PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ANTENATAL CORTICOSTEROIDS IN SPECIFIC GROUPS AT RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW
AUTHORS	Saito, KANA; Nishimura, Etsuko; Ota, Erika; Namba, Fumihiko; Swa, Toshiyuki; Ramson, Jenny; Lavin, Tina; Cao, Jenny; Vogel, Joshua

VERSION 1 – REVIEW

REVIEWER	Dehaene, Isabelle University Hospital Ghent
REVIEW RETURNED	19-Jun-2022

GENERAL COMMENTS	This study is an update of a systematic review published in 2016. It focusses on the value of ACS administration in subpopulations (late preterm before caesarean section, diabetes, chorioamnionitis and fetal growth restriction). English vocabular and grammar needs some revision. Some suggestions are made below. The tables are nice and informative. Introduction * “Chorioamnionitis is acute inflammation of the membranes and chorion of the placenta…” * “because most cases of SGA are caused by FGR”: FGR is not a cause, it is also the result of an etiology; “because most cases of SGA are also cases of FGR” * “Clarifying ACS effects in women at risk of imminent preterm birth of growth restricted fetuses is necessary.” * “Babies born in late preterm…” Do you also have prevalence’s of chorioamnionitis in pregnant women not giving birth? Not all SGA are growth restricted. If you are aiming to say something about both, I would mention them both consistently. If your definition of SGA is based on birthweight, than this is not a good inclusion criterion, since at study entry, you don’t know the birthweight of the infant. Methods For your PICO’s, I recommend you add the gestational ages. For example P1: do you mean preterm birth < 37 weeks? Or (I think)

	less than 34 weeks. And from which lower limit onwards? 24 weeks? Or less? Women at risk: also multiple pregnancies? Also pregnancies with other complications (for example a woman with preeclampsia and gestational diabetes)? SGA and histological chorioamnionitis are post-baseline characteristics. You need to know at baseline if your patient needs ACS or not. If for example your analysis would show that women with histological chorioamnionitis would experience harmful outcomes due to ACS administration, you would want to avoid ACS in this subgroup. But… you don't know which patients will have histological chorioamnionitis at the time that you have to take the decision whether or not to give ACS. It would help you, if you would think about how a randomised trial would look like if you want to get an answer to your research questions (target trial, see publications of Miguel Hernan from Harvard university on causal inference from observational studies). Is it not logical that there will be more PIH in the ACS group (when looking at FGR/SGA)? The chances of administrating ACS are higher if there is PIH. Is this PIH present at baseline or is it an outcome variable (in this case, PIH should be diagnosed post-baseline)? Table 4: what is NS? Not significant? Non-significant results should also be reported. Discussion * "…33 observational studies pertaining to the benefits…": pertaining is not a correct verb here, I think, could you replace it? * line 417: "in the setting of fetal growth restriction" (or change to "should not be withheld in case of fetal growth restriction") * line 417: "while the evidence was largely of low…" * line 419: "and no harms were reported" * line 447: "ACS have" instead of "has" I am missing more reflection on how the included studies were conducted. Why are almost all of the studies observational? What are the drawbacks of observational studies? How should observational data ideally be analysed to enable causal inference, because that is your aim: exploring the EFFECT of ACS on a maternal or neonatal outcome (cfr Hernan)? Say something on the different regimens and repeat courses of ACS in the studies? Supplementary files S3: is there a reason why there are no definitions of the outcomes? S5-8: nice! Congratulations.

REVIEWER	Soll, Roger University of Vermont
REVIEW RETURNED	11-Jul-2022

GENERAL COMMENTS	Thank you for the opportunity to review Saito and colleagues' manuscript "Antenatal corticosteroids in specific groups at risk of preterm birth: a systematic review". The authors synthesize available evidence on antenatal corticosteroids (ACS) effectiveness among women at risk of imminent preterm birth with pregestational/gestational diabetes, chorioamnionitis, or fetal growth restriction (FGR), or planned cesarean section (CS) in the late preterm period. The authors perform a comprehensive systemic search of bibliographic databases for all comparative randomized (RCT) or non-randomized interventional studies in the four subpopulations. The authors used standard methods for searching and evaluating risk of bias and GRADE recommendations. The authors identified 23 studies with 18003 pregnant women/neonates. All included articles were observational studies. Data on women with diabetes were limited and evidence on women undergoing planned CS was inconclusive. ACS was associated with possibly reduced odds of neonatal mortality, severe intraventricular hemorrhage, and IVH in women with histological chorioamnionitis. Among women with clinical chorioamnionitis, IVH and periventricular leukomalacia odds were possibly reduced. Among women with FGR, surfactant use, mechanical ventilation, and oxygen therapy were probably reduced, but hypoglycemia probably increased. The authors conclude that evidence is lacking for women with diabetes or undergoing planned CS. ACS might have benefits in women with chorioamnionitis. ACS is probably beneficial in FGR but can increase neonatal hypoglycemia. Well-designed studies with adequate follow-up are required. I am confused regarding the paucity of randomized controlled trials in the populations of interest. The obvious one is the use of ACS in planned cesarean section (CS) in the late preterm period. There are many RCTs of ACS in the late preterm period, albeit not restricted to mothers undergoing planned cesarean section. A recent systematic review and meta-analysis identified 7 RCTs (N = 4144) and reported moderate quality evidence that ANC exposure reduced need for respiratory support in late preterm neonates (Deshmukh M, Patole S (2021) Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries—A systematic review and meta-analysis of RCTs. PLoS ONE 16(3): e0248774. https://doi.org/10.1371/journal.pone.0248774). Trials included in this review had many infants delivered by cesarean section. Likewise, many randomized controlled trials included mothers with gestational diabetes, though reports on these subgroups are missing. The NIH statement is very broad and states that "antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs". Some acknowledgement and formal discussion of what is (and is not) provided by the myriad randomized controlled trials is needed to put this interesting report of the available observational data in focus.

