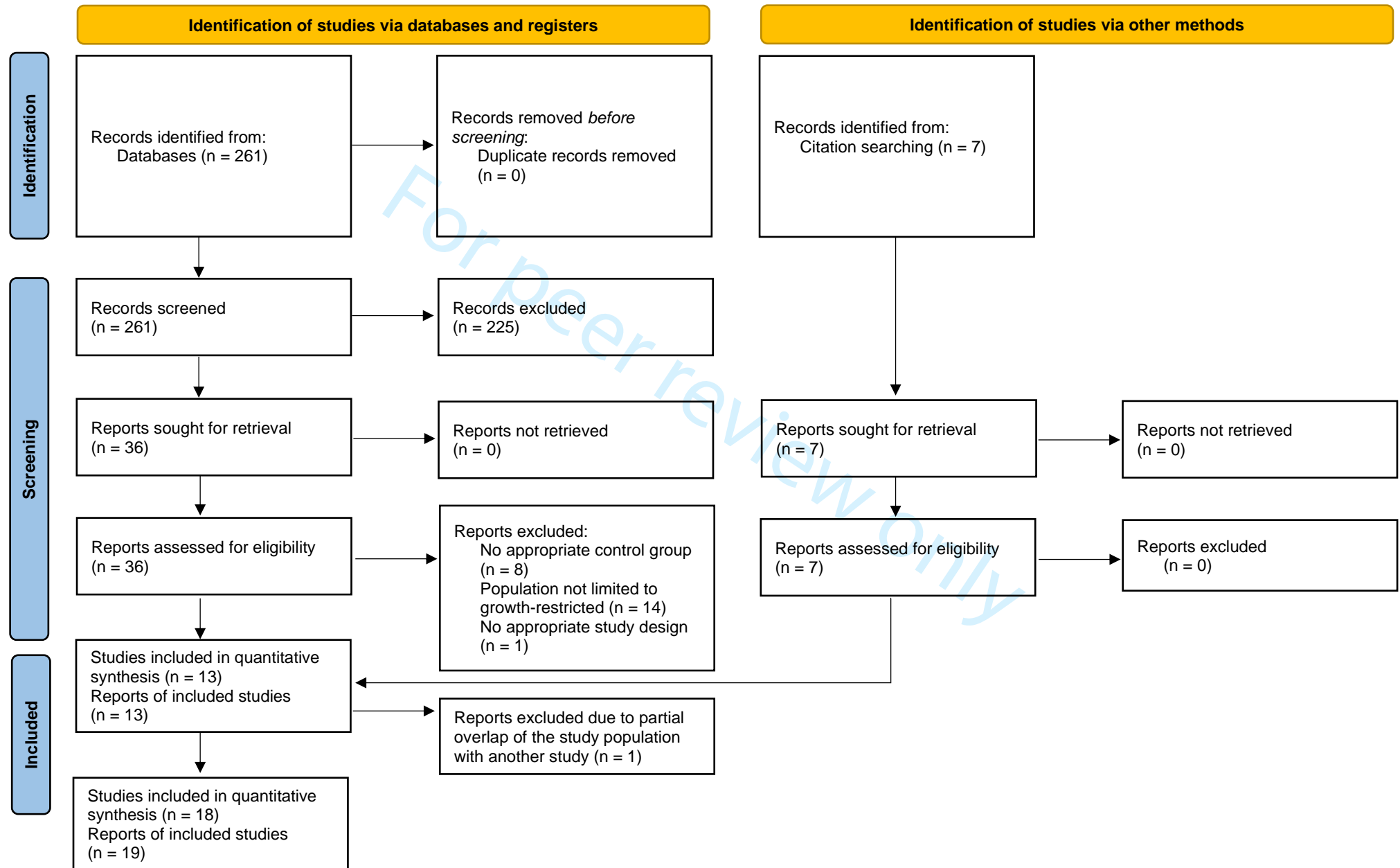


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure 1: 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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Battarbee 2020	+	-	+	+	+	+
Cassimatis 2020	+	-	+	+	+	+
Krispin 2018	+	-	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
de la Huerga Lopez 2019	+	-	+	+	+	+
Kirshenbaum 2018	+	-	+	+	+	+

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gyamfi-Bannerman 2016	+	+	+	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Ahn 2012	+	-	+	+	+	+
Baud 2000	+	-	+	+	+	+
Been 2009	+	-	+	+	+	+
Dempsey 2005	+	-	+	+	+	+
Elimian 2000	+	-	+	+	+	+
Foix-L'Helias 2005	+	-	+	+	+	+
Goldenberg 2006	+	-	+	+	+	+
Ryu 2019	+	-	+	+	+	+

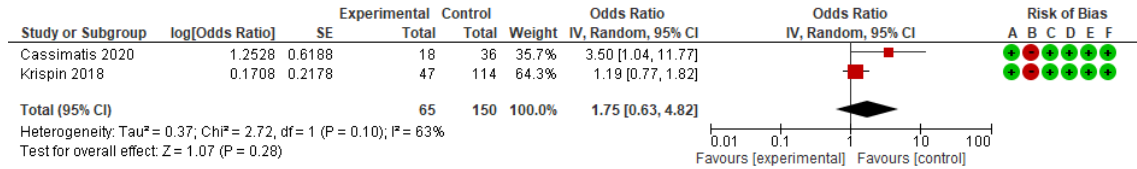
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
 Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Bernstein 2000	+	-	+	+	+	+
Bitar 2020	+	-	+	+	+	+
Cartwright 2019	+	-	+	+	+	+
DiLenardo 1990	?	-	+	+	+	+
Elimian 1999	+	-	+	+	+	+
Feng 2017	+	-	+	+	+	+
Foix-L'Helias 2005	+	-	+	+	+	+
Ishikawa 2015	+	-	+	+	+	+
Kim 2018	+	+	+	+	+	+
Kim Y.J. 2018	+	-	+	+	+	+
Ley 1997	+	-	+	+	+	+
Mitsiakos 2013	+	-	+	+	+	+
Riskin-Mashiah 2016	+	-	+	+	+	+
Riskin-Mashiah 2018	+	-	+	+	+	+
Schaap 2001	+	-	+	+	+	+
Spinillo 1995	+	-	+	+	+	+
Torrance 2007	+	-	+	+	+	+
vanStralen 2009	+	-	+	+	+	+

Supplementary file 4: Forest plots

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

1) Caesarean section



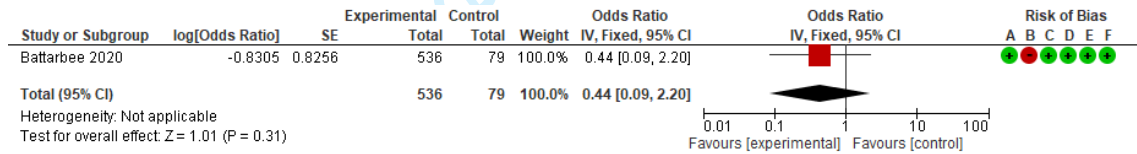
Risk of bias legend

- (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

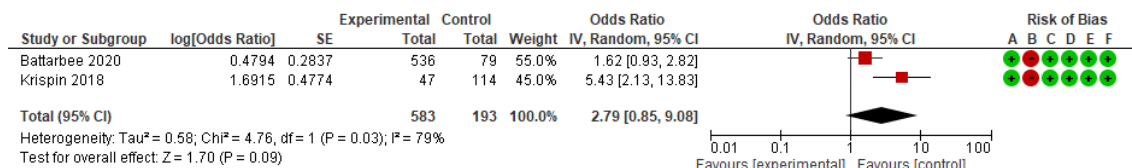


Risk of bias legend

- (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)

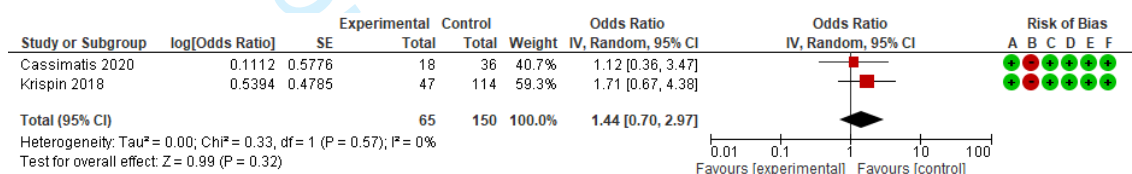


Risk of bias legend

- (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

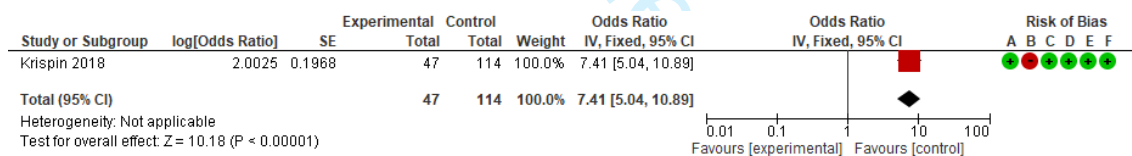


Risk of bias legend

- (A) Selection of participants (selection bias)
- (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) Admission to neonatal intensive care unit (NICU)



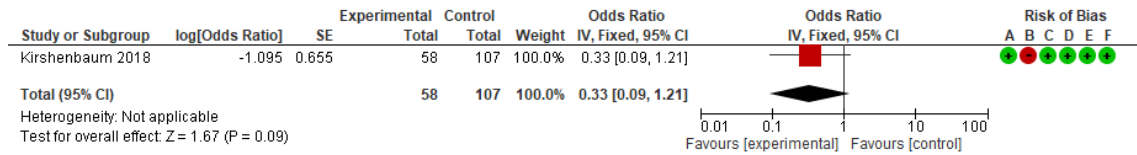
Risk of bias legend

- (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 undergoing elective cesarean section in the late preterm period

1) Hypertensive disorders

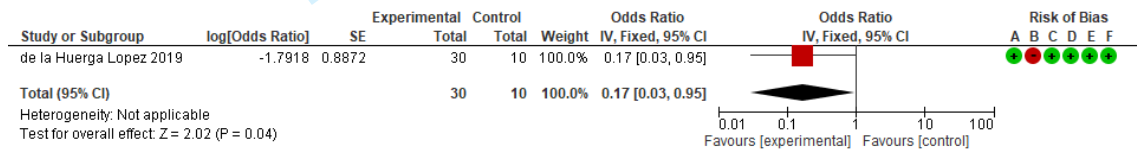


Risk of bias legend

- (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) Gestational diabetes mellitus



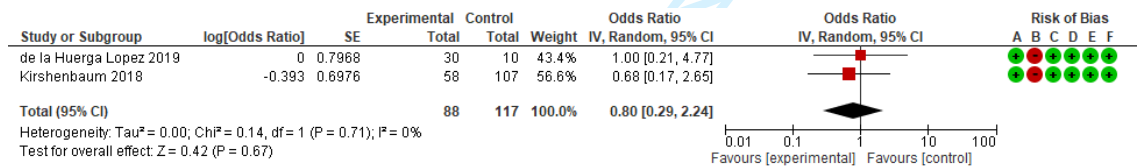
Risk of bias legend

- (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)

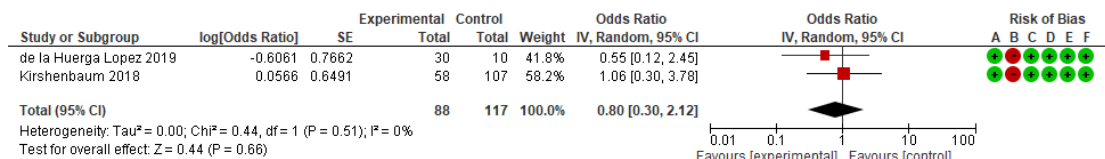


Risk of bias legend

- (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

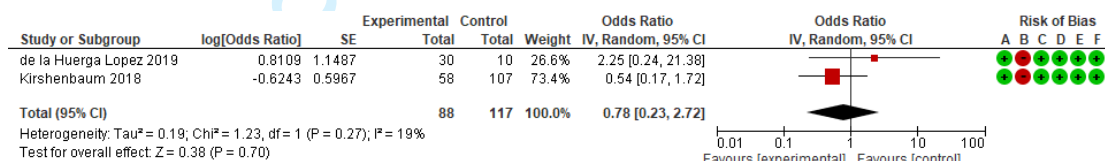


Risk of bias legend

- (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) Admission to neonatal intensive care unit (NICU)

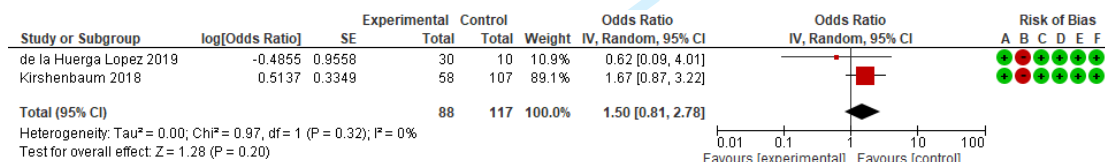


Risk of bias legend

- (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)
- (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)

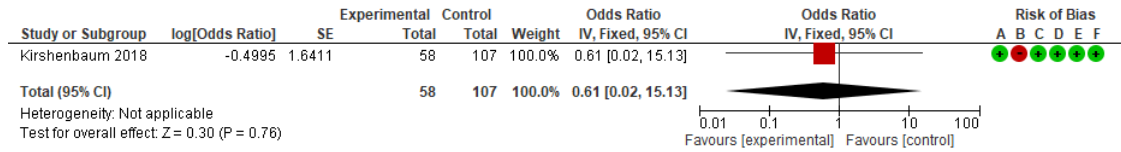


Risk of bias legend

- (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)

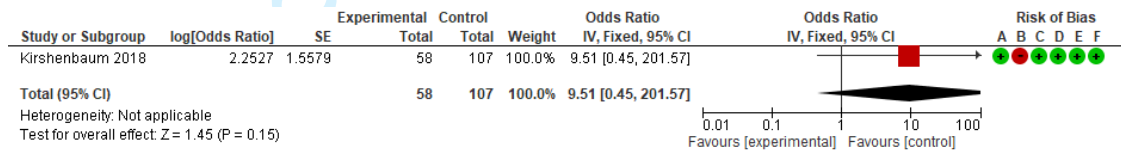


Risk of bias legend

- (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

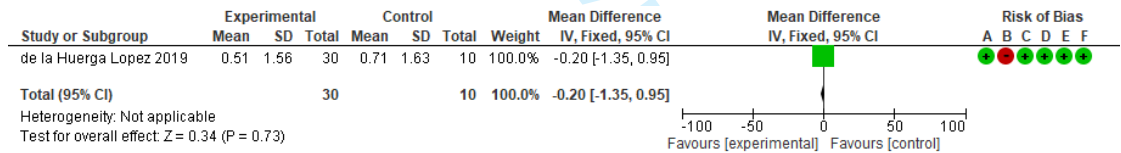


Risk of bias legend

- (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

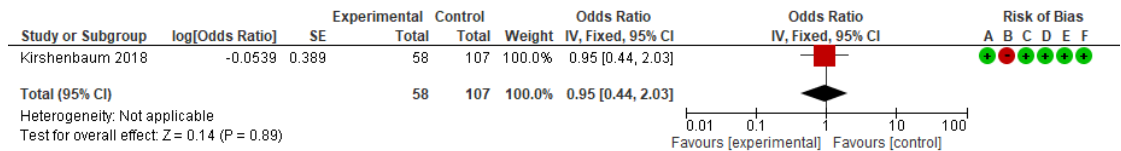


Risk of bias legend

- (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)



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

2) Gestational diabetes mellitus (HC)

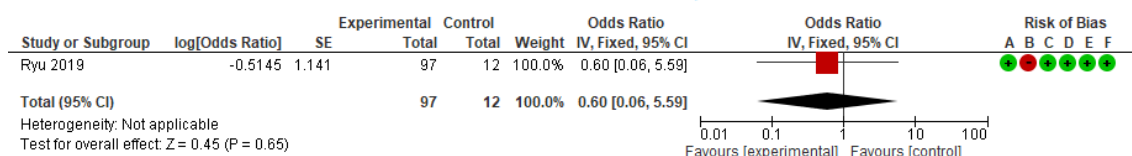


Risk of bias legend

- (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

3) Preeclampsia or eclampsia (HC)



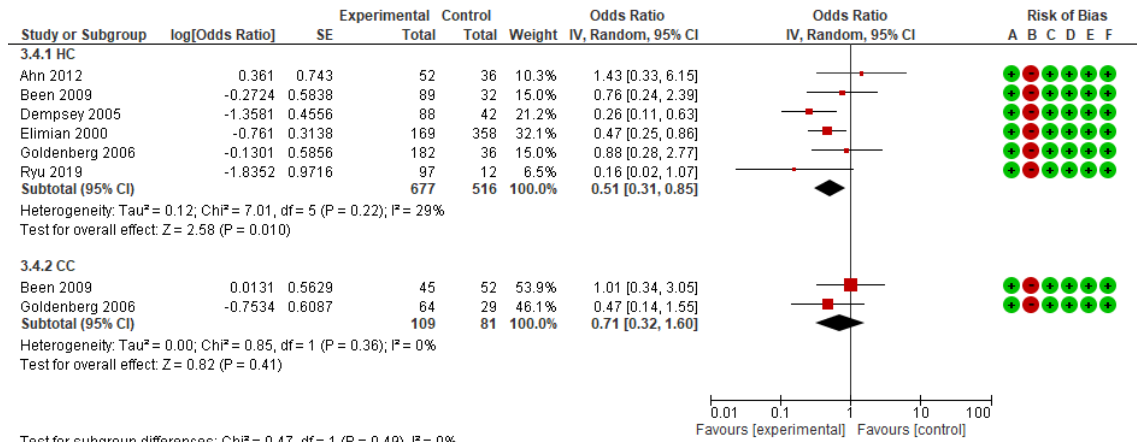
Risk of bias legend

- (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

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

1) Neonatal death



Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%

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; CC: Clinical chorioamnionitis

2) Death before discharge home (CC)

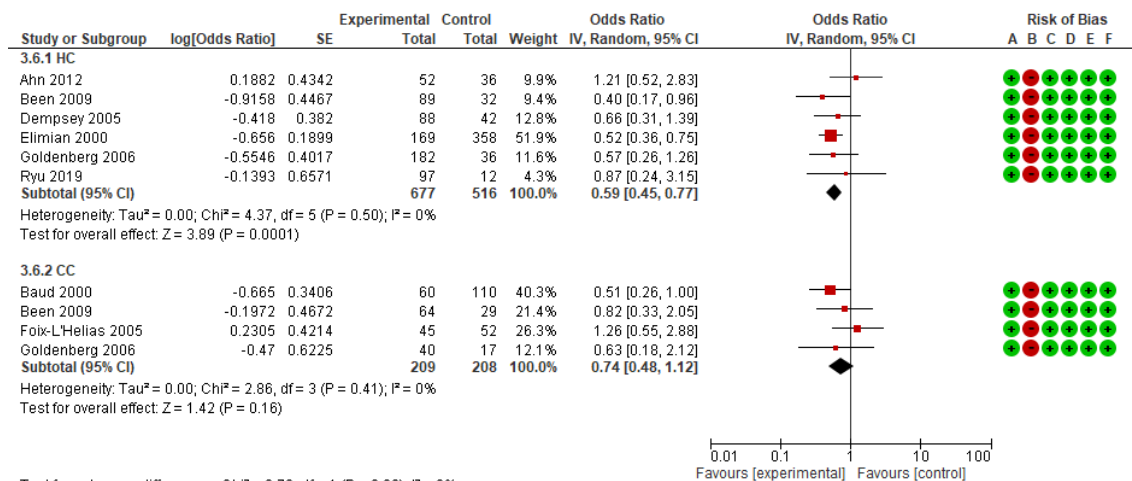


Risk of bias legend

- (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)

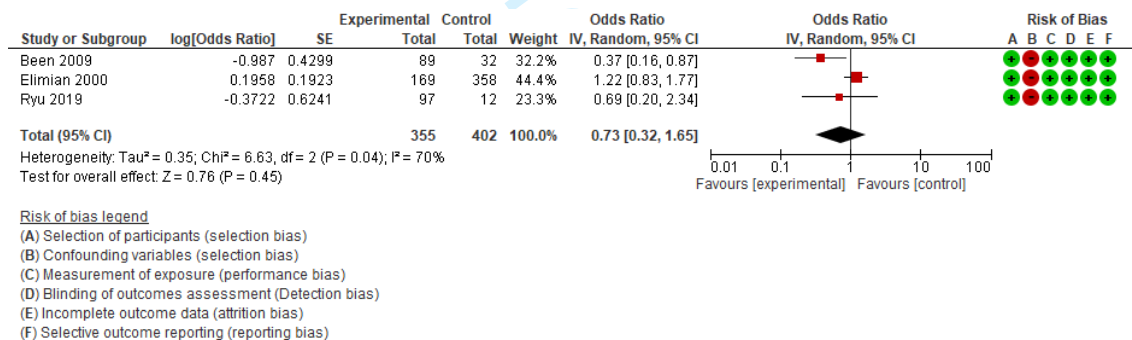
SE: Standard error; CI: Confidence interval; CC: Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



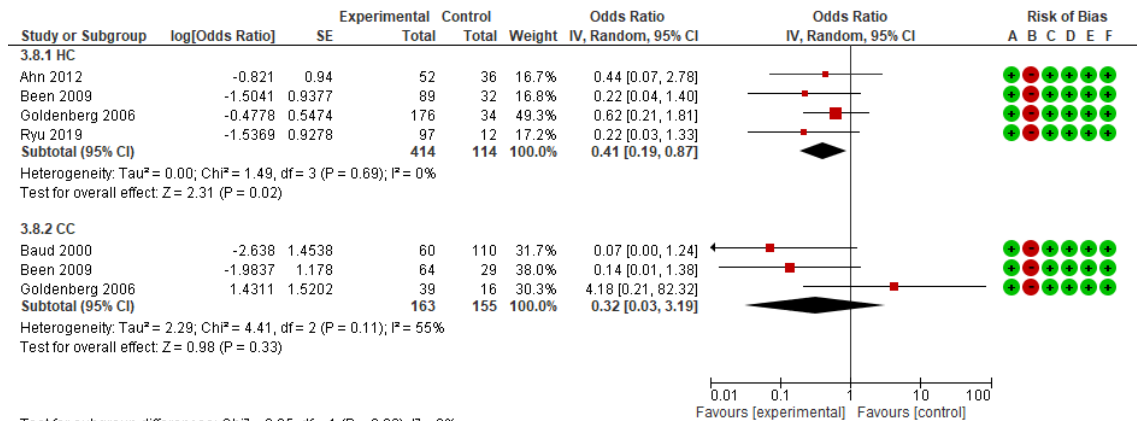
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

4) Surfactant use (HC)



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

5) Severe intraventricular hemorrhage (IVH)



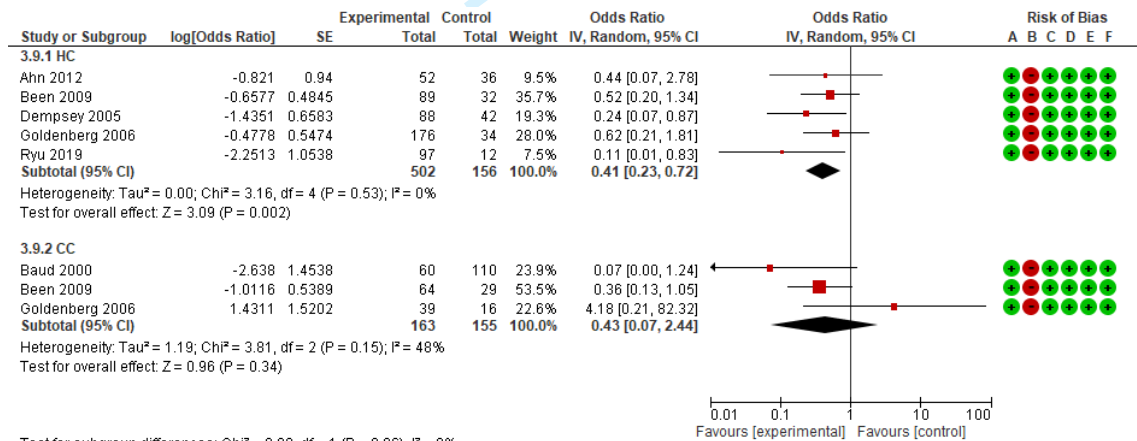
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%

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; CC: Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



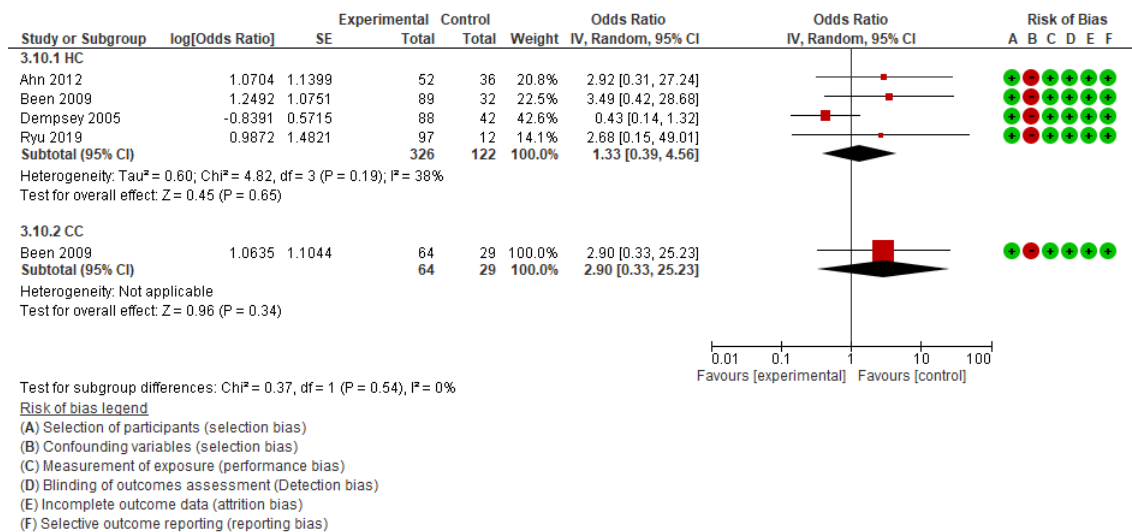
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

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)

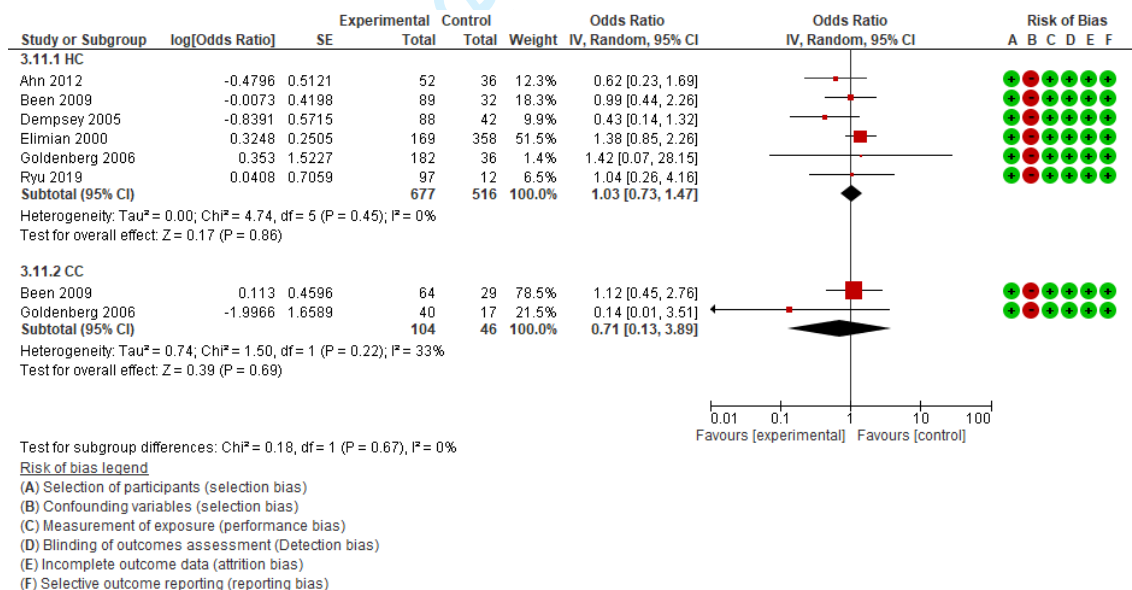
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

7) Early-onset sepsis



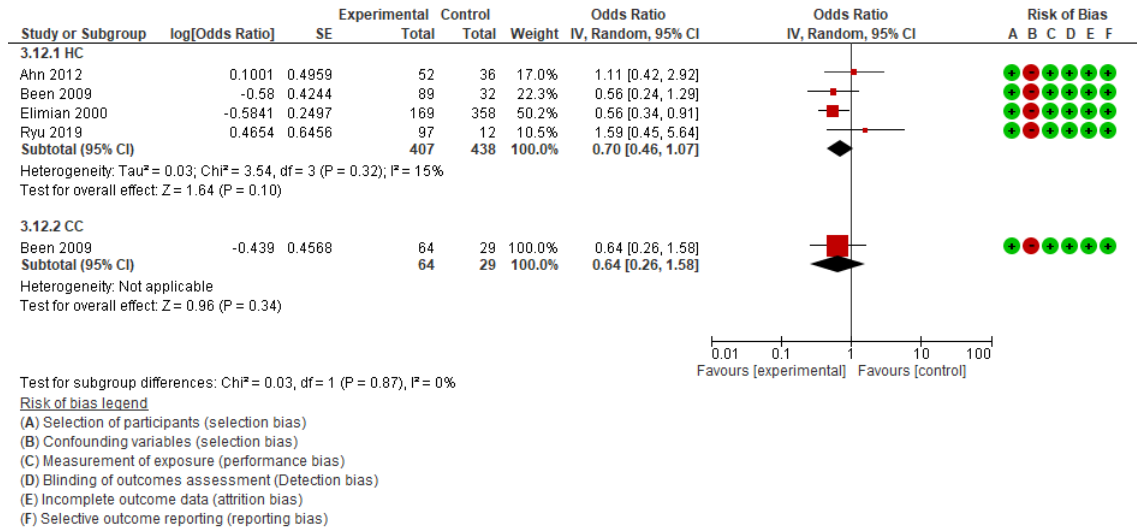
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

8) Sepsis



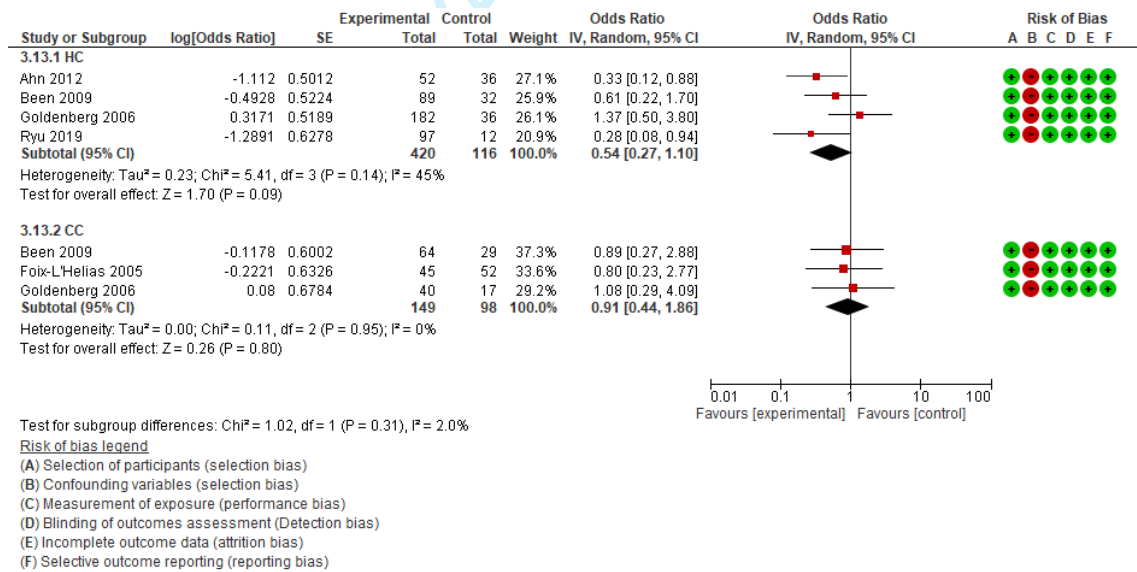
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



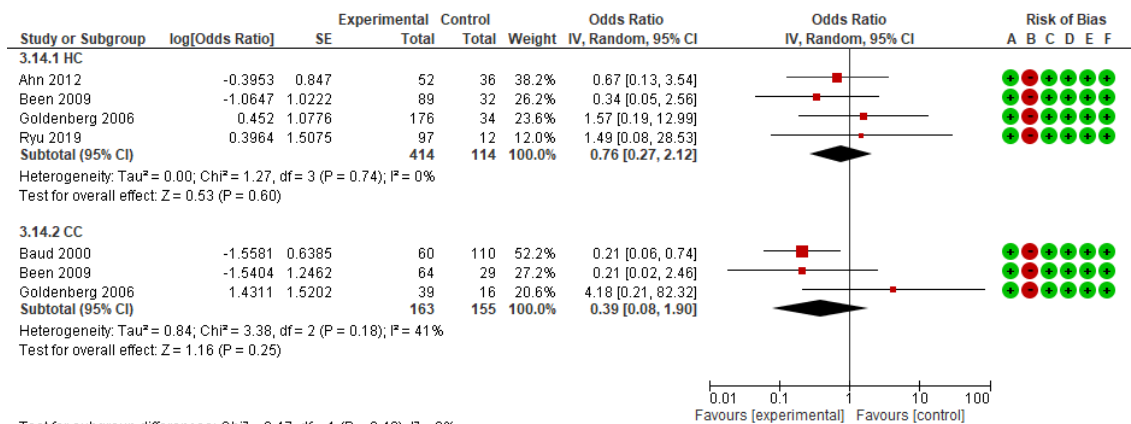
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



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

11) Periventricular leukomalacia (PVL)



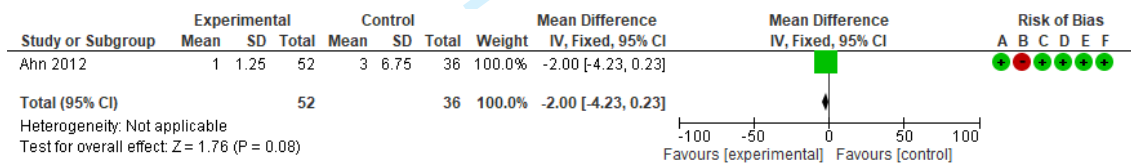
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%

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; CC: Clinical chorioamnionitis

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

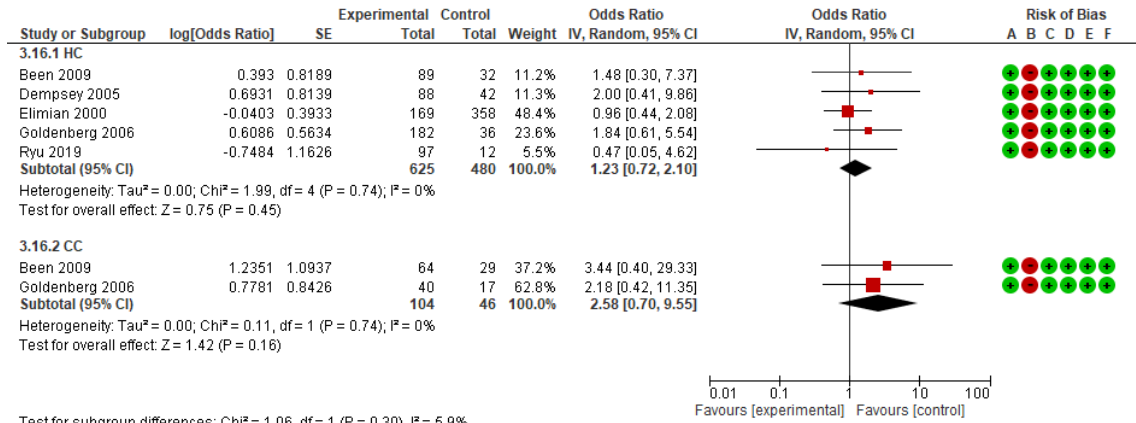


Risk of bias legend

- (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)

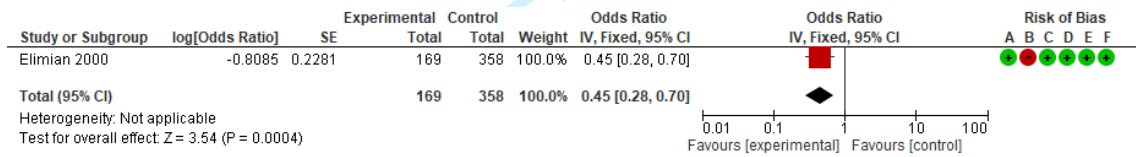
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

13) Necrotizing enterocolitis (NEC)



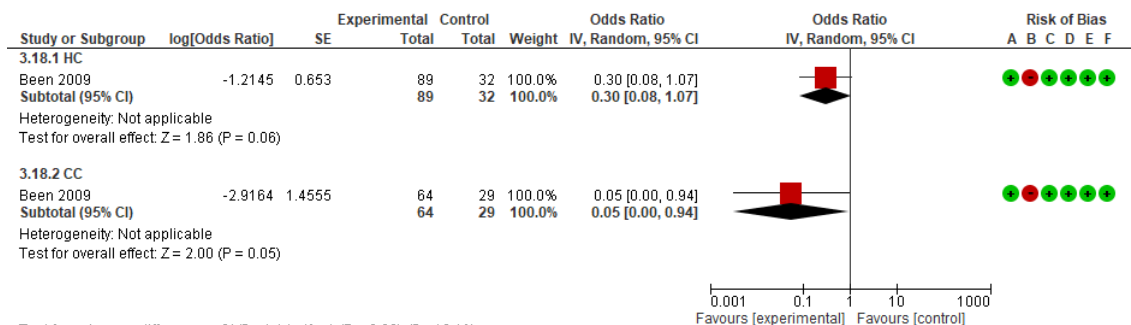
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



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

15) Use of mechanical ventilation



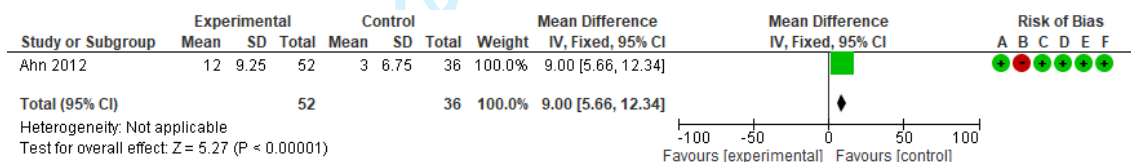
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.1%

