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Antenatal corticosteroids in specific groups at risk of preterm birth: a systematic review

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ABSTRACT

Objective This study aimed to synthesise 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 caesarean 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 randomised or non-randomised interventional studies in the four subpopulations on 6 June 2021. Risk of Bias Assessment tool for Non-randomised 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 10 819 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 to 0.85, low certainty), intraventricular haemorrhage (pooled OR: 0.41; 95% CI: 0.23 to 0.72, low certainty) and respiratory distress syndrome (pooled OR: 0.59; 95% CI: 0.45 to 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 to 0.62, moderate certainty), mechanical ventilation (pooled OR: 0.42; 95% CI: 0.26 to 0.66, moderate certainty) and oxygen therapy (pooled OR: 0.48; 95% CI: 0.30 to 0.77, moderate certainty) were probably reduced; however, the rate of hypoglycaemia probably increased (pooled OR: 2.06; 95% CI: 1.27 to 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.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review included a broad search strategy.
⇒ This review applied rigorous quality assessment and Grading of Recommendations Assessment, Development and Evaluation methodology.
⇒ Most included studies were observational studies.
⇒ Definitional differences between populations and outcomes complicated the meta-analysis.
⇒ Most studies were conducted in high-income countries.

INTRODUCTION

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

However, current evidence regarding the benefits and possible harms of ACS use in subpopulations of women with specific complications of pregnancy, such as women with diabetes, chorioamnionitis or fetal growth restriction (FGR), is controversial. Women with diabetes, chorioamnionitis or FGR are at a higher risk of adverse perinatal outcomes; however, they are generally

excluded from ACS efficacy trials.[2] Consequently, any subgroup analysis to explore the effects of ACS on women with these complications is unlikely to yield concrete evidence from which conclusions can be drawn.

While pregnant women with diabetes are at a higher risk of spontaneous preterm birth and may require ACS, glucocorticoids have hyperglycaemic effects and respiratory morbidities that affect preterm infants may be exacerbated in the setting of poor maternal glycaemic control.[7 8] Chorioamnionitis is estimated to affect 3.9% of women giving birth, causing 22.6–36.9% of stillbirths.[9–11] Chorioamnionitis treatment involves antibiotics and prompt delivery of the fetus; typically, ACS therapy is avoided due to concerns that its immunosuppressive effects may worsen outcomes for women and their babies. However, the relative benefits and harms of using ACS in clinical settings are unclear. FGR is associated with an increased risk of morbidity and mortality.[12–15] Small-for-gestational age (SGA) status does not accurately represent FGR as SGA neonates are constitutionally, rather than pathologically, small.[16] In most cases, FGR fetuses are delivered as SGA neonates.[17] In this study, we targeted pregnant women with both FGR fetuses and SGA neonates.

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

In 2016, members of our team published a systematic review assessing the effectiveness of ACS therapy in these four clinical situations.[27] No direct evidence of the effects of ACS therapy on pregnant women with diabetes who were at risk of preterm birth or for those undergoing elective CS in the late preterm period was found. The review could not draw firm conclusions regarding the effects of ACS on women with growth-restricted fetuses, although low-quality evidence suggested that ACS reduced neonatal IVH in women with chorioamnionitis.[27] The review's findings informed[28] WHO 2015 ACS recommendations.[28] Now, WHO's ACS recommendations are being updated as part of the WHO's living guidelines in maternal and perinatal health.[29] Our aim is to update the 2016 systematic review and provide a contemporary evidence base for researchers, clinicians and maternal and newborn health stakeholders on safe, effective clinical management in preterm birth.

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

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

P2: Effects of ACS therapy on women undergoing elective caesarean 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.

METHODS

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

Study eligibility criteria

Eligible studies were randomised or non-randomised primary studies that reported on the effects of ACS therapy in the four subpopulations. This included published, unpublished and ongoing randomised or quasi-randomised controlled trials, controlled before–after studies, interrupted-time-series studies, historically controlled studies, cohort studies and cross-sectional studies comparing any ACS (betamethasone,

dexamethasone or hydrocortisone) administered either parentally or enterally with placebo or no treatment. Study populations of interest were women at risk of imminent preterm birth or provider-initiated preterm birth and where the study population fulfilled one or more of the following conditions: women with pregestational and/or gestational diabetes, women undergoing elective CS in the late preterm period, women with chorioamnionitis and women with FGR fetuses or SGA infants.

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

Data sources and search strategy

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

Study selection, data extraction and quality assessment

Two reviewers (KS and EN) independently assessed the titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies were obtained and assessed in duplicate by two reviewers working independently, with disagreements resolved through discussions or by consulting a third reviewer. The two reviewers also independently extracted baseline and outcome data and assessed the quality, with these data compared and any discrepancies resolved through discussions or by consulting a third reviewer. Extracted data were entered into the Review Manager V.5.4 software (RevMan 5; The Cochrane Collaboration, Oxford, UK). For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomised Studies.[31] We used the Cochrane Risk of Bias tool for randomised trials.[32] Potential publication bias was inspected visually using funnel plots for asymmetry in situations where data for a single outcome were available from at least 10 studies.