REVIEWER	Socha, Peter McGill University
REVIEW RETURNED	07-Mar-2023

GENERAL COMMENTS	Primary concerns 1. Studies were eligible if they either restricted to the specific risk groups or reported subgroup analyses in the specific risk groups. Please clarify whether search strategy and eligibility criteria for full-text review would have identified studies that did not report subgroup analyses in their title, abstract, keywords (ie, only reported analyses for the specific groups in their main text). Eg, the ALPS trial (doi.org/10.1056/NEJMoa1516783) reported a subgroup analysis by mode of delivery (vaginal vs planned caesarean) in the main text and supplement, but not in the abstract. 2. Please update the selection and confounding domains for the risk of bias assessments (Supplementary file S6). Some justifications are unclear (see specific comments below) and some studies needed additional review (eg, Paul 2019 does indeed consider confounding in their design stage, by matching exposed/unexposed on ethnicity, mode of delivery, year of delivery—though in this case I agree these confounders are insufficient and the study is still at "high" risk of confounding). Please also list which confounders were considered for all studies. 3. I recommend the pooled analyses be limited to studies that were rated as "low" risk of bias (particularly bias due to confounding). If studies at "low" risk of bias are pooled with studies at "high" risk of bias, then the pooled results will be at higher risk of bias. 4. I recommend using random effects (not fixed effects) to pool all results. The assumption of fixed effects, that studies are estimating the same treatment effect, is unlikely to hold as these studies are in very different populations, use different methods, adjust for different confounders, etc. If there is little between-study heterogeneity, I would argue that this is due to chance rather than evidence that the studies are estimating the same treatment effect. 5. Please specify how the absolute effects (risk differences) in Tables 1-4 are being calculated. Other concerns 1. The Canadian recommendations for ACS in the late-preterm (ref. 3) were just updated in 2023 (doi.org/10.1016/j.jogc.2022.12.006), though the update does not change the authors' statement. 2. Please add the date the search was conducted. 3. Please clarify denominators for counts throughout the manuscript. Are these pregnant people, fetuses, or neonates? Eg, when studies include multiple gestations "women/neonates" would be inappropriate. 4. There is a typo in Figures 2, 4, 6, 8 which should read: "Confounding variables (confounding bias)". 5. Please clarify what is meant by "downgrading for imprecision" (page 25). Specific comments: Supplementary file S6 Krispin 2018: There is a typo where "ACS treatment" is listed as a confounder. de la Huerga Lopez 2019: The current justification for the selection domain is unclear. I do not think that excluding congenital malformations and transfers would lead to "high" selection bias. The last three comments (matching, proportion with planned cesareans, and proportion with preterm delivery) are related to

	confounding. Confounding (by gestational age) was considered in the design phase through matching. Ahn 2012: Please clarify this sentence in the confounding domain "did not control for NEC, PDA, or neonatal death in analyses". Goldenberg 2006/Dempsey 2005/Elimian 2000: Please clarify this sentence in the confounding domain "adjusted analysis for results stratified by corticosteroid administration not available". Torrance 2007: Unclear justification for "high" risk of selection bias. Is restricting to infants admitted to the NICU the primary concern? Please indicate whether individuals matched on outcome (cases/controls) or exposure (treated/untreated). Matching on post-treatment variables (gestational age at birth, birth weight) can induce collider bias, but I am not convinced that this warrants "high" selection bias. Torrence 2007/Elimian 1999/Spinillo 1995: Please clarify this comment in the selection domain, "but the control group was defined only by no-steroid treatment without further specification, so it is conceivable that fetal condition on hospitalization differed". Is this about confounding by indication? Kim YJ 2018: The current justification for the selection domain is unclear, how does a large difference in proportion between intervention/control lead to selection bais?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr Isabelle Dehaene, University Hospital Ghent

Comments to the Author:

1) English vocabulary and grammar needs some revision.

-We have highlighted all changes related to spelling and grammar errors using underlined, bold text.

2) Do you also have prevalence's of chorioamnionitis in pregnant women not giving birth?

-Chorioamnionitis accounts for 22.6–36.9% of total stillbirths [9-11]. Based on the data, we have revised the following on line 119-120:

"Chorioamnionitis is estimated to affect 3.9% of women giving birth, causing 22.6–36.9% of total stillbirths."

Ref)

[9] Lahra MM, Gordon A, Jeffery HE. Chorioamnionitis and fetal response in stillbirth. Am J Obstet Gynecol. 2007;196(3):229.e1-229.e2294. doi:10.1016/j.ajog.2006.10.900

[10] Gordon A, Lahra M, Raynes-Greenow C, Jeffery H. Histological chorioamnionitis is increased at extremes of gestation in stillbirth: a population-based study. Infect Dis Obstet Gynecol. 2011;2011:456728. doi:10.1155/2011/456728

[11] Woodd SL, Montoya A, Barreix M, et al. Incidence of maternal peripartum infection: A systematic review and meta-analysis. PLoS Med. 2019;16(12):e1002984. https:// doi: 10.1371/journal.pmed.1002984.