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; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)

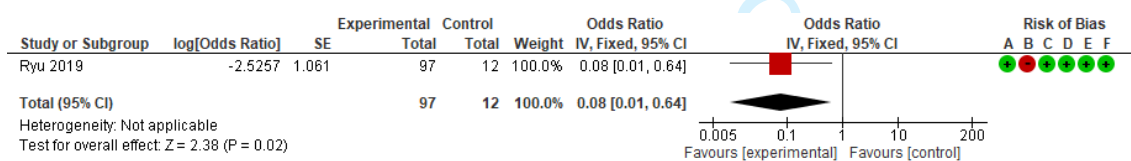


Risk of bias legend

- (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

17) Hypotension within 7 postnatal days (HC)

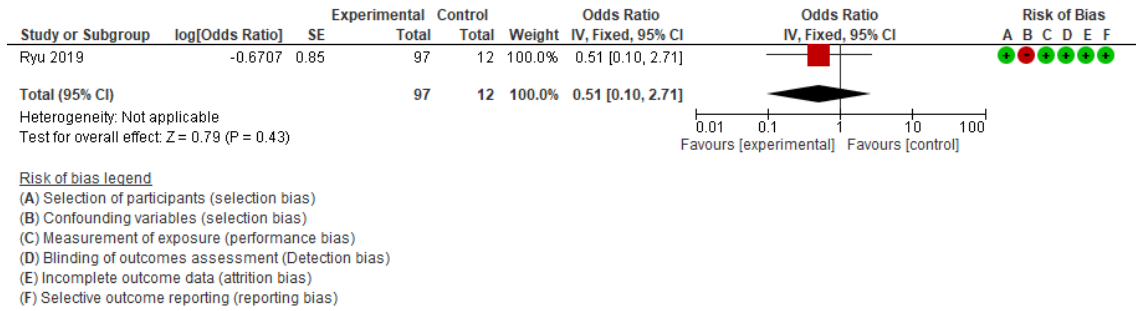


Risk of bias legend

- (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)

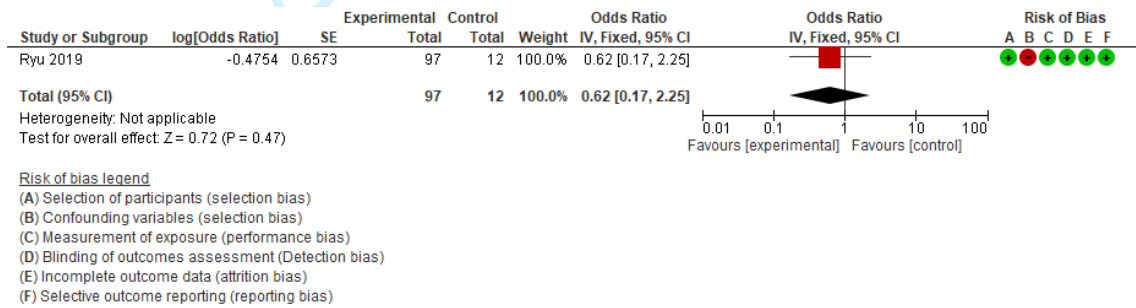
SE: Standard error; **CI:** Confidence interval; **HC:** Histological chorioamnionitis

18) Retinopathy of prematurity requiring treatment (HC)



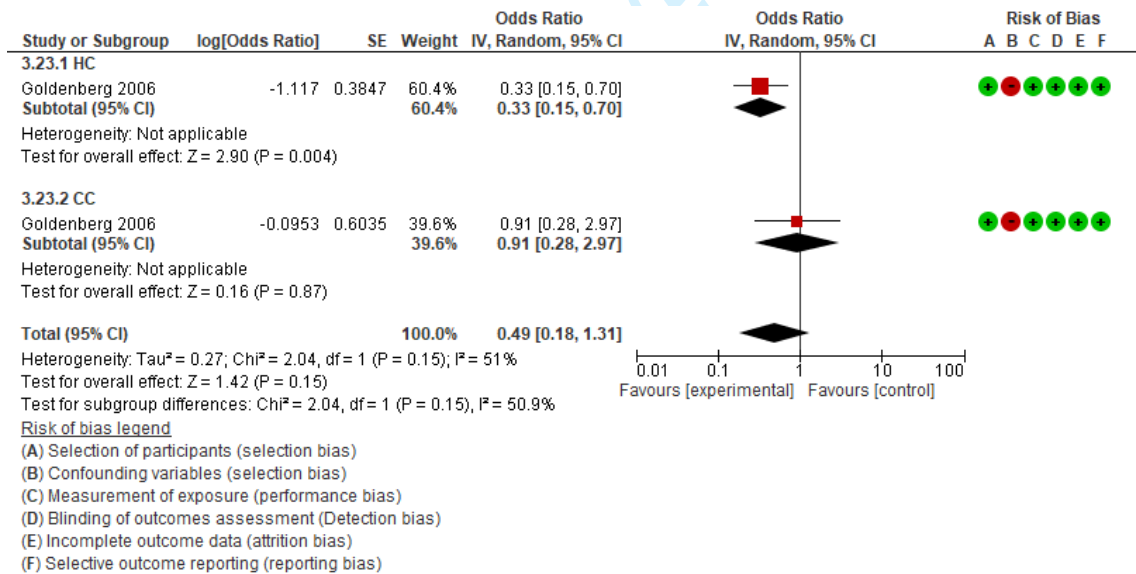
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

19) Discharge with respiratory support (HC)



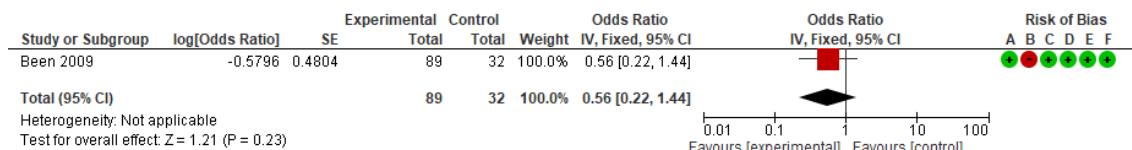
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

20) Systemic inflammatory response syndrome



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

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

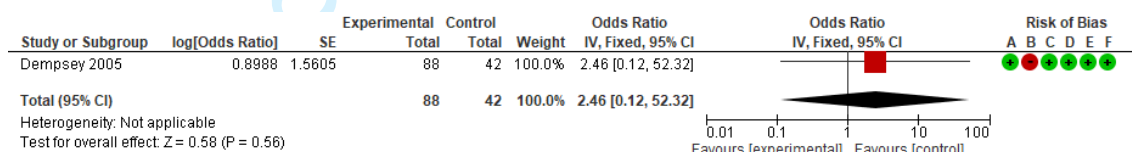


Risk of bias legend

- (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)

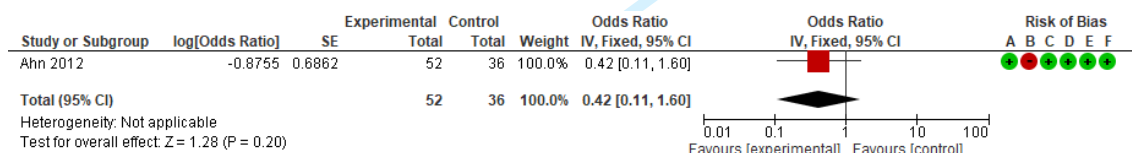


Risk of bias legend

- (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)

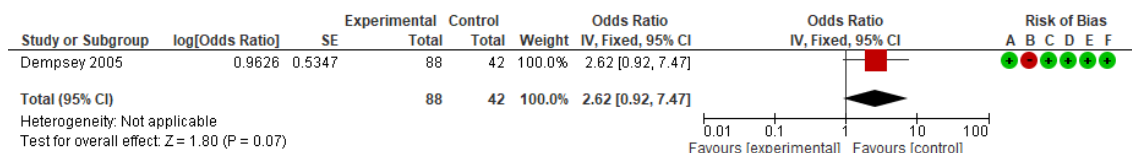


Risk of bias legend

- (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)



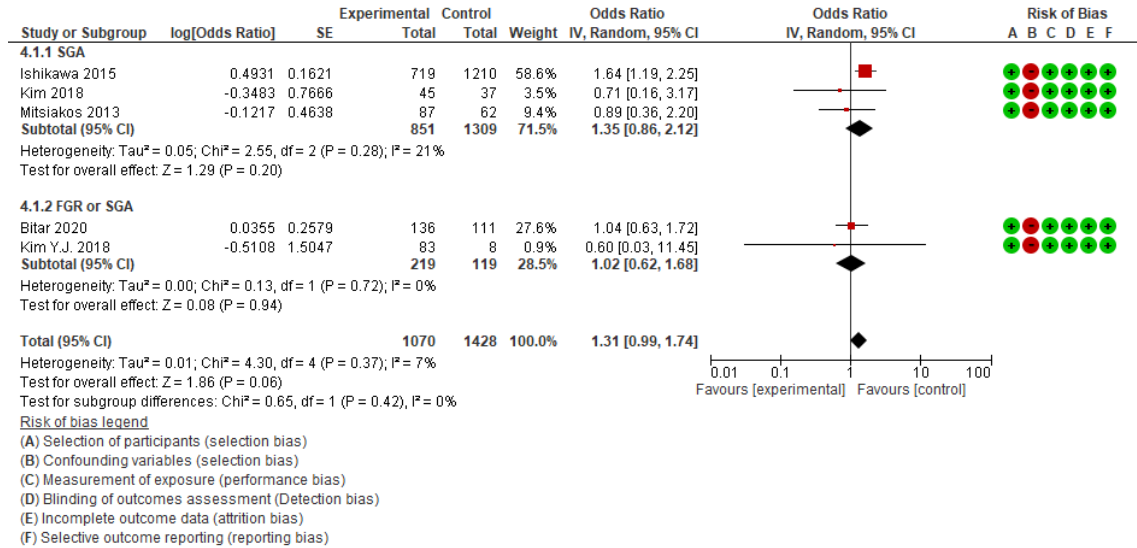
Risk of bias legend

- (A) Selection of participants (selection bias)
- (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

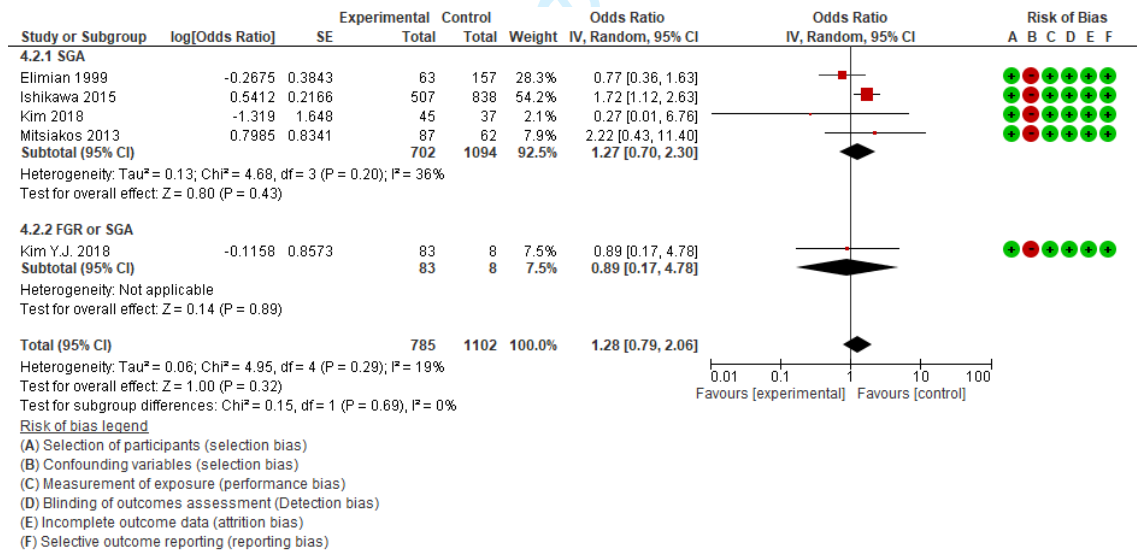
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



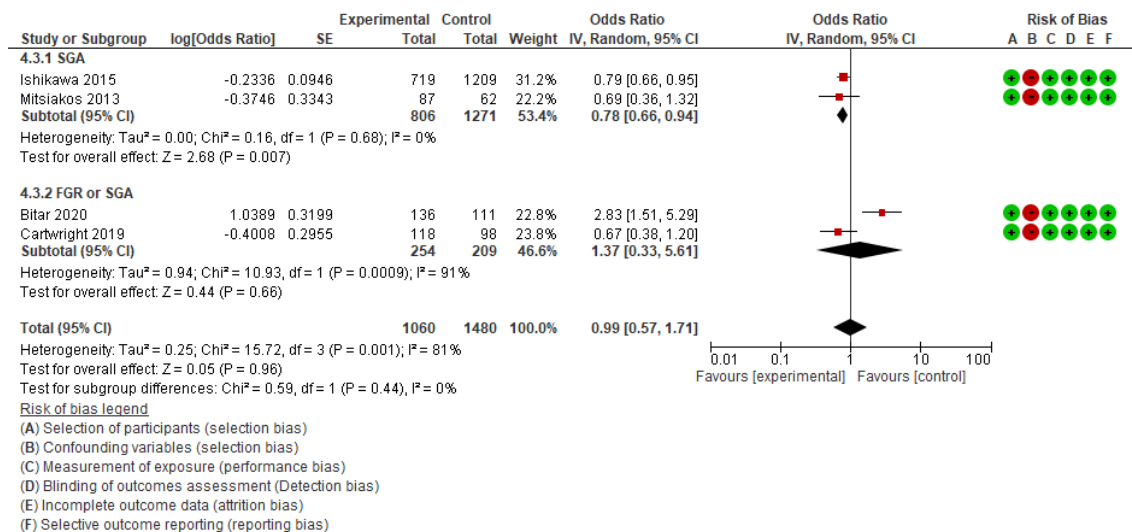
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

2) Chorioamnionitis (histologic and /or clinical)



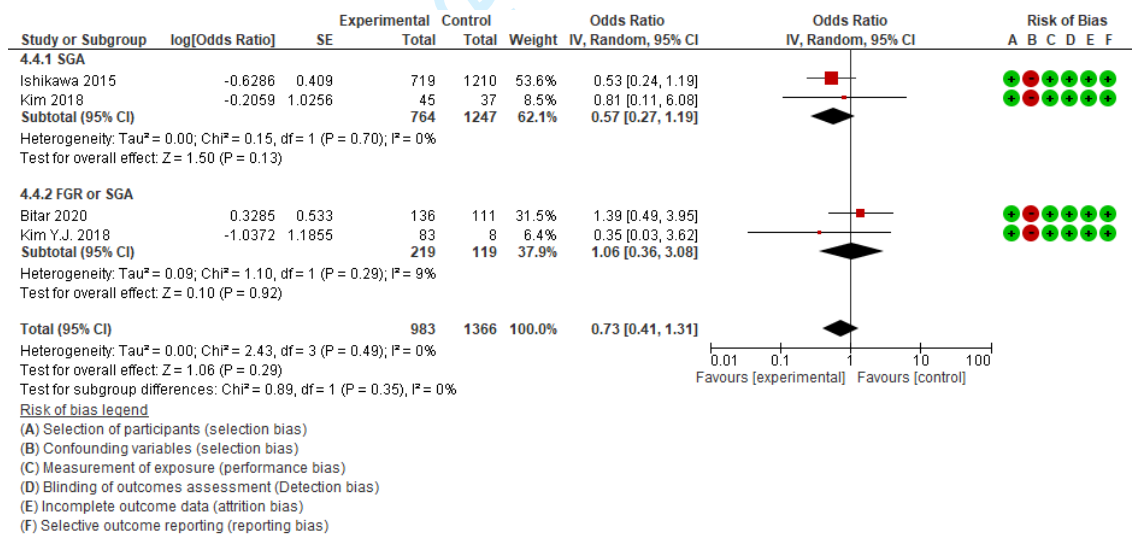
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

3) Preeclampsia.



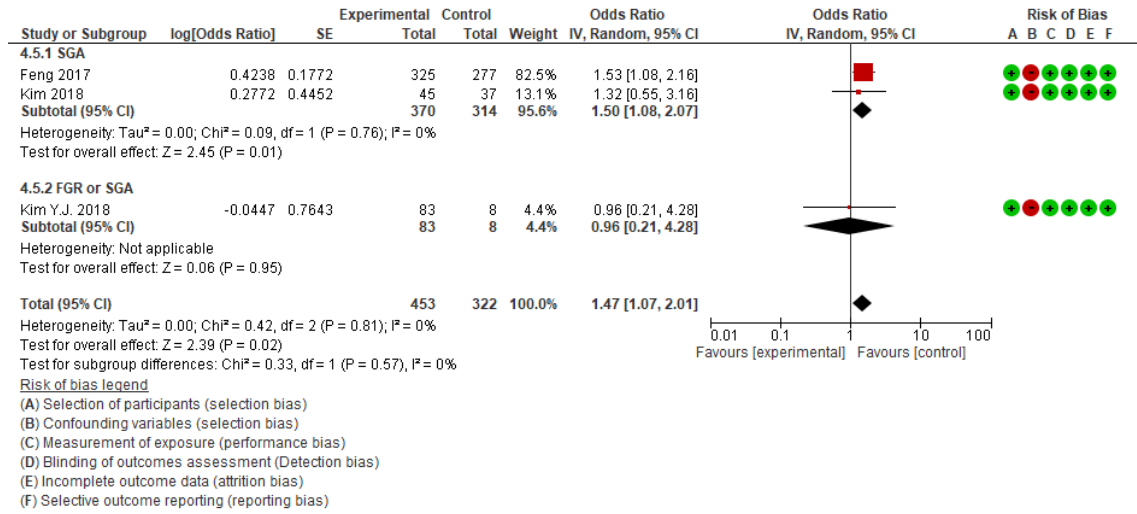
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Gestational diabetes mellitus.



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

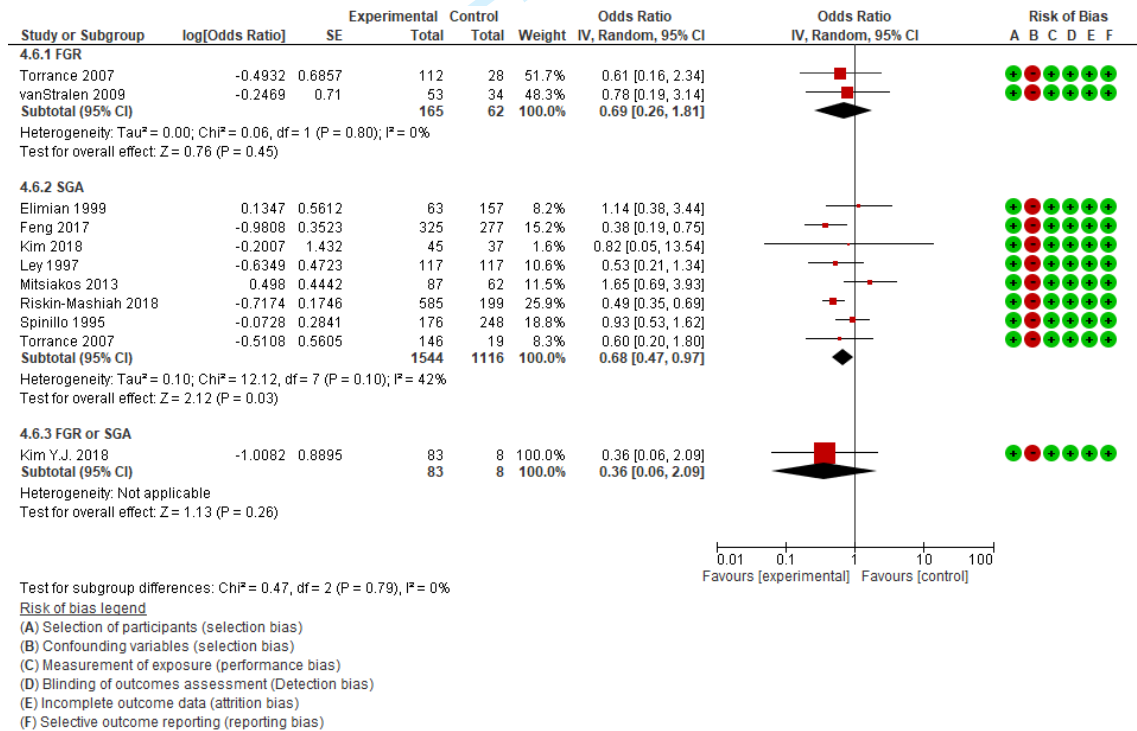
5) Pregnancy induced hypertension.



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

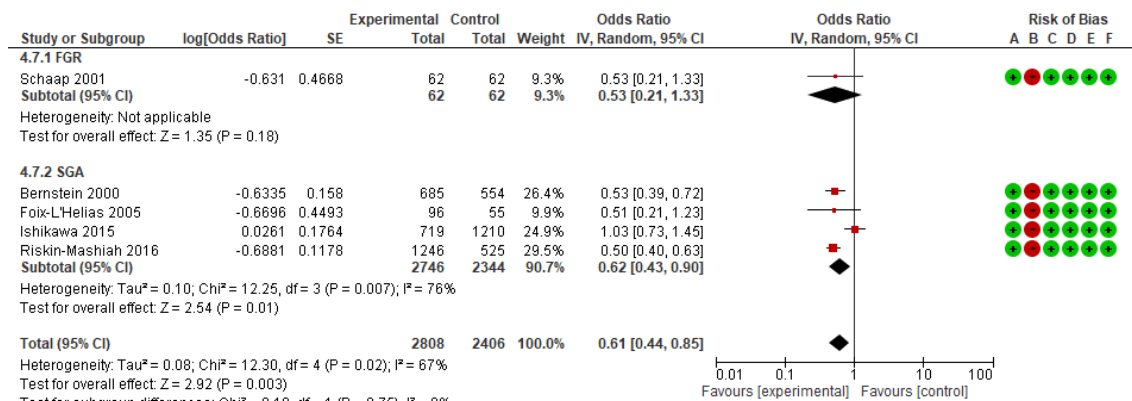
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



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

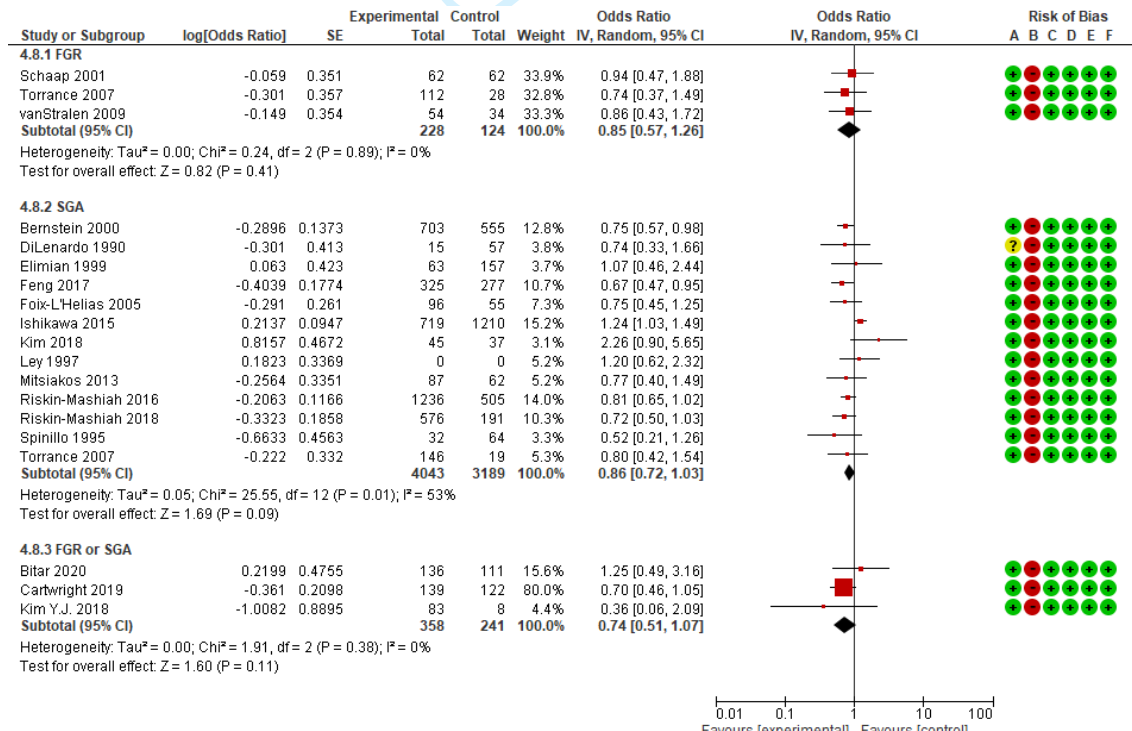
2) Death before discharge home



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

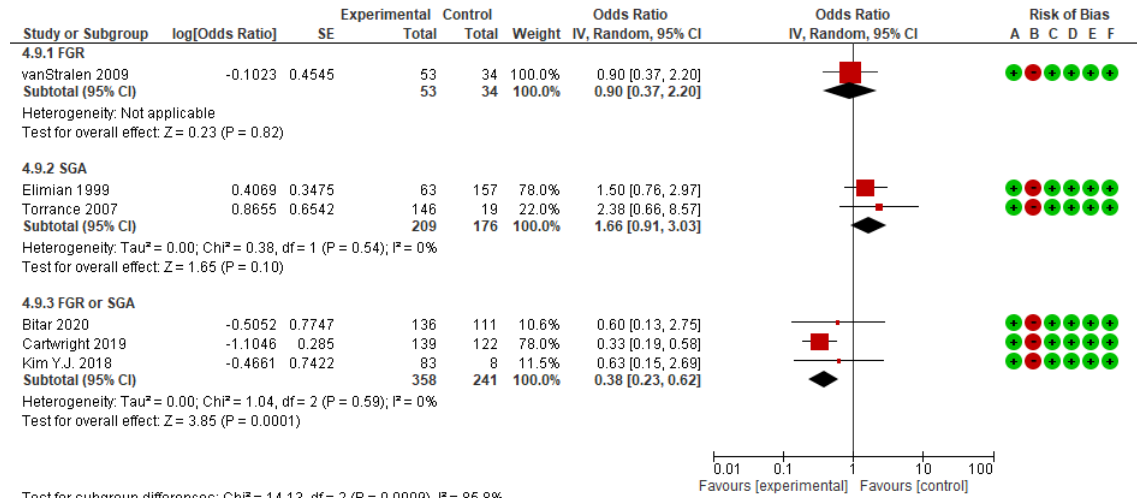
3) Respiratory distress syndrome (RDS) and moderate / severe RDS



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; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Surfactant use



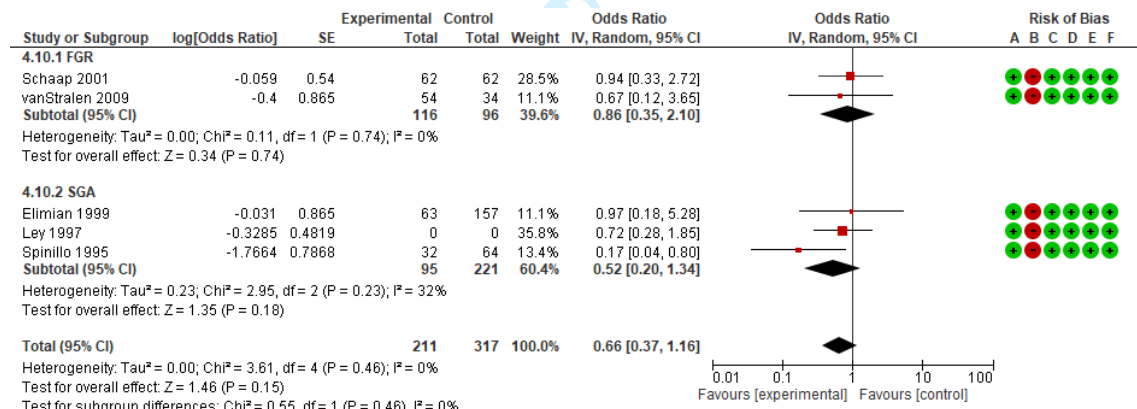
Test for subgroup differences: Chi² = 14.13, df = 2 (P = 0.0009), I² = 85.8%

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

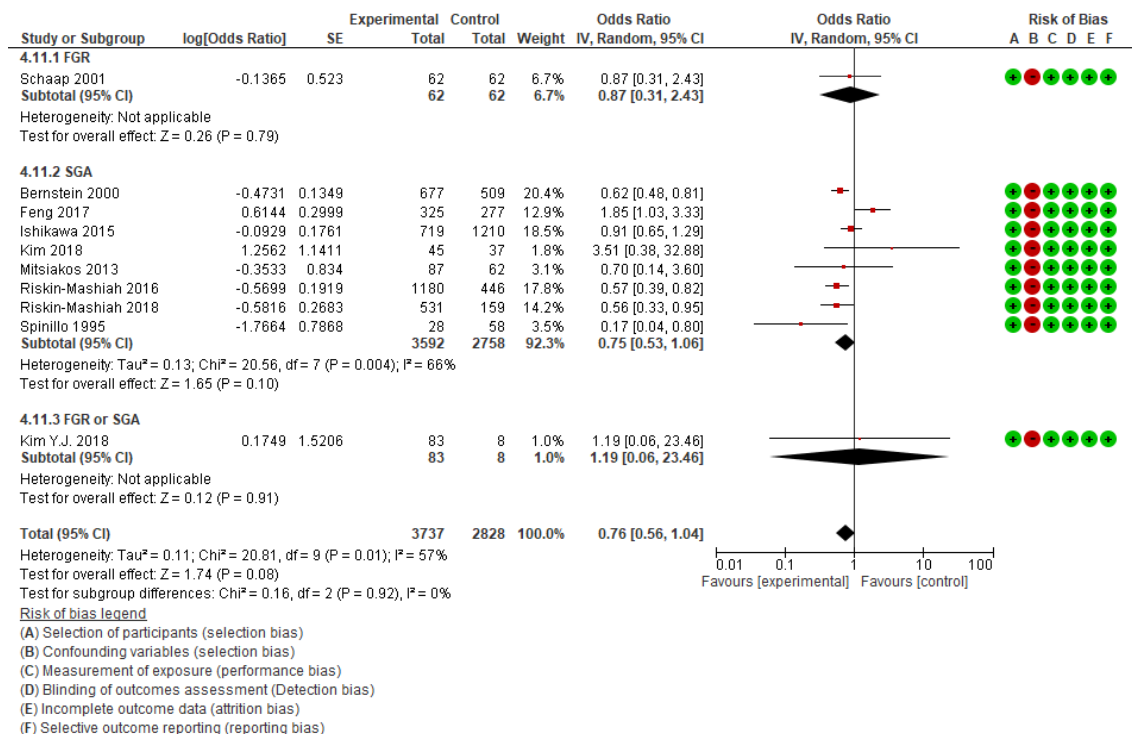
5) Major brain lesion (IVH, ICH, PVH, PVL)

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)

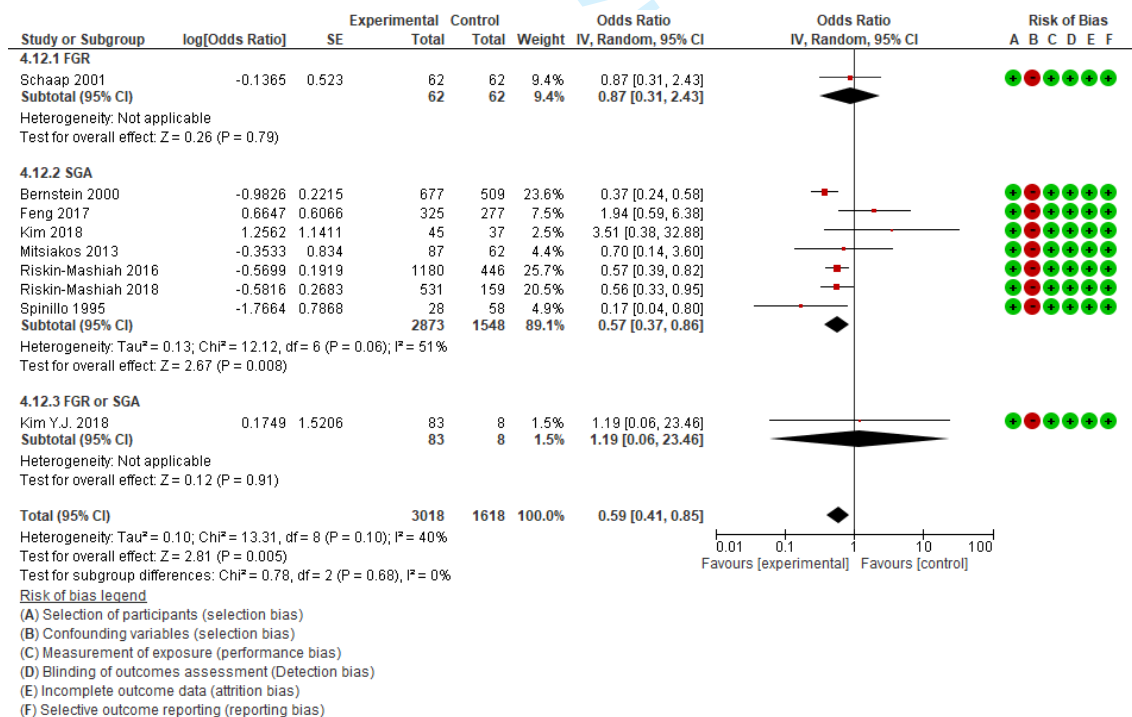
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

6) Interventricular haemorrhage



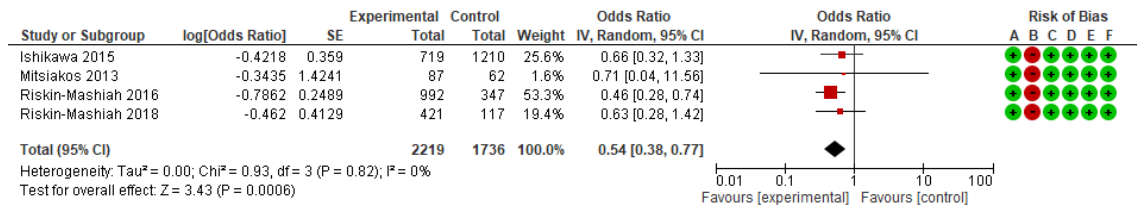
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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)

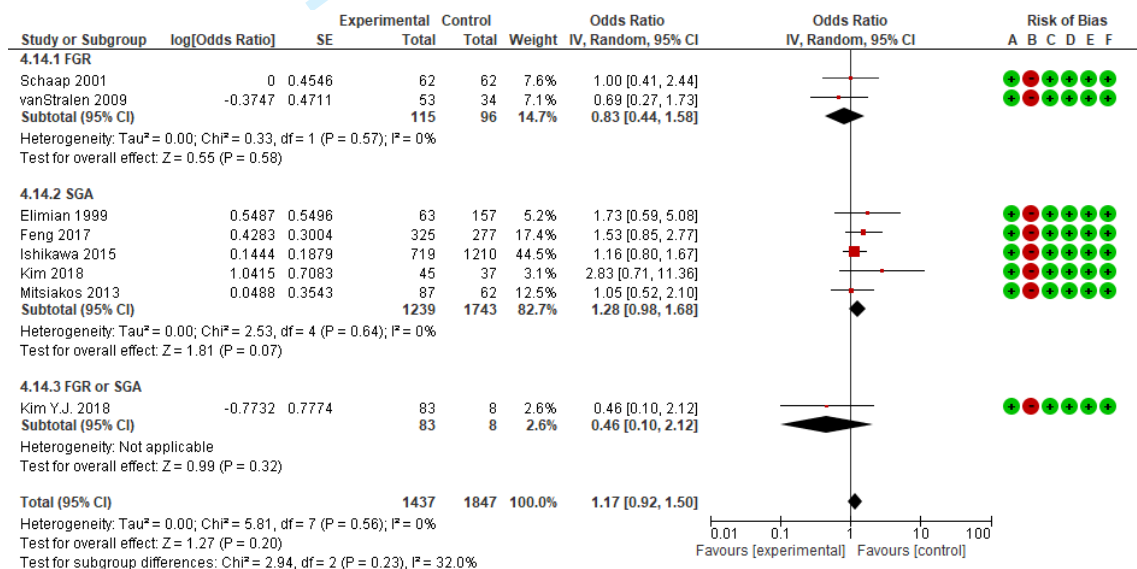


Risk of bias legend

- (A) Selection of participants (selection bias)
- (B) Confounding variables (selection bias)
- (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

9) Neonatal sepsis

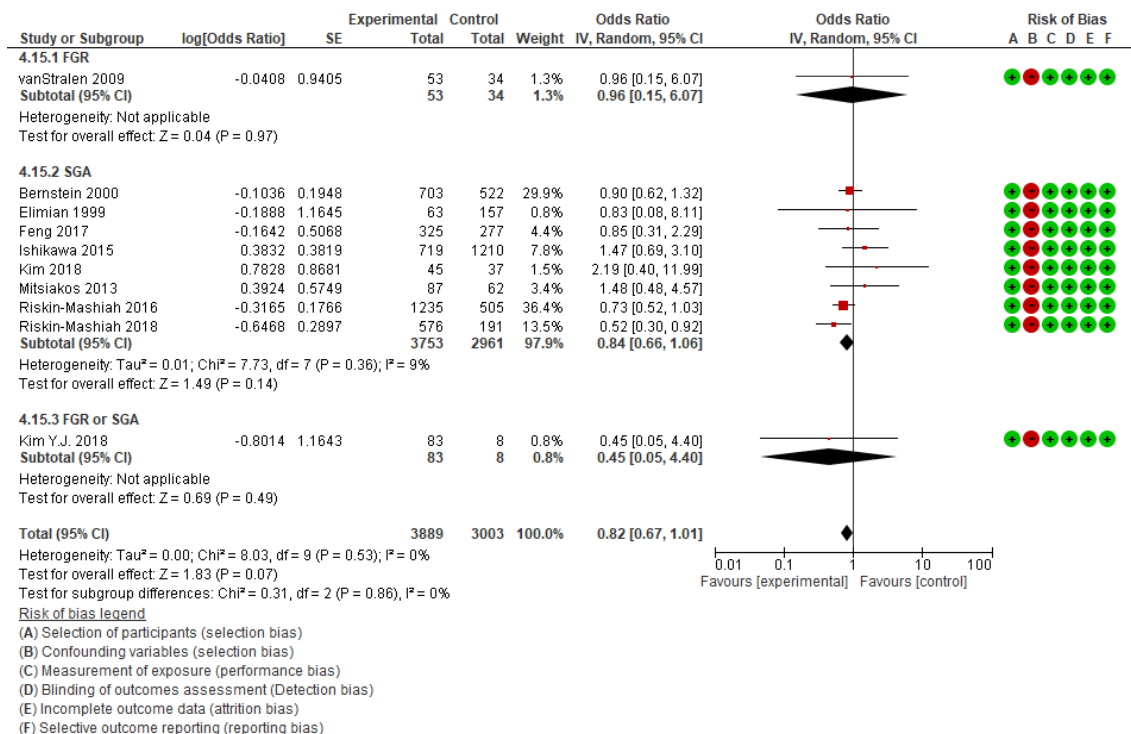


Risk of bias legend

- (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)