Data synthesis and analysis

Aggregate ORs and relative risks with 95% CIs were determined for dichotomous data using the random-effects model. Crude data were used when the numbers of events were available and crude OR were employed when events were not available. We integrated crude ORs to mitigate confounding bias associated with varying covariates, as using adjusted ORs would introduce potential bias. This approach follows the methodology outlined in Yoneoka *et al*.[33 34] For continuous data, mean differences (MDs) with 95% CIs were used. Statistical heterogeneity was determined for each meta-analysis using I^2 and χ^2 statistics. Heterogeneity was deemed substantial if I^2 was greater than 60% or $p<0.05$ in the χ^2 test for heterogeneity. For the analysis of women with FGR fetuses and/or SGA babies, we reported results for three subpopulations (SGA only, FGR only and SGA or FGR). Data from the three populations were combined, and pooled ORs were calculated if the heterogeneity for that outcome was less than 60%. Based on the evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at high risk of bias. All statistical analyses were performed using RevMan 5. The threshold for statistical significance was set at an alpha level of 0.05 for all analyses. Evidence profiles were prepared for each research question using GRADEpro (https://gradepro.org/). Grading of Recommendations Assessment, Development and Evaluation (GRADE), an approach for grading the certainty of evidence in systematic reviews and clinical practice guidelines, was used in this review.

Patients and public involvement

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

RESULTS

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

The search identified 179 citations: 11 potentially eligible studies were evaluated, and 3 studies met the eligibility criteria, providing data on 725 pregnant women and 830 neonates (online supplemental file 2).[35–37] All studies were conducted in high-income countries and data collection was performed between 2008 and 2017 (online supplemental table 1). One study involved women with pregestational diabetes only, one study involved women with gestational diabetes only and one study involved women with either pregestational or gestational diabetes. All included studies were judged as having a low risk of bias across all domains except high risk of bias at confounding variables (online supplemental file 3), (online supplemental table 5). Data were available for six outcomes (table 1). One retrospective cohort study found that in women with gestational diabetes, the likelihood of neonatal intensive care unit (NICU) admission is possibly increased (one study, 162 infants; OR: 7.41; 95% CI: 5.04

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

Neonatal outcomes	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Caesarean section	2	31/65 (47.7%)	58/150 (38.7%)	1.75 (0.63 to 4.82)	138 more per 1000 (from 102 fewer to 366 more)	Very low
Neonatal death within 48 hours of birth	1	6/536 (1.1%)	2/79 (2.5%)	0.44 (0.09 to 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 to 9.08)	207 more per 1000 (from 24 fewer to 4 91 more)	Very low
Neonatal hypoglycaemia	2	14/65 (21.5%)	66/150 (44.0%)	1.44 (0.70 to 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 to 5.89)	33 fewer per 1000 (from 162 fewer to 387 more)	Very l ow
Admission to NICU	1	19/47 (40.4%)	36/114 (31.6%)	7.41 (5.04 to 10.89)	458 more per 1000 (from 384 more to 518 more)	Low

ACS, antenatal corticosteroid; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome.

to 10.89, *low-certainty evidence*); however, the effect of ACS therapy on neonatal hypoglycaemia was uncertain (two studies, 215 infants; pooled OR: 1.44; 95% CI: 0.70 to 2.97, *very-low-certainty evidence*).[35] The certainty of evidence was also very low for other outcomes; hence, no meaningful conclusions could be drawn.

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

The search identified 211 citations: 17 potentially eligible studies were evaluated, and 3 studies were included (online supplemental file 2).[38–40] These were two observational studies and a randomised controlled trial (RCT). All studies were conducted in high-income countries between 2010 and 2017, providing data on 205 pregnant women/neonates (online supplemental table 1). The two observational studies were judged as having a high risk of bias for confounding variables (online supplemental file 3), (online supplemental table 5). Data on 11 outcomes were available but all had very low certainty; so, no meaningful conclusions could be drawn (table 2).

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

The search identified 418 citations: 12 potentially eligible studies were evaluated, and 8 were found to be eligible (online supplemental file 2).[41–48] Two were prospective cohort studies and six were retrospective, providing data on 1372 pregnant women and 1460 neonates (online supplemental table 1). Four studies included pregnant women with clinical chorioamnionitis, and there were variations in the diagnostic criteria (online supplemental table 1). All studies were conducted in high-income countries between 1989 and 2014. Additional unpublished crude data from the four included studies were extracted from a previous meta-analysis identified through the search process.[41 44–46 49] All included studies were judged as having a low risk of bias overall except high risk of bias at confounding variables (online supplemental file 3), (online supplemental table 5). Data for 27 outcomes were available, with data reported separately for women with histological chorioamnionitis and women with clinical chorioamnionitis (table 3; online supplemental 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 to 0.85, *low-certainty evidence*), severe IVH (four studies, 528 infants; pooled OR: 0.41; 95% CI: 0.19 to 0.87, *low-certainty evidence*), IVH (five studies, 658 infants; pooled OR: 0.41; 95% CI: 0.23 to 0.72, *low-certainty evidence*), RDS (six studies, 1193 infants; pooled OR: 0.59; 95% CI: 0.45 to 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 to 1.47, *very-low-certainty evidence*). The certainty of evidence was very low for other outcomes (online supplemental 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 to 3.89). The certainty of evidence was very low for all other outcomes (online supplemental table 6).