3) Not all SGA are growth restricted. If you are aiming to say something about both, I would mention them both consistently. If your definition of SGA is based on birthweight, than this is not a good inclusion criterion, since at study entry, you don't know the birthweight of the infant.

-We agree with your comment. When ACS is considered for women at risk of imminent preterm birth, fetal growth restriction (FGR) is the only available data. However, if we include only the studies that targeted FGR without small for gestational age (SGA) infants, only two studies and 212 neonates would be included in our meta-analysis [van Stralen et al. 2009, Schaap et al. 2001]. The GRADE table in the supplementary file S8 for exclusively FGR revealed very low certainty in all outcomes, and no meaningful conclusion could be drawn. We found 12 ACS studies targeting women giving birth to SGA infants preterm [Kim WJ et al. 2018, Riskin-Mashiah et al. 2018, Feng et al. 2017, Riskin-Mashiah et al. 2016, Ishikawa et al. 2015, Mitsiakos et al. 2013, Torrance et al. 2007, Foix-L'Helias et al. 2005, Bernstein et al. 2000, Elimian et al. 1999, Ley et al. 1997, Spinillo et al. 1995, Lenardo et al. 1990]. Battaglia FC et al. reported that FGR fetuses are delivered as SGA neonates in most cases [Battaglia FC et al. 1967]. However, SGA status does not accurately represent FGR as SGA neonates include those who are constitutionally small [Nardozza LMM et al. 2017]. Hence, we separately analyzed the data in each of the three populations: SGA, FGR, SGA or FGR. In the discussion, we encourage the study evaluating ACS effects in pregnant women with FGR.

Considering the above, we have revised as follows on line 124-128 in the introduction:

"FGR is associated with an increased risk of morbidity and mortality [12-15]. Small for gestational age (SGA) status does not accurately represent FGR as SGA neonates include constitutionally small ones [16]. In most cases, FGR fetuses are delivered as SGA neonates [17]. In this study, we targeted pregnant women with both FGR fetuses and SGA neonates."

Ref)

[12] Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and neonatal encephalopathy. Am J Obstet Gynecol. 2003;188(4):1011-1015. https://doi: 10.1067/mob.2003.233.

[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(6):660-668. https:// doi: 10.1001/jama.2009.1111.

[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(4):869-877. https:// doi: 10.1097/AOG.0b013e3182a265ab.

[15] MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. PLoS Med. 2010;7(6):e1000289. https:// doi: 10.1371/journal.pmed.1000289.

[16] Nardozza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017;295(5):1061-1077. https:// doi: 10.1007/s00404-017-4341-9.

[17] Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71(2):159-163. https://doi: 10.1016/s0022-3476(67)80066-0.

We have revised as follows on line 159-161 in the methods:

“SGA infants are all neonates with birth weights below the 10th percentile. In this survey, FGR fetuses were defined with each included study criterion.”

We have revised as follows on line 315-318 in the results:

“Among the studies that included FGR fetuses, the definitions of FGR varied widely. Since SGA status is insufficient to determine FGR, we separately analyzed the three populations: SGA, FGR, and SGA or FGR. Three populations were combined, and the pooled OR in total were calculated.”

We have revised as follows on line 456-458 in the discussion:

“In this meta-analysis, only two studies targeted pregnant women with FGR. Since the SGA status does not accurately represent FGR, studies evaluating the effects of ACS therapy on pregnant women with FGR fetuses should be encouraged.”

4) Methods: For your PICO’s, I recommend you add the gestational ages. For example P1: do you mean preterm birth < 37 weeks? Or (I think) less than 34 weeks. And from which lower limit onwards? 24 weeks? Or less?

- We have revised as follows in P1 in the Box 1.

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

We have revised as follows in P2 in the Box 1.

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

We have revised as follows in P3 in the Box 1.

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

We have revised as follows in P4 in the Box 1.

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

During the process, we decided to exclude two studies in P1; Paul et al. (2019) and Touhy et al. (2020) in this review. This is because Paul et al. targeted term pregnant women with GDM. The study by Touhy et al. targeted both preterm and term pregnant women, but the maternal outcome, CS, did not provide data for preterm pregnant women. Based on this change, we have revised Supplementary file 2, Supplementary file 3, Supplementary file 4, Supplementary table 5, and Supplementary table 6.

5) Women at risk: also multiple pregnancies? Also pregnancies with other complications (for example a woman with preeclampsia and gestational diabetes)?

- Since this SR aims to update the above-mentioned WHO guideline, we did not aim to include pregnant women at risk of imminent preterm birth with other complications, multiple pregnancies, and preeclampsia [27].

Ref)

[27] 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. Published 2016 Feb 3. doi:10.1371/journal.pone.0147604

6-a) SGA and histological chorioamnionitis are post-baseline characteristics. You need to know at baseline if your patient needs ACS or not. If for example your analysis would show that women with histological chorioamnionitis would experience harmful outcomes due to ACS administration, you would want to avoid ACS in this subgroup. But… you don't know which patients will have histological chorioamnionitis at the time that you have to take the decision whether or not to give ACS.

- We answered the question related to SGA in 3). Please find it in 3).

We agree with your opinion. When ACS treatment is considered for women at risk of imminent preterm birth, clinical chorioamnionitis (CC) is the only available data. However, if we include the study that targeted only CC except for histological chorioamnionitis (HC), only four studies and 453 pregnant women/neonates could be included in our meta-analysis [Been et al. 2009, Goldenberg et al. 2006, Foix-L'Helias et al. 2005, Baud et al. 2000]. There is a significant overlap between clinical and histological chorioamnionitis [Dong Y et al. 1987]. Histological chorioamnionitis more accurately reflects antenatal inflammatory exposure than clinical chorioamnionitis [Redline RW 2006]. Hence, we separately analyzed the data in CC and HC. We encourage future studies evaluating ACS effects in pregnant women with CC in the discussion.