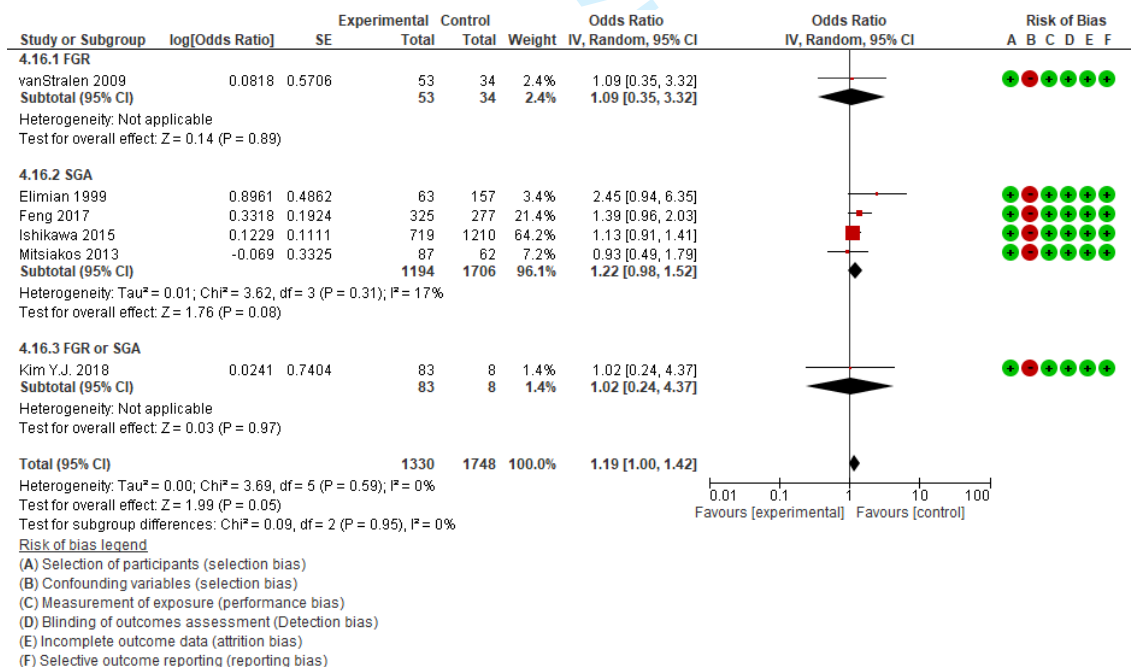
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

10) Necrotizing enterocolitis



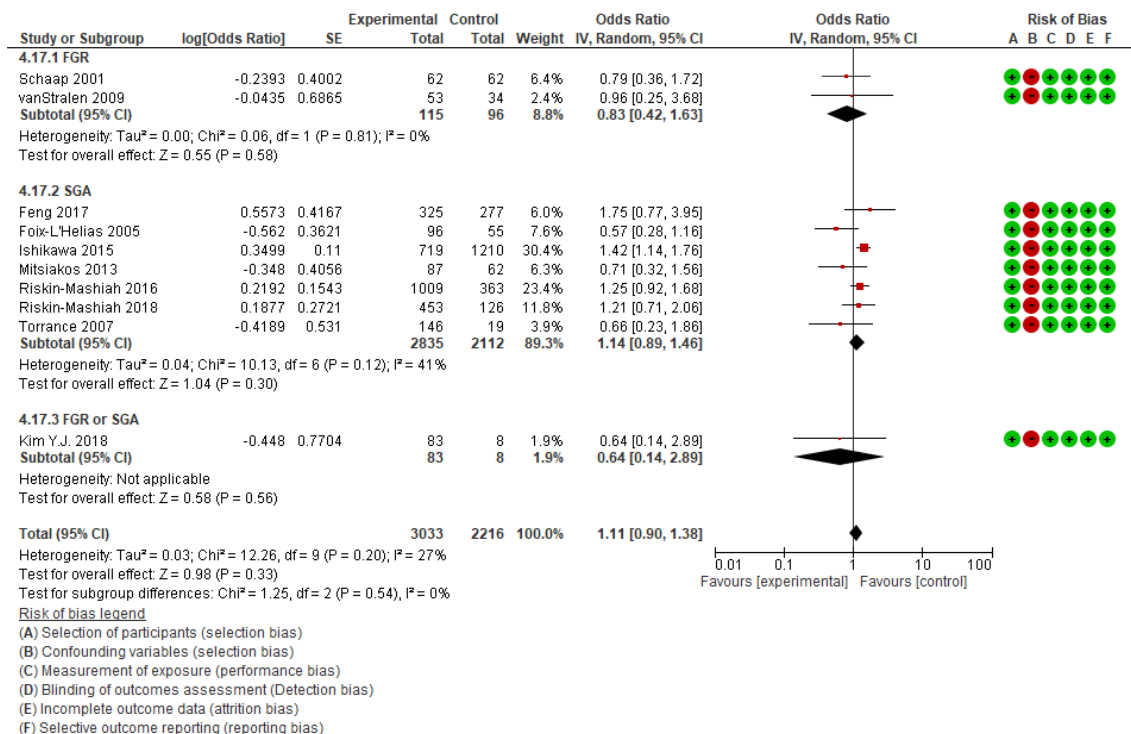
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

11) Patent ductus arteriosus



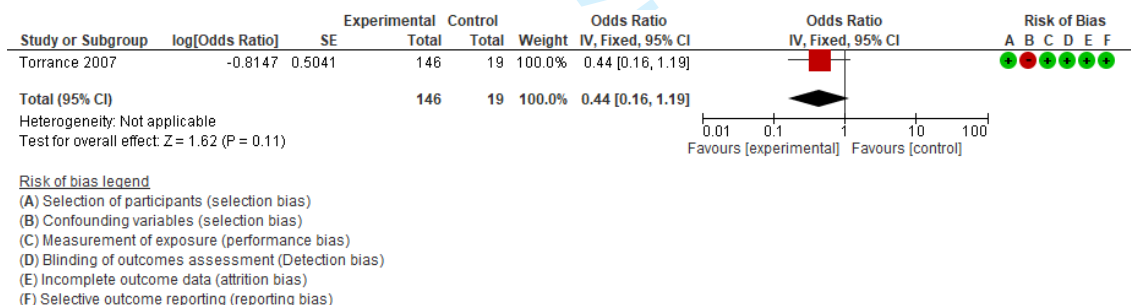
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



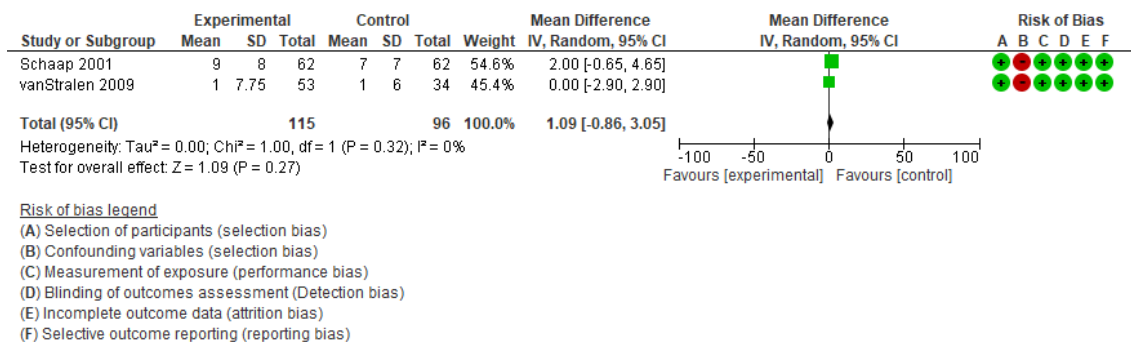
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



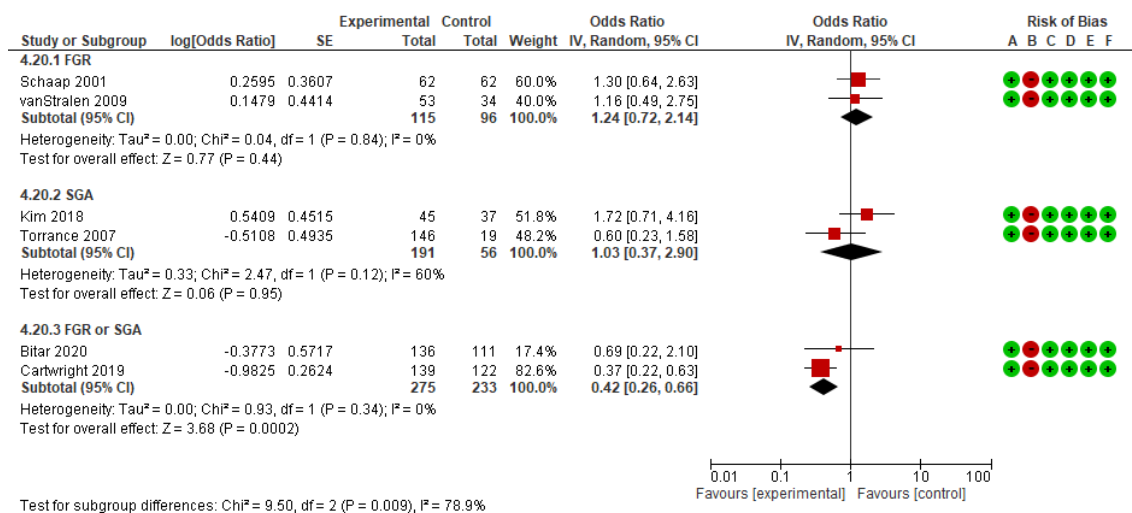
SE: Standard error; CI: Confidence interval

14) Duration of mechanical ventilation (FGR)



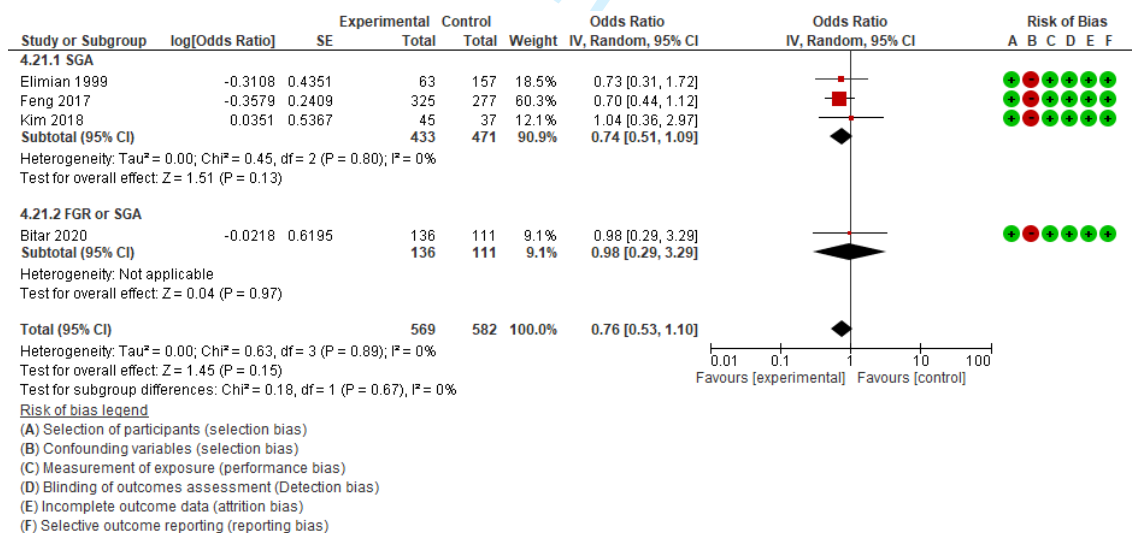
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction

15) Use of mechanical ventilation



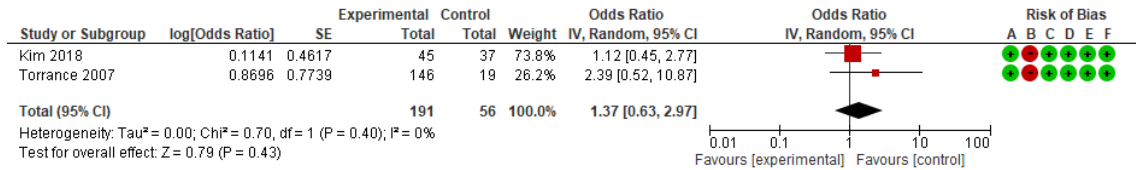
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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)

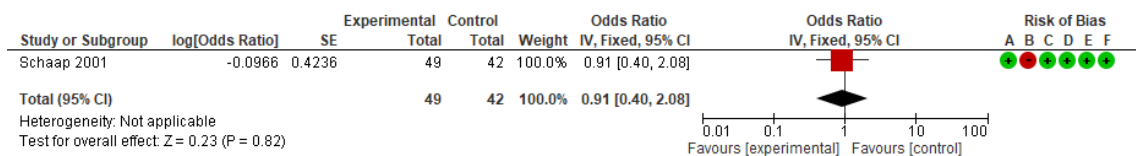


Risk of bias legend

- (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)

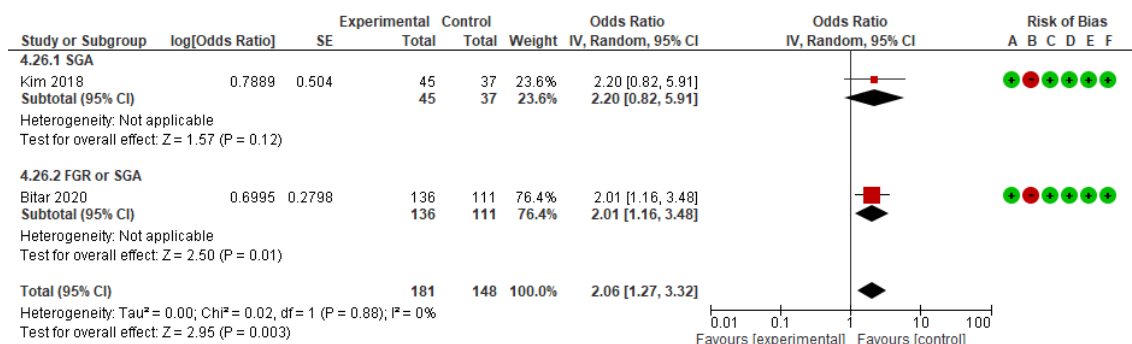


Risk of bias legend

- (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

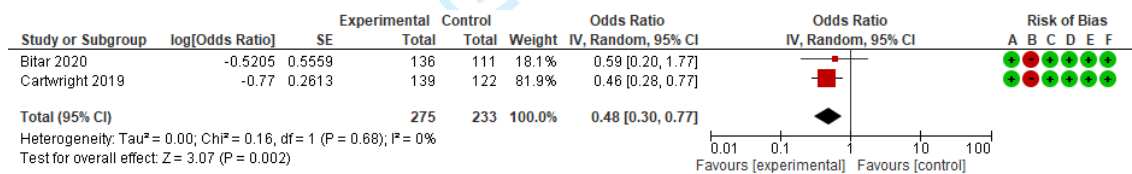
21) Neonatal hypoglycemia



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

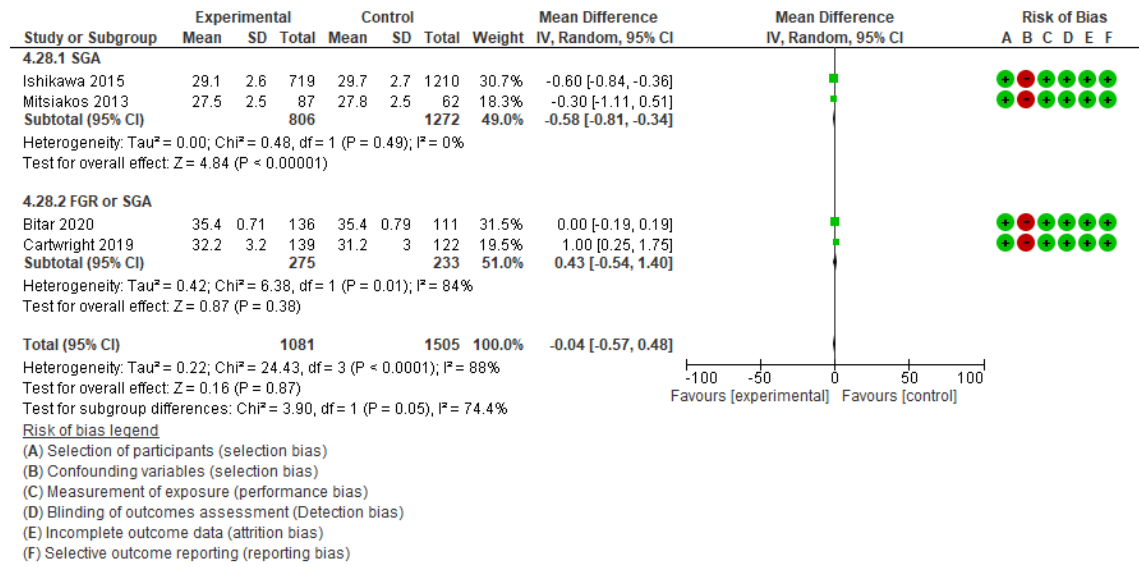
22) Oxygen therapy (FGR or SGA)



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)

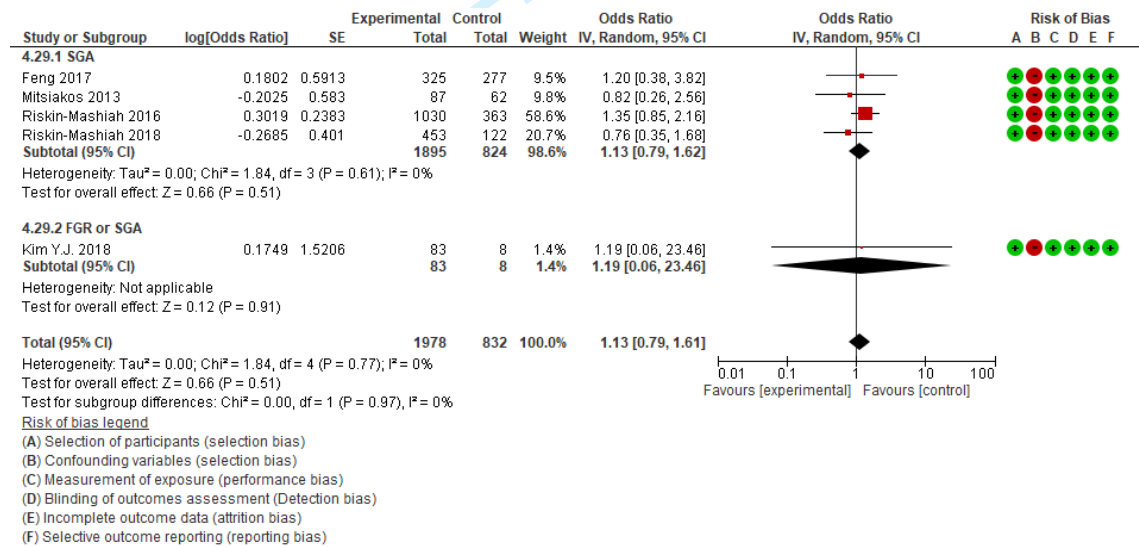
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

23) Gestational age at birth



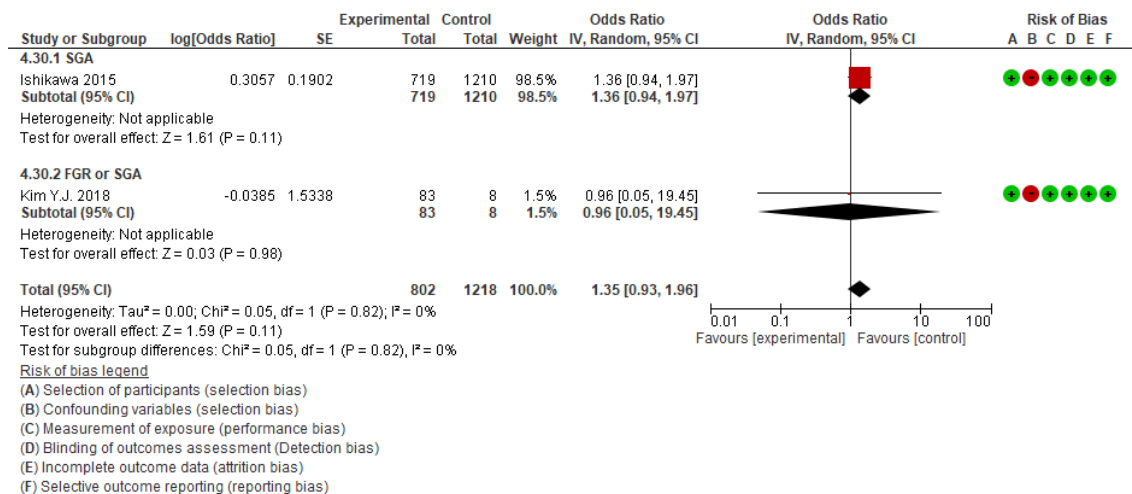
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

24) Retinopathy of prematurity



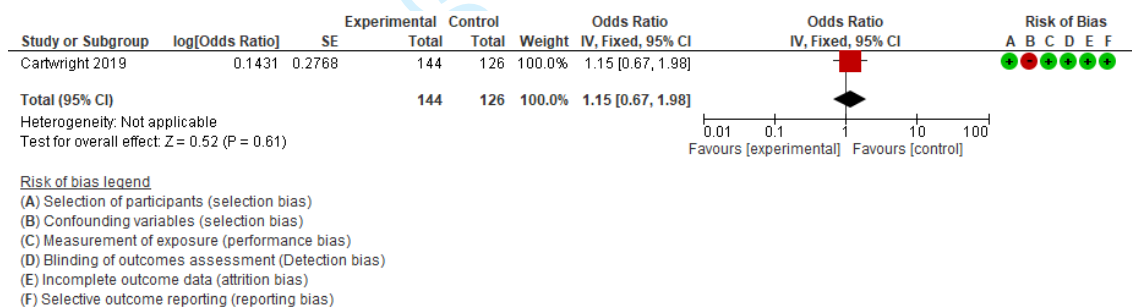
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

25) Neonatal adrenal insufficiency



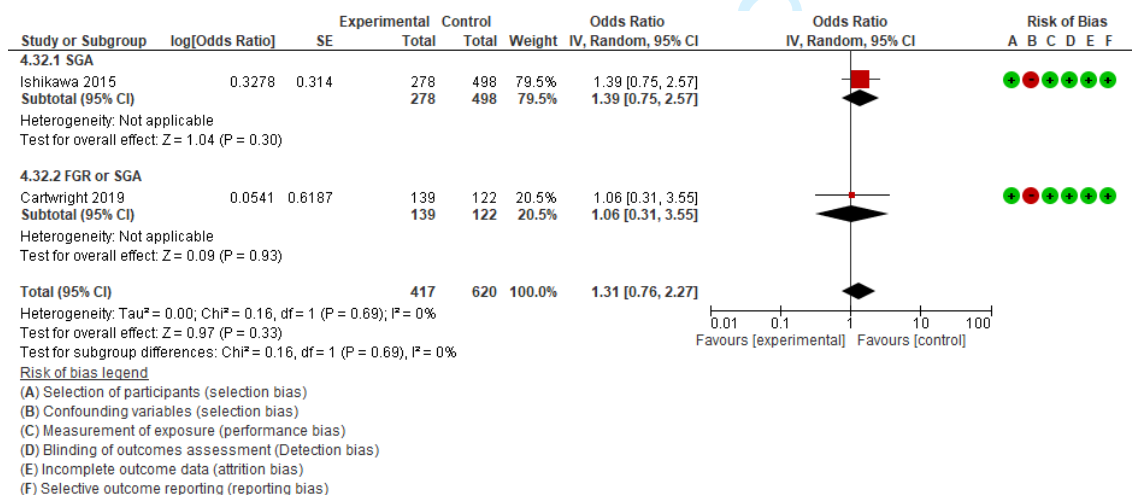
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

26) Survival free of disability (FGR or SGA)



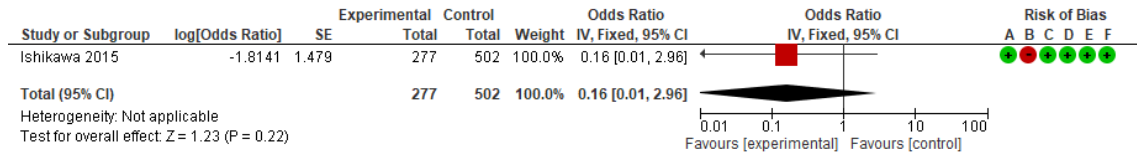
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

27) Cerebral palsy



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

28) Severe hearing impairment (SGA)

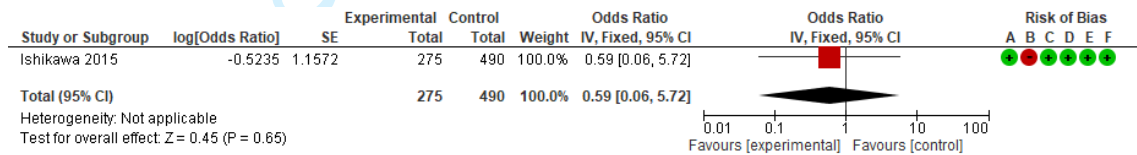


Risk of bias legend

- (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)

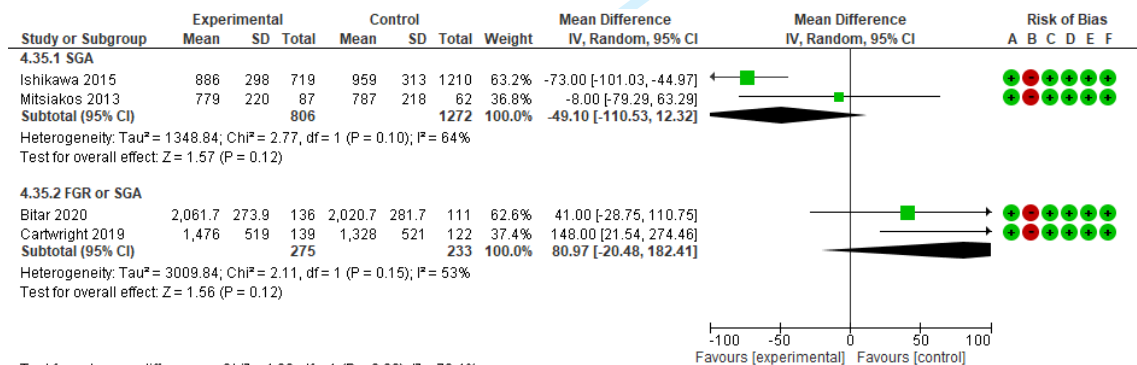


Risk of bias legend

- (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

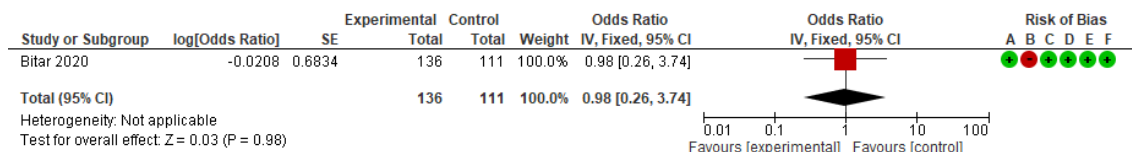


Risk of bias legend

- (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)

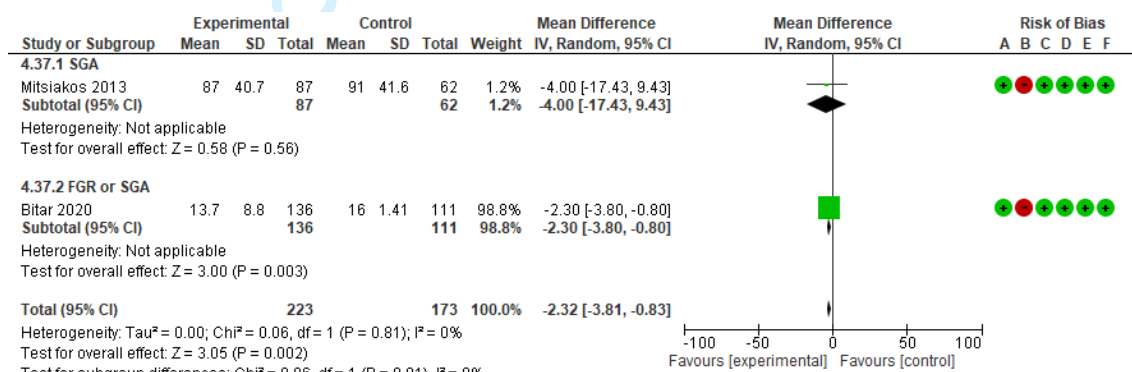


Risk of bias legend

- (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

32) Duration of hospital stay

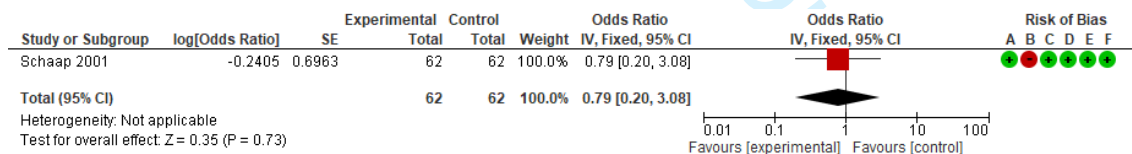


Risk of bias legend

- (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

33) Death at long-term follow-up (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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-065070.R3
Article Type:	Original research
Date Submitted by the Author:	09-Jul-2023
Complete List of Authors:	Saito, KANA; Saitama Medical Center, Pediatrics Nishimura, Etsuko; St Luke's International University, Graduate School of Nursing Science Ota, Erika; St Luke's International University, Graduate School of Nursing Science; The Tokyo Foundation for Policy Research Namba, Fumihiko; Saitama Medical Center, Pediatrics Swa, Toshiyuki; Osaka University School of Medicine Graduate School of Medicine Ramson, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Lavin, Tina; World Health Organization, Department of Sexual and Reproductive Health and Research Cao, Jenny; Burnet Institute, Maternal, Child and Adolescent Health Program Vogel, Joshua; Burnet Institute, Maternal, Child and Adolescent Health Program
Primary Subject Heading:	Paediatrics
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

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF 2 PRETERM BIRTH: A SYSTEMATIC REVIEW

3
4 Kana Saito^a, Etsuko Nishimura^b, Erika Ota^{b,c}, Fumihiko Namba^a, Toshiyuki Swa^d,
5 Jenny Ramson^e, Tina Lavin^f, Jenny Cao^e, Joshua P. Vogel^e

7 Affiliations

8 ^a Saitama Medical Center, Saitama Medical University, Saitama, Japan

9 ^b St. Luke's International University, Tokyo, Japan

10 ^c Tokyo Foundation for Policy Research, Tokyo, Japan

11 ^d Osaka University, Graduate School of Medicine, Osaka, Japan

12 ^e Maternal, Child, and Adolescent Health Program, Burnet Institute, Melbourne,
13 Australia

14 ^f UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research,
15 Development and Research Training in Human Reproduction, Department of Sexual
16 and Reproductive Health and Research, World Health Organization, Geneva,
17 Switzerland.

19 Correspondence to: Kana Saito

20 Department of Pediatrics, Saitama Medical Center, Saitama Medical University

21 1981 Kamoda, Kawagoe-city, Saitama 350-8550, Japan,

22 Phone:81-49-228-3400

23 E-mail: kana988@live.jp

24 ORCID: 0000-0001-7781-1870

25
26 **Word count:** 4416 words

27
28 **Short title:** Systematic review: antenatal steroids in specific women

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.

94 INTRODUCTION

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

107 However, current evidence regarding the benefits and possible harms of ACS use in
108 subpopulations of women with specific complications of pregnancy, such as women
109 with diabetes, chorioamnionitis, or fetal growth restriction (FGR), is controversial.
110 Women with diabetes, chorioamnionitis, or FGR are at a higher risk of adverse perinatal
111 outcomes; however, they are generally excluded from ACS efficacy trials [2].

112 Consequently, any subgroup analysis to explore the effects of ACS on women with
113 these complications is unlikely to yield concrete evidence from which conclusions can
114 be drawn.

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

1
2
3
4 118 maternal glycaemic control [7,8]. Chorioamnionitis is estimated to affect 3.9% of women
5
6 119 giving birth, causing 22.6–36.9% of stillbirths [9-11]. Chorioamnionitis treatment
7
8
9 120 involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided
10
11 121 due to concerns that its immunosuppressive effects may worsen outcomes for women
12
13 122 and their babies. However, the relative benefits and harms of using ACS in clinical
14
15 123 settings are unclear. FGR is associated with an increased risk of morbidity and mortality
16
17 124 [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as
18
19 125 SGA neonates are constitutionally, rather than pathologically, small [16]. In most cases,
20
21 126 FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant
22
23 127 women with both FGR fetuses and SGA neonates.

24
25
26
27 128 Another clinical scenario where there is uncertainty is around ACS efficacy in women
28
29 129 undergoing elective Cesarean section (CS) in the late preterm period (i.e., 34 to <37
30
31 130 weeks' gestation). Babies born in the late preterm period have lower risks of mortality
32
33 131 and morbidity than those born before 34 weeks' gestation; however, they have higher
34
35 132 risks of adverse outcomes than those born at term [18-21]. In many countries, the rising
36
37 133 rate of provider-initiated late preterm birth has been linked to the generalized increase in
38
39 134 the CS rate [22]. Regardless of gestational age, babies born via elective CS do not have
40
41 135 the usual physical and hormonal stimuli of passage through the birth canal; thus, they
42
43 136 tend to have higher rates of respiratory morbidity [23-25]. Some studies have suggested
44
45 137 that the risk of neonatal hypoglycemia is greater following CS; however, this may be
46
47 138 confounded by the underlying indication for CS [26].