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 (online supplemental file 2).[44 50–66] Of these, 12 studies included women with SGA infants only, 4 studies included women with FGR or SGA infants and 2 studies included women with FGR infants only (online supplemental table 1). Among the studies that included FGR fetuses, the definitions of FGR varied widely (online supplemental table 1). Since SGA status is insufficient to determine FGR, we separately analysed the three populations: SGA, FGR and

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

	No of studies	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes						
Hypertensive disorders	1	3/58 (5.2%)	15/107 (14.0%)	0.33 (0.09 to 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 to 0.95)	298 fewer per 1000 (from 380 to 12 fewer)	Very low
Neonatal outcomes						
RDS	2	12/88 (13.6%)	11/117 (9.4%)	0.80 (0.29 to 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 to 15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very low
Necrotising enterocolitis	1	0/58 (0.0%)	1/107 (0.9%)	0.61 (0.02 to 15.13)	4 fewer per 1000 (from 9 fewer to 116 more)	Very low
Neonatal hypoglycaemia	2	30/88 (34.1%)	37/117 (31.6%)	1.50 (0.81 to 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 to 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 to 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 to 201.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	Very low
Mean duration of mechanical ventilation	1	30	10	–	Mean difference 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 to 2.03)	9 fewer per 1000 (from 115 fewer to 149 more)	Very low

ACS, antenatal corticosteroid; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome.

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*, Torrance *et al* 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*[56] were extracted from a review paper published in 2009 identified through the search strategy.[56 67] We extracted crude data from the included studies except Ley *et al*.[52] The study by Ley *et al* only provided the adjusted ORs, controlled by birth weight deviation, gestational age, pre-eclampsia, premature rupture of membranes and mode of delivery.[52] Most of these studies were judged as having a low risk of bias across all domains except high risk of bias at confounding variables (online supplemental file 3), (online supplemental table 5). For SGA infants only, 12 studies provided data on 30 outcomes (online supplemental file 4), (online supplemental table 6). The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (two studies, 684 women; pooled OR 1.50, 95% CI: 1.08 to 2.07, *low-certainty evidence*) although the odds of pre-eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95% CI: 0.66 to 0.94, *low-certainty evidence*), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95% CI: 0.47 to 0.97, *low-certainty evidence*), periventricular leucomalacia (four studies, 3955 infants; pooled OR: 0.54; 95% CI: 0.38 to 0.77, *low-certainty evidence*) were possibly reduced (table 4). Two studies involving FGR infants only provided data for 18 review outcomes; the odds of death or disability/handicap at 2 years' corrected age (one study, 124 infants; pooled OR: 0.39; 95% CI: 0.17 to 0.90, *low-certainty evidence*) were possibly reduced (table 4). Four studies involved SGA or FGR infants, providing data for 25 outcomes (online supplemental file 4), (online supplemental table 6). The administration of ACS for women with SGA or FGR was associated with a possible reduction in the odds of surfactant use (three studies, 599 infants; pooled OR: 0.38; 95% CI: 0.23 to 0.62, *moderate-certainty evidence*), mechanical ventilation use (two studies, 508 infants; pooled OR: 0.42; 95% CI: 0.26 to 0.66, *moderate-certainty evidence*), oxygen use (two studies, 508 infants; pooled OR: 0.48; 95% CI: 0.30 to 0.77, *moderate-certainty*

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

Outcomes	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes (histological chorioamnionitis)						
Caesarean section	1	42/97 (43.3%)	2/12 (16.7%)	3.82 (0.79 to 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 to 1.86)	105 fewer per 1000 (from 155 fewer to 104 more)	Very low
Pre-eclampsia or eclampsia	1	5/97 (5.2%)	1/12 (8.3%)	0.60 (0.06 to 5.59)	32 fewer per 1000 (from 78 fewer to 254 more)	Very low
Neonatal outcomes (histological chorioamnionitis)						
Neonatal death	6	63/677 (9.3%)	87/516 (16.9%)	0.51 (0.31 to 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 to 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 to 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 to 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 to 1.47)	4 more per 1000 (from 38 fewer to 59 more)	Very low
Neonatal outcomes (clinical chorioamnionitis)						
Neonatal death	2	14/109 (12.8%)	14/81 (17.3%)	0.71 (0.32 to 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 to 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 to 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 to 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 to 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; IVH, intraventricular haemorrhage ; RDS, respiratory distress syndrome.