Considering the above, we have revised as follows on line 158-159 in the methods:

"Diagnostic criteria used to define clinical and histological chorioamnionitis are explained in Supplementary table 1."

We have revised as follows on line 282-284 in the result:

"Four studies included pregnant women with clinical chorioamnionitis, and there were variations in the diagnostic criteria (Supplementary table 1)."

We have revised as follows on line 432-437 in the discussion:

"Significant overlap exists between clinical and histological chorioamnionitis [70]. Histological chorioamnionitis reflects antenatal inflammatory exposure more accurately than clinical chorioamnionitis [71]. However, since physicians must decide the indications for ACS therapy when

clinical chorioamnionitis occurs, studies evaluating the effects of ACS in pregnant women with clinical chorioamnionitis should be encouraged."

Ref)

[70] Dong Y, St Clair PJ, Ramzy I, Kagan-Hallet KS, Gibbs RS. A microbiologic and clinical study of placental inflammation at term. Obstet Gynecol. 1987;70(2):175-182

[71] Redline RW. Inflammatory responses in the placenta and umbilical cord. Semin Fetal Neonatal Med. 2006;11(5):296-301. doi:10.1016/j.siny.2006.02.011

6-b) It would help you, if you would think about how a randomised trial would look like if you want to get an answer to your research questions (target trial, see publications of Miguel Hernan from Harvard university on causal inference from observational studies).

- Encouraging RCT trials in our targeting four special populations is challenging since the latest SRs reported the ACS positive effect on neonatal outcomes with moderate to high certainty [McGoldric E et al. 2020, Deshmukh M et al. 2021]. On the other hand, the review by McGoldrick E et al. did not show our targeting maternal and fetus background data; pregestational/gestational diabetes, undergoing elective CS in late preterm, chorioamnionitis, and FGR fetuses. Deshmukh M et al.'s review targeted women undergoing vaginal delivery and CS in late preterm. Hence, the evidence in these two SRs could not simply apply to our targeting four special populations.

Considering the above, we have revised as follows on line 471-488 in the discussion:

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

Ref)

[74] 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(1):11-25. https:// doi: 10.1111/j.1471-0528.1990.tb01711.x.

[75] 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(5):413-418. https:// doi:10.1001/jama.1995.03520290065031.

[40] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. *Am J Perinatol*. 2005;22(3):155-159. https:// doi: 10.1055/s-2005-865020.

[49] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in infants with impaired intrauterine growth. *Acta Paediatr*. 1997;86(10):1090-1096. https:// doi: 10.1111/j.1651-2227.1997.tb14814.x.

[52] 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(6):954-960. https:// doi: 10.1016/s0029-7844(01)01343-6.

[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. https://doi:10.1002/14651858.CD004454.pub.4.

[67] 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(3):e0248774. https:// doi: 10.1371/journal.pone.0248774.

7) Is it not logical that there will be more PIH in the ACS group (when looking at FGR/SGA)? The chances of administrating ACS are higher if there is PIH. Is this PIH present at baseline or is it an outcome variable (in this case, PIH should be diagnosed post-baseline)?

- Based on your comment, we reviewed all maternal outcomes in this SR. Throughout this process, we determined that three studies in P4 did not provide the number of pregnant women. Since these three studies included multiple gestations, there are the risks of double, triple, or more counts of one maternal outcome. Hence, we excluded the three studies for the ACS effects comparisons in maternal outcomes [Eiliminant et al. 1999, Torrance et al. 2007, Feng et al. 2017]. Because of the process, the evidence certainty of ACS's negative effect on PIH changed to very low. The evidence certainty of ACS's negative effect on chorioamnionitis changed to low in P4.

All studies in this review did not provide data on the time sequence between ACS admission and maternal outcomes' onset. Therefore, it is impossible to determine the relationship between ACS admission and maternal outcomes. Considering this circumstance, we recommend future studies which report the time sequence between ACS admission and maternal outcomes' onset in the discussion.

Considering the above, we have revised as follows on line 318-323 and 331-335, and table 4 in the results:

" Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 [50.53.58]. These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event.”

Ref)

[50] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids in obstetric subgroups. *Obstet Gynecol*. 1999;93(2):174-179. https:// doi: 10.1016/s0029-7844(98)00400-1.

[53] Torrance HL, Mulder EJ, Brouwers HA, 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(8):613-621. https:// doi: 10.1080/14767050701463662.

[58] 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(8):613-618. https:// doi: 10.3760/cma.j.issn.0578-1310.2017.08.013.

"The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95% CI:1.08－2.07, *low-certainty evidence*) although the odds of neonatal mortality (eight studies, 2660 infants; pooled OR 0.68, 95%CI:0.47－0.97, *low-certainty evidence*) were possibly reduced (Table 4)."

We have added as follow on line 487-490 in the discussion:

" 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."

8) Table 4: what is NS? Not significant? Non-significant results should also be reported.

- NS means "not stated" in table 4. Ley et al.'s study was the only one that did not provide the exact numerator numbers. Based on the crude OR in the study by Ley et al., We calculated the numerators and updated the data on neonatal death in SGA. we have revised the table 4 data and footnote as follows.

"In the neonatal death in SGA groups, the ACS group was 242/1544 (15.7%), and non-ACS group was 196/1116 (17.6%)."