48
49
50
51 139 In 2016, members of our team published a systematic review assessing the effectiveness
52
53 140 of ACS therapy in these four clinical situations [27]. No direct evidence of the effects of
54
55 141 ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for
56
57
58
59
60

1
2
3
4 142 those undergoing elective CS in the late preterm period was found. The review could
5
6 143 not draw firm conclusions regarding the effects of ACS on women with growth-
7
8 144 restricted fetuses, although low-quality evidence suggested that ACS reduced neonatal
9
10 145 IVH in women with chorioamnionitis [27]. The review's findings informed WHO 2015
11
12 146 ACS recommendations [28]. Now, WHO's ACS recommendations are being updated as
13
14 147 part of the WHO's living guidelines in maternal and perinatal health [29]. Our aim is to
15
16 148 update the 2016 systematic review and provide a contemporary evidence base for
17
18 149 researchers, clinicians, and maternal and newborn health stakeholders on safe, effective
19
20 150 clinical management in preterm birth.
21
22
23
24
25

151

152 **METHODS**

153 The specific review objectives are presented in Box 1, comprising four related questions
154 on ACS benefits and harms in 1) women with pregestational diabetes mellitus and/or
155 gestational diabetes mellitus; 2) women undergoing elective CS in the late preterm
156 period; 3) women with chorioamnionitis; and 4) women with FGR fetuses and/or SGA
157 infants. Diagnostic criteria used to define clinical and histological chorioamnionitis are
158 explained in Supplementary table 1. SGA infants are all neonates with birth weights
159 below the 10th percentile. In this study, FGR fetuses were defined using the operational
160 definition used in eligible studies (Supplementary table 1). The review protocol was
161 registered on PROSPERO (CRD42021267816) and reported per the Preferred
162 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist
163 (Supplementary file 1, Supplementary table 2) [30].
164
165

164

165

1
2
3
4 166 Box 1. Four Participant, Intervention, Comparison, and Outcome questions for a
5 167 systematic review
6

7 **P1: Effects of antenatal corticosteroids (ACS) on women with pregestational and/or gestational diabetes**

8 P: Women at risk of imminent preterm birth less than 37 weeks with pregestational diabetes mellitus
9 and/or gestational diabetes mellitus

10 I: ACS administration

11 C: Placebo or no treatment

12 O: World Health Organization (WHO) priority outcomes for preterm birth
13

14 **P2: Effects of ACS therapy on women undergoing elective cesarean section (CS) during the late preterm period**

15 P: Women undergoing elective CS in the late preterm period between 34 weeks and 0 days and 36
16 weeks and 6 days

17 I: ACS administration

18 C: Placebo or no treatment

19 O: WHO priority outcomes for preterm birth
20
21

22 **P3: Effects of ACS therapy on women with chorioamnionitis**

23 P: Women at risk of imminent preterm birth less than 37 weeks with chorioamnionitis

24 I: ACS administration

25 C: Placebo or no treatment

26 O: WHO priority outcomes for preterm birth
27

28 **P4: Effects of ACS therapy on women with growth-restricted fetuses and/or small-for-gestational-age infants**

29 P: Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or
30 small-for-gestational-age infants

31 I: ACS administration

32 C: Placebo or no treatment

33 O: WHO priority outcomes for preterm birth
34

35 168

36 169 **Study eligibility criteria**

37
38
39 170 Eligible studies were randomized or non-randomized primary studies that reported on
40
41 171 the effects of ACS therapy in the four subpopulations. This included published,
42
43 172 unpublished, and ongoing randomized or quasi-randomized controlled trials, controlled
44
45 173 before-after studies, interrupted-time-series studies, historically controlled studies,
46
47 174 cohort studies, and cross-sectional studies comparing any ACS (betamethasone,
48
49 175 dexamethasone, or hydrocortisone) administered either parentally or enterally with
50
51 176 placebo or no treatment. Study populations of interest were women at risk of imminent
52
53 177 preterm birth or provider-initiated preterm birth and where the study population fulfilled
54
55 178 one or more of the following conditions: women with pregestational and/or gestational
56
57
58
59
60

1
2
3
4 179 diabetes, women undergoing elective CS in the late preterm period, women with
5
6 180 chorioamnionitis, and women with FGR fetuses or SGA infants.
7
8
9 181 Articles in any language and from any country were eligible for inclusion if they
10
11 182 reported on one or more of WHO's priority outcomes for preterm birth guideline
12
13 183 development [28]. Maternal outcomes were death, maternal morbidity, and therapy side
14
15 184 effects. Newborn and child outcomes of interest were perinatal mortality, fetal
16
17 185 mortality, neonatal mortality, neonatal morbidity, neurodevelopment, anthropometric
18
19 186 status, and therapy side effects (Supplementary table 3).
20
21
22
23
24

25 188 **Data sources and search strategy**

26
27 189 An information specialist was consulted for the development of the search strategy. A
28
29 190 systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of
30
31 191 Science, and Global Index Medicus was conducted with no date restrictions on June 6,
32
33 192 2021. Controlled vocabularies supplemented with free keywords were used to search for
34
35 193 the relevant concept areas, with duplicates removed in the process to yield a total
36
37 194 number of abstracts for each database (Supplementary table 4). Reference lists of the
38
39 195 included articles, including any recent systematic reviews, were also hand-searched for
40
41 196 further potentially relevant studies. All citations were imported into a Rayyan
42
43 197 (<http://rayyan.qcri.org>) library for eligibility assessment.
44
45
46
47
48
49

50 199 **Study selection, data extraction, and quality assessment**

51
52 200 Two reviewers (KS, EN) independently assessed the titles and abstracts of identified
53
54 201 citations for eligibility. Any disagreement resulted in automatic inclusion into the next
55
56 202 level of screening. Subsequently, full-text publications of potentially eligible studies
57
58
59
60

1
2
3
4 203 were obtained and assessed in duplicate by two reviewers working independently, with
5
6 204 disagreements resolved through discussions or by consulting a third reviewer. The two
7
8
9 205 reviewers also independently extracted baseline and outcome data and assessed the
10
11 206 quality, with these data compared and any discrepancies resolved through discussions or
12
13 207 by consulting a third reviewer. Extracted data were entered into the Review Manager
14
15 208 version 5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study
16
17 209 quality, observational studies were assessed using the Risk of Bias Assessment tool for
18
19 210 Non-randomized Studies (RoBANS) [31]. We used the Cochrane Risk of Bias tool for
20
21 211 randomized trials [32]. Potential publication bias was inspected visually using funnel
22
23 212 plots for asymmetry in situations where data for a single outcome were available from at
24
25 213 least ten studies.
26
27
28
29
30

214

215 **Data synthesis and analysis**

216 Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs)
217 were determined for dichotomous data using the random-effects model. Crude data were
218 used when the numbers of events were available and crude OR were employed when
219 events were not available. We integrated crude odds ratios to mitigate confounding bias
220 associated with varying covariates, as using adjusted odds ratios would introduce
221 potential bias. This approach follows the methodology outlined in Yoneoka et al. (2015,
222 2017) [33,34]. For continuous data, mean differences (MDs) with 95% CIs were used.
223 Statistical heterogeneity was determined for each meta-analysis using I^2 and Chi^2
224 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p < 0.05$
225 in the Chi^2 test for heterogeneity. For the analysis of women with FGR fetuses and/or
226 SGA babies, we reported results for three subpopulations (SGA only, FGR only, and

1
2
3
4 227 SGA or FGR). Data from the three populations were combined, and pooled ORs were
5
6 228 calculated if the heterogeneity for that outcome was less than 60%. Based on the
7
8
9 229 evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at
10
11 230 high risk of bias. All statistical analyses were performed using RevMan5. The threshold
12
13 231 for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence
14
15 232 profiles were prepared for each research question using GRADEpro
16
17 233 (<https://gradepr.org/>). Grading of Recommendations Assessment, Development, and
18
19 234 Evaluation (GRADE), an approach for grading the certainty of evidence in systematic
20
21 235 reviews and clinical practice guidelines, was used in this review.
22
23
24
25
26

27 237 **Patients and public involvement**

28
29 238 Since this is a systematic review of previously published data, there was no direct
30
31 239 involvement of patients or the public.
32
33
34
35

36 241 **RESULTS**

37 242 **Associations of ACS therapy on women with pregestational and/or gestational** 38 39 243 **diabetes mellitus**

40
41 244 The search identified 179 citations: 11 potentially eligible studies were evaluated, and
42
43 245 three studies met the eligibility criteria, providing data on 725 pregnant women and 830
44
45 246 neonates (Supplementary file 2) [35-37]. All studies were conducted in high-income
46
47 247 countries and data collection was performed between 2008 and 2017 (Supplementary
48
49 248 table 1). One study involved women with pregestational diabetes only, one study
50
51 249 involved women with gestational diabetes only, and one study involved women with
52
53 250 either pregestational or gestational diabetes. All included studies were judged as having
54
55
56
57
58
59
60

251 a low risk of bias across all domains except high risk of bias at confounding variables
 252 (Supplementary file 3, Supplementary table 5). Data were available for six outcomes
 253 (Table 1). One retrospective cohort study found that in women with gestational
 254 diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly
 255 increased (one study, 162 infants; OR: 7.41; 95%CI: 5.04–10.89, *low-certainty*
 256 *evidence*); however, the effect of ACS therapy on neonatal hypoglycemia was uncertain
 257 (two studies, 215 infants; pooled OR: 1.44; 95%CI: 0.702.97, *very-low-certainty*
 258 *evidence*) [35]. The certainty of evidence was also very low for other outcomes; hence,
 259 no meaningful conclusions could be drawn.

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

Neonatal outcomes	No of studies	No of the patients		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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 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 (31.6%)	7.41 (5.04–10.89)	458 more per 1000 (from 384 more to 518 more)	Low

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

265 Associations of ACS therapy on women undergoing elective CS in the late preterm 266 period

267 The search identified 211 citations: 17 potentially eligible studies were evaluated, and
 268 three studies were included (Supplementary file 2) [38,39,40]. These were two
 269 observational studies and a randomized controlled trial (RCT). All studies were
 270 conducted in high-income countries between 2010 and 2017, providing data on 205
 271 pregnant women/neonates (Supplementary table 1). The two observational studies were
 272 judged as having a high risk of bias for confounding variables (Supplementary file 3,

273 Supplementary table 5). Data on eleven outcomes were available but all had very low
274 certainty; so, no meaningful conclusions could be drawn (Table 2).

275

276

277

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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS		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

278

279

280

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

281

Associations of ACS therapy on women with chorioamnionitis (histological or

282

clinical)

283

The search identified 418 citations: 12 potentially eligible studies were evaluated, and

284

eight were found to be eligible (Supplementary file 2) [41–48]. Two were prospective

285

cohort studies and six were retrospective, providing data on 1372 pregnant women and

286

1460 neonates (Supplementary table 1). Four studies included pregnant women with

287

clinical chorioamnionitis, and there were variations in the diagnostic criteria

288

(Supplementary table 1). All studies were conducted in high-income countries between

289

1989 and 2014. Additional unpublished crude data from the four included studies were

290

extracted from a previous meta-analysis identified through the search process [41,44–

291

46,49]. All included studies were judged as having a low risk of bias overall except high

292 risk of bias at confounding variables (Supplementary file 3, Supplementary table 5).

293 Data for 27 outcomes were available, with data reported separately for women with

294 histological chorioamnionitis and women with clinical chorioamnionitis (Table 3;

295 Supplementary file 4). Among women with histological chorioamnionitis, ACS

296 administration was associated with a possible reduction in the odds of neonatal death

297 (six studies, 1193 infants; pooled OR: 0.51; 95%CI: 0.31–0.85, *low-certainty evidence*),

298 severe intraventricular hemorrhage (IVH) (four studies, 528 infants; pooled OR: 0.41;

299 95%CI: 0.19–0.87, *low-certainty evidence*), IVH (five studies, 658 infants; pooled OR:

300 0.41; 95%CI: 0.23–0.72, *low-certainty evidence*), RDS (six studies, 1193 infants;

301 pooled OR: 0.59; 95%CI: 0.45–0.77, *low-certainty*). ACS might result in no difference

302 in neonatal sepsis; however, the evidence was uncertain (six studies, 1193 infants:

303 pooled OR: 1.03; 95%CI: 0.73–1.47, *very-low-certainty evidence*). The certainty of

304 evidence was very low for other outcomes (Supplementary table 6). In women with

305 clinical chorioamnionitis, only very-low-certainty evidence was available for neonatal

306 sepsis (two studies, 150 infants, pooled OR: 0.71; 95%CI: 0.13–3.89). The certainty of

307 evidence was very low for all other outcomes (Supplementary table 6).

308
309 Table 3: Maternal and neonatal outcomes for women with chorioamnionitis (histological or clinical)

Outcomes	No of study	No of the patients		OR (95% CI)	Effect	Certainty
		ACS	Non-ACS			
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)	131 fewer 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

1
2
3
4 333 included studies except Ley et al. (1997) [52]. The study by Ley et al. only provided the
5
6 334 adjusted ORs, controlled by birthweight deviation, gestational age, pre-eclampsia,
7
8
9 335 premature rupture of membranes, and mode of delivery [52]. Most of these studies were
10
11 336 judged as having a low risk of bias across all domains except high risk of bias at
12
13 337 confounding variables (Supplementary file 3, Supplementary table 5). For SGA infants
14
15 338 only, 12 studies provided data on 30 outcomes (Supplementary file 4, Supplementary
16
17 339 table 6). The administration of ACS for women with SGA was associated with
18
19 340 increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women;
20
21 341 pooled OR 1.50, 95%CI: 1.08–2.07, *low-certainty evidence*) although the odds of pre-
22
23 342 eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95%CI: 0.66–0.94, *low-*
24
25 343 *certainty evidence*), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68;
26
27 344 95%CI: 0.47–0.97, *low-certainty evidence*), periventricular leukomalacia (PVL) (four
28
29 345 studies, 3955 infants; pooled OR: 0.54; 95%CI: 0.38–0.77, *low-certainty evidence*) were
30
31 346 possibly reduced (Table 4). Two studies involving FGR infants only provided data for
32
33 347 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age
34
35 348 (one study, 124 infants; pooled OR: 0.39; 95%CI: 0.17–0.90, *low-certainty evidence*)
36
37 349 were possibly reduced (Table 4). Four studies involved SGA or FGR infants, providing
38
39 350 data for 25 outcomes (Supplementary file 4, Supplementary table 6). The administration
40
41 351 of ACS for women with SGA or FGR was associated with a possible reduction in the
42
43 352 odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95%CI: 0.23–0.62,
44
45 353 *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants;
46
47 354 pooled OR: 0.42; 95%CI: 0.26–0.66, *moderate-certainty evidence*), oxygen use (two
48
49 355 studies, 508 infants; pooled OR: 0.48; 95%CI: 0.30–0.77, *moderate-certainty evidence*)
50
51 356 although the odds of hypoglycemia increased (one study, 247 infants; pooled OR: 2.01;
52
53
54
55
56
57
58
59
60

357 95%CI: 1.16–3.48, *low-certainty evidence*) (Table 4). Pooled ORs involving women
 358 and newborns from all three populations (i.e., FGR only, SGA only, and FGR or SGA
 359 combined into SGA and/or FGR) could be determined for 20 outcomes (Supplementary
 360 file 4, Supplementary table 6). ACS administration for women with SGA and/or FGR
 361 was associated with a possible reduction in severe IVH (nine studies, 4636 infants;
 362 pooled OR: 0.59, 95%CI: 0.41–0.85, *low-certainty evidence*) and duration of hospital
 363 stay (two studies, 396 infants; MD –2.23 days; 95%CI: –3.81––0.83, *low-certainty*
 364 *evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47,
 365 95%CI: 1.07–2.01, *low-certainty evidence*) and neonatal hypoglycemia (two studies,
 366 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, *moderate-certainty evidence*) were
 367 possibly increased (Table 4).

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

Maternal outcomes	No of study	No of the patients		OR (95% CI)	Effect Absolute (95% CI)	Certainty
		ACS	Non-ACS			
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						
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

370
371
372
373
374
375

*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).

For peer review only

1
2
3
4
5
6 376 **DISCUSSION**
7

8
9 377 This systematic review identified 31 observational studies and a RCT on the benefits
10
11
12 378 and harms of using ACS in subgroups of women with specific pregnancy complications.
13
14
15 379 In women with diabetes and those undergoing elective late preterm CS, the available
16
17
18 380 evidence on the effects of ACS therapy was largely very-low-certainty; thus,
19
20
21 381 conclusions could not be drawn. In women with histological and clinical
22
23
24 382 chorioamnionitis, ACS therapy was associated with the benefit of neonatal death, IVH
25
26
27 383 and RDS reduction. In women with FGR and/or SGA babies, ACS therapy possibly has
28
29
30 384 benefits regarding neonatal morbidity and mortality, as well as the reduced use of
31
32
33 385 respiratory support interventions for the newborn; however, neonatal hypoglycemia
34
35
36 386 might be increased.
37

38
39 387

40
41
42 388 **Associations of ACS therapy on women with pregestational and/or gestational**
43
44
45 389 **diabetes**
46

47
48 390 A clinical concern regarding ACS use in women with diabetes is the possibility of
49
50
51 391 steroid-induced insulin resistance and consequent hyperglycemia, which causes
52
53
54 392 avoidable harm to the neonate. For example, in women with insulin-dependent diabetes,
55
56
57 393 ketoacidosis may occur if insulin dosing is not increased following steroid
58
59
60

1
2
3
4
5
6 394 administration [68]. A 2002 Danish study conducted on 24 pregnant women with
7
8
9 395 diabetes who received steroids suggested that insulin dose adjustment may be required
10
11
12 396 for up to five days after ACS administration [69]. However, in the current review, there
13
14
15 397 was insufficient evidence to determine whether ACS increased neonatal hypoglycemia,
16
17
18 398 respiratory morbidity, or mortality. One retrospective study suggested that ACS use in
19
20
21 399 women with gestational diabetes increases the risk of NICU admission; however, the
22
23
24 400 authors noted that average birthweight in the ACS group was significantly lower than
25
26
27 401 that in the unexposed group, which may explain this finding [35]. Well-designed studies
28
29
30 402 are needed that describe adjustments to maternal diabetic regimens at the time of ACS
31
32
33 403 therapy and from the time of ACS administration to birth and report on important
34
35
36 404 newborn health outcomes.
37
38

39 405

40
41
42 406 **Associations of ACS therapy on women undergoing elective CS in the late preterm**
43
44
45 407 **period**
46
47

48 408 The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup
49
50
51 409 analysis on gestational age at trial entry reported findings from seven trials recruiting
52
53
54 410 women in the late preterm period [2]. This subgroup analysis suggested that ACS
55
56
57 411 reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh et
58
59
60

1
2
3
4
5
6 412 al. reported that ACS reduced the need for respiratory support and increased the risk of
7
8
9 413 hypoglycemia with moderate certainty in late preterm [70]. However, no subgroup
10
11
12 414 analyses were conducted on CS [70]. Hence, these findings cannot be generalized to all
13
14
15 415 women undergoing CS in the late preterm period. The trial by Gyamfi-Bannerman et al.
16
17
18 416 reported that ACS in the late preterm period reduced their primary outcome and severe
19
20
21 417 newborn respiratory complications [40]. Their subgroup analysis showed that these
22
23
24 418 beneficial effects persisted among women admitted for planned CS only [40]. Their
25
26
27 419 primary outcome was defined as any of the following occurrences within 72 hours after
28
29
30 420 birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for
31
32
33 421 at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen
34
35
36 422 of at least 0.30 for at least four continuous hours, mechanical ventilation, or the need for
37
38
39 423 extracorporeal membrane oxygenation (ECMO) [40]. Severe respiratory complications
40
41
42 424 were defined as any of the following occurrences within 72 hours after birth: CPAP,
43
44
45 425 HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of
46
47
48 426 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death
49
50
51 427 within 72 hours after delivery, or the need for ECMO [40]. Their outcomes did not
52
53
54 428 adequately fit our outcomes, and the study did not provide their outcome data. Our
55
56
57 429 review suggests there is insufficient evidence to draw firm conclusions on the benefits
58
59
60

1
2
3
4
5
6 430 and possible harms of ACS when used in this subpopulation. At the same time, the
7
8
9 431 multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective
10
11
12 432 effects from ACS for neonatal respiratory morbidity amongst women with late preterm
13
14
15 433 CS [40]. An ongoing randomized trial in New Zealand will provide further information
16
17
18 434 on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and
19
20
21 435 39 weeks 6 days [71].
22
23

24 436

27 437 **Associations of ACS on women with chorioamnionitis**

28
29
30 438 Women with chorioamnionitis are typically excluded from ACS efficacy trials due to
31
32
33 439 concerns that the prolongation of pregnancy and/or immunosuppression may worsen
34
35
36 440 outcomes for these women and their newborns. Although ACS appears to be associated
37
38
39 441 with reduced neonatal death, IVH and RDS rates in women with histological
40
41
42 442 chorioamnionitis, there was insufficient evidence of other important infection-related
43
44
45 443 maternal and neonatal outcomes in this review. While these conclusions are similar to
46
47
48 444 those of a 2011 review by Been et al., we do not consider that the available evidence
49
50
51 445 supports the routine use of ACS therapy in women with chorioamnionitis, as clinical
52
53
54 446 trials comparing ACS therapy to no ACS therapy in this population and reliable
55
56
57 447 evidence regarding infection-related outcomes are still lacking [49]. Significant overlap
58
59
60

1
2
3
4
5
6 448 exists between clinical and histological chorioamnionitis [72]. Histological
7
8
9 449 chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical
10
11
12 450 chorioamnionitis [73]. However, since physicians must decide the indications for ACS
13
14
15 451 therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in
16
17
18 452 pregnant women with clinical chorioamnionitis should be encouraged.
19
20

21 453

22
23
24 454 **Associations of ACS therapy on women with growth-restricted fetuses and/or**
25
26
27 455 **small-for-gestational-age infants**
28

29
30 456 The totality of the evidence identified in this review suggests that ACS therapy should
31
32
33 457 be used in the fetal growth restriction setting. Although the evidence was mainly of low
34
35
36 458 or very low certainty, benefits were observed for several outcomes, and no harm was
37
38
39 459 reported. The current review identified more substantial evidence than that identified in
40
41
42 460 our 2016 systematic review, which was unable to draw solid conclusions about the
43
44
45 461 effects of ACS therapy in this subpopulation [27]. It is also noteworthy that the largest
46
47
48 462 trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled
49
50
51 463 2852 women and reported preterm newborn mortality and morbidity benefits, recruited
52
53
54 464 189 women with known or suspected fetal growth restriction [74]. The current review
55
56
57 465 did not identify the benefits regarding the outcome RDS, which might be attributable to
58
59
60

1
2
3
4
5
6 466 a single retrospective cohort study in Japan in which neonates in the ACS group were
7
8
9 467 delivered significantly earlier than those in the control group [59]. A sensitivity analysis
10
11
12 468 in which we excluded this study suggested that RDS is significantly lower for SGA
13
14
15 469 babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal
16
17
18 470 hypoglycemia in this subpopulation, which warrants further exploration in future
19
20
21 471 research. In this meta-analysis, two studies targeted pregnant women with FGR while
22
23
24 472 the other 16 included pregnant women with SGA. SGA status does not perfectly
25
26
27 473 represent FGR [16]. Since physicians must decide the indication for ACS therapy when
28
29
30 474 FGR is detected, studies evaluating the effects of ACS therapy on pregnant women with
31
32
33 475 FGR fetuses should be encouraged.

34
35
36 47637
38
39 477 **Strengths and limitations**

40
41
42 478 The strengths of this review were its broad search strategy, which included studies
43
44
45 479 published in languages other than English, rigorous quality assessments, and the use of
46
47
48 480 the GRADE methodology to assess the reliability of the review's findings. Thus, we
49
50
51 481 consider the risk of missing potentially eligible studies to be low, although we
52
53
54 482 acknowledge that publication bias may affect these results. One limitation of the present
55
56
57 483 review is the difference in how studies defined, identified, or diagnosed the subgroup
58
59
60

1
2
3
4
5
6 484 conditions and outcomes of interest. These differences might have created a bias in the
7
8
9 485 review conclusions. However, we explored and reported heterogeneity for meta-
10
11
12 486 analyses. This analysis extracted all data from observational studies. Since adjusted
13
14
15 487 confounding variables showed a wide variety in each included study, crude data were
16
17
18 488 employed in our review. No included studies adequately considered their study design
19
20
21 489 to adjust the confounding bias. Therefore, confounding bias should be cautiously
22
23
24 490 considered in our results' interpretation. Another limitation is that most of the included
25
26
27 491 studies were conducted in high-income countries, although over 60% of all preterm
28
29
30 492 births globally occur in African and South Asian countries [75]. This review did not
31
32
33 493 lead to any evidence of high certainty, and one reason for this observation is that all
34
35
36 494 studies were observational. In 1990, Crowley P et al. reported a structured review of
37
38
39 495 ACS for preterm birth [76]. The review revealed that ACS significantly reduced the risk
40
41
42 496 of IVH and respiratory morbidity [76]. In 1995, the National Institutes of Health
43
44
45 497 developed a consensus on recommending ACS treatment for preterm birth [77]. In our
46
47
48 498 review, only one study targeting women with chorioamnionitis and two studies
49
50
51 499 targeting women with FGR started before 1990 [43,52,55]. It would be challenging to
52
53
54 500 conduct the RCTs on ACS efficacy even in these special populations after the review by
55
56
57 501 Crowley P et al. [76]. The latest Cochrane review on ACS treatment for preterm birth
58
59
60

1
2
3
4
5
6 502 involved a subgroup analysis in the seven special conditions [2]. However, the review
7
8
9 503 did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis,
10
11
12 504 and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not
13
14
15 505 perform any subgroup analysis due to the lack of stratified data based on the mode of
16
17
18 506 delivery [70]. Considering the circumstances, guidelines on ACS therapy by
19
20
21 507 international bodies are yet to develop solid recommendations for these special
22
23
24 508 populations. Hence, we consider this review valid. Prospective cohort studies on ACS
25
26
27 509 efficacy for these four special populations should be encouraged. The studies should
28
29
30 510 include precise data on the time sequence between ACS admission and the onset of
31
32
33 511 maternal outcomes to determine the effect of ACS therapy on maternal outcomes. Our
34
35
36 512 search was last conducted in June 2021 and required time for publication. Despite
37
38
39 513 scrutinizing additional sources between June 2021 and February 2023, we did not find
40
41
42 514 any further relevant studies.
43
44

45 515

48 516 **CONCLUSION**

51 517 ACS has possible benefits in the setting of FGR and/or SGA; however, direct trial
52
53
54 518 evidence of its efficacy and safety for pregnant women with pregestational and/or
55
56
57 519 gestational diabetes mellitus and those undergoing elective CS in the late preterm period
58
59
60

1
2
3
4
5
6 520 is still lacking. Although ACS may have some benefits in the context of histological
7
8
9 521 chorioamnionitis, more evidence is required. Well-designed studies (ideally trials) with
10
11
12 522 adequate follow-up for long-term child outcomes are needed to confirm the upsides and
13
14
15 523 downsides of ACS use in these subpopulations.
16
17

18 524

21 525 **AUTHOR CONTRIBUTIONS**

23
24 526 Dr. Saito participated in the conceptualization and design of the study, conducted title,
25
26
27 527 abstract, and full-text screening, performed data extraction, analysis, and interpretation,
28
29
30 528 assessed the risk of bias, drafted the initial manuscript, and critically reviewed the
31
32
33 529 manuscript. Ms. Nishimura conducted the title abstract and full-text screening,
34
35
36 530 performed data extraction, analysis, and interpretation, assessed the risk of bias, and
37
38
39 531 critically reviewed the manuscript. Dr. Swa conceptualized and designed the search
40
41
42 532 strategy, conducted a systematic search, and critically reviewed the manuscript for
43
44
45 533 important intellectual content. Dr. Ramson assisted in the interpretation of data and the
46
47
48 534 assessment of the risk of bias and critically reviewed the manuscript for important
49
50
51 535 intellectual content. Drs Namba, Cao, and Lavin critically reviewed the protocol and
52
53
54 536 manuscript for important intellectual content. Prof. Ota and Associate Prof. Vogel
55
56
57 537 designed and planned the study, assisted with developing the literature search strategy
58
59
60

1
2
3
4
5
6 538 and resolving inclusion conflicts, critically reviewed the manuscript, and supervised the
7
8
9 539 execution of the study. All authors approved the final manuscript as submitted and
10
11
12 540 agreed to be accountable for all aspects of the work.
13
14

15 541

18 542 **DATA SHARING STATEMENT**

21 543 Data were obtained from the published journal article, and extracts are available from
22
23
24 544 the corresponding author upon reasonable request.
25
26

27 545

30 546 **FUNDING**

33 547 This work was supported by UNDP/UNFPA/ UNICEF/WHO/World Bank Special
34
35
36 548 Program of Research, Development and Research Training in Human Reproduction,
37
38
39 549 WHO (Grand Number: not applicable) and Research Program on Rare and Intractable
40
41
42 550 Diseases co-sponsored program supported with grants from the Japanese Ministry of
43
44
45 551 Health, Labour and Welfare Science (Grant Number: JPMH22FC117) and the grant
46
47
48 552 from the Japanese Ministry of Education, Culture, Sports, Science and Technology
49
50
51 553 (Grant Number: 22K20865).
52
53

54 554

57 555 **COMPETING INTERESTS**

1
2
3
4
5
6 556 None declared.
7
8

9 557
10
11

12 558 **SUPPLEMENTARY FILES**
13
14

15 559 Supplementary table 1: Characteristic tables
16
17

18 560 Supplementary table 2: PRISMA 2020 Checklist
19
20

21 561 Supplementary table 3: Review outcomes
22
23

24 562 Supplementary table 4: Database-specific search terms and strategies
25
26

27 563 Supplementary table 5: Risk of bias tables
28
29

30 564 Supplementary table 6: GRADE tables
31
32

33 565 Supplementary file 1: PROSPERO
34
35

36 566 Supplementary file 2: PRISMA flow diagrams
37
38

39 567 Supplementary file 3: Risk of bias figures
40
41

42 568 Supplementary file 4: Forest plots
43
44

45 569
46
47

48 570 **ETHICS APPROVAL**
49
50

51 571 This study is a systematic review of published studies; thus, ethical approval was not
52
53

54 572 required.
55
56

57 573
58
59
60

574

575 **REFERENCES**

- 576 [1] Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for
577 prevention of the respiratory distress syndrome in premature infants. *Pediatrics*.
578 1972;50(4):5155-25. <https://doi.org/10.1542/peds.50.4.515>.
- 579 [2] McGoldrick E, Stewart F, Parker R, et al. Antenatal corticosteroids for accelerating
580 fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*.
581 2020;12:CD004454. <https://doi:10.1002/14651858.CD004454.pub.4>.
- 582 [3] Committee on Obstetric Practice. Committee opinion no. 713 summary: antenatal
583 corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130(2):493-494.
584 <https://doi:10.1097/AOG.0000000000002231>.
- 585 [4] World Health Organization. Managing complications in pregnancy and childbirth: a
586 guide for midwives and doctors, 2nd ed. 2017.
587 <https://apps.who.int/iris/handle/10665/255760>. (accessed 24 Mar 2022).
- 588 [5] Skoll A, Boutin A, Bujold E, et al. No. 364-antenatal corticosteroid therapy for
589 improving neonatal outcomes. *J Obstet Gynaecol Can*. 2018;40(9):1219-1239.
590 <https://doi:10.1016/j.jogc.2018.04018>.
- 591 [6] Japan Society of Obstetrics and Gynecology. Obstetrics and Gynecology clinical
592 guideline 2020. https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf (accessed 24 Mar
593 2022).
- 594 [7] McGillick EV, Morrison JL, McMillen IC, et al. Intrafetal glucose infusion alters
595 glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of
596 the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol*.
597 2014;307(5):R538-R545. <https://doi:10.1152/ajpregu.00053.2014>.
- 598 [8] Kawakita T, Bowers K, Hazrati S, et al. Increased Neonatal Respiratory Morbidity
599 Associated with Gestational and Pregestational Diabetes: A Retrospective Study. *Am J*
600 *Perinatol*. 2017;34(11):1160-1168. <https://doi:10.1055/s-0037-1604414>.
- 601 [9] Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth.
602 *Am J Obstet Gynecol*. 2007;196(3):229 e1-4. <https://doi:10.1016/j.ajog.2006.10.900>.
- 603 [10] Gordon A, Lahra M, Raynes-Greenow C, et al. Histological chorioamnionitis is
604 increased at extremes of gestation in stillbirth: a population-based study. *Infect Dis Obstet*
605 *Gynecol*. 2011;2011:456728. <https://doi:10.1155/2011/456728>.
- 606 [11] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection:
607 A systematic review and meta-analysis. *PLoS Med*. 2019;16(12):e1002984. [https:// doi:](https://doi:)

- 1
2
3
4
5
6 608 10.1371/journal.pmed.1002984.
7 609 [12] Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and
8 610 neonatal encephalopathy. *Am J Obstet Gynecol*. 2003;188(4):1011-1015. [https://doi:](https://doi.org/10.1067/mob.2003.233)
9 611 10.1067/mob.2003.233.
10 612 [13] Pasupathy D, Wood AM, Pell JP, et al. Rates of and factors associated with delivery-
11 613 related perinatal death among term infants in Scotland. *JAMA*. 2009;302(6):660-668.
12 614 [https:// doi: 10.1001/jama.2009.1111](https://doi.org/10.1001/jama.2009.1111).
13 615 [14] McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal
14 616 death in term and late preterm singletons. *Obstet Gynecol*. 2013;122(4):869-877. [https://](https://doi.org/10.1097/AOG.0b013e3182a265ab)
15 617 [doi: 10.1097/AOG.0b013e3182a265ab](https://doi.org/10.1097/AOG.0b013e3182a265ab).
16 618 [15] MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special
17 619 educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med*.
18 620 2010;7(6):e1000289. [https:// doi: 10.1371/journal.pmed.1000289](https://doi.org/10.1371/journal.pmed.1000289).
19 621 [16] Nardoza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current
20 622 knowledge. *Arch Gynecol Obstet*. 2017;295(5):1061-1077. [https:// doi: 10.1007/s00404-](https://doi.org/10.1007/s00404-017-4341-9)
21 623 [017-4341-9](https://doi.org/10.1007/s00404-017-4341-9).
22 624 [17] Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight
23 625 and gestational age. *J Pediatr*. 1967;71(2):159-163. [https://doi: 10.1016/s0022-](https://doi.org/10.1016/s0022-3476(67)80066-0)
24 626 [3476\(67\)80066-0](https://doi.org/10.1016/s0022-3476(67)80066-0).
25 627 [18] Wang ML, Dorer DJ, Fleming MP, et al. Clinical outcomes of near-term infants.
26 628 *Pediatrics*. 2004;114(2):372-6. [https:// doi: 10.1542/peds.114.2.372](https://doi.org/10.1542/peds.114.2.372).
27 629 [19] Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm
28 630 birth and maternal medical conditions on newborn morbidity risk. *Pediatrics*.
29 631 2008;121(2):e223-232. [https:// doi: 10.1542/peds.2006-3629](https://doi.org/10.1542/peds.2006-3629).
30 632 [20] Leone A, Ersfeld P, Adams M, et al. Neonatal morbidity in singleton late preterm
31 633 infants compared with full-term infants. *Acta Paediatr*. 2012;101(1):e6-10. [https:// doi:](https://doi.org/10.1111/j.1651-2227.2011.02459.x)
32 634 [10.1111/j.1651-2227.2011.02459.x](https://doi.org/10.1111/j.1651-2227.2011.02459.x).
33 635 [21] Mitha A, Chen R, Altman M, et al. Neonatal Morbidities in Infants Born Late
34 636 Preterm at 35-36 Weeks of Gestation: A Swedish Nationwide Population-based Study. *J*
35 637 *Pediatr*. 2021;233:43-50 e5. [https:// doi: 10.1016/j.jpeds.2021.02.066](https://doi.org/10.1016/j.jpeds.2021.02.066).
36 638 [22] Richards JL, Kramer MS, Deb-Rinker P, et al. Temporal Trends in Late Preterm and
37 639 Early Term Birth Rates in 6 High-Income Countries in North America and Europe and
38 640 Association With Clinician-Initiated Obstetric Interventions. *JAMA*. 2016;316(4):410-
39 641 419. [https:// doi: 10.1001/jama.2016.9635](https://doi.org/10.1001/jama.2016.9635).
40 642 [23] Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of
41 643 delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol*.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 644 1995;102(2):101-106. [https:// doi: 10.1111/j.1471-0528.1995.tb09060.x](https://doi.org/10.1111/j.1471-0528.1995.tb09060.x).
- 7 645 [24] Zanardo V, Simbi AK, Franzoi M, et al. Neonatal respiratory morbidity risk and
8 646 mode of delivery at term: influence of timing of elective caesarean delivery. *Acta*
9 647 *Paediatr*. 2004;93(5):643-647. [https:// doi: 10.1111/j.1651-2227.2004.tb02990.x](https://doi.org/10.1111/j.1651-2227.2004.tb02990.x).
- 10 648 [25] Hansen AK, Wisborg K, Uldbjerg N, et al. Risk of respiratory morbidity in term
11 649 infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336(7635):85-
12 650 87. [https:// doi: 10.1136/bmj.39405.539282.BE](https://doi.org/10.1136/bmj.39405.539282.BE).
- 13 651 [26] Groom KM. Antenatal corticosteroids after 34weeks' gestation: Do we have the
14 652 evidence? *Semin Fetal Neonatal Med*. 2019;24(3):189-196. [https:// doi:](https://doi.org/10.1016/j.siny.2019.03.001)
15 653 [10.1016/j.siny.2019.03.001](https://doi.org/10.1016/j.siny.2019.03.001).
- 16 654 [27] Amiya RM, Mlunde LB, Ota E, et al. Antenatal Corticosteroids for Reducing
17 655 Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of
18 656 Imminent Preterm Birth: A Systematic Review and Meta-Analysis. *PLoS One*.
19 657 2016;11(2):e0147604. [https:// doi: 10.1371/journal.pone.0147604](https://doi.org/10.1371/journal.pone.0147604).
- 20 658 [28] World Health Organization. WHO recommendations on intervention to improve
21 659 preterm birth outcomes. World Health Organizaiton; 2015.
22 660 <https://www.who.int/publications/i/item/9789241508988> (accessed 24 Mar 2022).
- 23 661 [29] Vogel JP, Dowswell T, Lewin S, et al. Developing and applying a 'living guidelines'
24 662 approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health*.
25 663 2019;4(4):e001683. [https:// doi: 10.1136/bmjgh-2019-001683](https://doi.org/10.1136/bmjgh-2019-001683).
- 26 664 [30] PRISMA. PRISMA Checklist. 2020. [http://prisma-](http://prisma-statement.org/PRISMAStatement/Checklist)
27 665 [statement.org/PRISMAStatement/Checklist](http://prisma-statement.org/PRISMAStatement/Checklist) (accessed 24 Mar 2022).
- 28 666 [31] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for
29 667 nonrandomized studies showed moderate reliability and promising validity. *J Clin*
30 668 *Epidemiol*. 2013;66(4):408-414. [https:// doi: 10.1016/j.jclinepi.2012.09.016](https://doi.org/10.1016/j.jclinepi.2012.09.016).
- 31 669 [32] Cochrane Methods. Risk of Bias 2 (ROB2) tool. 2020.
32 670 <https://methods.cochrane.org/risk-bias-2>. (accessed 24 Mar 2022).
- 33 671 [33] Yoneoka D, Henmi M, Sawada N, et al. Synthesis of clinical prediction models under
34 672 different sets of covariates with one individual patient data. *BMC Med Res Methodol*.
35 673 2015;15:101. [https:// doi:10.1186/s12874-015-0087-x](https://doi.org/10.1186/s12874-015-0087-x).
- 36 674 [34] Yoneoka D, Henmi M. Meta-analytical synthesis of regression coefficients under
37 675 different categorization scheme of continuous covariates. *Stat Med*. 2017;36(27):4336-
38 676 4352. [https:// doi:10.1002/sim.7434](https://doi.org/10.1002/sim.7434)
- 39 677 [dataset] [35] Krispin E, Hochberg A, Chen R, et al. Neonatal outcome in gestational-
40 678 diabetic mothers treated with antenatal corticosteroids delivering at the late preterm and
41 679 term. *Arch Gynecol Obstet*. 2018;298(4):689-695. [https:// doi: 10.1007/s00404-018-](https://doi.org/10.1007/s00404-018-)
- 42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 680 4848-8.
- 7 681 [dataset] [36] Battarbee AN, Sandoval G, Grobman WA, et al. Antenatal corticosteroids
8 682 and preterm neonatal morbidity and mortality among women with and without diabetes
9 683 in pregnancy. *Am J Perinatol*. 2022;39:67-74. [https:// doi: 10.1055/s-0040-1714391](https://doi.org/10.1055/s-0040-1714391).
- 11 684 [dataset] [37] Cassimatis IR, Battarbee AN, Allshouse AA, et al. Neonatal outcomes
12 685 associated with late preterm betamethasone administration in women with pregestational
13 686 diabetes. *Pediatr Neonatol*. 2020;61(6):645-646. [https:// doi:](https://doi.org/10.1016/j.pedneo.2020.07.002)
15 687 [10.1016/j.pedneo.2020.07.002](https://doi.org/10.1016/j.pedneo.2020.07.002).
- 17 688 [dataset] [38] Kirshenbaum M, Mazaki-Tovi S, Amikam U, et al. Does antenatal steroids
18 689 treatment prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal
19 690 morbidity? Evidence from a case control study. *Arch Gynecol Obstet*. 2018;297(1):101-
20 691 107. [http:// doi: 10.1007/s00404-017-4557-8](http://doi.org/10.1007/s00404-017-4557-8).
- 22 692 [dataset] [39] de la Huerga Lopez A, Sendarrubias Alonso M, Jimenez Jimenez AP, et al.
23 693 [Antenatal corticosteroids and incidence of neonatal respiratory distress after elective
24 694 caesarean section in late preterm and term neonates]. *An Pediatr (Engl Ed)*.
25 695 2019;91(6):371-377. Corticoides antenatales e incidencia de distrés respiratorio del recién
26 696 nacido en las cesáreas programadas del pretérmino tardío y término precoz. [https:// doi:](https://doi.org/10.1016/j.anpedi.2018.12.004)
27 697 [10.1016/j.anpedi.2018.12.004](https://doi.org/10.1016/j.anpedi.2018.12.004).
- 29 698 [dataset] [40] Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal
30 699 Betamethasone for Women at Risk for Late Preterm Delivery. *N Engl J Med*.
31 700 2016;374(14):1311-1320. [https:// doi: 10.1056/NEJMoa1516783](https://doi.org/10.1056/NEJMoa1516783).
- 32 701 [dataset] [41] Baud O, Zupan V, Lacaze-Masmonteil T, et al. The relationships between
33 702 antenatal management, the cause of delivery and neonatal outcome in a large cohort of
34 703 very preterm singleton infants. *BJOG*. 2000;107(7):877-884. [https:// doi: 10.1111/j.1471-](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x)
35 704 [0528.2000.tb11086.x](https://doi.org/10.1111/j.1471-0528.2000.tb11086.x).
- 36 705 [dataset] [42] Elimian A, Verma U, Beneck D, et al. Histologic chorioamnionitis,
37 706 antenatal steroids, and perinatal outcomes. *Obstet Gynecol*. 2000;96(3):333-6. [https://](https://doi.org/10.1016/s0029-7844(00)00928-5)
38 707 [doi: 10.1016/s0029-7844\(00\)00928-5](https://doi.org/10.1016/s0029-7844(00)00928-5).
- 39 708 [dataset] [43] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30
40 709 weeks gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22(3):155-159.
41 710 [https:// doi: 10.1055/s-2005-865020](https://doi.org/10.1055/s-2005-865020).
- 42 711 [dataset] [44] Foix-L'heliás L, Baud O, Lenclen R, et al. Benefit of antenatal
43 712 glucocorticoids according to the cause of very premature birth. *Arch Dis Child Fetal*
44 713 *Neonatal Ed*. 2005;90(1):F46-48. [https:// doi: 10.1136/adc.2003.042747](https://doi.org/10.1136/adc.2003.042747).
- 45 714 [dataset] [45] Goldenberg RL, Andrews WW, Faye-Petersen OM, et al. The Alabama
46 715 preterm birth study: corticosteroids and neonatal outcomes in 23- to 32-week newborns