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

	No of study	No of the patients		Effect		Certainty
		ACS	Non-ACS	OR (95% CI)	Absolute (95% CI)	
Maternal outcomes						
Pregnancy induced hypertension						
Total†	3	195/453 (43.0%)	99/322 (30.7%)	1.47 (1.07 to 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 to 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 to 0.94)	62 fewer per 1000 (from 103 fewer to 15 fewer)	Low
Neonatal outcomes						
Neonatal death*						
SGA	8	242/1544 (15.7%)	196/1116 (17.6%)	0.68 (0.47 to 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 to 0.85)	41 fewer per 1000 (from 59 fewer to 14 fewer)	Low
Neonatal hypoglycaemia						
Total†	2	72/181 (39.8%)	36/148 (24.3%)	2.06 (1.27 to 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 to 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 to 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 to 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 to 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 to 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 2 years' corrected age						
FGR	1	11/62 (17.7%)	22/62 (35.5%)	0.39 (0.17 to 0.90)	178 fewer per 1000 (from 269 fewer to 24 fewer)	Low

*We calculated the numerators using the adjusted OR in the study by Ley et al.[52] (1997).
†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; FGR, fetal growth restriction; IVH, intraventricular haemorrhage ; MD, mean difference; PIH, pregnancy induced hypertension; PVL, periventricular leucomalacia; SGA, small-for-gestational age.

evidence) although the odds of hypoglycaemia increased (one study, 247 infants; pooled OR: 2.01; 95% CI: 1.16 to 3.48, *low-certainty evidence*) (table 4). Pooled ORs involving women and newborns from all three populations (ie, FGR only, SGA only and FGR or SGA combined into SGA and/or FGR) could be determined for 20 outcomes (online supplemental file 4), (online supplemental table 6). ACS administration for women with SGA and/or FGR was associated with a possible reduction in severe IVH (nine studies, 4636 infants; pooled OR: 0.59, 95% CI: 0.41 to 0.85, *low-certainty evidence*) and duration of hospital stay (two studies, 396 infants; MD −2.23 days; 95% CI: −3.81 to −0.83, *low-certainty evidence*). However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95% CI: 1.07 to 2.01, *low-certainty evidence*) and neonatal hypoglycaemia (two studies, 329 infants; pooled OR: 2.06, 95% CI: 1.27

to 3.32, *moderate-certainty evidence*) were possibly increased (table 4).

DISCUSSION

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

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

A clinical concern regarding ACS use in women with diabetes is the possibility of steroid-induced insulin resistance and consequent hyperglycaemia, which causes avoidable harm to the neonate. For example, in women with insulin-dependent diabetes, ketoacidosis may occur if insulin dosing is not increased following steroid administration.[68] A 2002 Danish study conducted on 24 pregnant women with diabetes who received steroids suggested that insulin dose adjustment may be required for up to 5 days after ACS administration.[69] However, in the current review, there was insufficient evidence to determine whether ACS increased neonatal hypoglycaemia, respiratory morbidity or mortality. One retrospective study suggested that ACS use in women with gestational diabetes increases the risk of NICU admission; however, the authors noted that average birth weight in the ACS group was significantly lower than that in the unexposed group, which may explain this finding.[35] Well-designed studies are needed that describe adjustments to maternal diabetic regimens at the time of ACS therapy and from the time of ACS administration to birth and report on important newborn health outcomes.

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

The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from 7 trials recruiting women in the late preterm period.[2] This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period.[2] Deshmukh and Patole reported that ACS reduced the need for respiratory support and increased the risk of hypoglycaemia with moderate certainty in late preterm.[70] However, no subgroup analyses were conducted on CS.[70] Hence, these findings cannot be generalised to all women undergoing CS in the late preterm period. The trial by Gyamfi-Bannerman and Thom reported that ACS in the late preterm period reduced their primary outcome and severe newborn respiratory complications.[40] Their subgroup analysis showed that these beneficial effects persisted among women admitted for planned CS only.[40] Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, mechanical ventilation or the need for extracorporeal membrane oxygenation (ECMO).[40] Severe respiratory complications were defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death within 72 hours after delivery or the need for ECMO.[40] Their outcomes did not adequately fit our outcomes, and the study did not provide their outcome data. Our review suggests there is insufficient evidence to draw firm conclusions on the benefits and possible harms of ACS when used in this subpopulation. At the same time, the multicentre trial by Gyamfi-Bannerman and Thom is suggestive that there are protective effects from ACS for neonatal respiratory morbidity among women with late preterm CS.[40] An ongoing randomised trial in New Zealand will provide further information on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and 39 weeks 6 days.[71]

Associations of ACS on women with chorioamnionitis

Women with chorioamnionitis are typically excluded from ACS efficacy trials due to concerns that the prolongation of pregnancy and/or immunosuppression may worsen outcomes for these women and their newborns. Although ACS appears to be associated with reduced neonatal death, IVH and RDS rates in women with histological chorioamnionitis, there was insufficient evidence of other important infection-related maternal and neonatal outcomes in this review. While these conclusions are similar to those of a 2011 review by Been *et al*, we do not consider that the available evidence supports the routine use of ACS therapy in women with chorioamnionitis, as clinical trials comparing ACS therapy to no ACS therapy in this population and reliable evidence regarding infection-related outcomes are still lacking.[49] Significant overlap exists between clinical and histological chorioamnionitis.[72] Histological chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis.[73] However, since physicians must decide the indications for ACS therapy when clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant women with clinical chorioamnionitis should be encouraged.