"We calculated the numerators by the crude OR in the study by Ley et al. (1997)."

Ref)

[49] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in infants with impaired intrauterine growth. *Acta Paediatr*. 1997;86(10):1090-1096. https:// doi: 10.1111/j.1651-2227.1997.tb14814.x.

9) "…33 observational studies pertaining to the benefits…": pertaining is not a correct verb here, I think, could you replace it?

- We have revised as follow on line 366-368 in the discussion:

"This systematic review identified 31 observational studies on the benefits and drawbacks of using ACS in subgroups of women with specific pregnancy complications."

10) line 417: “in the setting of fetal growth restriction” (or change to “should not be withheld in case of fetal growth restriction”)

- We have revised as follow on line 441-442 in the discussion:

“The totality of evidence identified in this review suggests that ACS therapy should be used in the fetal growth restriction setting.”

11) line 417: “while the evidence was largely of low…”

12) line 419: “and no harms were reported”

- We have revised as follow on line 442-444 in the discussion:

“Although the evidence was mainly of low or very low certainty, benefits were observed for several outcomes, and no harm was reported.”

13) line 447: “ACS have” instead of “has”

- We have revised as follow on line 493-496 in the discussion:

“ACS has possible benefits in the setting of FGR and/or SGA; however, direct evidence of its efficacy and safety for pregnant women with pregestational and/or gestational diabetes mellitus and those undergoing elective CS in late preterm period is still lacking.”

14) I am missing more reflection on how the included studies were conducted.

Why are almost all of the studies observational?

- In 1990, Crowley P et al. reported a structured review on antenatal corticosteroids (ACS) for preterm birth [Crowley P et al. 1990]. The review revealed that ACS significantly reduced the risk of IVH and respiratory morbidity [Crowley P et al. 1990]. In 1995, the National Institutes of Health (NIH) developed the consensus on the recommendation of ACS treatment for preterm birth [JAMA 1995].

In our review, only one study in P3 and two in P4 started before 1990 [Dempsey et al. 2005, Schaap et al. 2001, Ley et al. 1997]. No study included in P1 and P2 was conducted before 1990. We assumed that it would be challenging to conduct the RCTs on ACS efficacy even in the special populations after the review by Crowley P et al. since solid evidence on ACS effectiveness for preterm birth had been reported [Crowley P et al. 1990]. However, women with diabetes, chorioamnionitis, or babies with FGR are generally excluded from ACS efficacy trials [McGoldrick E et al. 2020]. Considering the circumstance, the guidelines of ACS by international bodies have yet to develop a solid recommendation for these special populations. However, women with these complications are at higher risk of adverse perinatal outcomes. Hence, we consider this review valid.

Based on the above, we have revised it on line 471-490 in the discussion.

“This review did not lead to any evidence of high certainty, and one reason for this observation is that all 31 studies were observational. In 1990, Crowley P et al. reported a structured review of ACS for preterm birth [74]. The review revealed that ACS significantly reduced the risk of IVH and respiratory

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

Ref)

[74] Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol. 1995;173(1):322-335. doi:10.1016/0002-9378(95)90222-8

[75] 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(5):413-418. doi:10.1001/jama.1995.03520290065031

[40] Dempsey E, Chen MF, Kokottis T, et al. Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. Am J Perinatol. 2005;22(3):155-159. https:// doi: 10.1055/s-2005-865020.

[49] Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in infants with impaired intrauterine growth. Acta Paediatr. 1997;86(10):1090-1096. https:// doi: 10.1111/j.1651-2227.1997.tb14814.x.

[52] 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(6):954-960. https:// doi: 10.1016/s0029-7844(01)01343-6.

15) What are the drawbacks of observational studies?

- Observational studies are more prone to bias and confounding and cannot be used to demonstrate causality.

16)How should observational data ideally be analysed to enable causal inference, because that is your aim: exploring the EFFECT of ACS on a maternal or neonatal outcome (cfr Hernan)?

- Causal relationships cannot be directly inferred from meta-analysis of observational studies. Meta-analysis is intended to increase statistical power and obtain consistent results by integrating the results of multiple independent observational studies. However, many factors, such as design limitations of observational studies, heterogeneity among different studies, and unmeasured confounding factors, may prevent meta-analysis from providing strong evidence to infer causality. In addition, studies that provide stronger evidence, such as experimental studies or randomized controlled trials, are needed to infer causal relationships.

17) Say something on the different regimens and repeat courses of ACS in the studies?

-This review evaluated the ACS efficacy in the targeted special population. We did not compared the ACS regimens, so this review did not lead to any recommendation on ACS regimens. The latest Cohoran review on repeat doses of ACS for women at risk of preterm birth revealed that the repeated ACS regimen reduced the risk of RDS and severe infant morbidity [Walters A et al. 2022]. The future study should determine whether the repeat doses of ACS regimens would be effective in pregnant women with special conditions.

Ref)

Walters A, McKinlay C, Middleton P, Harding JE, Crowther CA. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2022;4(4):CD003935. Published 2022 Apr 4. doi:10.1002/14651858.CD003935.pub5

18) Supplementary files

S3: is there a reason why there are no definitions of the outcomes?

- We updated Supplementary table 1, including the outcome definitions.

19) S5-8: nice! Congratulations.

- Thank you.