- 1
2
3
4
5
6 716 with various markers of intrauterine infection. *Am J Obstet Gynecol.* 2006;195(4):1020-
7 717 1024. [https:// doi: 10.1016/j.ajog.2006.06.033](https://doi.org/10.1016/j.ajog.2006.06.033).
- 8
9 718 [dataset] [46] Been JV, Rours IG, Kornelisse RF, et al. Histologic chorioamnionitis, fetal
10 719 involvement, and antenatal steroids: effects on neonatal outcome in preterm infants. *Am*
11 720 *J Obstet Gynecol.* 2009;201(6):587 e1-8. [https:// doi: 10.1016/j.ajog.2009.06.025](https://doi.org/10.1016/j.ajog.2009.06.025).
- 12
13 721 [dataset] [47] Ahn HM, Park EA, Cho SJ, et al. The association of histological
14 722 chorioamnionitis and antenatal steroids on neonatal outcome in preterm infants born at
15 723 less than thirty-four weeks' gestation. *Neonatology.* 2012;102(4):259-64. [https:// doi:](https://doi.org/10.1159/000339577)
16 724 [10.1159/000339577](https://doi.org/10.1159/000339577).
- 17
18 725 [dataset] [48] Ryu YH, Oh S, Sohn J, Lee J. The Associations between Antenatal
19 726 Corticosteroids and In-Hospital Outcomes of Preterm Singleton Appropriate for
20 727 Gestational Age Neonates according to the Presence of Maternal Histologic
21 728 Chorioamnionitis. *Neonatology.* 2019;116(4):369-375. [https:// doi: 10.1159/000502650](https://doi.org/10.1159/000502650).
- 22
23 729 [49] Been JV, Degraeuwe PL, Kramer BW, et al. Antenatal steroids and neonatal outcome
24 730 after chorioamnionitis: a meta-analysis. *BJOG.* 2011;118(2):113-122. [https://doi:](https://doi.org/10.1111/j.1471-0528.2010.02751.x)
25 731 [10.1111/j.1471-0528.2010.02751.x](https://doi.org/10.1111/j.1471-0528.2010.02751.x).
- 26
27 732 [dataset] [50] Di Lenardo D, Piermarocchi P, Cazzaro L, et al. Betamethasone and
28 733 theophylline in the prevention of the Respiratory Distress Syndrome (RDS) : Trend up-
29 734 date. *J FOET Med.* 1990; 10 (1-4):27-31. Retrieved from [https://pascal-](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
30 735 [francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214](https://pascal-francis.inist.fr/vibad/index.php?action=getRecordDetail&idt=19590214)
- 31
32 736 [dataset] [51] Spinillo A, Capuzzo E, Ometto A, et al. Value of antenatal corticosteroid
33 737 therapy in preterm birth. *Early Hum Dev.* 1995;42(1):37-47. [https:// doi: 10.1016/0378-](https://doi.org/10.1016/0378-3782(95)01638-j)
34 738 [3782\(95\)01638-j](https://doi.org/10.1016/0378-3782(95)01638-j).
- 35
36 739 [dataset] [52] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome
37 740 in infants with impaired intrauterine growth. *Acta Paediatr.* 1997;86(10):1090-1096.
38 741 [https:// doi: 10.1111/j.1651-2227.1997.tb14814.x](https://doi.org/10.1111/j.1651-2227.1997.tb14814.x).
- 39
40 742 [dataset] [53] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids
41 743 in obstetric subgroups. *Obstet Gynecol.* 1999;93(2):174-179. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-7844(98)00400-1)
42 744 [7844\(98\)00400-1](https://doi.org/10.1016/s0029-7844(98)00400-1).
- 43
44 745 [dataset] [54] Bernstein IM, Horbar JD, Badger GJ, et al. Morbidity and mortality among
45 746 very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford
46 747 Network. *Am J Obstet Gynecol.* 2000;182:198-206. [https:// doi: 10.1016/s0002-](https://doi.org/10.1016/s0002-9378(00)70513-8)
47 748 [9378\(00\)70513-8](https://doi.org/10.1016/s0002-9378(00)70513-8).
- 48
49 749 [dataset] [55] Schaap AH, Wolf H, Bruinse HW, et al. Effects of antenatal corticosteroid
50 750 administration on mortality and long-term morbidity in early preterm, growth-restricted
51 751 infants. *Obstet Gynecol.* 2001;97(6):954-960. [https:// doi: 10.1016/s0029-](https://doi.org/10.1016/s0029-)

- 1
2
3
4
5
6 752 7844(01)01343-6.
- 7 753 [dataset] [56] Torrance HL, Mulder EJ, Brouwers HA, et al. Respiratory outcome in
8 754 preterm small for gestational age fetuses with or without abnormal umbilical artery
9 755 Doppler and/or maternal hypertension. *J Matern Fetal Neonatal Med.* 2007;20(8):613-
10 756 621. [https:// doi: 10.1080/14767050701463662](https://doi.org/10.1080/14767050701463662).
- 11
12
13 757 [dataset] [57] van Stralen G, van der Bos J, Lopriore E, et al. No short-term benefits of
14 758 antenatal corticosteroid treatment in severely preterm growth restricted fetuses: a case-
15 759 control study. *Early Hum Dev.* 2009;85(4):253-257. [https:// doi:](https://doi.org/10.1016/j.earlhumdev.2008.10.010)
16 760 [10.1016/j.earlhumdev.2008.10.010](https://doi.org/10.1016/j.earlhumdev.2008.10.010).
- 17
18
19 761 [dataset] [58] Mitsiakos G, Kovacs L, Papageorgiou A. Are antenatal steroids beneficial
20 762 to severely growth restricted fetuses? *J Matern Fetal Neonatal Med.* 2013;26(15):1496-
21 763 1499. [https:// doi: 10.3109/14767058.2013.789852](https://doi.org/10.3109/14767058.2013.789852).
- 22
23
24 764 [dataset] [59] Ishikawa H, Miyazaki K, Ikeda T, et al. The Effects of Antenatal
25 765 Corticosteroids on Short- and Long-Term Outcomes in Small-for-Gestational-Age
26 766 Infants. *Int J Med Sci.* 2015;12(4):295-300. [https:// doi: 10.7150/ijms.11523](https://doi.org/10.7150/ijms.11523).
- 27
28 767 [dataset] [60] Riskin-Mashiah S, Riskin A, Bader D, et al. Antenatal corticosteroid
29 768 treatment in singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a
30 769 population-based study. *BJOG.* 2016;123(11):1779-1786. [https:// doi: 10.1111/1471-](https://doi.org/10.1111/1471-0528.13723)
31 770 [0528.13723](https://doi.org/10.1111/1471-0528.13723).
- 32
33
34 771 [dataset] [61] Collaborative Study Group for Respiratory Distress Syndrome in Preterm
35 772 I. [Effect of antenatal corticosteroids therapy on the mortality and morbidity of small for
36 773 gestational age infants born at 24-34 completed weeks: a retrospective multicenter study].
37 774 *Zhonghua Er Ke Za Zhi.* 2017;55(8):613-618. [https:// doi: 10.3760/cma.j.issn.0578-](https://doi.org/10.3760/cma.j.issn.0578-1310.2017.08.013)
38 775 [1310.2017.08.013](https://doi.org/10.3760/cma.j.issn.0578-1310.2017.08.013).
- 39
40
41 776 [dataset] [62] Kim WJ, Han YS, Ko HS, et al. Antenatal corticosteroids and outcomes of
42 777 preterm small-for-gestational-age neonates in a single medical center. *Obstet Gynecol Sci.*
43 778 2018;61(1):7-13. [https:// doi: 10.5468/ogs.2018.61.1.7](https://doi.org/10.5468/ogs.2018.61.1.7).
- 44
45
46 779 [dataset] [63] Kim YJ, Choi SH, Oh S, et al. Antenatal Corticosteroids and clinical
47 780 outcomes of preterm singleton neonates with intrauterine growth restriction. *Neonatal*
48 781 *Med.* 2018;25(4):161-169. <https://doi.org/10.5385/nm.2018.25.4.161>.
- 49
50
51 782 [dataset] [64] Riskin-Mashiah S, Reichman B, Bader D, et al. Population-based study on
52 783 antenatal corticosteroid treatment in preterm small for gestational age and non-small for
53 784 gestational age twin infants. *J Matern Fetal Neonatal Med.* 2018;31(5):553-559. [https://](https://doi.org/10.1080/14767058.2017.1292242)
54 785 [doi: 10.1080/14767058.2017.1292242](https://doi.org/10.1080/14767058.2017.1292242).
- 55
56
57 786 [dataset] [65] Cartwright RD, Crowther CA, Anderson PJ, et al. Association of fetal
58 787 growth restriction with neurocognitive function after repeated antenatal betamethasone

- 1
2
3
4
5
6 788 treatment vs placebo: secondary analysis of the ACTORDS randomized clinical trial.
7 789 *JAMA Netw Open.* 2019;2(2):e187636. [https:// doi:](https://doi.org/10.1001/jamanetworkopen.2018.7636)
8 790 10.1001/jamanetworkopen.2018.7636.
9
10 791 [dataset] [66] Bitar G, Merrill SJ, Sciscione AC, et al. Antenatal corticosteroids in the late
11 792 preterm period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM.*
12 793 2020;2(3):100153. [https:// doi: 10.1016/j.ajogmf.2020.100153.](https://doi.org/10.1016/j.ajogmf.2020.100153)
13 794 [67] Torrance HL, Derks JB, Scherjon SA, et al. Is antenatal steroid treatment effective
14 795 in preterm IUGR fetuses? *Acta Obstet Gynecol Scand.* 2009;88(10):1068-1073. [https://](https://doi.org/10.1080/00016340903176784)
15 796 doi: 10.1080/00016340903176784.
16 797 [68] Whiteman VE, Homko CJ, Reece EA. Management of hypoglycemia and diabetic
17 798 ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am.* 1996;23(1):87-107. [https://](https://doi.org/10.1016/s0889-8545(05)70246-1)
18 799 doi: 10.1016/s0889-8545(05)70246-1.
19 800 [69] Mathiesen ER, Christensen AB, Hellmuth E, et al. Insulin dose during glucocorticoid
20 801 treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction
21 802 of analgoritm]. *Acta Obstet Gynecol Scand.* 2002;81(9):835-839. [https:// doi:](https://doi.org/10.1034/j.1600-0412.2002.810906.x)
22 803 10.1034/j.1600-0412.2002.810906.x.
23 804 [70] Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-
24 805 36+6 weeks) deliveries-A systematic review and meta-analysis of RCTs. *PLoS One.*
25 806 2021;16(3):e0248774. [https:// doi: 10.1371/journal.pone.0248774.](https://doi.org/10.1371/journal.pone.0248774)
26 807 [71] University of Auckland. The C*Steroid trial.
27 808 [https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html)
28 809 [studies-pregnancy/c-steroid-trial.html](https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html) (accessed 24 Mar 2022).
29 810 [72] Dong Y, St Clair PJ, Ramzy I, et al. A microbiologic and clinical study of placental
30 811 inflammation at term. *Obstet Gynecol.* 1987;70(2):175-182. Retrieved from
31 812 [https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clin](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx)
32 813 [ical_Study_of_Placental.7.aspx](https://journals.lww.com/greenjournal/Abstract/1987/08000/A_Microbiologic_and_Clinical_Study_of_Placental.7.aspx).
33 814 [73] Redline RW. Inflammatory responses in the placenta and umbilical cord. *Semin Fetal*
34 815 *Neonatal Med.* 2006;11(5):296-301. [https:// doi: 10.1016/j.siny.2006.02.011.](https://doi.org/10.1016/j.siny.2006.02.011)
35 816 [74] WHO ACTION Trials Collaborators, Oladapo OT, Vogel JP, et al. Antenatal
36 817 Dexamethasone for Early Preterm Birth in Low-Resource Countries. *N Engl J Med.*
37 818 2020;383(26):2514-2525. [https:// doi:10.1056/NEJMoa2022398.](https://doi.org/10.1056/NEJMoa2022398)
38 819 [75] World Health Organization. Born too soon: the global action report on preterm birth.
39 820 World Health Organization; 2012. <https://apps.who.int/iris/handle/10665/44864>
40 821 (accessed 24 Mar 2022).
41 822 [76] Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration
42 823 before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet*
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 824 *Gynaecol.* 1990;97(1):11-25. [https:// doi: 10.1111/j.1471-0528.1990.tb01711.x](https://doi.org/10.1111/j.1471-0528.1990.tb01711.x).
7 825 [77] Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus
8 826 Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal
9 827 Outcomes. *JAMA.* 1995;273(5):413-418. [https://](https://doi.org/10.1001/jama.1995.03520290065031)
10 828 [doi:10.1001/jama.1995.03520290065031](https://doi.org/10.1001/jama.1995.03520290065031).
11
12
13

14 829

15
16 830
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Supplementary table 1: Characteristic 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

^aGyamfi-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	CC	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	CC	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
Goldenberg 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	CC	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	HC	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	HC	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	CC	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 amniotic 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 \geq 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 \geq 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 percetile 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/>

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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

1
2
3
4
5 Periventricular leukomalacia (PVL)
6 Major brain lesion damage
7 Necrotizing enterocolitis (NEC)
8 Sepsis
9
10 Early onset sepsis
11
12 Systemic inflammatory response syndrome
13 Meningitis
14 Neonatal hypoglycemia
15 Neonatal adrenal insufficiency
16 Intrahepatic cholestasis
17 Retinopathy of prematurity (ROP)
18 Gestational age at birth
19 Birth weight
20 Neonatal intensive care unit (NICU) admission
21 Duration of hospital stay
22 Survival free from disability
23 Death at long-term follow up
24 Death or disability/handicap at 2 years
25 Cerebral palsy
26 Severe hearing impairment
27 Visual impairment
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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	<p>P3 Ryu et al. (2019): Listed in the online supplementary Table1*1.</p>
Preeclampsia	<p>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 \geq 90mmHg measured at least twice and proteinuria \geq0.3g/24g.</p>
Hypertensive disorders	<p>P2 Kirshenbaum et al. (2018): No data.</p>
Pregnancy induced hypertension (PIH)	<p>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.</p>
Chorioamnionitis	<p>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.</p>
Gestational diabetes mellitus	<p>P2 de la Hueruga et al. (2019): No data.</p>
	<p>P3 Ryu et al. (2019): Listed in the online supplementary Table1*1.</p>

	<u>P4</u> 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	<u>P1</u> Battarbee et al. (2020): Death within 48h after birth.
Death before discharge home	<u>P3</u> Foix-L'Helias et al. (2005): Death before discharge home. <u>P4</u> 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	<u>P2</u> Kishenbaum et al. (2018): Apgar score ≤ 7 at 5 min after birth.
Apgar score < 7 at 5min after birth	<u>P1</u> Krispin et al. (2018): Apgar score < 7 at 5 min after birth. <u>P3</u> Elimian et al. (2000): Apgar score < 7 at 5 min after birth. <u>P4</u> 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	<u>P4</u> 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)	<u>P1</u> Battarbee et al. (2020). Defined as a clinical diagnosis of respiratory distress syndrome, hyaline

1
2
3 membrane disease, or respiratory insufficiency requiring oxygen therapy with $FiO_2 \geq 0.40$ started
4 within the first 24 hours after birth and continued for ≥ 24 hours or until neonatal demise.

5 Krispin et al. (2018): No data.

6
7 **P2**

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

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

12
13 **P3**

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

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

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

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

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

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

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

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

34
35 **P4**

36 Kim et al. (2018): No data.

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

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

40 Feng et al. (2017): No data.

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

42 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

43 Mitsiakos et al. (2013): Diagnosed based on clinical and radiological criteria and oxygen requirements
44
45
46

≥ 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.
For peer review only (http://www.bmj.com/site/about/guidelines.xhtml)

	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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

1 2 3 4 5 6 7	Mean duration of mechanical ventilations	P2 de la Huerga Lopez et al. (2019): No data. P3 Ahn et al. (2012): No data.
8 9	Duration of oxygen use	P3 Ahn et al. (2012): No data.
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27	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. (2009): 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 to a left-to-right shunt. Mitsiakos et al. (2013): No data. van Stralen et al. (2009): No data. Elimian et al. (1999): No data.
28 29 30	Hypotension within 7 postnatal days	P3 Ryu et al. (2019): Listed in the online supplementary Table1.*1
31 32 33 34	Hypotension	P4 van Stralen et al. (2009): Defined as a mean arterial pressure ≤ 30 mmHg requiring treatment with volume expanders and/or inotropic support.
35 36 37 38 39 40 41 42 43 44 45 46	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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.

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

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.

For peer review only: <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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 \(SDG 3.2.2\) \(who.int\)](https://www.who.int/indicators/mortality-rates/neonatal-mortality-rate).

*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.

- 1
2
3 *7. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, ed. Neurology of the newborn. Philadelphia: Saunders; 2001: 331-94.
4 *8. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg.
5 1978;187(1):1-7. doi:10.1097/0000658-197801000-00001.
6 *9. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol.
7 1984;102(8):1130-1134. doi:10.1001/archopht.1984.01040030908011.
8 *10. Frederiks AM, Nederlandse groeidoagrammen 1997 in historisch perspectief. In: Wit JM, ed. De Vierde Landelijke Groeistudie 1997. Presentatie
9 nieuwe groeidoagrammen. Bureau Boerhaave Commissie. Leiden: Rijksuniversiteit Leiden, 1998:1-14.
10 *11. Barkley RA. Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press, 1990: 39-73.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

For peer review only

1
2
3
4
5
6
7
8
9

Supplementary table 4: Database-specific search terms and strategies

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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	(MH "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

1 **Supplementary table 5: Risk of bias**

2
3 **Risk of bias assessments for studies of women with pregestational and/or with gestational diabetes**

4
5
6 ***Risk of bias assessments (RoBANS)***

7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 (\geq 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							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with PGDM	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section												
2	observational studies	not serious	serious ^a	not serious	serious ^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 =\leq7 at 5minutes												
1	observational studies	not serious	not serious	not serious	very serious ^{a,b}	none	2/58 (3.4%)	0/107 (0.0%)	OR 9.51 (0.45 to 201.57)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	
Mean duration of mechanical ventilation												

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

Oxygen requirement for at least 4 hours

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

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

Explanations

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

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Author(s): Kana Saito, Etsuko Nishimura, Toshiyuki Swa, Jenny Cao, Jenny Ramson, Fumihiko Namba, Erika Ota, Joshua P. Vogel
Question: Is antenatal corticosteroid therapy effective and safe for reducing adverse maternal and child outcomes in women with chorioamnionitis?
Setting: 8 studies (observational studies in the USA, the Netherlands, France, and Republic of Korea)

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

1	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	
2	Chronic lung disease / bronchopulmonary dysplasia (CC)												
3	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	
4	Periventricular leukomalacia (HC)												
5	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	
6	Periventricular leukomalacia (CC)												
7	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	
8	Mean duration of mechanical ventilation, days (HC)												
9	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	
10	Necrotizing enterocolitis (HC)												
11	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	
12	Necrotizing enterocolitis (CC)												
13	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	
14	Apgar score <7 at 5 minutes (HC)												
15	1	observational studies	not serious	not serious	not serious	serious ^{b,a}	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	
16	Use of mechanical ventilation (HC)												
17	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	
18	Use of mechanical ventilation (CC)												
19	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	
20	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

- 1
- 2
- 3 a. Estimate based on wide confidence interval crossing the line of no effect.
- 4 b. Estimate based on small sample size.
- 5 c. Heterogeneity is high (I-square \geq 60%).
- 6 d. Wide difference of denominators between ACS and control group.
- 7 e. The data were extracted from one study.
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

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 ^s	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	none	386/3592 (10.7%)	378/2758 (13.7%)	OR 0.75 (0.53 to 1.06)	31 fewer per 1,000 (from 59 fewer to 7 more)	⊕○○○ Very low
Severe interventricular haemorrhage (grade3-4) (SGA)											
7	observational studies	not serious	serious ^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

Appgar score < 5 at 1 minute (SGA)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	49/191 (25.7%)	15/56 (26.8%)	OR 1.37 (0.63 to 2.97)	66 more per 1,000 (from 81 fewer to 253 more)	⊕○○○ Very low
Neonatal hypoglycemia (SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	17/45 (37.8%)	8/37 (21.6%)	OR 2.20 (0.82 to 5.91)	161 more per 1,000 (from 32 fewer to 404 more)	⊕○○○ Very low
Gestational age at birth (SGA)											
2	observational studies	not serious	not serious	not serious	serious ^d	none	806	1272	-	MD 0.58 lower (0.81 lower to 0.34 lower)	⊕○○○ Very low
Small for gestational age (< 2.3rd percentile for gestational age) (SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	63/146 (43.2%)	12/19 (63.2%)	OR 0.44 (0.16 to 1.19)	202 fewer per 1,000 (from 416 fewer to 39 more)	⊕○○○ Very low
Neonatal adrenal insufficiency (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	53/719 (7.4%)	67/1210 (5.5%)	OR 1.36 (0.94 to 1.97)	18 more per 1,000 (from 3 fewer to 48 more)	⊕○○○ Very low
Cerebral palsy (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	19/278 (6.8%)	25/498 (5.0%)	OR 1.39 (0.75 to 2.57)	18 more per 1,000 (from 12 fewer to 69 more)	⊕○○○ Very low
Severe hearing impairment (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	0/277 (0.0%)	5/502 (1.0%)	OR 0.16 (0.01 to 2.96)	8 fewer per 1,000 (from 10 fewer to 19 more)	⊕○○○ Very low
Visual impairment (SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	none	1/275 (0.4%)	3/490 (0.6%)	OR 0.59 (0.06 to 5.72)	3 fewer per 1,000 (from 6 fewer to 28 more)	⊕○○○ Very low
Birth weight (SGA)											
2	observational studies	not serious	serious ^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 ^{ab}	none	87	62	-	MD 4 lower (17.43 lower to 9.43 higher)	⊕○○○ Very low

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

Explanations

- 1
- 2
- 3 a. Estimate based on wide confidence interval crossing the line of no effect.
- 4 b. Estimate based on small sample size.
- 5 c. Heterogeneity is high (I-square=>60%).
- 6 d. Estimate based on the risk of selection bias.
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

For peer review only

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 ^{ab}	none	20/165 (12.1%)	6/62 (9.7%)	OR 0.69 (0.26 to 1.81)	28 fewer per 1,000 (from 70 fewer to 66 more)	⊕○○○ Very low	
Death before discharge home (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	9/62 (14.5%)	15/62 (24.2%)	OR 0.53 (0.21 to 1.33)	97 fewer per 1,000 (from 179 fewer to 56 more)	⊕○○○ Very low	
Respiratory distress syndrome (RDS) and moderate / severe RDS (FGR)												
3	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	-	-	OR 0.85 (0.57 to 1.26)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ Very low	
Surfactant use (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	19/53 (35.8%)	13/34 (38.2%)	OR 0.90 (0.37 to 2.20)	25 fewer per 1,000 (from 196 fewer to 194 more)	⊕○○○ Very low	
Major brain lesion (IVH, ICH, PVH, PVL) (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	12/116 (10.3%)	10/96 (10.4%)	OR 0.86 (0.35 to 2.10)	13 fewer per 1,000 (from 65 fewer to 92 fewer)	⊕○○○ Very low	
Interventricular haemorrhage (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Severe interventricular haemorrhage (grade3-4) (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	8/62 (12.9%)	9/62 (14.5%)	OR 0.87 (0.31 to 2.43)	16 fewer per 1,000 (from 95 fewer to 147 more)	⊕○○○ Very low	
Neonatal sepsis (FGR)												
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	45/115 (39.1%)	36/96 (37.5%)	OR 0.83 (0.44 to 1.58)	43 fewer per 1,000 (from 166 fewer to 112 more)	⊕○○○ Very low	
Necrotizing enterocolitis (FGR)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	3/53 (5.7%)	2/34 (5.9%)	OR 0.96 (0.15 to 6.07)	2 fewer per 1,000 (from 50 fewer to 216 more)	⊕○○○ Very low	
Patent ductus arteriosus (FGR)												

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	10/53 (18.9%)	6/34 (17.6%)	OR 1.09 (0.35 to 3.32)	13 more per 1,000 (from 107 fewer to 239 more)	⊕○○○ Very low
Chronic lung disease / bronchopulmonary dysplasia (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	22/115 (19.1%)	23/96 (24.0%)	OR 0.83 (0.42 to 1.63)	32 fewer per 1,000 (from 123 fewer to 100 more)	⊕○○○ Very low
Duration of mechanical ventilation (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	115	96	-	MD 1.09 higher (0.86 lower to 3.05 higher)	⊕○○○ Very low
Use of mechanical ventilation (FGR)											
2	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	61/115 (53.0%)	45/96 (46.9%)	OR 1.24 (0.72 to 2.14)	54 more per 1,000 (from 80 fewer to 185 more)	⊕○○○ Very low
Hypotension (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	15/53 (28.3%)	5/34 (14.7%)	OR 2.29 (0.75 to 7.03)	136 more per 1,000 (from 33 fewer to 401 more)	⊕○○○ Very low
Growth <10th percentile in early childhood (FGR)											
1	observational studies	not serious	not serious	not serious	serious ^b	none	14/49 (28.6%)	3/42 (7.1%)	OR 5.20 (1.38 to 19.62)	214 more per 1,000 (from 25 more to 530 more)	⊕○○○ Very low
Abnormal behavior at long-term follow-up at school age (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	21/49 (42.9%)	19/42 (45.2%)	OR 0.91 (0.40 to 2.08)	23 fewer per 1,000 (from 204 fewer to 180 more)	⊕○○○ Very low
Death at long-term follow-up (school age) (FGR)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	4/62 (6.5%)	5/62 (8.1%)	OR 0.79 (0.20 to 3.08)	16 fewer per 1,000 (from 63 fewer to 132 more)	⊕○○○ Very low
Death or disability/handicap at 2yrs' corrected age (FGR)											
1	observational studies	not serious	not serious	not serious	serious ^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							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	women with growth-restricted fetuses	placebo	Relative (95% CI)	Absolute (95% CI)		
Caesarean section (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	136/219 (62.1%)	56/119 (47.1%)	OR 1.02 (0.62 to 1.68)	5 more per 1,000 (from 115 fewer to 128 more)	⊕○○○	Very low
Chorioamnionitis (histologic and /or clinical) (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	19/83 (22.9%)	2/8 (25.0%)	OR 0.89 (0.17 to 4.78)	21 fewer per 1,000 (from 196 fewer to 364 more)	⊕○○○	Very low
Preeclampsia (FGR or SGA)												
2	observational studies	<u>not serious</u>	serious ^c	not serious	serious ^a	none	78/254 (30.7%)	52/209 (24.9%)	OR 1.37 (0.33 to 5.61)	63 more per 1,000 (from 150 fewer to 401 more)	⊕○○○	Very low
Gestational diabetes mellitus (FGR or SGA)												
2	observational studies	not serious	not serious	not serious	serious ^a	none	14/219 (6.4%)	7/119 (5.9%)	OR 1.06 (0.36 to 3.08)	3 more per 1,000 (from 37 fewer to 103 more)	⊕○○○	Very low
Pregnancy induced hypertension (FGR or SGA)												
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	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 ^{ab}	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 ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○	Very low
Severe interventricular haemorrhage (grade3-4) (FGR or SGA)												

1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	0/8 (0.0%)	OR 1.19 (0.06 to 23.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low
Neonatal sepsis (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	18/83 (21.7%)	3/8 (37.5%)	OR 0.46 (0.10 to 2.12)	159 fewer per 1,000 (from 318 fewer to 185 more)	⊕○○○ Very low
Necrotizing enterocolitis (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	5/83 (6.0%)	1/8 (12.5%)	OR 0.45 (0.05 to 4.40)	65 fewer per 1,000 (from 118 fewer to 261 more)	⊕○○○ Very low
Patent ductus arteriosus (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	42/83 (50.6%)	4/8 (50.0%)	OR 1.02 (0.24 to 4.37)	5 more per 1,000 (from 306 fewer to 314 more)	⊕○○○ Very low
Chronic lung disease / bronchopulmonary dysplasia (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	23/83 (27.7%)	3/8 (37.5%)	OR 0.64 (0.14 to 2.89)	98 fewer per 1,000 (from 298 fewer to 259 more)	⊕○○○ Very low
Use of mechanical ventilation (FGR or SGA)											
2	observational studies	not serious	not serious	not serious	not serious	strong association	73/275 (26.5%)	94/233 (40.3%)	OR 0.42 (0.26 to 0.66)	182 fewer per 1,000 (from 254 fewer to 95 fewer)	⊕⊕⊕○ Moderate
Apgar score < 7 at 5 minutes (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	very serious ^{ab}	none	6/136 (4.4%)	5/111 (4.5%)	OR 0.98 (0.29 to 3.29)	1 fewer per 1,000 (from 32 fewer to 89 more)	⊕○○○ Very low
Neonatal hypoglycemia (FGR or SGA)											
1	observational studies	not serious	not serious	not serious	serious ^a	strong association	55/136 (40.4%)	28/111 (25.2%)	OR 2.01 (1.16 to 3.48)	152 more per 1,000 (from 29 more to 288 more)	⊕⊕○○ Low
Oxygen therapy (FGR or SGA)											
2	observational studies	not serious	not serious	not serious	not serious	strong association	79/275 (28.7%)	94/233 (40.3%)	OR 0.48 (0.30 to 0.77)	158 fewer per 1,000 (from 235 fewer to 61 fewer)	⊕⊕⊕○ Moderate
Gestational age at birth (FGR or SGA)											
2	observational studies	not serious	serious ^s	not serious	serious ^a	none	275	233	-	MD 0.43 higher (0.54 lower to 1.4 higher)	⊕○○○ Very low
Retinopathy of prematurity (FGR or SGA)											

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

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

Explanations

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

1	8	observational studies	not serious	not serious	not serious	serious*	none	191/1437 (13.3%)	165/1847 (8.9%)	OR 1.17 (0.92 to 1.50)	14 more per 1,000 (from 7 fewer to 39 more)	⊕○○○ Very low	
2	Necrotizing enterocolitis (total)												
3	10	observational studies	not serious	not serious	not serious	serious*	none	246/3889 (6.3%)	165/3003 (5.5%)	OR 0.82 (0.67 to 1.01)	9 fewer per 1,000 (from 17 fewer to 1 more)	⊕○○○ Very low	
4	Patent ductus arteriosus (total)												
5	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	
6	Chronic lung disease / bronchopulmonary dysplasia (total)												
7	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	
8	Apgar score < 7 at 5 minutes (total)												
9	4	observational studies	not serious	not serious	not serious	serious*	none	58/569 (10.2%)	67/582 (11.5%)	OR 0.76 (0.53 to 1.10)	25 fewer per 1,000 (from 51 fewer to 10 more)	⊕○○○ Very low	
10	Neonatal hypoglycemia (total)												
11	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	
12	Gestational age at birth (total)												
13	4	observational studies	not serious	serious*	not serious	serious*	none	1081	1505	-	MD 0.04 lower (0.57 lower to 0.48 higher)	⊕○○○ Very low	
14	Retinopathy of prematurity (total)												
15	5	observational studies	not serious	not serious	not serious	serious*	none	135/1978 (6.8%)	44/832 (5.3%)	OR 1.13 (0.79 to 1.61)	6 more per 1,000 (from 11 fewer to 30 more)	⊕○○○ Very low	
16	Neonatal adrenal insufficiency (total)												
17	2	observational studies	not serious	not serious	not serious	serious*	none	57/802 (7.1%)	67/1218 (5.5%)	OR 1.35 (0.93 to 1.96)	18 more per 1,000 (from 4 fewer to 47 more)	⊕○○○ Very low	
18	Cerebral palsy (total)												
19	2	observational studies	not serious	not serious	not serious	serious*	none	25/417 (6.0%)	30/620 (4.8%)	OR 1.31 (0.76 to 2.27)	14 more per 1,000 (from 11 fewer to 55 more)	⊕○○○ Very low	
20	Duration of hospital stay (total)												
21	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	

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

2

3 Explanations

- 4 a. Estimate based on wide confidence interval crossing the line of no effect.
5 b. Estimate based on small sample size.
6 c. Heterogeneity is high (I-square=>60%).
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only

PROSPERO
International prospective register of systematic reviews

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

PROSPERO

International prospective register of systematic reviews

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

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.

PROSPERO

International prospective register of systematic reviews

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.

Exclusion: Pregnant women with the population at 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.

PROSPERO

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 fulfil one or more of the following criteria:

1. undergoing elective caesarean birth in late preterm (from 34 weeks 0 days to 36 weeks 6 days);
2. having intrauterine inflammation, infection, or both; or
3. 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.

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)

PROSPERO

International prospective register of systematic reviews

- 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.

PROSPERO International prospective register of systematic reviews

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

PROSPERO**International prospective register of systematic reviews**

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 T^2 , I^2 , and τ^2 statistics.

Heterogeneity will be deemed substantial if T^2 will be greater than zero and either I^2 will be greater than 50% or $p < 0.10$ in the τ^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 $p < 0.10$ 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

PROSPERO

International prospective register of systematic reviews

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

PROSPERO**International prospective register of systematic reviews**1
2
3
4 No

5 Education

6 No

7
8 Endocrine and metabolic disorders

9 No

10 Eye disorders

11 No

12
13 General interest

14 No

15 Genetics

16 No

17
18 Health inequalities/health equity

19 No

20
21 Infections and infestations

22 No

23
24 International development

25 No

26 Mental health and behavioural conditions

27 No

28
29 Musculoskeletal

30 No

31
32 Neurological

33 No

34
35 Nursing

36 No

37
38 Obstetrics and gynaecology

39 No

40
41 Oral health

42 No

43
44 Palliative care

45 No

46
47 Perioperative care

48 No

49
50 Physiotherapy

51 No

52
53 Pregnancy and childbirth

54 Yes

55
56 Public health (including social determinants of health)

57 No

58
59 Rehabilitation

60 No

Respiratory disorders

No

PROSPERO**International prospective register of systematic reviews**

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?