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

The totality of the evidence identified in this review suggests that ACS therapy should be used in the FGR setting. Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes and no harm was reported. The current review identified more substantial evidence than that identified in our 2016 systematic review, which was unable to draw solid conclusions about the effects of ACS therapy in this subpopulation.[27] It is also noteworthy that the largest trial on ACS therapy in low-resource countries, the WHO ACTION-I Trial that enrolled 2852 women and reported preterm newborn mortality and morbidity benefits, recruited 189 women with known or suspected FGR.[74] The current review did not identify the benefits regarding the outcome RDS, which might be attributable to a single retrospective cohort study in Japan in which neonates in the ACS group were delivered significantly earlier than those in the control group.[59] A sensitivity analysis in which we excluded this study suggested that RDS is significantly lower for SGA babies exposed to ACS. It cannot be ruled out that ACS increases the rate of neonatal hypoglycaemia in this subpopulation, which warrants further exploration in future research. In this meta-analysis, two studies targeted pregnant women with FGR while the other 16 included pregnant women with SGA. SGA status does not perfectly represent FGR.[16] Since physicians must decide the indication for ACS therapy when FGR is detected, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.

Strengths and limitations

The strengths of this review were its broad search strategy, which included studies published in languages other than English, rigorous quality assessments and the use of the GRADE methodology to assess the reliability of the review's findings. Thus, we consider the risk of missing potentially eligible studies to be low, although we acknowledge that publication bias may affect these results. One limitation of the present review is the difference in how studies defined, identified or diagnosed the subgroup conditions and outcomes of interest. These differences might have created a bias in the review conclusions. However, we explored and reported heterogeneity for meta-analyses. This analysis extracted all data from observational studies. Since adjusted confounding variables showed a wide variety in each included study, crude data were employed in our review. No included studies adequately considered their study design to adjust the confounding bias. Therefore, confounding bias should be cautiously considered in our results' interpretation. Another limitation is that most of the included studies were conducted in high-income countries, although over 60% of all preterm births globally occur in African and South Asian countries.[75] This review did not lead to any evidence of high certainty, and one reason for this observation is that all studies were observational. In 1990, Crowley *et al* reported a structured review of ACS for preterm birth.[76] The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity.[76] In 1995, the National Institutes of Health developed a consensus on recommending ACS treatment for preterm birth.[77] In our review, only one study targeting women with chorioamnionitis and two studies targeting women with FGR started before 1990.[43 52 55] It would be challenging to conduct the RCTs on ACS efficacy even in these special populations after the review by Crowley *et al*.[76] The latest Cochrane review on ACS treatment for preterm birth involved a subgroup analysis in the seven special conditions.[2] However, the review did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis and FGR.[2] Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery.[70] Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes. Our search was last conducted in June 2021 and required time for publication. Despite scrutinising additional sources between June 2021 and February 2023, we did not find any further relevant studies.

CONCLUSION

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

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Contributors KS participated in the conceptualisation and design of the study, conducted title, abstract and full-text screening, performed data extraction, analysis and interpretation, assessed the risk of bias, drafted the initial manuscript and critically reviewed the manuscript. EN conducted the title abstract and full-text screening, performed data extraction, analysis and interpretation, assessed the risk of bias and critically reviewed the manuscript. TS conceptualised and designed the search strategy, conducted a systematic search and critically reviewed the manuscript for important intellectual content. JR assisted in the interpretation of data and the assessment of the risk of bias and critically reviewed the manuscript for important intellectual content. FN, JC and TL critically reviewed the protocol and manuscript for important intellectual content. EO and JPV designed and planned the study, assisted with developing the literature search strategy and resolving inclusion conflicts, critically reviewed the manuscript and supervised the execution of the study. EO accepts full responsibility for the work and/or the conduct of the

study, had access to the data, and controlled the decision to publish. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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REFERENCES