Reviewer: 2

Dr. Roger Soll, University of Vermont

Comments to the Author:

1) I am confused regarding the paucity of randomized controlled trials in the populations of interest. The obvious one is the use of ACS in planned cesarean section (CS) in the late preterm period. There are many RCTs of ACS in the late preterm period, albeit not restricted to mothers undergoing planned cesarean section. A recent systematic review and meta-analysis identified 7 RCTs (N = 4144) and reported moderate quality evidence that ANC exposure reduced need for respiratory support in late preterm neonates (Deshmukh M, Patole S (2021) Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries—A systematic review and meta-analysis of RCTs. PLoS ONE 16(3): e0248774.
https://apac01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1371%2Fjournal.pone.0248774&data=05%7C01%7C%7Cd785ad98c1f246a0eb3e08db257433f7%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C638144953238906330%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=LxsEQauxKIGfTfZdlHs6uO%2FOFR0zMXDjbnHaIwL8FQo%3D&reserved=0). Trials included in this review had many infants delivered by cesarean section. Likewise, many randomized controlled trials included mothers with gestational diabetes, though reports on these subgroups are missing. The NIH statement is very broad and states that “antenatal corticosteroid therapy is indicated

for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs". Some acknowledgement and formal discussion of what is (and is not) provided by the myriad randomized controlled trials is needed to put this interesting report of the available observational data in focus.

- Based on your comment, we have revised line 395-401 in the discussion.

"The 2020 Cochrane review on ACS efficacy identified 27 trials; however, a subgroup analysis on gestational age at trial entry reported findings from seven trials recruiting women in the late preterm period [2]. This subgroup analysis suggested that ACS reduces the rates of neonatal death and RDS in the late preterm period [2]. Deshmukh M et al. reported that ACS reduced the need for respiratory support and increased the risk of hypoglycemia with moderate certainty [67]. However, no subgroup analyses were conducted on CS [67]. Hence, these findings cannot be generalized to all women undergoing CS in the late preterm period."

We have added and revised as follows in line 479-490 in the discussion.

"The latest Cochrane review on ACS treatment for preterm birth involved a subgroup analysis in the seven special conditions [2]. However, the review did not conduct a subgroup analysis regarding women with diabetes, chorioamnionitis, and FGR [2]. Furthermore, the latest review on ACS for later preterm birth did not perform any subgroup analysis due to the lack of stratified data based on the mode of delivery [67]. Considering the circumstances, guidelines on ACS therapy by international bodies are yet to develop solid recommendations for these special populations. Hence, we consider this review valid. Prospective cohort studies on ACS efficacy for these four special populations should be encouraged. The studies should include precise data on the time sequence between ACS admission and the onset of maternal outcomes to determine the effect of ACS therapy on maternal outcomes."

Ref)

[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. https://doi:10.1002/14651858.CD004454.pub.4.

[67] 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(3):e0248774. https:// doi: 10.1371/journal.pone.0248774.

Reviewer: 3

Dr. Peter Socha, McGill University

Comments to the Author:

Primary concerns

1) Studies were eligible if they either restricted to the specific risk groups or reported subgroup analyses in the specific risk groups. Please clarify whether search strategy and eligibility criteria for full-text review would have identified studies that did not report subgroup analyses in their title, abstract, keywords (ie, only reported analyses for the specific groups in their main text). Eg, the ALPS

trial (doi.org/10.1056/NEJMoa1516783) reported a subgroup analysis by mode of delivery (vaginal vs planned caesarean) in the main text and supplement, but not in the abstract.

- We explained the study selection in this survey on line 200-204 in the methods below.

“Two reviewers (KS, EN) independently assessed titles and abstracts of identified citations for eligibility. Any disagreement resulted in automatic inclusion into the next level of screening. Subsequently, full-text publications of potentially eligible studies were obtained and assessed in duplicate by two reviewers independently, with disagreements resolved through discussion or by consulting a third reviewer.”

Based on the screening of titles and abstracts, we evaluated full-text publications. Hence, we have a risk of missing the data of subgroup analysis through the screening of titles and abstracts.

Regarding the RCT by Gyamfi-Bannerman CEA et al., we picked it up by screening titles and abstracts. In the full-text evaluation, their outcomes did not adequately fit our outcomes, and the study was not included in this review. However, we agree that this review should mention the RCT’s results. Therefore, we added the following in line 402-416 in the discussion.

“The RCT by Gyamfi-Bannerman CEA et al. reported that ACS in the late preterm period reduced the risk of transient tachypnea of the newborn, surfactant use, and BPD [68]. Their subgroup analysis of planned CS showed ACS resulted in no significant difference in their primary outcome and severe respiratory complication [68]. Their primary outcome was defined as any of the following occurrences within 72 hours after birth: continuous positive airway pressure (CPAP), a high-flow nasal cannula (HFN) for at least two continuous hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least four continuous hours, mechanical ventilation, stillbirth, neonatal death, or the need for extracorporeal membrane oxygenation (ECMO) [68]. Their severe respiratory complication was defined as any of the following occurrences within 72 hours after birth: CPAP, HFN for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth, neonatal death, or the need for ECMO [68]. Their outcomes did not adequately fit our outcomes, and the study was not included in this review.”

Ref)

[68] Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016;374(14):1311-1320. https:// doi: 10.1056/NEJMoa1516783.

2) Please update the selection and confounding domains for the risk of bias assessments (Supplementary file S6). Some justifications are unclear (see specific comments below) and some studies needed additional review (eg, Paul 2019 does indeed consider confounding in their design stage, by matching exposed/unexposed on ethnicity, mode of delivery, year of delivery—though in this case I agree these confounders are insufficient and the study is still at “high” risk of confounding). Please also list which confounders were considered for all studies.