PROSPERO**International prospective register of systematic reviews**

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

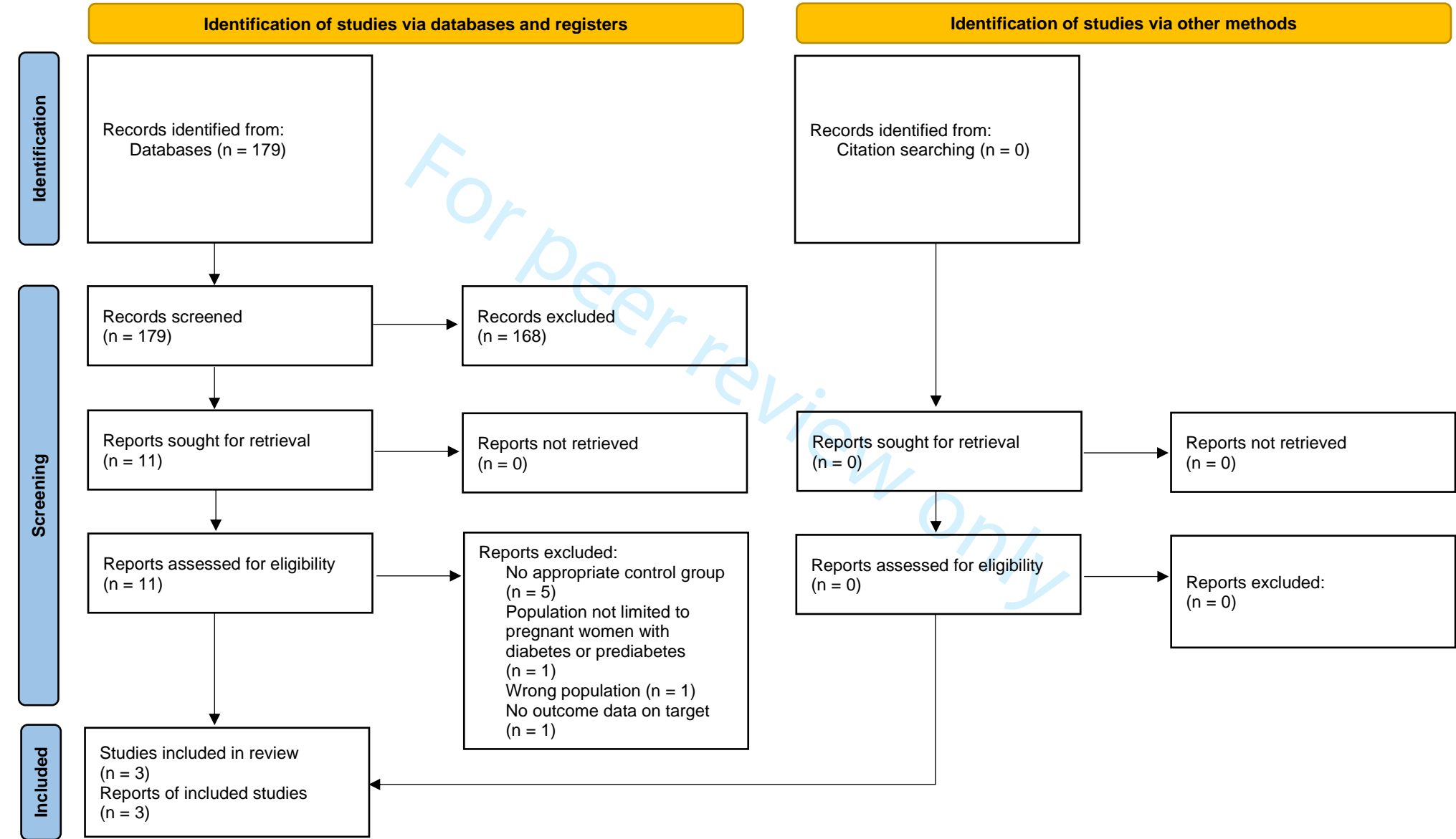


Figure 2: Flow diagram of search results and study selection for women undergoing elective Cesarean section in late preterm period

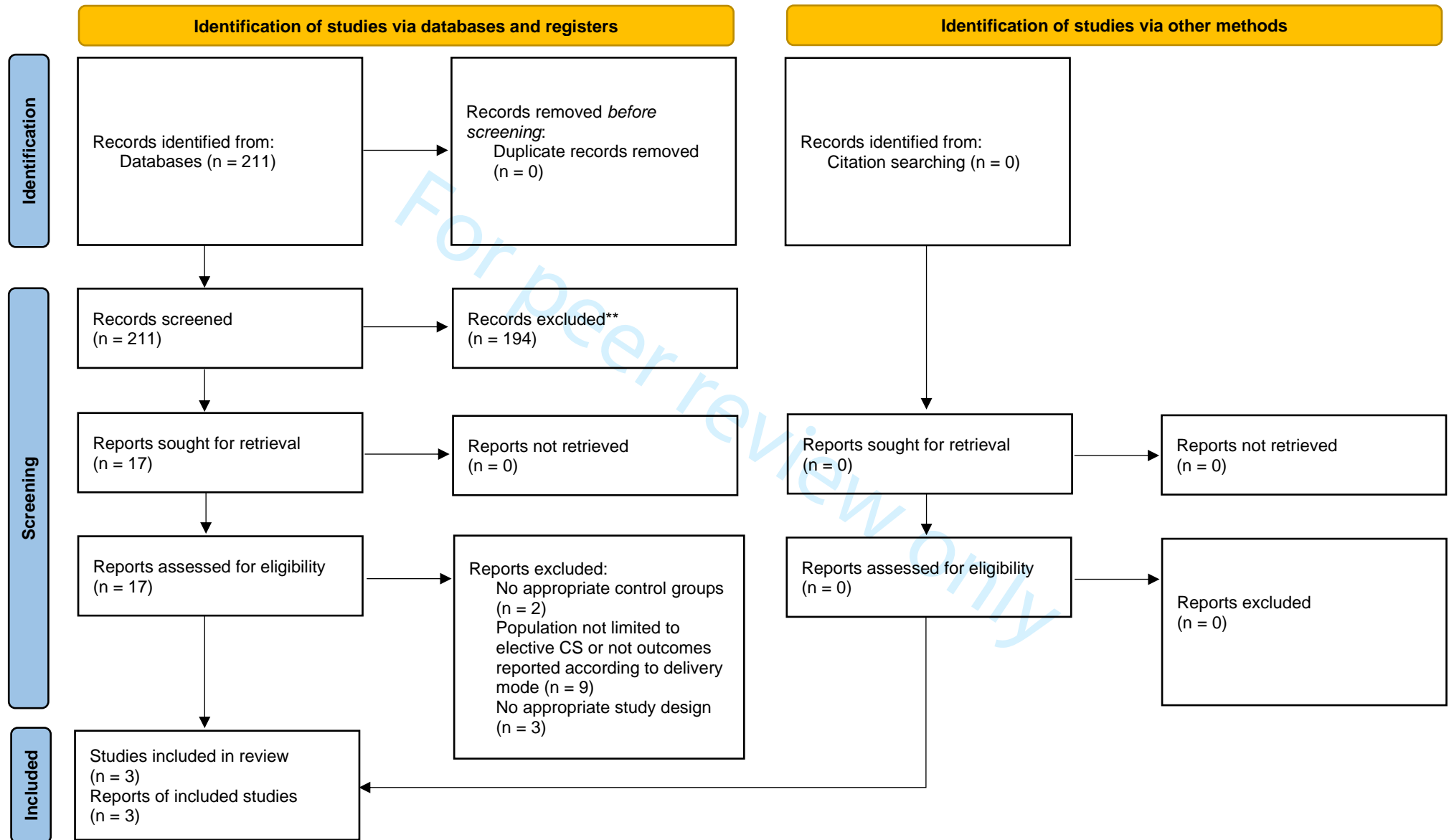


Figure 3: Flow diagram of search results and study selection for women with chorioamnionitis (histological or clinical)

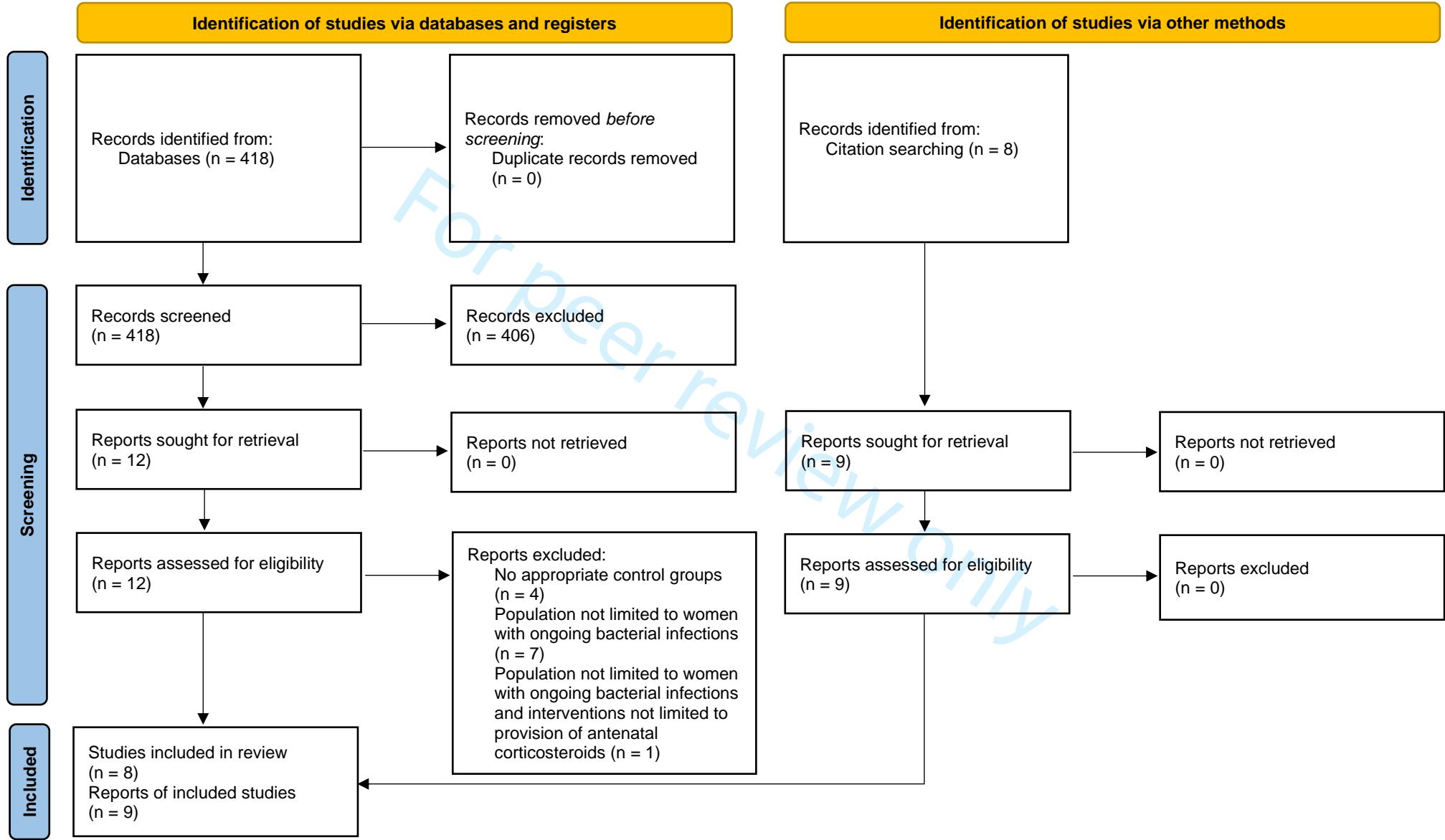
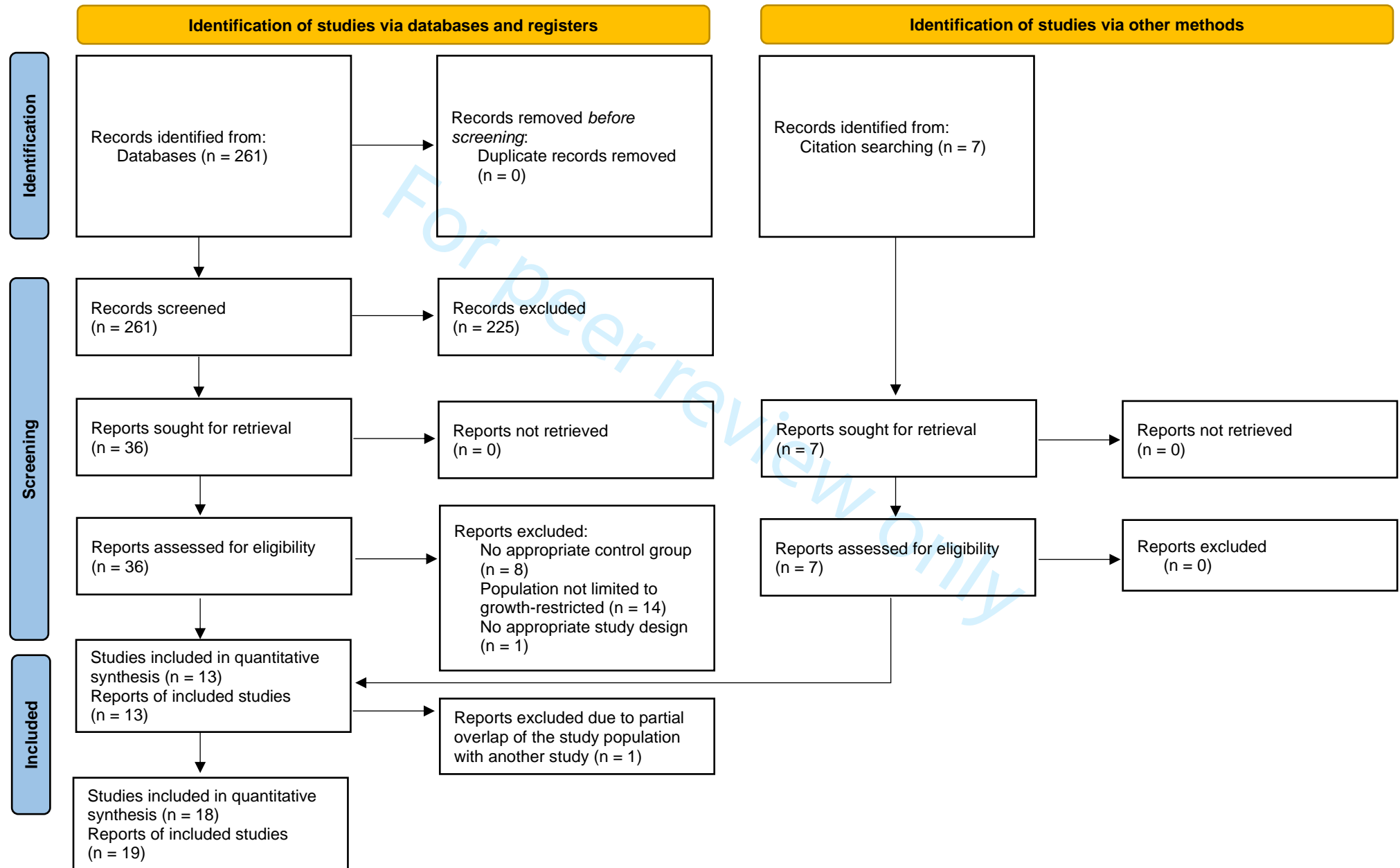


Figure 4: Flow diagram of search results and study selection for women with growth-restricted fetuses and/or small-for-gestational-age infants



Supplementary file 3: Risk of bias figures

Figure 1: 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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Battarbee 2020	+	-	+	+	+	+
Cassimatis 2020	+	-	+	+	+	+
Krispin 2018	+	-	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
de la Huerga Lopez 2019	+	-	+	+	+	+
Kirshenbaum 2018	+	-	+	+	+	+

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gyamfi-Bannerman 2016	+	+	+	+	+	+	+

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

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Ahn 2012	+	-	+	+	+	+
Baud 2000	+	-	+	+	+	+
Been 2009	+	-	+	+	+	+
Dempsey 2005	+	-	+	+	+	+
Elimian 2000	+	-	+	+	+	+
Foix-L'Helias 2005	+	-	+	+	+	+
Goldenberg 2006	+	-	+	+	+	+
Ryu 2019	+	-	+	+	+	+

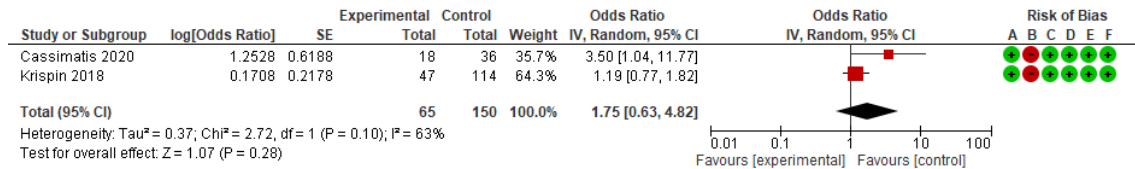
Figure 4: Summary of risk of bias for each trial for women with growth-restricted fetuses and/or small-for-gestational-age infants
 Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias

	Selection of participants (selection bias)	Confounding variables (selection bias)	Measurement of exposure (performance bias)	Blinding of outcomes assessment (Detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Bernstein 2000	+	-	+	+	+	+
Bitar 2020	+	-	+	+	+	+
Cartwright 2019	+	-	+	+	+	+
DiLenardo 1990	?	-	+	+	+	+
Elimian 1999	+	-	+	+	+	+
Feng 2017	+	-	+	+	+	+
Foix-L'Helias 2005	+	-	+	+	+	+
Ishikawa 2015	+	-	+	+	+	+
Kim 2018	+	+	+	+	+	+
Kim Y.J. 2018	+	-	+	+	+	+
Ley 1997	+	-	+	+	+	+
Mitsiakos 2013	+	-	+	+	+	+
Riskin-Mashiah 2016	+	-	+	+	+	+
Riskin-Mashiah 2018	+	-	+	+	+	+
Schaap 2001	+	-	+	+	+	+
Spinillo 1995	+	-	+	+	+	+
Torrance 2007	+	-	+	+	+	+
vanStralen 2009	+	-	+	+	+	+

Supplementary file 4: Forest plots

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

1) Caesarean section

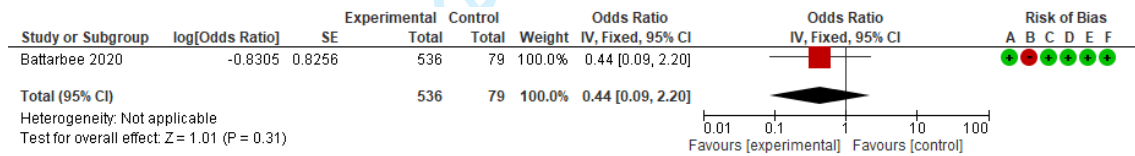
Risk of bias legend

- (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

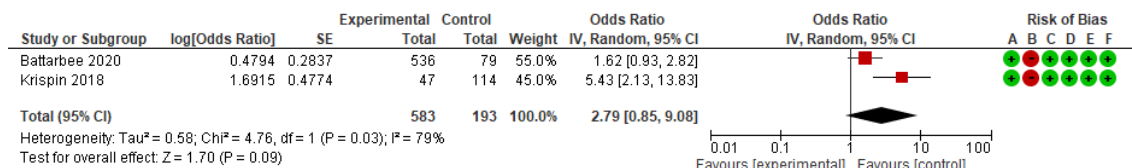
2) Apgar score < 7 at 5 min

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)

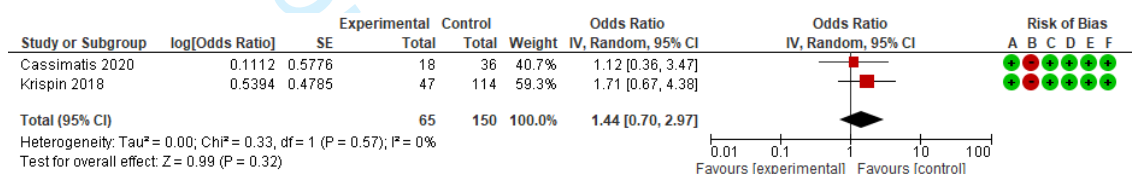


Risk of bias legend

- (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

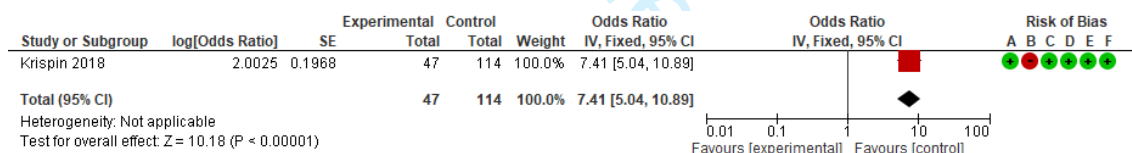


Risk of bias legend

- (A) Selection of participants (selection bias)
- (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) Admission to neonatal intensive care unit (NICU)



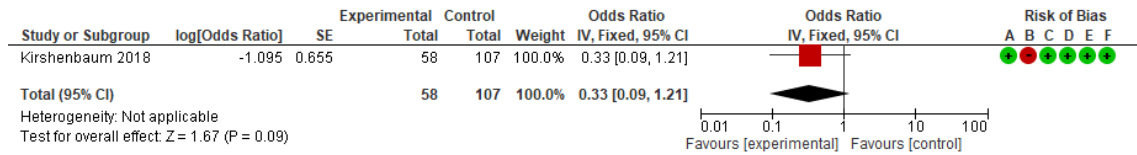
Risk of bias legend

- (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 undergoing elective cesarean section in the late preterm period

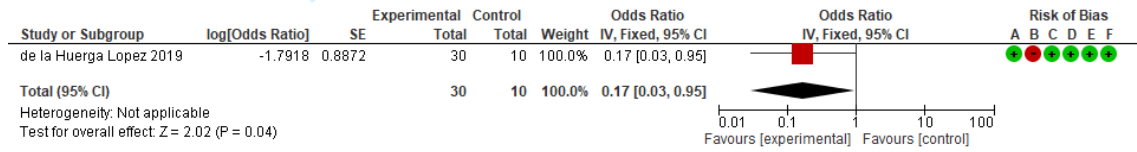
1) Hypertensive disorders



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) Gestational diabetes mellitus

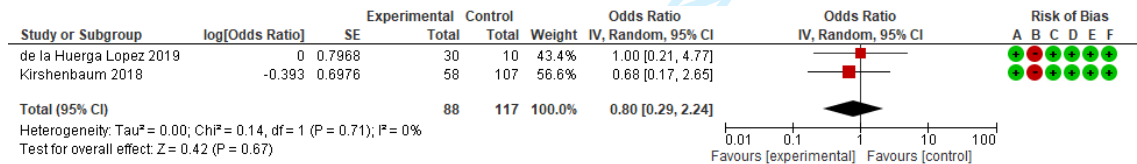


Risk of bias legend
 (A) Selection of participants (selection bias)
 (B) Confounding variables (selection bias)
 (C) Measurement of exposure (performance bias)
 (D) Blinding of outcomes assessment (Detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective outcome reporting (reporting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

SE: Standard error; CI: Confidence interval

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

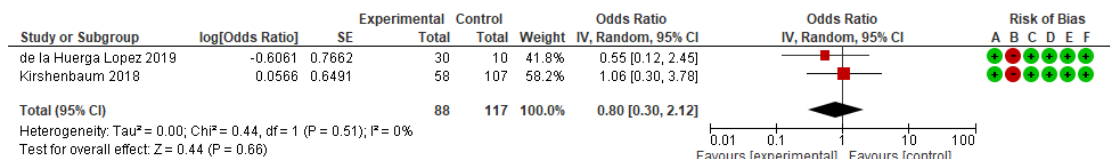
1) Respiratory distress syndrome (RDS)



Risk of bias legend
 (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

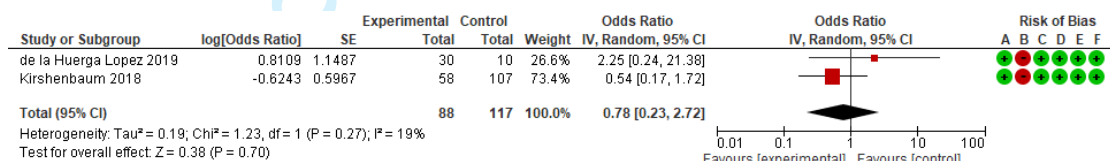


Risk of bias legend

- (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) Admission to neonatal intensive care unit (NICU)

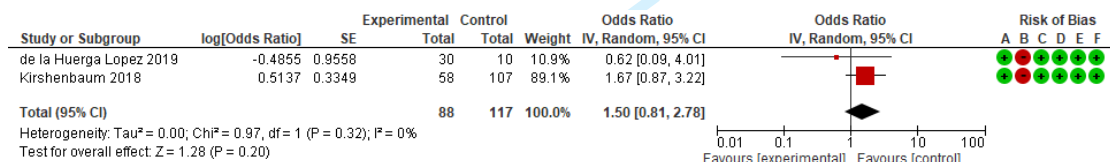


Risk of bias legend

- (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)
- (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)

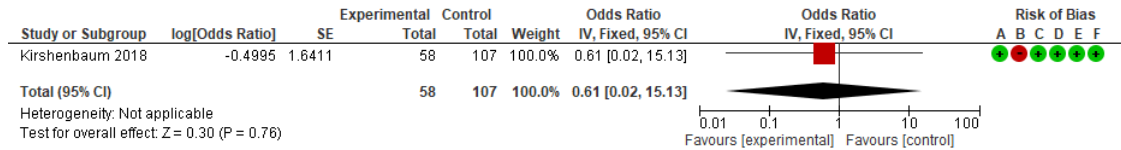


Risk of bias legend

- (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

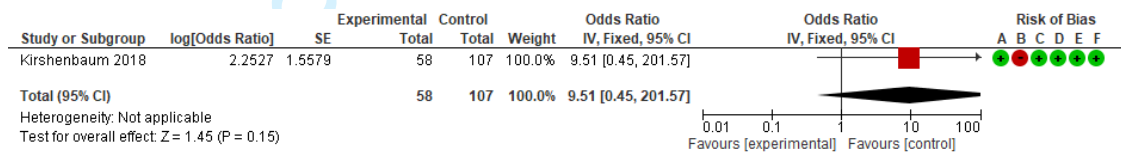
6) Necrotizing enterocolitis (NEC)



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

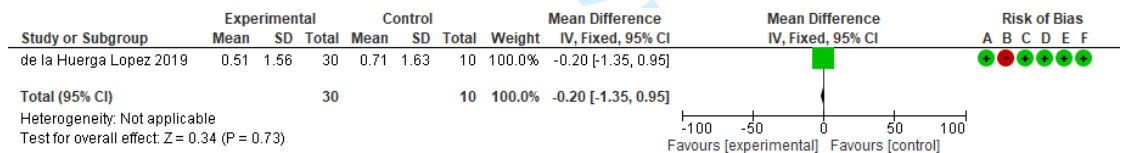
7) Apgar score ≤ 7 at 5min



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

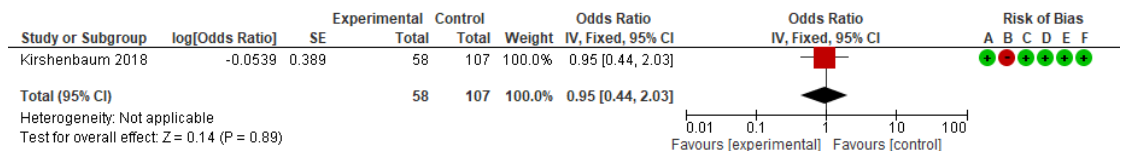
8) Mean duration of mechanical ventilation, days



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)



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

2) Gestational diabetes mellitus (HC)

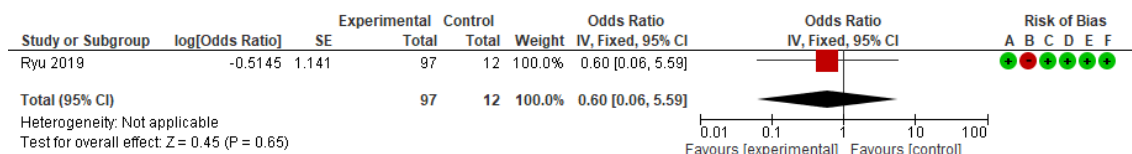


Risk of bias legend

- (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

3) Preeclampsia or eclampsia (HC)



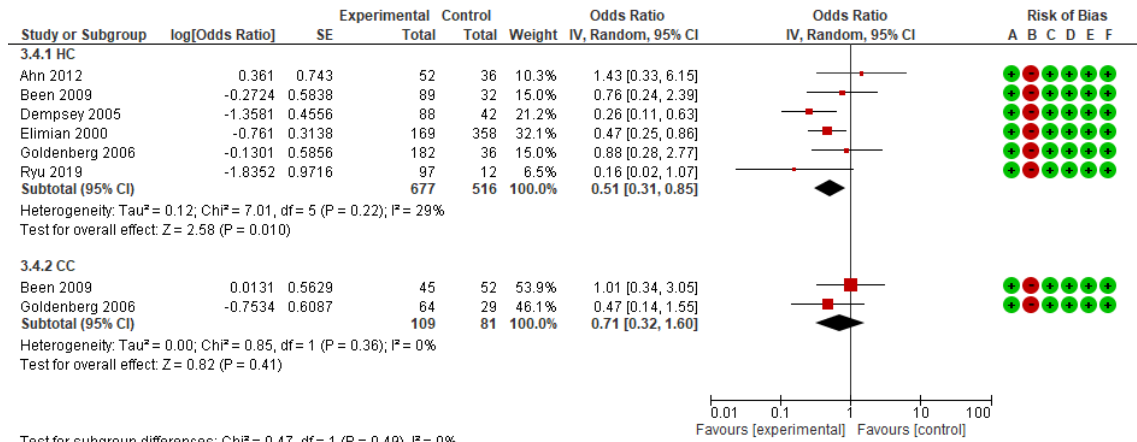
Risk of bias legend

- (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

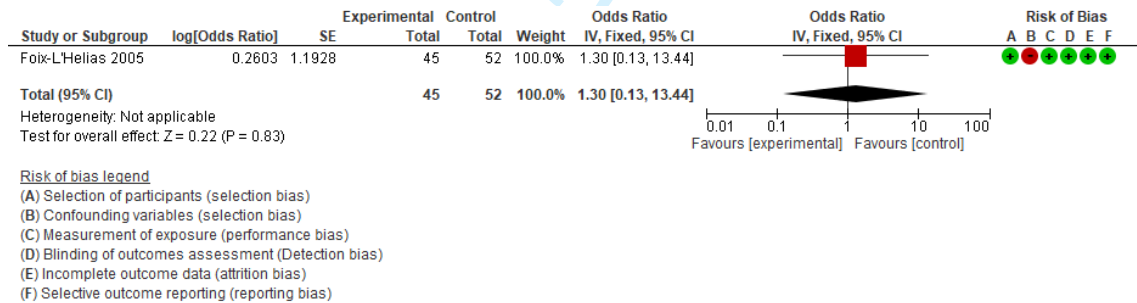
Neonatal outcomes for women with histological chorioamnionitis (HC) and clinical chorioamnionitis (CC)

1) Neonatal death



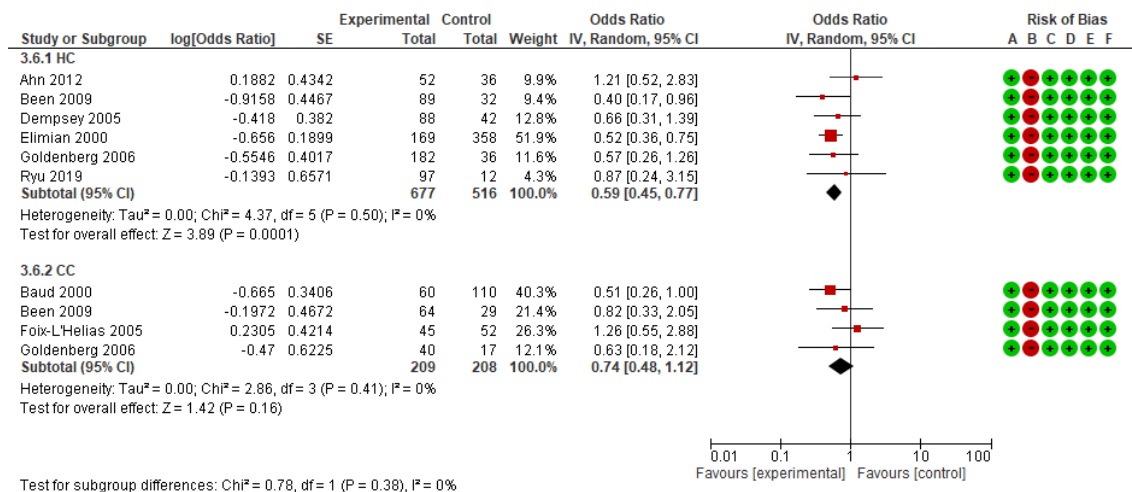
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

2) Death before discharge home (CC)



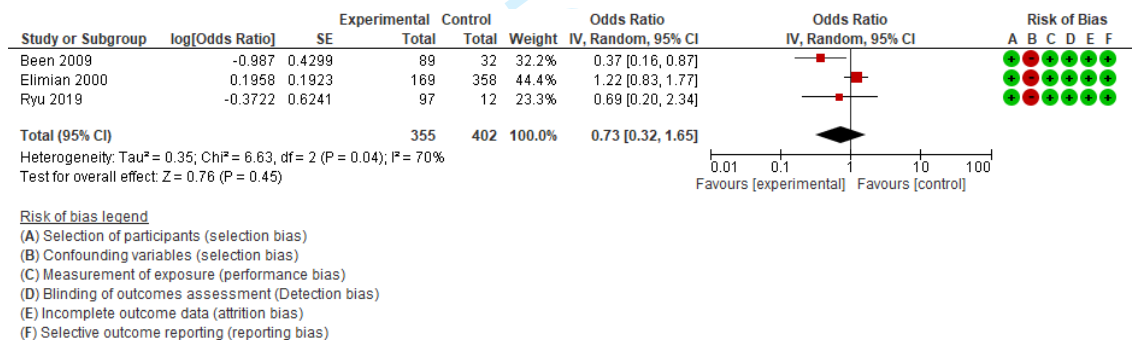
SE: Standard error; CI: Confidence interval; CC: Clinical chorioamnionitis

3) Respiratory distress syndrome (RDS)



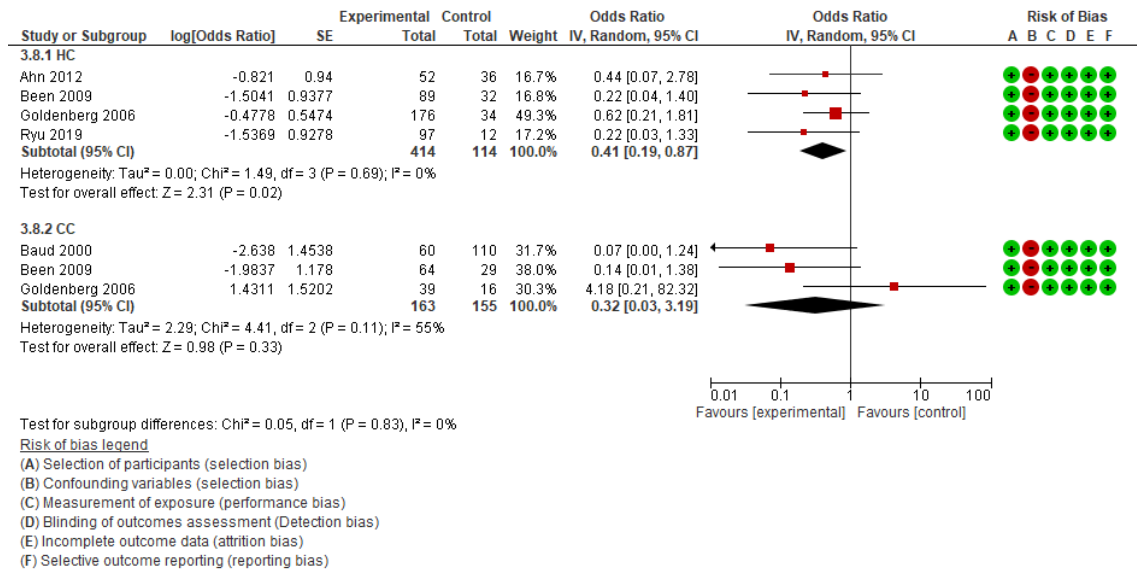
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

4) Surfactant use (HC)



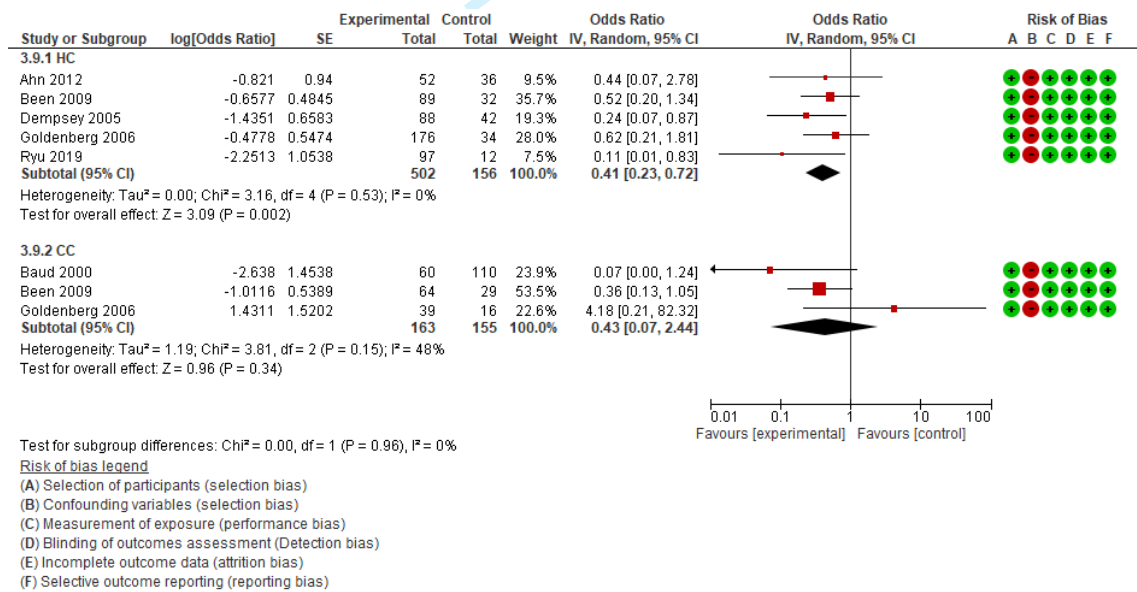
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis

5) Severe intraventricular hemorrhage (IVH)



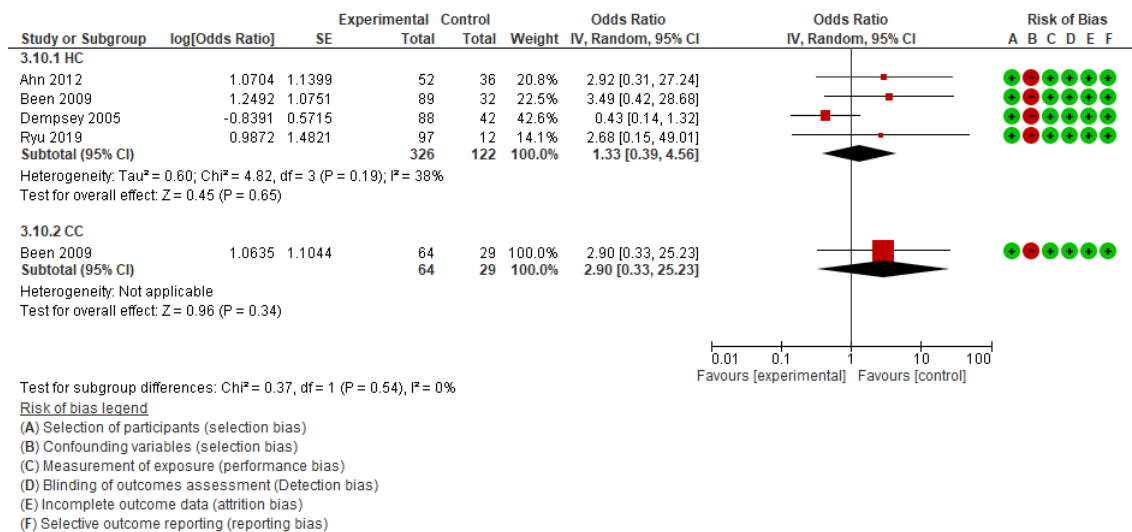
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

6) Intraventricular hemorrhage (IVH)