1 Liggins GC, Howie RN. A controlled trial of Antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;50:515–25.
2 McGoldrick E, Stewart F, Parker R, *et al*. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of Preterm birth. *Cochrane Database Syst Rev* 2020;12:CD004454.
3 Committee on obstetric practice. Committee opinion No.713 summary: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2017;130:493–4.
4 World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors, 2017. Available: https://apps.who.int/iris/handle/10665/255760 [Accessed 24 Mar 2022].
5 Skoll A, Boutin A, Bujold E, *et al*. No. 364-Antenatal corticosteroid therapy for improving neonatal outcomes. *J Obstet Gynaecol Can* 2018;40:1219–39.
6 Japan Society of Obstetrics and Gynegology. Obsterics and Gynecology clinical guideline, 2020. Available: https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf [Accessed 24 Mar 2022].
7 McGillick EV, Morrison JL, McMillen IC, *et al*. Intrafetal glucose infusion alters glucocorticoid signaling and reduces surfactant protein mRNA expression in the lung of the late-gestation sheep fetus. *Am J Physiol Regul Integr Comp Physiol* 2014;307:R538–45.
8 Kawakita T, Bowers K, Hazrati S, *et al*. Increased neonatal respiratory morbidity associated with gestational and Pregestational diabetes: A retrospective study. *Am J Perinatol* 2017;34:1160–8.
9 Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in Stillbirth. *Am J Obstet Gynecol* 2007;196:229.
10 Gordon A, Lahra M, Raynes-Greenow C, *et al*. Histological Chorioamnionitis is increased at extremes of gestation in Stillbirth: a population-based study. *Infect Dis Obstet Gynecol* 2011;2011:456728.
11 Woodd SL, Montoya A, Barreix M, *et al*. Incidence of maternal Peripartum infection: A systematic review and meta-analysis. *PLoS Med* 2019;16:e1002984.
12 Bukowski R, Burgett AD, Gei A, *et al*. Impairment of fetal growth potential and neonatal encephalopathy. *Am J Obstet Gynecol* 2003;188:1011–5.
13 Pasupathy D, Wood AM, Pell JP, *et al*. Rates of and factors associated with delivery-related perinatal death among term infants in Scotland. *JAMA* 2009;302:660–8.
14 McIntyre S, Blair E, Badawi N, *et al*. Antecedents of cerebral palsy and perinatal death in term and late Preterm Singletons. *Obstet Gynecol* 2013;122:869–77.
15 MacKay DF, Smith GCS, Dobbie R, *et al*. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med* 2010;7:e1000289.
16 Nardozza LMM, Caetano ACR, Zamarian ACP, *et al*. Fetal growth restriction: Current knowledge. *Arch Gynecol Obstet* 2017;295:1061–77.
17 Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J Pediatr* 1967;71:159–63.
18 Wang ML, Dorer DJ, Fleming MP, *et al*. Clinical outcomes of near-term infants. *Pediatrics* 2004;114:372–6.
19 Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, *et al*. Effect of late-Preterm birth and maternal medical conditions on newborn morbidity risk. *Pediatrics* 2008;121:e223–32.
20 Leone A, Ersfeld P, Adams M, *et al*. Neonatal morbidity in Singleton late Preterm infants compared with full-term infants. *Acta Paediatr* 2012;101:e6–10.
21 Mitha A, Chen R, Altman M, *et al*. Neonatal morbidities in infants born late Preterm at 35-36 weeks of gestation: A Swedish nationwide population-based study. *J Pediatr* 2021;233:43–50.
22 Richards JL, Kramer MS, Deb-Rinker P, *et al*. Temporal trends in late Preterm and early term birth rates in 6 high-income countries in North America and Europe and association with clinician-initiated obstetric interventions. *JAMA* 2016;316:410–9.
23 Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective Caesarean section. *Br J Obstet Gynaecol* 1995;102:101–6.
24 Zanardo V, Simbi AK, Franzoi M, *et al*. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective Caesarean delivery. *Acta Paediatr* 2004;93:643–7.
25 Hansen AK, Wisborg K, Uldbjerg N, *et al*. Risk of respiratory morbidity in term infants delivered by elective Caesarean section: cohort study. *BMJ* 2008;336:85–7.
26 Groom KM. Antenatal corticosteroids after 34 weeks' gestation: do we have the evidence? *Semin Fetal Neonatal Med* 2019;24:189–96.
27 Amiya RM, Mlunde LB, Ota E, *et al*. 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:e0147604.
28 World Health Organization. WHO recommendations on intervention to improve Preterm birth outcomes. 2015. Available: https://www.who.int/publications/i/item/9789241508988 [Accessed 24 Mar 2022].
29 Vogel JP, Dowswell T, Lewin S, *et al*. "Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health". *BMJ Glob Health* 2019;4:e001683. 10.1136/bmjgh-2019-001683 Available: https
30 PRISMA. PRISMA Checklist, 2020. Available: http://presma-statement.org/PRISMAStatement/Checklist [Accessed 24 Mar 2022].
31 Kim SY, Park JE, Lee YJ, *et al*. Testing a tool for assessing the risk of bias for Nonrandomized studies showed moderate Reliability and promising validity. *J Clin Epidemiol* 2013;66:408–14.
32 Methods. Risk of Bias 2 (ROB2) tool, 2020. Available: https://methods.cochrane.org/risk-bias-2 [Accessed 24 Mar 2022].
33 Yoneoka D, Henmi M, Sawada N, *et al*. Synthesis of clinical prediction models under different sets of covariates with one individual patient data. *BMC Med Res Methodol* 2015;15:101.
34 Yoneoka D, Henmi M. Meta-Analytical synthesis of regression coefficients under different Categorization scheme of continuous covariates. *Stat Med* 2017;36:4336–52.
35 Krispin E, Hochberg A, Chen R, *et al*. Neonatal outcome in gestational-diabetic mothers treated with Antenatal corticosteroids delivering at the late Preterm and term. *Arch Gynecol Obstet* 2018;298:689–95.