- Based on your comment, we have revised Supplementary table 5 and Supplementary file 3.

3) I recommend the pooled analyses be limited to studies that were rated as “low” risk of bias (particularly bias due to confounding). If studies at “low” risk of bias are pooled with studies at “high” risk of bias, then the pooled results will be at higher risk of bias.

- We consulted a statistician for a meta-analysis of observational studies and decided to include unadjusted variables. Therefore, confounding bias is not relevant to the results of the meta-analysis. If we do a sensitivity analysis, we should do it when the selection and attrition biases are high risk. However, there was no study of selection bias with high risk of bias, and there were three cases of attrition bias with high risk of bias. The three studies with high risk of bias in attrition bias reported long-term child outcomes. In this review, all long-term outcomes were extracted from these three studies, which were high risk of bias in attrition bias. Hence, we did not perform the sensitivity analysis.

4) I recommend using random effects (not fixed effects) to pool all results. The assumption of fixed effects, that studies are estimating the same treatment effect, is unlikely to hold as these studies are in very different populations, use different methods, adjust for different confounders, etc. If there is little between-study heterogeneity, I would argue that this is due to chance rather than evidence that the studies are estimating the same treatment effect.

-We agreed and we used random effect model for all results when the outcomes included two or more studies.

5) Please specify how the absolute effects (risk differences) in Tables 1-4 are being calculated.

- We use the GRADEpro system to calculate the absolute effects. In this review, we determined the ORs transferred to RRs with the control even rates (CERs). I describe the formulas below.

CRE= (the number of event occurrences in the control group)÷ (the total number in the control group)

RR= OR÷ (1-CER×(1-OR))

Absolute effect (per 1000)= 1000×(CER×(1-RR))

Ref)

-Skoetz N, Goldkuhle M, van Dalen EC, Akl EA, Trivela M, Mustafa RA,

Nowak A, Dahm P, Schünemann H, Bender R, GRADE Working Group, GRADE guidelines 27: How to calculate absolute effects for time-to-event outcomes in Summary of Findings tables and Evidence Profiles, Journal of Clinical Epidemiology (2019), doi: https://doi.org/10.1016/j.jclinepi.2019.10.015.

Other concerns

6) The Canadian recommendations for ACS in the late-preterm (ref. 3) were just updated in 2023 (doi.org/10.1016/j.jogc.2022.12.006), though the update does not change the authors' statement.

- We appreciate your information. We believe that ACS efficacy in the special populations in this review should be determined to provide personalized medicine for pregnant women.

7) Please add the date the search was conducted.

- We have revised as followed on the line 189-192 in the methods.

“A systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Library, Web of Science, and Global Index Medicus was conducted with no date restrictions on 6th June 2021.”

8) Please clarify denominators for counts throughout the manuscript. Are these pregnant people, fetuses, or neonates? Eg, when studies include multiple gestations “women/neonates” would be inappropriate.

- We reviewed all denominators in this review and revised the following points.

In P1, we had a typo in Supplementary table 1 on the number of the study by Battarbee et al. We had revised it as a total infants’ number: 615 (treatment 536, control 79). In the Review Manager, we made a typo in the denominators related to the study by Krispin et al. (2018). We updated all the denominators and recalculated the ORs in CS, NICU admission, Apgar score at 5 mins <7, RDS, and neonatal hypoglycemia. The ORs did not change significantly, and we changed the GRADE table in the Supplementary table 6.

In P3, we had a typo in Supplementary table 1 on the number of the study by Ryu et al. We revised it to a total infants’/pregnant women’s number: of 109 (treatment 97, control 12). We had a typo in Supplementary table 1 on the number of the study by Ahn et al. We had revised it as a total pregnant women number: 88 (treatment 52, control 36). We added the numbers of HC and CC in the studies by Been et al. and Goldenberg et al. in Supplementary table 1. We made a typo in the Revman data of the study by Foix-L'Helias et al.: the denominators in the outcomes, death before discharge, and BPD. We updated them and revised Supplementary file 4 and Supplementary table 6. These changes did not make any impact on the result in this review.

In P4, we determined that three studies did not provide the number of pregnant women. Since these three studies included multiple gestations, there are the risks of double, triple, or more counts of one maternal outcome. Hence, we excluded the three studies for the ACS effects comparisons in maternal outcomes [Elimian et al. 1999, Torrance et al. 2007, Feng et al. 2017]. Because of the process, the evidence certainty of ACS's negative effect on PIH changed to very low. The evidence certainty of ACS's negative effect on chorioamnionitis changed to low in P4.

All studies in this review did not provide data on the time sequence between ACS admission and maternal outcomes' onset. Therefore, it is impossible to determine the relationship between ACS admission and maternal outcomes. Considering this circumstance, we recommend future studies which report the time sequence between ACS admission and maternal outcomes' onset in the discussion.

Considering the above, we have revised as follows on line 318-323, 331-335, and 353-357, and table 4 in the results:

" Data were available from 2714 pregnant women and 8324 neonates enrolled between 1984 and 2019. We excluded three studies on maternal outcomes for omitting the number of pregnant women: Elimian et al., 1999, Torrance et al., 2007, and Feng et al., 2017 [50,53,58]. These studies included multiple gestations; hence, there was the risk of double, triple, or more counts to one maternal outcome event.”

Ref)

[50] Elimian A, Verma U, Canterino J, et al. Effectiveness of antenatal steroids in obstetric subgroups. Obstet Gynecol. 1999;93(2):174-179. https:// doi: 10.1016/s0029-7844(98)00400-1.