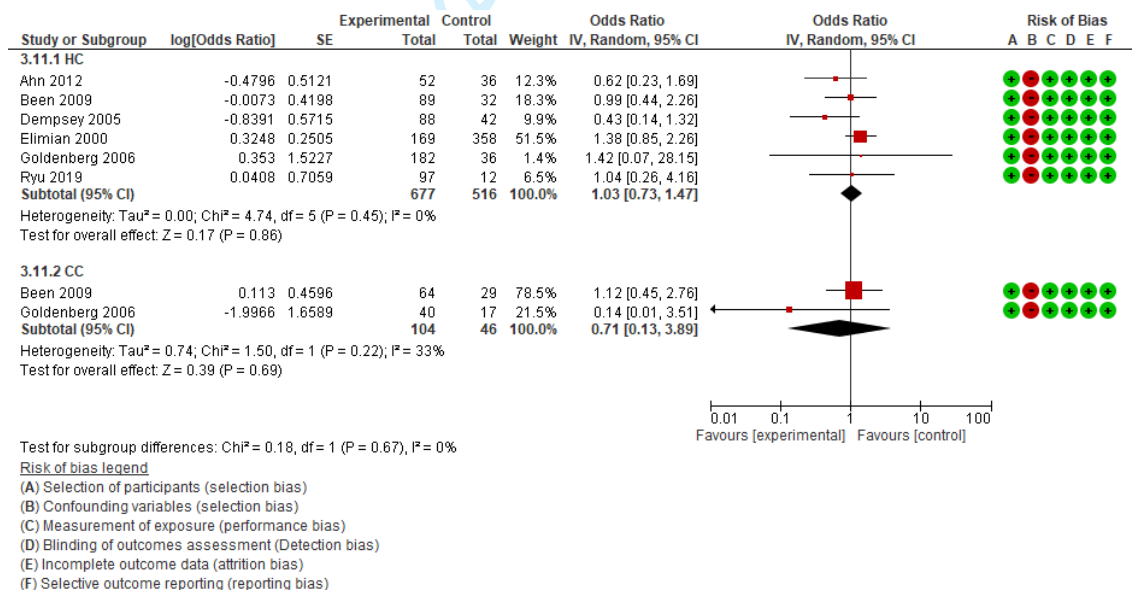
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

7) Early-onset sepsis



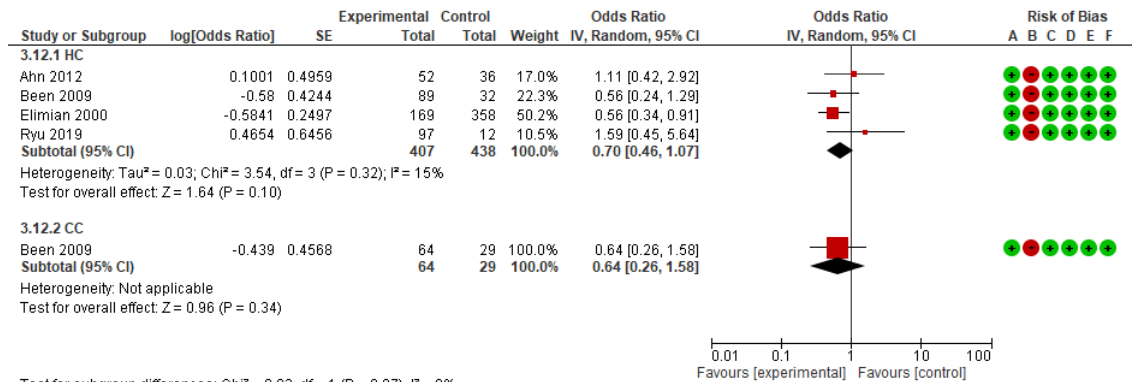
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

8) Sepsis



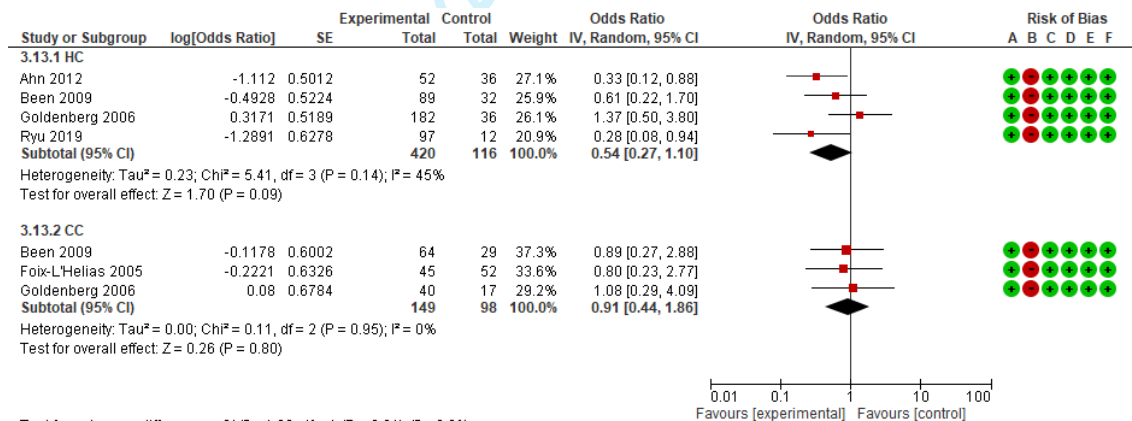
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

9) Patent ductus arteriosus (PDA)



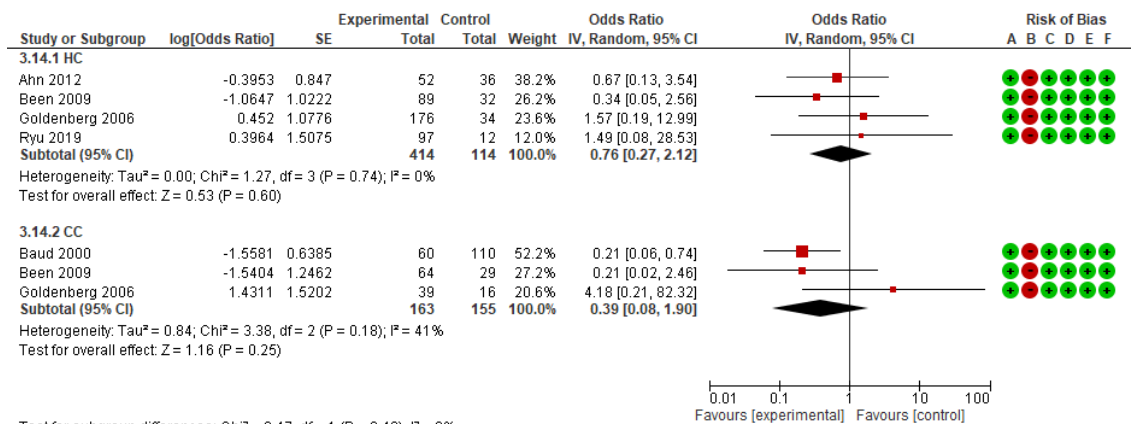
SE: Standard error; CI: Confidence interval; HC: Histological chorioamnionitis; CC: Clinical chorioamnionitis

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



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

11) Periventricular leukomalacia (PVL)



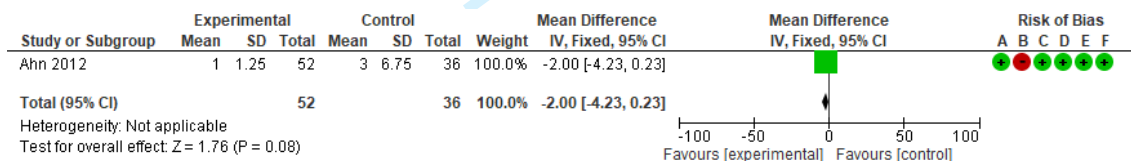
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%

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; **CC:** Clinical chorioamnionitis

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

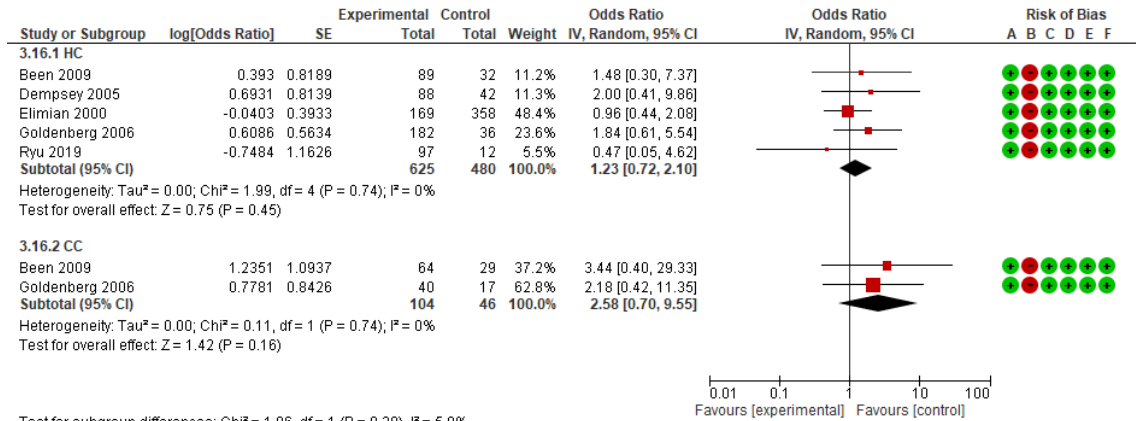


Risk of bias legend

- (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

13) Necrotizing enterocolitis (NEC)



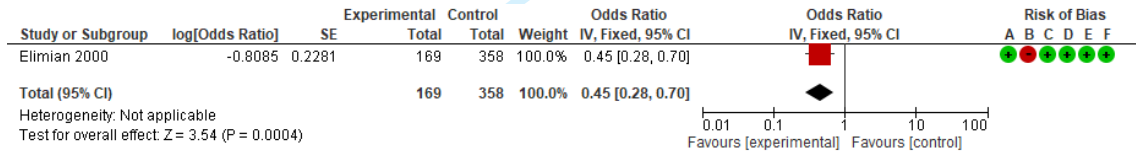
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² = 5.9%

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; CC: Clinical chorioamnionitis

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

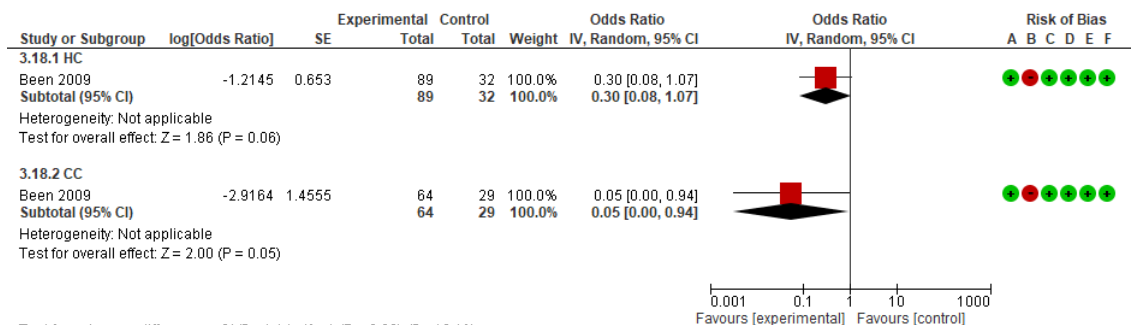


Risk of bias legend

- (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

15) Use of mechanical ventilation



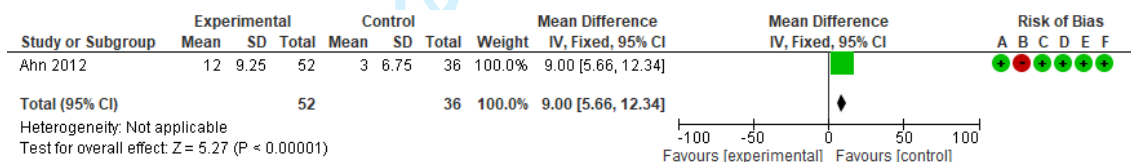
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.1%

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; **CC:** Clinical chorioamnionitis

16) Duration of oxygen use, days (HC)

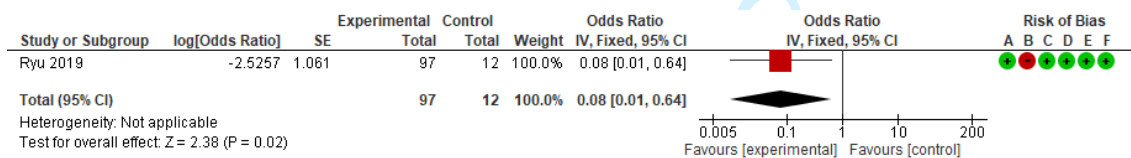


Risk of bias legend

- (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

17) Hypotension within 7 postnatal days (HC)

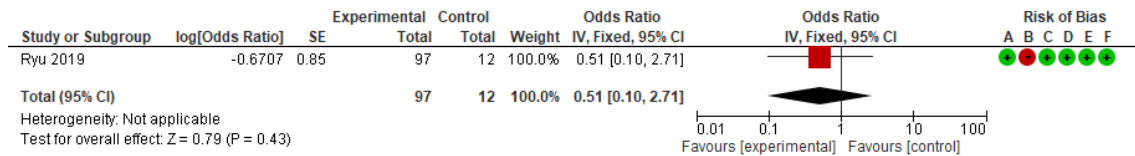


Risk of bias legend

- (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

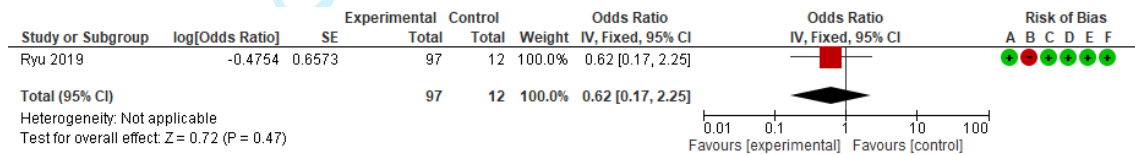
18) Retinopathy of prematurity requiring treatment (HC)

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

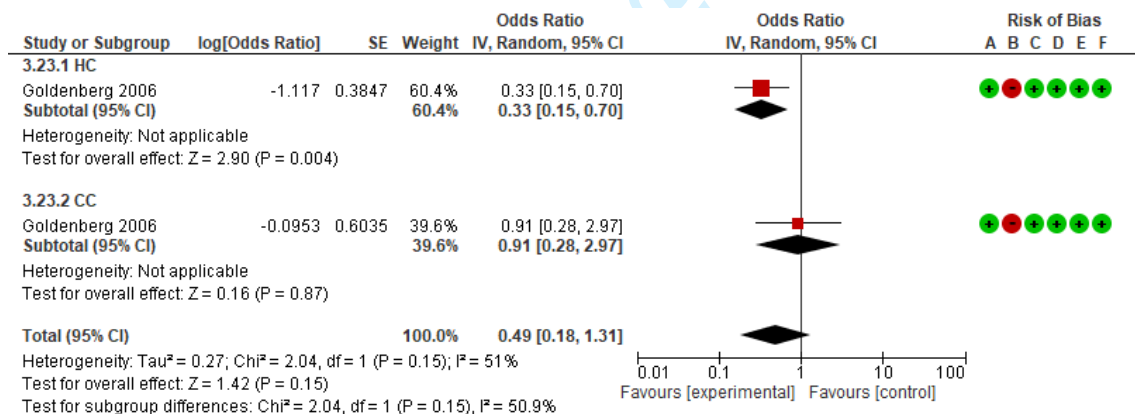
19) Discharge with respiratory support (HC)

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

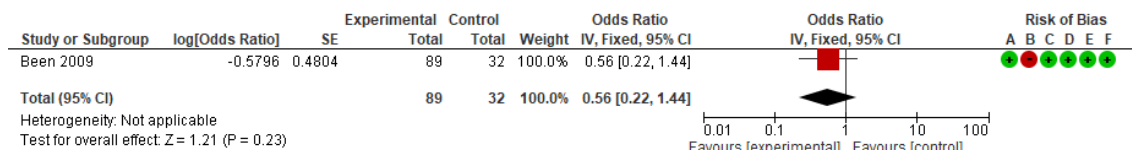
20) Systemic inflammatory response syndrome

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; 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)

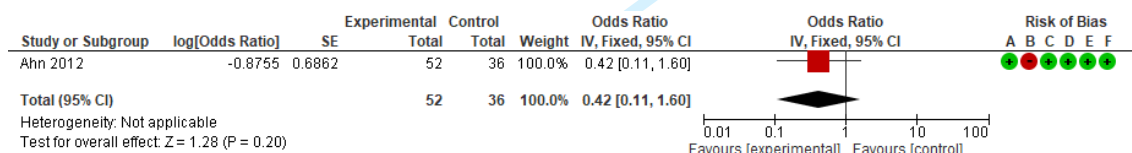


Risk of bias legend

- (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)



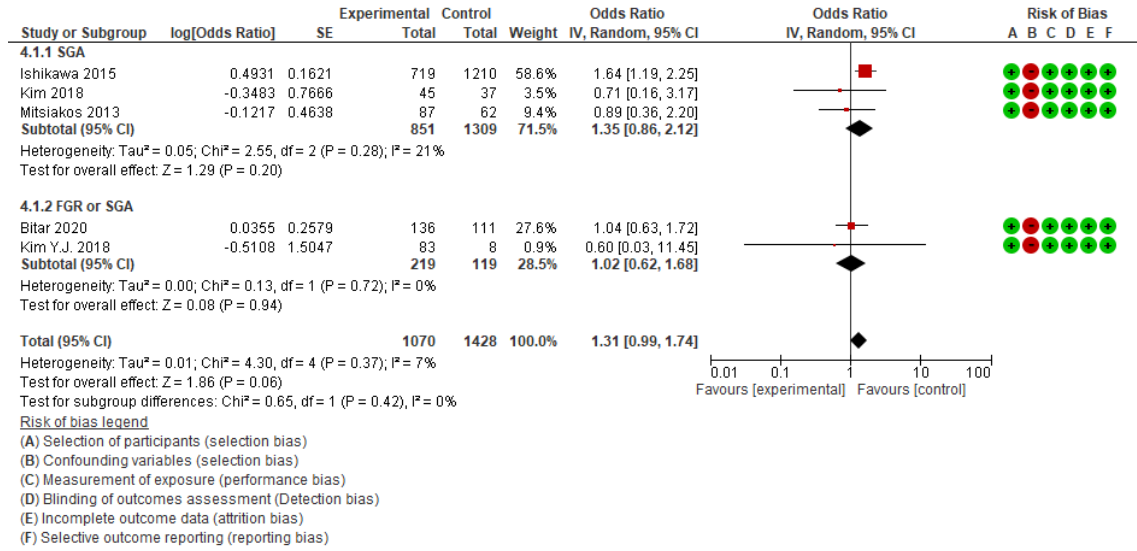
Risk of bias legend

- (A) Selection of participants (selection bias)
- (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

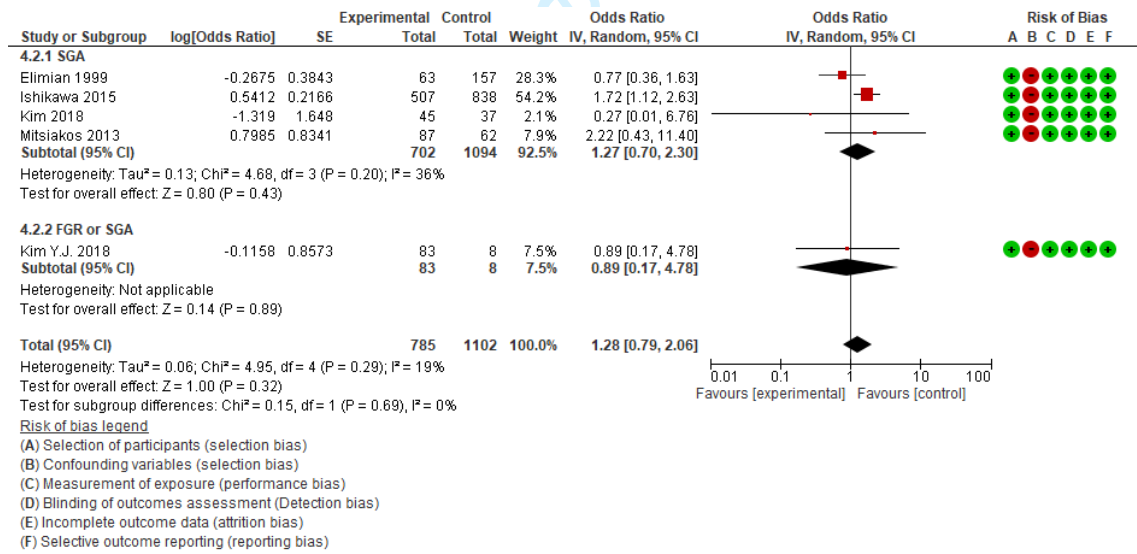
Maternal outcomes for women with growth-restricted fetuses and/or small-for-gestational age infants

1) Caesarean section



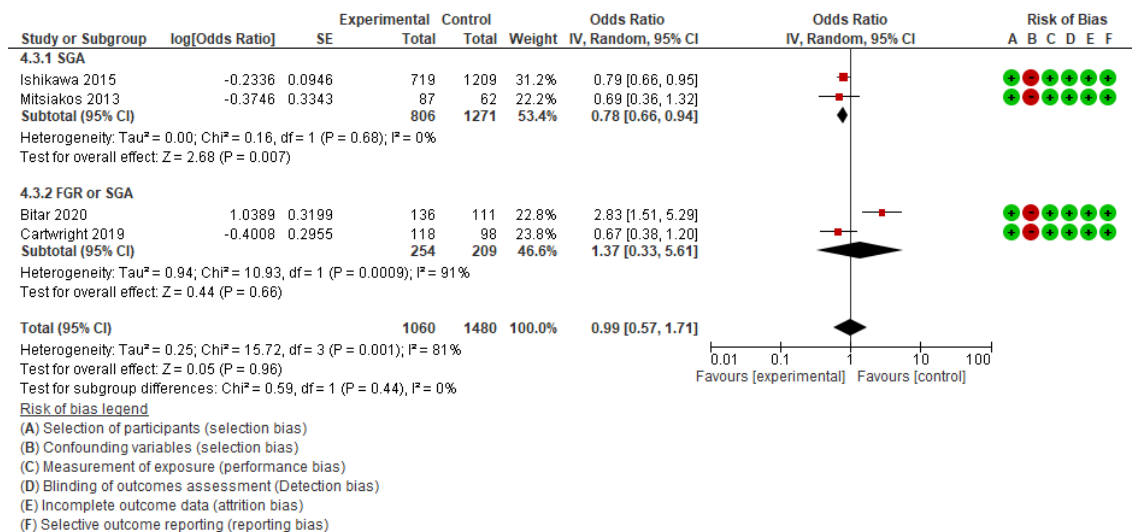
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

2) Chorioamnionitis (histologic and/or clinical)



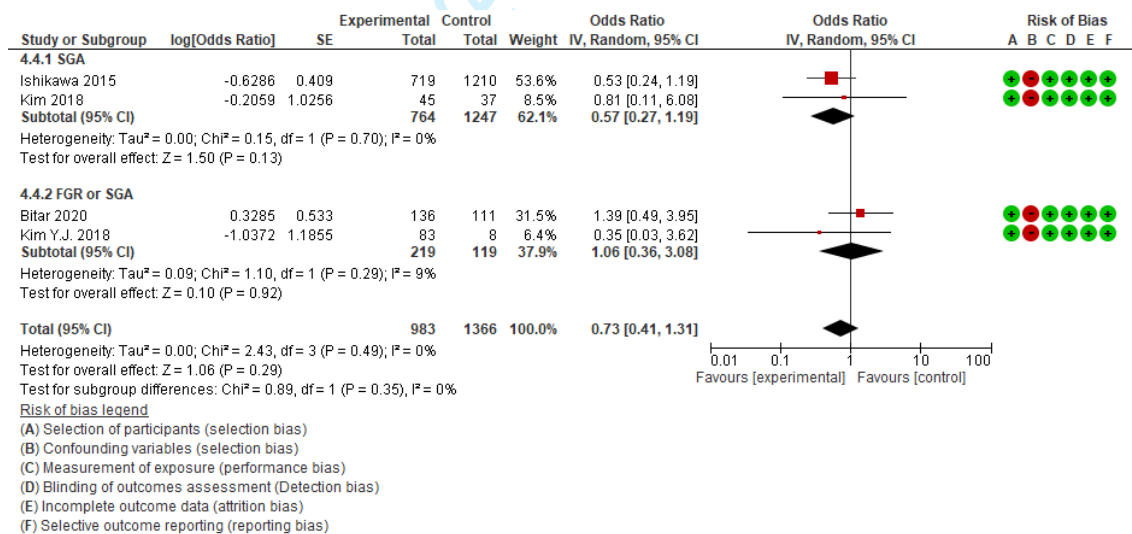
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

3) Preeclampsia.



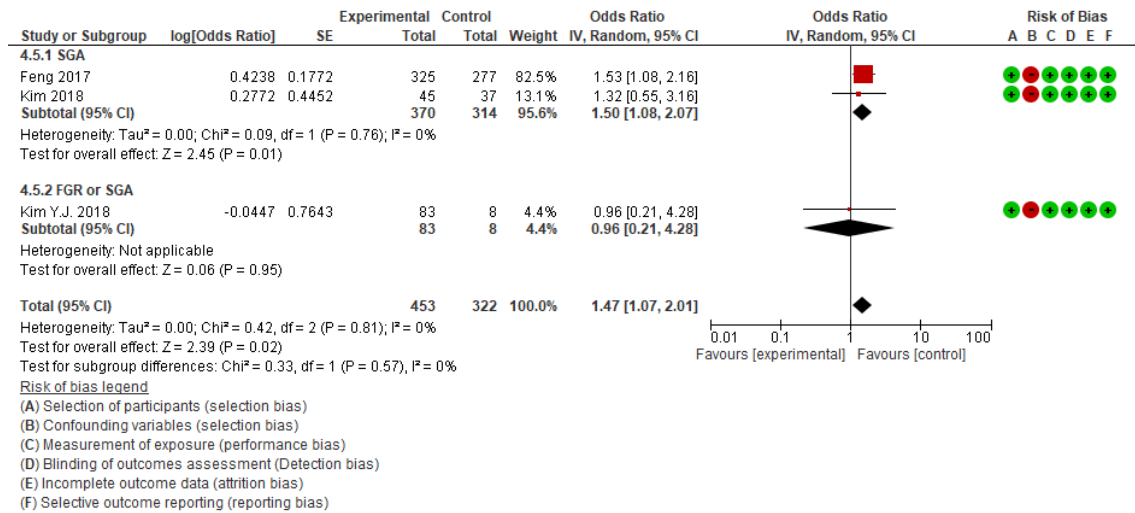
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Gestational diabetes mellitus.



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

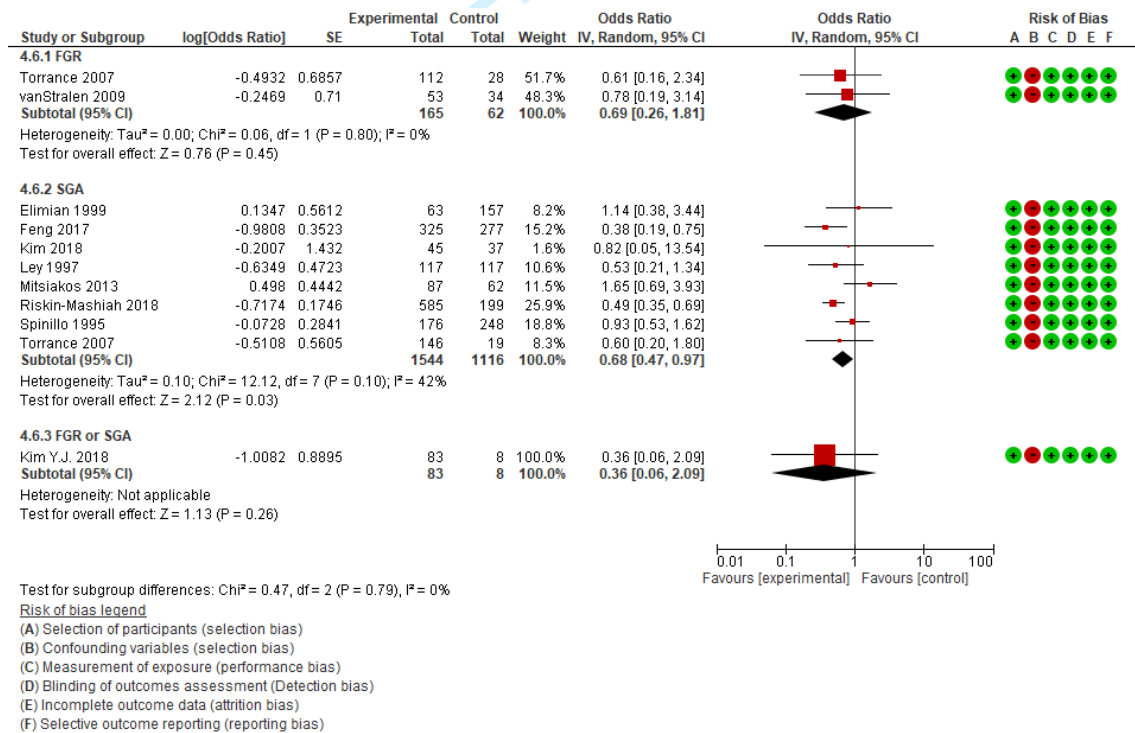
5) Pregnancy induced hypertension.



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

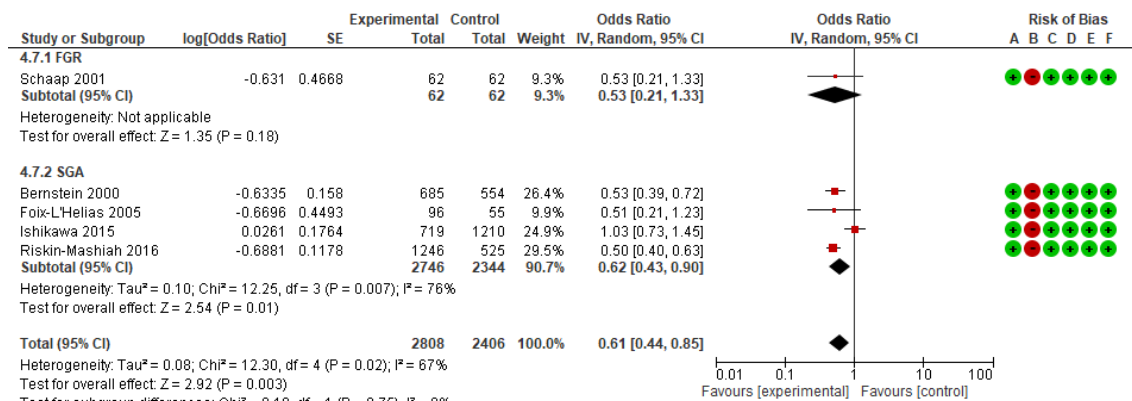
Neonatal outcomes for women with growth-restricted fetuses

1) Neonatal death



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

2) Death before discharge home

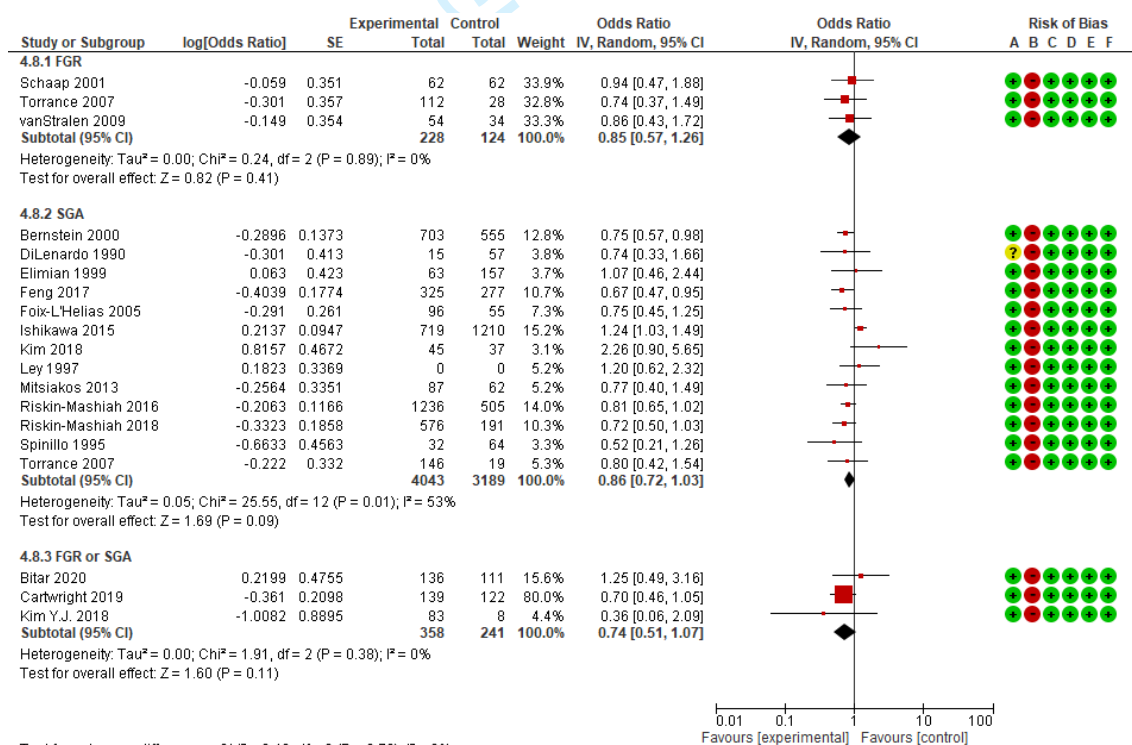


Risk of bias legend

- (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

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

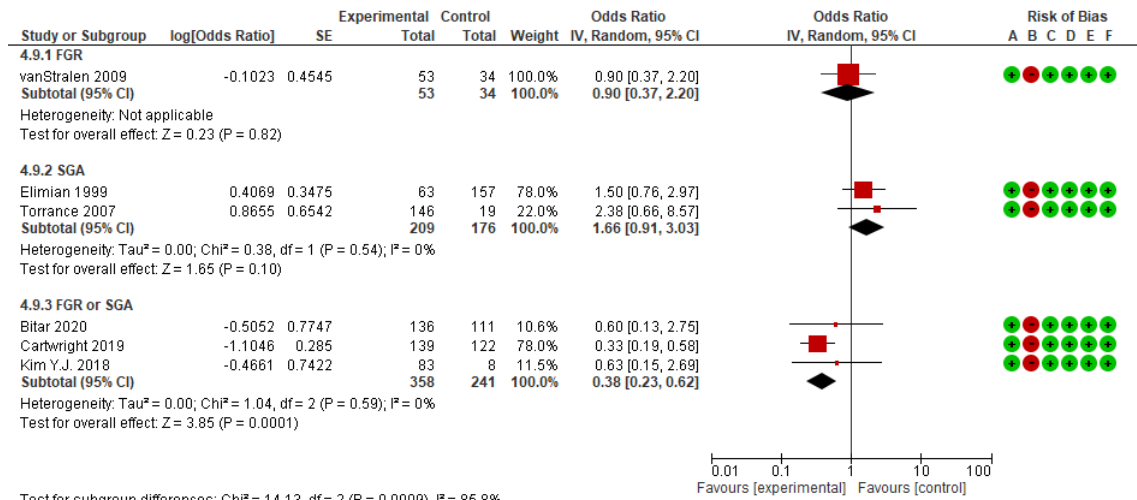


Risk of bias legend

- (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; FGR: Fetus growth restriction; SGA: Small for gestational age

4) Surfactant use



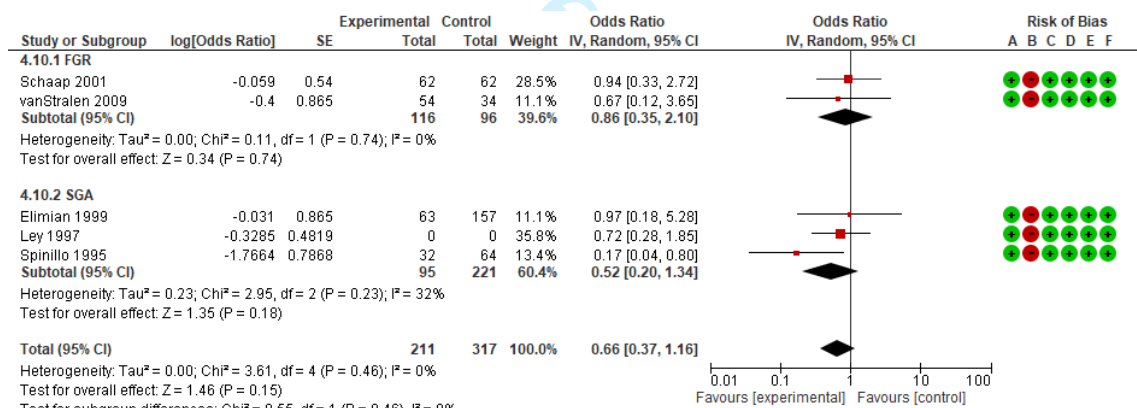
Test for subgroup differences: Chi² = 14.13, df = 2 (P = 0.0009), I² = 85.8%