36 Battarbee AN, Sandoval G, Grobman WA, *et al*. Antenatal corticosteroids and Preterm neonatal morbidity and mortality among women with and without diabetes in pregnancy. *Am J Perinatol* 2022;39:67–74.
37 Cassimatis IR, Battarbee AN, Allshouse AA, *et al*. Neonatal outcomes associated with late Preterm Betamethasone administration in women with Pregestational diabetes. *Pediatr Neonatol* 2020;61:645–6.
38 Kirshenbaum M, Mazaki-Tovi S, Amikam U, *et al*. Does Antenatal steroids treatment prior to elective cesarean section at 34-37 weeks of gestation reduce neonatal morbidity? evidence from a case control study. *Arch Gynecol Obstet* 2018;297:101–7.
39 de la Huerga López A, Sendarrubias Alonso M, Jiménez Jiménez AP, *et al*. Antenatal corticosteroids and incidence of neonatal respiratory distress after elective Caesarean section in late Preterm and term neonates. *Anales de Pediatría (English Edition)* 2019;91:371–7.
40 Gyamfi-Bannerman C, Thom EA. Antenatal Betamethasone for women at risk for late Preterm delivery. *N Engl J Med* 2016;375:486–7.
41 Baud O, Zupan V, Lacaze-Masmonteil T, *et al*. The relationships between Antenatal management, the cause of delivery and neonatal outcome in a large cohort of very Preterm Singleton infants. *BJOG* 2000;107:877–84.
42 Elimian A, Verma U, Beneck D, *et al*. Histologic Chorioamnionitis, Antenatal steroids, and perinatal outcomes. *Obstet Gynecol* 2000;96:333–6.
43 Dempsey E, Chen M-F, Kokottis T, *et al*. Outcome of neonates less than 30 weeks gestation with histologic Chorioamnionitis. *Am J Perinatol* 2005;22:155–9.
44 Foix-L'helias L, Baud O, Lenclen R, *et al*. Benefit of Antenatal glucocorticoids according to the cause of very premature birth. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F46–8.
45 Goldenberg RL, Andrews WW, Faye-Petersen OM, *et al*. The Alabama Preterm birth study: corticosteroids and neonatal outcomes in 23- to 32-week newborns with various markers of Intrauterine infection. *Am J Obstet Gynecol* 2006;195:1020–4.
46 Been JV, Rours I, Kornelisse RF, *et al*. Histologic Chorioamnionitis, fetal involvement, and Antenatal steroids: effects on neonatal outcome in Preterm infants. *Am J Obstet Gynecol* 2009;201:587.
47 Ahn HM, Park EA, Cho SJ, *et al*. The Association of histological Chorioamnionitis and Antenatal steroids on neonatal outcome in Preterm infants born at less than thirty-four weeks' gestation. *Neonatology* 2012;102:259–64.
48 Ryu YH, Oh S, Sohn J, *et al*. The associations between Antenatal corticosteroids and in-hospital outcomes of Preterm Singleton appropriate for gestational age neonates according to the presence of maternal histologic Chorioamnionitis. *Neonatology* 2019;116:369–75.
49 Been JV, Degraeuwe PL, Kramer BW, *et al*. Antenatal steroids and neonatal outcome after Chorioamnionitis: a meta-analysis. *BJOG* 2011;118:113–22.
50 Di Lenardo D D, Piermarocchi P, Cazzaro L, *et al*. Betamethasone and theophylline in the prevention of the respiratory distress syndrome (RDS): trend up-date. *J FOET Med* 1990;10:27–31.
51 Spinillo A, Capuzzo E, Ometto A, *et al*. Value of Antenatal corticosteroid therapy in Preterm birth. *Early Hum Dev* 1995;42:37–47.
52 Ley D, Wide-Swensson D, Lindroth M, *et al*. Respiratory distress syndrome in infants with impaired Intrauterine growth. *Acta Paediatr* 1997;86:1090–6.
53 Elimian A, Verma U, Canterino J, *et al*. Effectiveness of Antenatal steroids in obstetric subgroups. *Obstet Gynecol* 1999;93:174–9.
54 Bernstein IM, Horbar JD, Badger GJ, *et al*. Morbidity and mortality among very-low-birth-weight neonates with Intrauterine growth restriction. The Vermont Oxford network. *Am J Obstet Gynecol* 2000;182(1 Pt 1):198–206.
55 Schaap AH, Wolf H, Bruinse HW, *et al*. Effects of Antenatal corticosteroid administration on mortality and long-term morbidity in early Preterm, growth-restricted infants. *Obstet Gynecol* 2001;97:954–60.
56 Torrance HL, Mulder EJH, Brouwers HAA, *et al*. Respiratory outcome in Preterm small for gestational age fetuses with or without abnormal umbilical artery Doppler and/or maternal hypertension. *J Matern Fetal Neonatal Med* 2007;20:613–21.
57 van Stralen G, van der Bos J, Lopriore E, *et al*. No short-term benefits of Antenatal corticosteroid treatment in severely Preterm growth restricted fetuses: a case-control study. *Early Hum Dev* 2009;85:253–7.
58 Mitsiakos G, Kovacs L, Papageorgiou A. Are Antenatal steroids beneficial to severely growth restricted fetuses? *J Matern Fetal Neonatal Med* 2013;26:1496–9.
59 Ishikawa H, Miyazaki K, Ikeda T, *et al*. The effects of Antenatal corticosteroids on Short- and long-term outcomes in small-for-gestational-age infants. *Int J Med Sci* 2015;12:295–300.
60 Riskin-Mashiah S, Riskin A, Bader D, *et al*. Antenatal corticosteroid treatment in Singleton, small-for-gestational-age infants born at 24-31 weeks' gestation: a population-based study. *BJOG* 2016;123:1779–86.
61 Collaborative Study Group for Respiratory Distress Syndrome in Preterm I. Effect of Antenatal corticosteroids therapy on the mortality and morbidity of small for gestational age infants born at 24-34 completed weeks: a retrospective multicenter study. *Zhonghua Er Ke Za Zhi* 2017;55:613–8.
62 Kim WJ, Han YS, Ko HS, *et al*. Antenatal corticosteroids and outcomes of Preterm small-for-gestational-age neonates in a single medical center. *Obstet Gynecol Sci* 2018;61:7–13.
63 Kim YJ, Choi SH, Oh S, *et al*. Antental corticosteroids and clinical outcomes of Preterm Singleton neonates with Intrauterine growth restriction. *Neonatal Med* 2018;25:161–9.
64 Riskin-Mashiah S, Reichman B, Bader D, *et al*. Population-based study on Antenatal corticosteroid treatment in Preterm small for gestational age and non-small for gestational age twin infants. *J Matern Fetal Neonatal Med* 2018;31:553–9.
65 Cartwright RD, Crowther CA, Anderson PJ, *et al*. Association of fetal growth restriction with Neurocognitive function after repeated Antenatal Betamethasone treatment vs placebo: secondary analysis of the ACTORDS randomized clinical trial. *JAMA Netw Open* 2019;2:e187636.
66 Bitar G, Merrill SJ, Sciscione AC, *et al*. Antenatal corticosteroids in the late Preterm period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM* 2020;2:100153.
67 Torrance HL, Derks JB, Scherjon SA, *et al*. Is Antenatal steroid treatment effective in Preterm IUGR fetuses? *Acta Obstet Gynecol Scand* 2009;88:1068–73.
68 Whiteman VE, Homko CJ, Reece EA. Management of Hypoglycemia and diabetic Ketoacidosis in pregnancy. *Obstet Gynecol Clin North Am* 1996;23:87–107.
69 Mathiesen ER, Christensen A-BL, Hellmuth E, *et al*. Insulin dose during glucocorticoid treatment for fetal lung maturation in diabetic pregnancy: test of an algorithm [correction of analgoritm]. *Acta Obstet Gynecol Scand* 2002;81:835–9.
70 Deshmukh M, Patole S. Antenatal corticosteroids for impending late Preterm (34-36+6 weeks) deliveries-A systematic review and meta-analysis of Rcts. *PLoS One* 2021;16:e0248774.
71 University of Auckland. The C*Steroid trial, Available: https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-trial.html [Accessed 24 Mar 2022].
72 Dong Y, St Clair PJ, Ramzy I, *et al*. A Microbiologic and clinical study of Placental inflammation at term. *Obstet Gynecol* 1987;70:175–82.
73 Redline RW. Inflammatory responses in the Placenta and umbilical cord. *Semin Fetal Neonatal Med* 2006;11:296–301.
74 Oladapo OT, Vogel JP, Piaggio G, *et al*. Antenatal dexamethasone for early Preterm birth in low-resource countries. *N Engl J Med* 2020;383:2514–25.
75 World Health Organization. World health organization. born Toon soon: the global action report on Preterm birth. 2012. Available: https://apps.who.int/iris/handle/10665/44864 [Accessed 24 Mar 2022].
76 Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration before Preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol* 1990;97:11–25.
77 Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH consensus development panel on the effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;273:413–8.