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

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

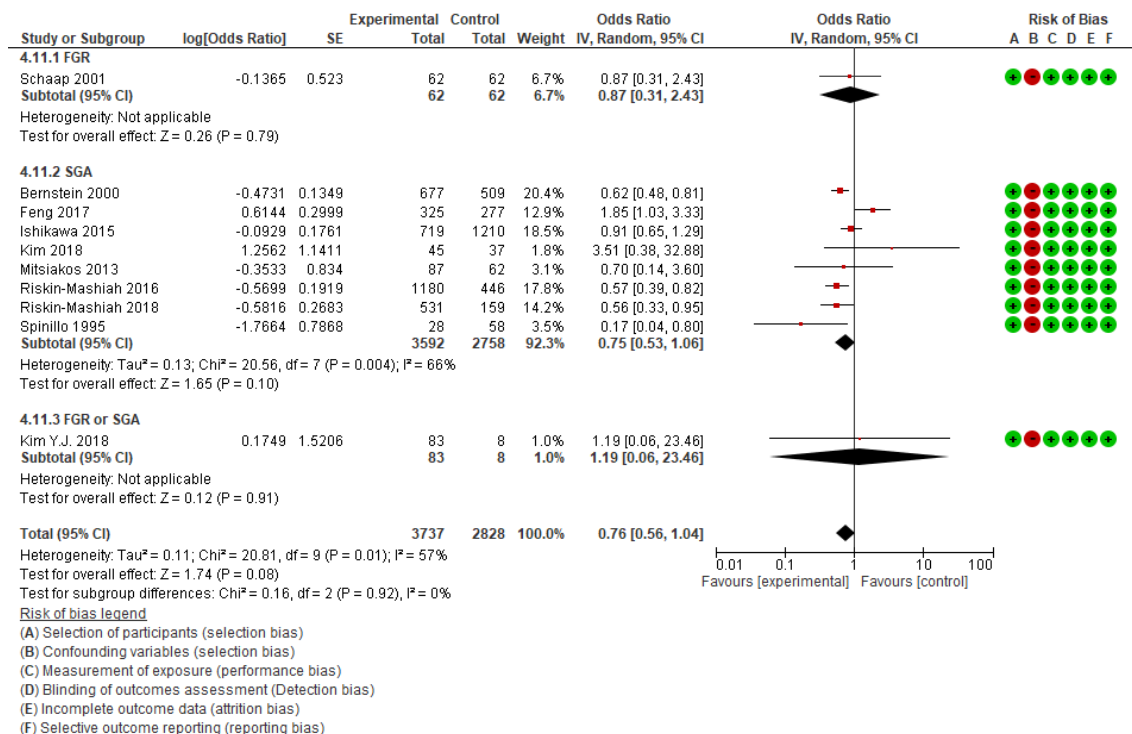


Risk of bias legend

- (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)

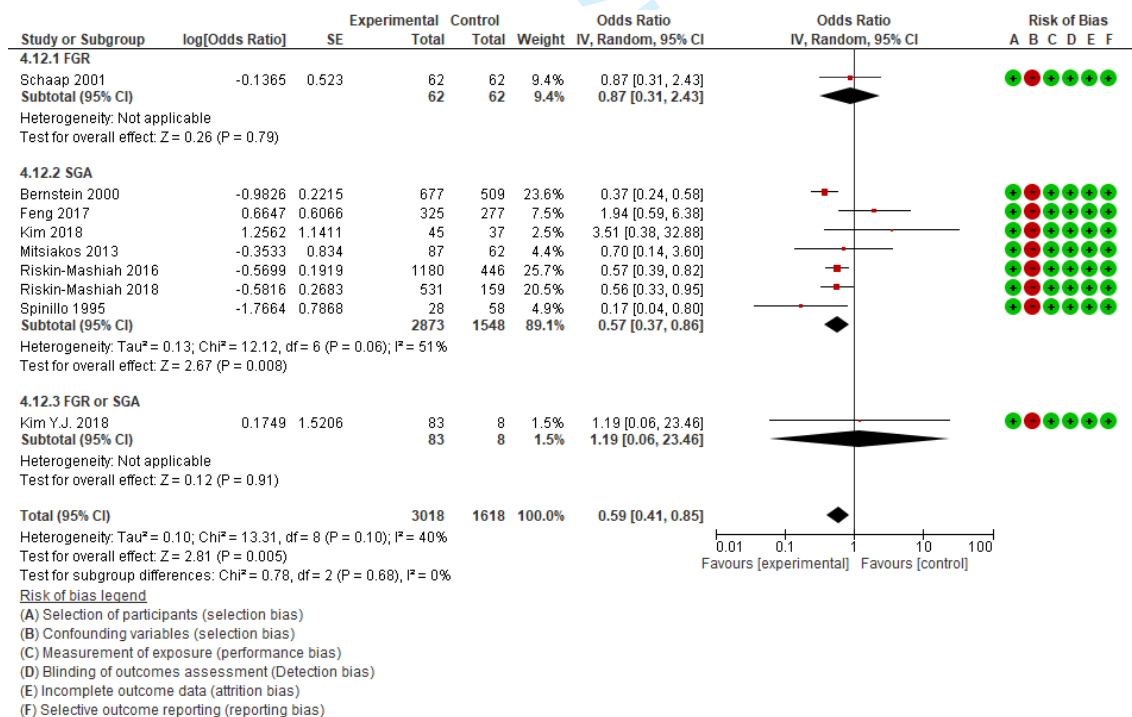
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

6) Interventricular haemorrhage



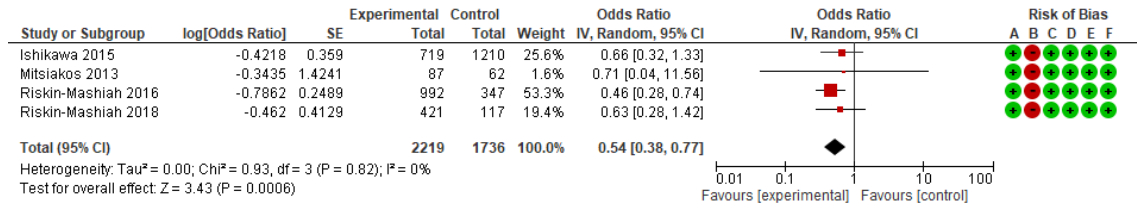
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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)

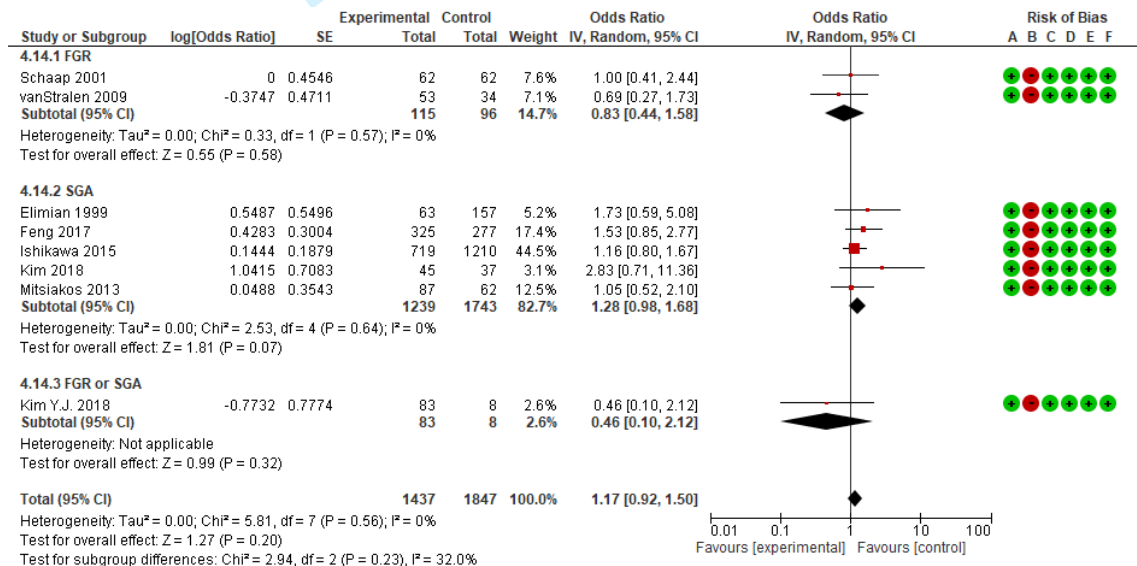


Risk of bias legend

- (A) Selection of participants (selection bias)
- (B) Confounding variables (selection bias)
- (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

9) Neonatal sepsis

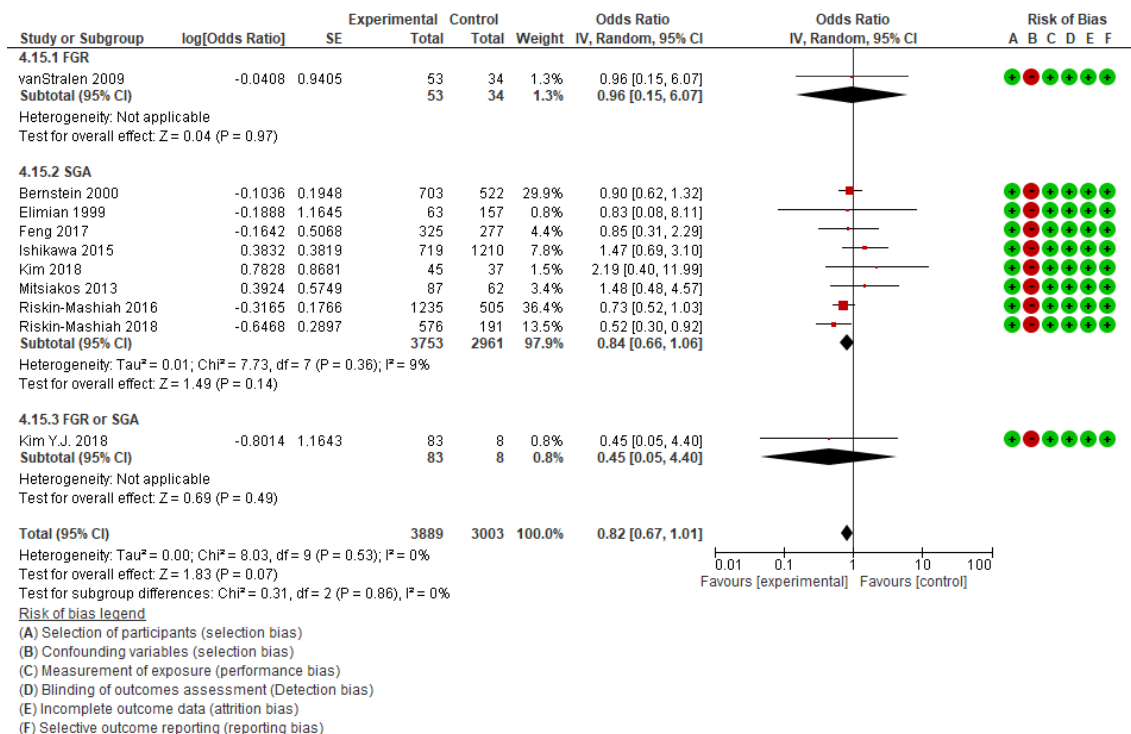


Risk of bias legend

- (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)

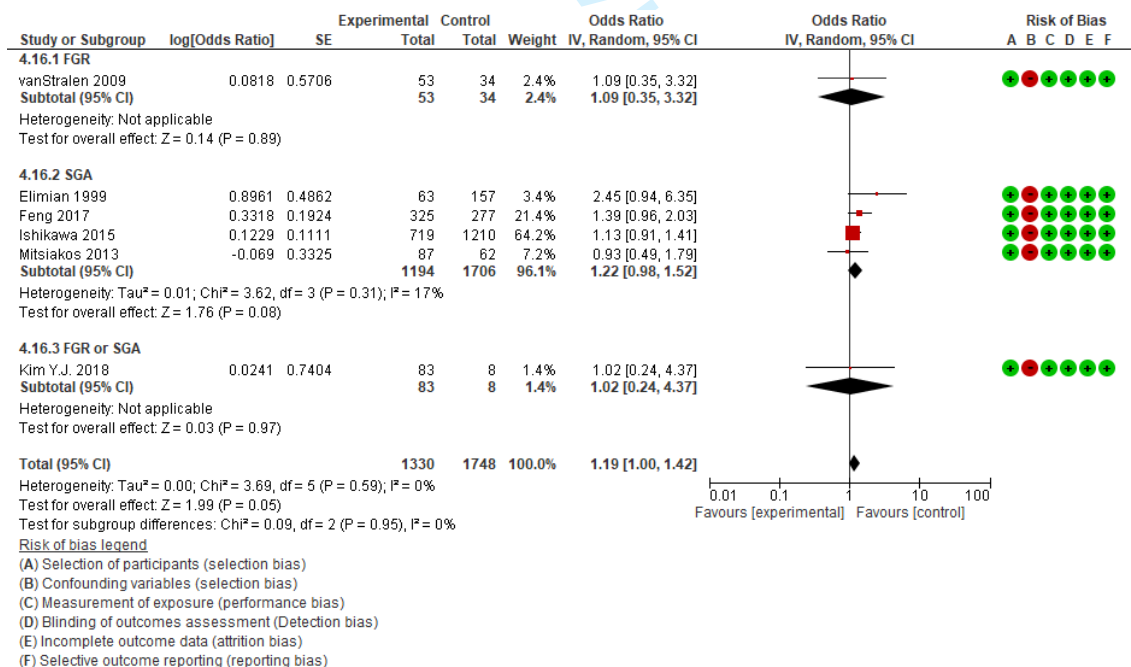
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

10) Necrotizing enterocolitis



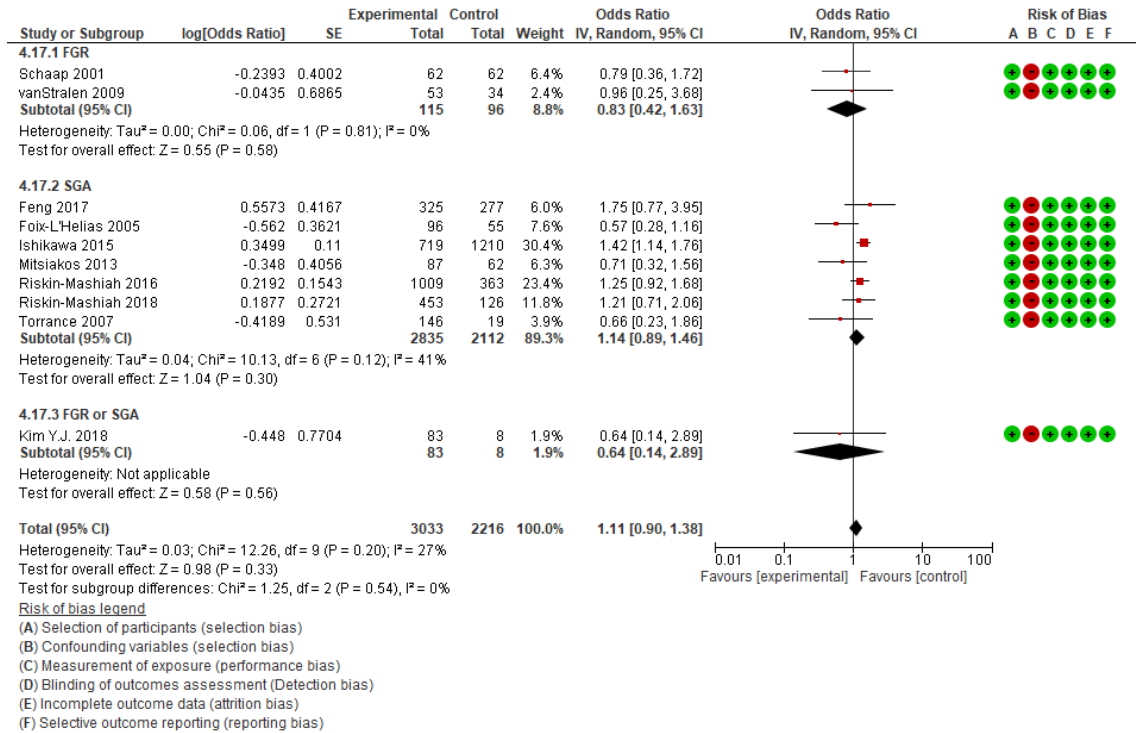
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

11) Patent ductus arteriosus



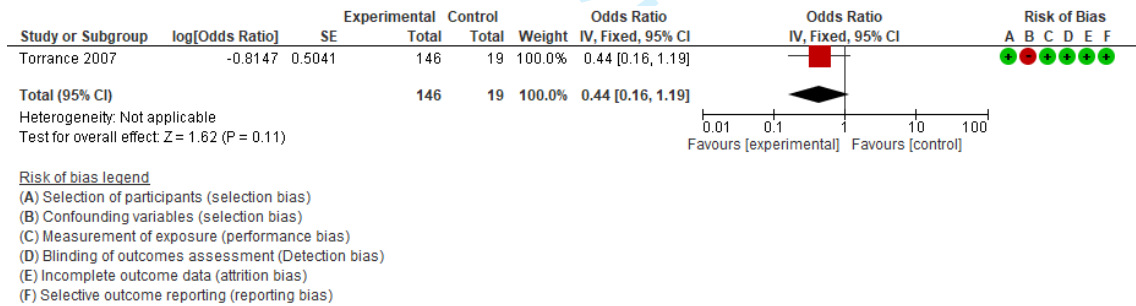
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

12) Chronic lung disease / bronchopulmonary dysplasia



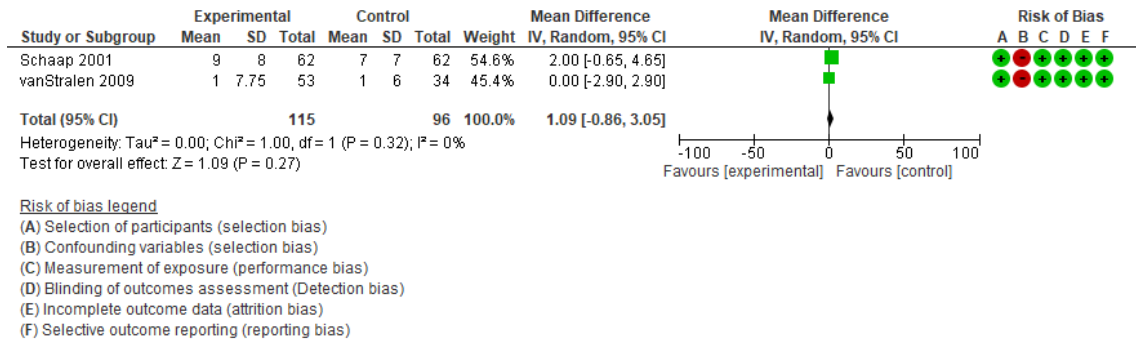
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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



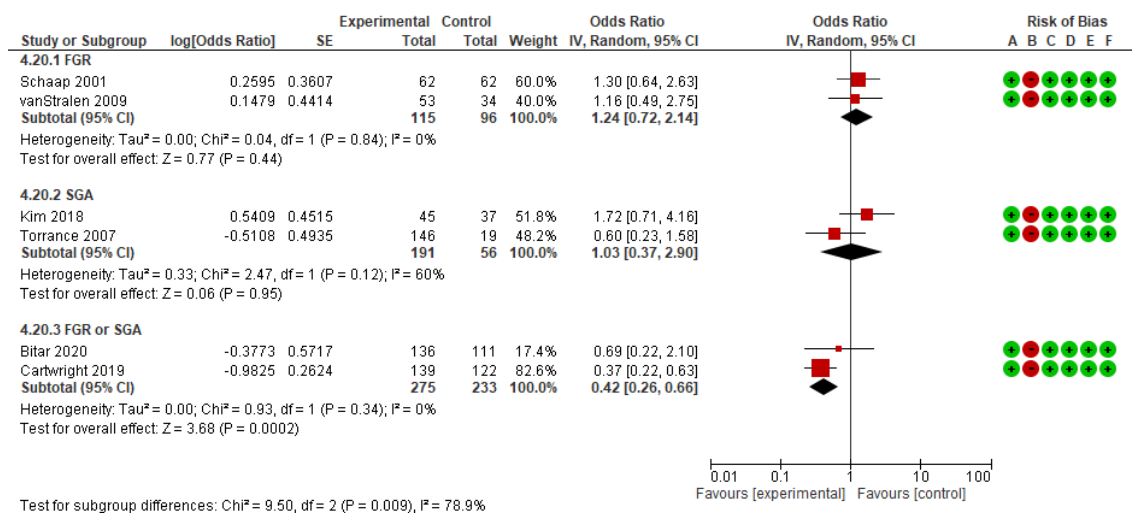
SE: Standard error; CI: Confidence interval

14) Duration of mechanical ventilation (FGR)



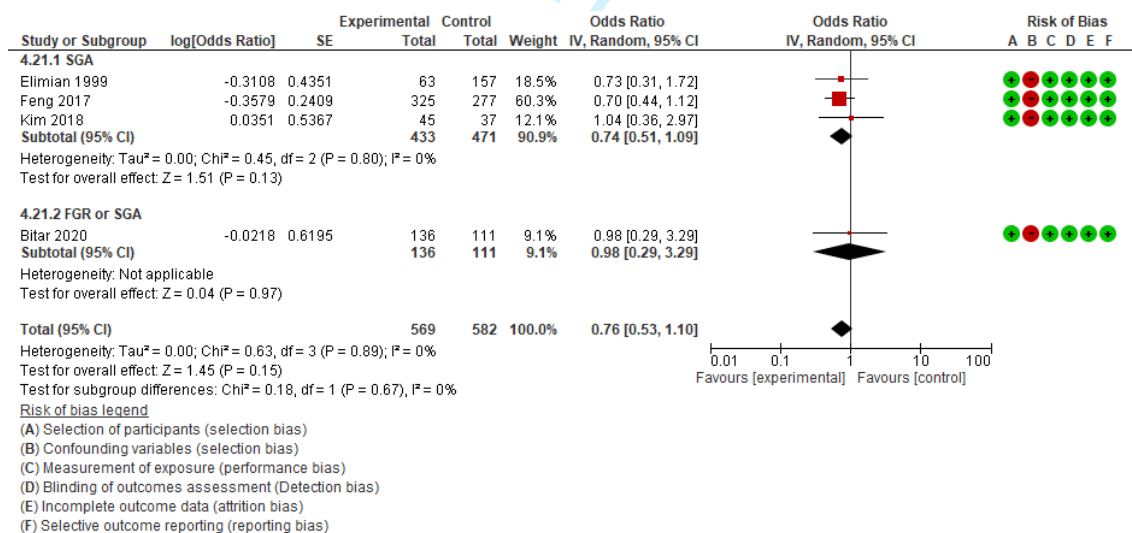
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction

15) Use of mechanical ventilation



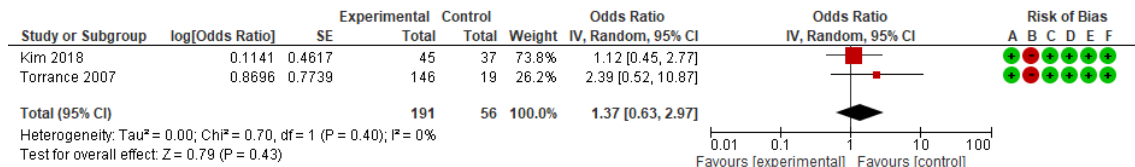
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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

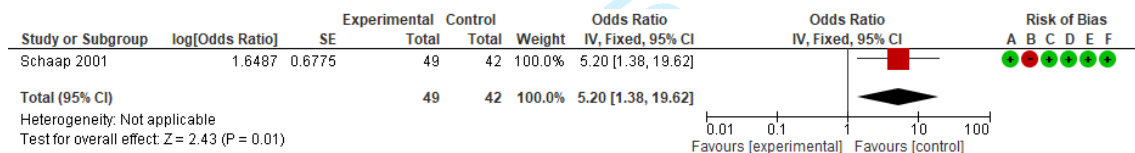
18) Hypotension (FGR)

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

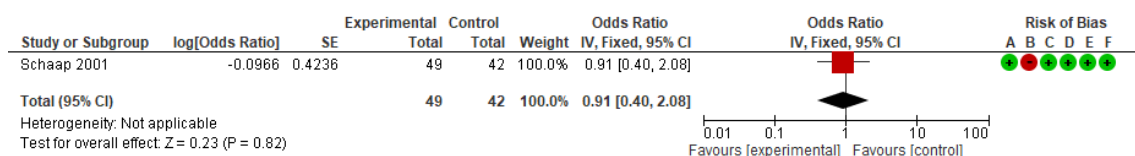
19) Growth < 10th percentile in early childhood (FGR)

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

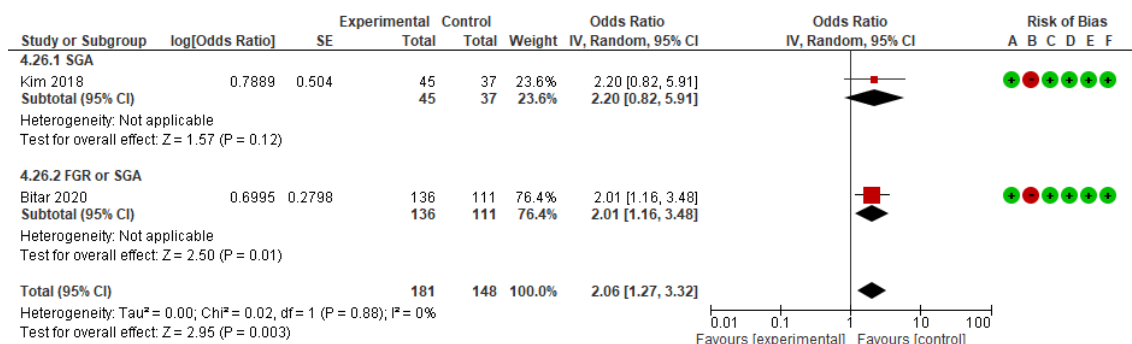
20) Abnormal behavior at long-term follow-up at school age (FGR)

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

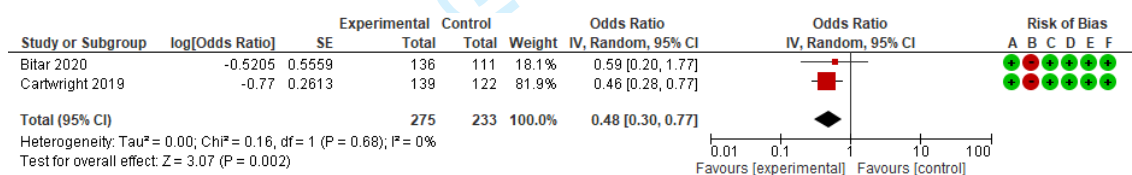
21) Neonatal hypoglycemia



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

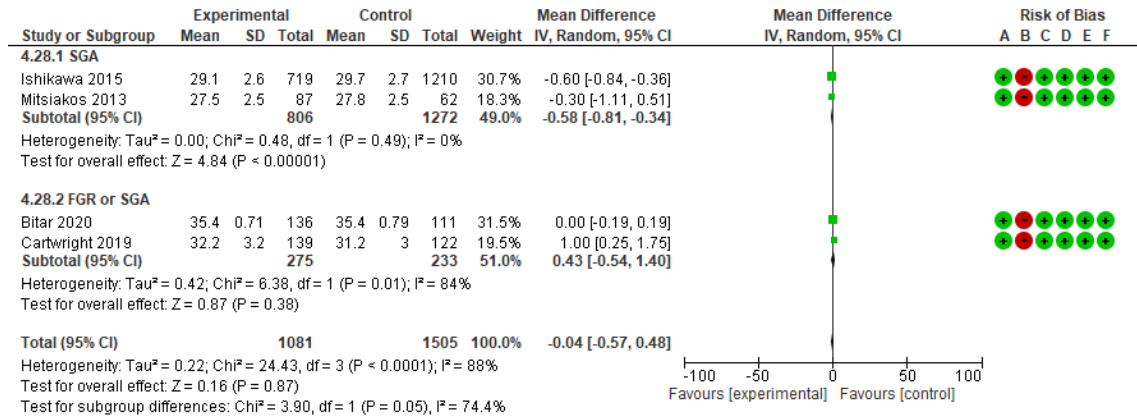
22) Oxygen therapy (FGR or SGA)



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; FGR: Fetus growth restriction; SGA: Small for gestational age

23) Gestational age at birth

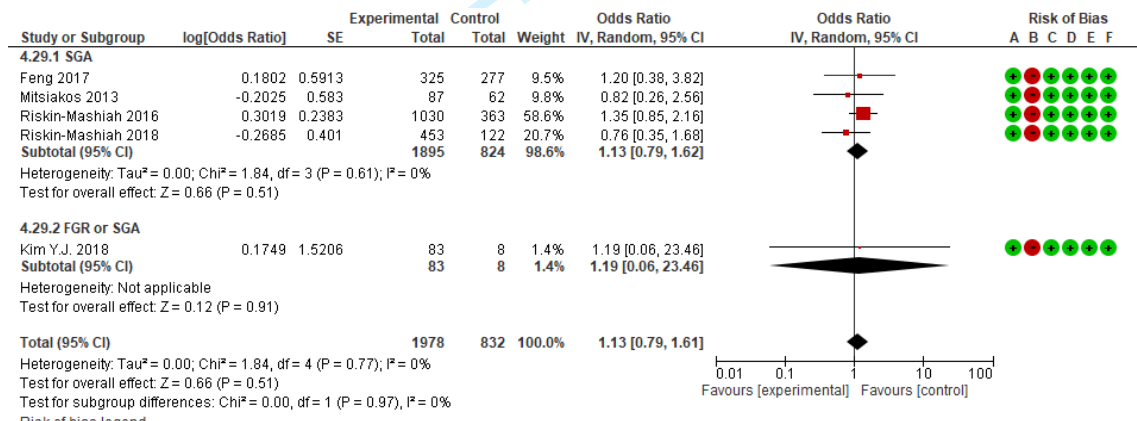


Risk of bias legend

- (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; FGR: Fetus growth restriction; SGA: Small for gestational age

24) Retinopathy of prematurity

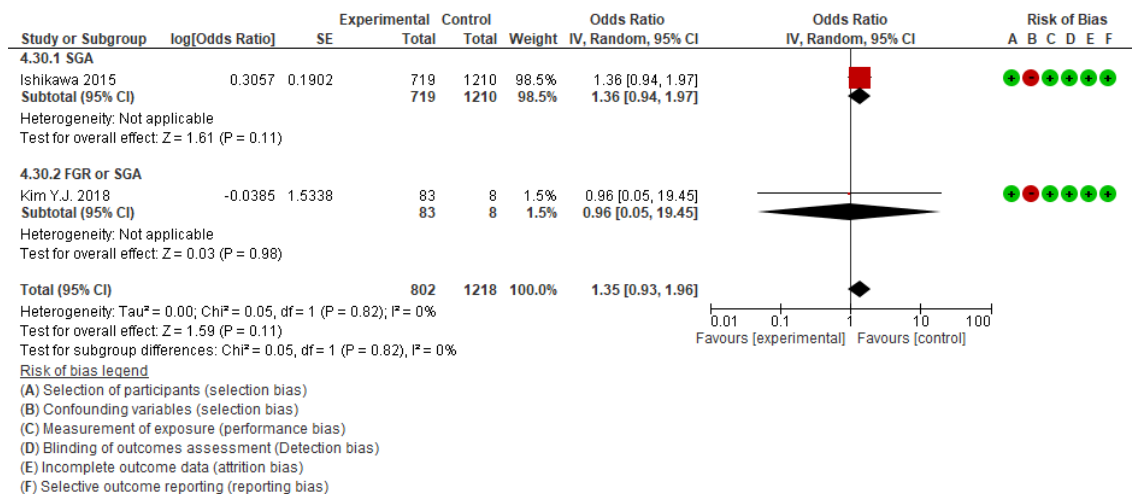


Risk of bias legend

- (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)

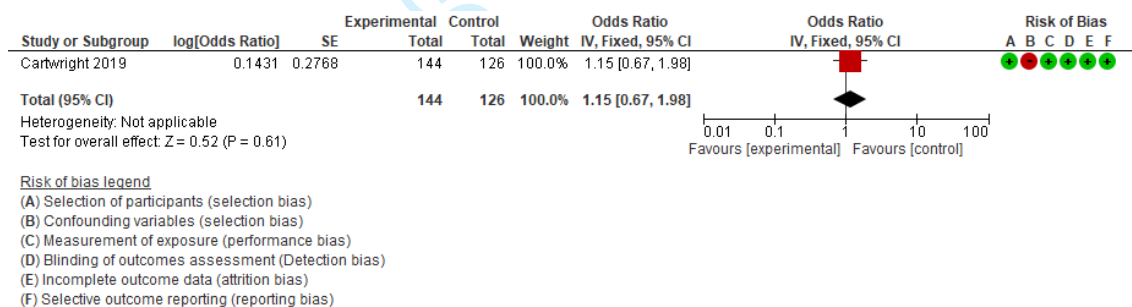
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

25) Neonatal adrenal insufficiency



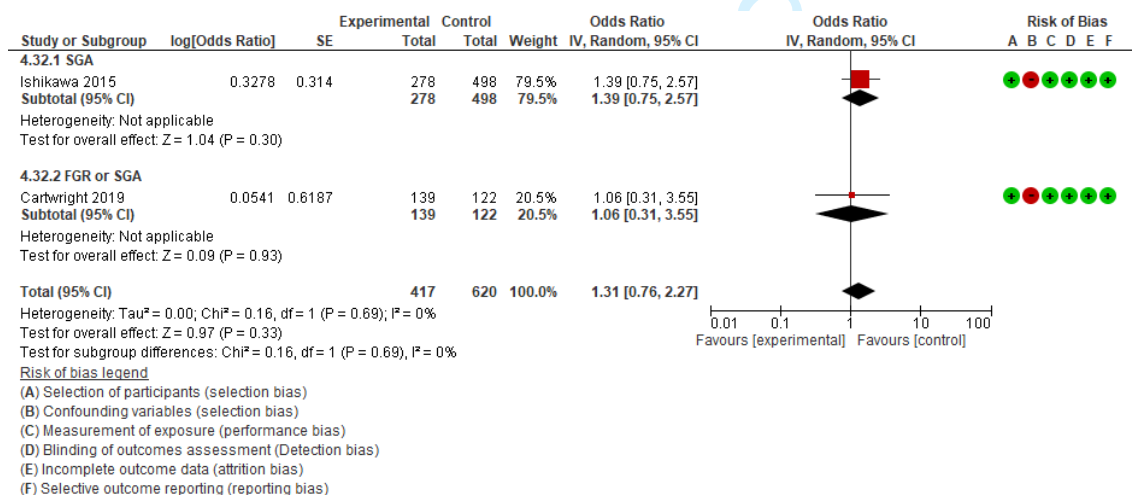
SE: Standard error; CI: Confidence interval; FGR: Fetus growth restriction; SGA: Small for gestational age

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

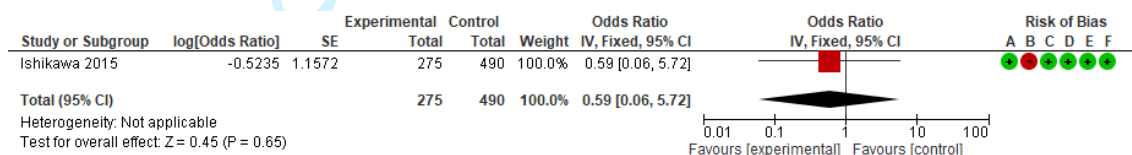
28) Severe hearing impairment (SGA)



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

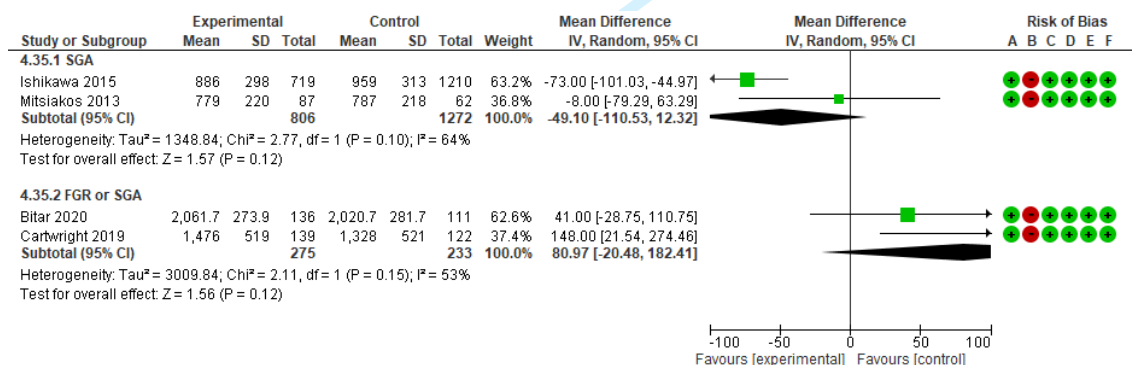
29) Visual impairment (SGA)



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

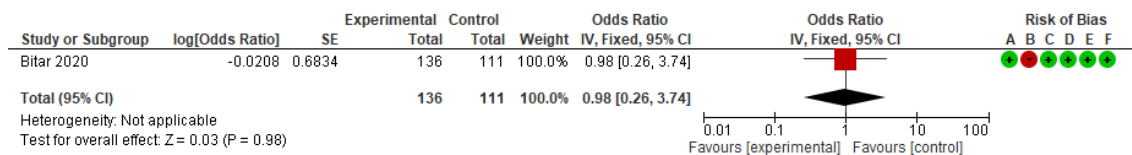
30) Birth weight



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)

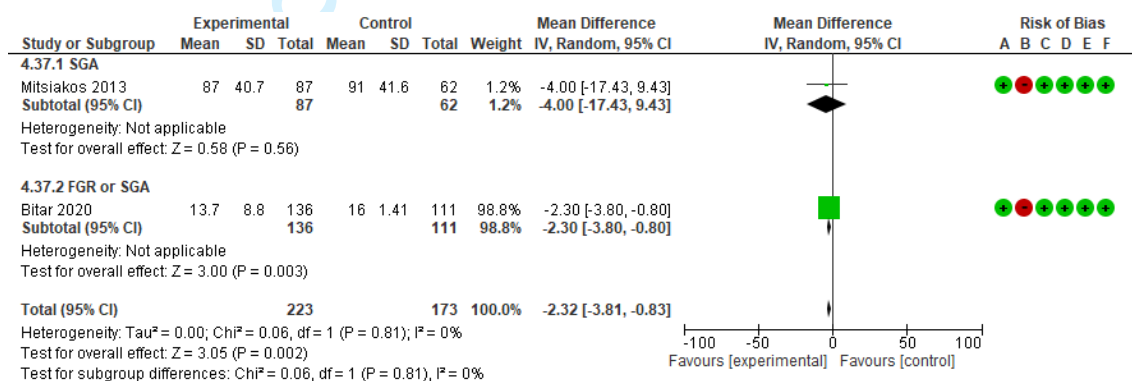


Risk of bias legend

- (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

32) Duration of hospital stay

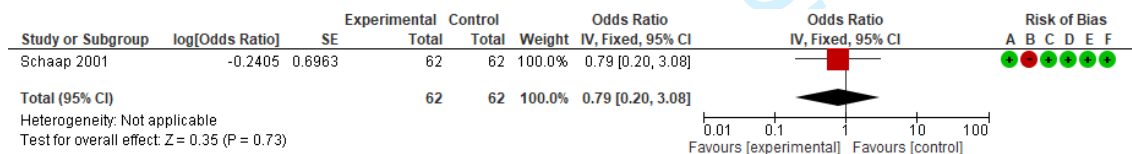


Risk of bias legend

- (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

33) Death at long-term follow-up (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

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

For peer review only