[53] Torrance HL, Mulder EJ, Brouwers HA, 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(8):613-621. https:// doi: 10.1080/14767050701463662.

[58] 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(8):613-618. https:// doi: 10.3760/cma.j.issn.0578-1310.2017.08.013.

" The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI:1.08–2.07, low-certainty evidence) although the odds of neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–0.97, low-certainty evidence) were possibly reduced (Table 4).

" However, the odds of PIH (three studies, 775 women; pooled OR 1.47, 95%CI: 1.07–2.01, low-certainty evidence) and neonatal hypoglycemia (two studies, 329 infants; pooled OR: 2.06, 95%CI: 1.27–3.32, moderate-certainty evidence) were possibly increased (Table 4)”

We have added as follow on line 487-490 in the discussion:

" 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.”

Based on the change above in P4, we have revised Supplementary table 6, and Supplementary file 4.

In the Review Manager, we made a typo in the denominators in neonatal death related to the study by Torrance et al. (2007) in P4. We updated all the denominators and recalculated the odd ratio (OR) in neonatal death. The OR did not change significantly, and we changed the GRADE table in the Supplementary table 6.

9) There is a typo in Figures 2, 4, 6, 8 which should read: “Confounding variables (confounding bias)”.

- For study quality, observational studies were assessed using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) in this review (Kim SY et al. 2013). In the RoBANS, confounding variables are categorized in selection bias. Hence, we prefer to keep Supplementary file 3.

Ref) 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(4):408-414. doi:10.1016/j.jclinepi.2012.09.016

10) Please clarify what is meant by “downgrading for imprecision” (page 25).

- Imprecision in the GRADE approach is evaluated with the number of included patients and events and the confidence interval (Guyatt GJ et al. 2011). Therefore, the mention of imprecision is inappropriate, and we removed it. We have revised it as a follow in line 468-469 in the discussion.

“However, we explored and reported heterogeneity for meta-analyses.”

Ref)

Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision [published correction appears in J Clin Epidemiol. 2021 Sep;137:265]. J Clin Epidemiol. 2011;64(12):1283-1293. doi:10.1016/j.jclinepi.2011.01.012

11) Specific comments: Supplementary file S6

11-a) Krispin 2018: There is a typo where “ACS treatment” is listed as a confounder.

-We have revised it as the following in Supplementary table 5:

“No differences in maternal age, gravidity, body mass index, and hypertensive disorders were confirmed between the exposed and unexposed groups. Women treated with corticosteroids had higher rates of nulliparity than women who were not treated (55% vs. 34%, respectively, p = 0.001). Multivariate analysis adjusting for gravity, parity, primiparity, hypertensive disorders, BMI, birth weight and gestational age at delivery was conducted in adverse composite neonatal outcome.”

11-b) de la Huerga Lopez 2019: The current justification for the selection domain is unclear. I do not think that excluding congenital malformations and transfers would lead to “high” selection bias. The last three comments (matching, proportion with planned cesareans, and proportion with preterm delivery) are related to confounding. Confounding (by gestational age) was considered in the design phase through matching.

- We have revised as the following.

Selection of participants: Low. All participants admitted/delivered and treated at the same tertiary hospital over the same period (from January 2013 to April 2017).

Confounding variables: High. No confirmation or consideration on confounding variables in the analysis phase.

11-c) Ahn 2012: Please clarify this sentence in the confounding domain “did not control for NEC, PDA, or neonatal death in analyses”.

-We have revised the following: Multiple logistic regression models were used for several outcomes (RDS, mechanical ventilation, use of oxygen, BPD, sepsis, IHC, IVH, PVL), controlling for gestational age. Confounding was not considered in the analysis phase for NEC, PDA, and neonatal death.

11-d) Goldenberg 2006/Dempsey 2005/Elimian 2000: Please clarify this sentence in the confounding domain “adjusted analysis for results stratified by corticosteroid administration not available”.

- We have revised the following.

i) Goldenberg 2006; 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.

ii) Dempsey 2006; High. Multiple logistic regression models with and without corticosteroid administration were not performed, and results adjusted for confounding factors were not available.

iii) Elimian 2000; High. Multiple logistic regression models with and without corticosteroid administration were not performed, and results adjusted for confounding factors were not available.

11-e) Torrance 2007: Unclear justification for “high” risk of selection bias. Is restricting to infants admitted to the NICU the primary concern? Please indicate whether individuals matched on outcome (cases/controls) or exposure (treated/untreated). Matching on post-treatment variables (gestational age at birth, birth weight) can induce collider bias, but I am not convinced that this warrants “high” selection bias.

-We changed from high to low risk of bias on selection of participants. We have revised the following: 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).

11-f) Torrence 2007/Elimian 1999/Spinillo 1995: Please clarify this comment in the selection domain, “but the control group was defined only by no-steroid treatment without further specification, so it is conceivable that fetal condition on hospitalization differed”. Is this about confounding by indication?

-We have revised the following in the risk of bias on selection of participants.

i) Torrance 2007: 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).

ii) Elimian 1999: Low. All participants from the same institution during the same period (January 1990–July 1997).

iii) Spinillo 1995: Low. All participants from the same institution during the same period (1988–1993).

11-g) Kim YJ 2018: The current justification for the selection domain is unclear, how does a large difference in proportion between intervention/control lead to selection bais?

- We changed from unclear to low risk of bias in selection of participants. We changed the comment in the confounding variables to the following: 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.

VERSION 2 – REVIEW

REVIEWER	Dehaene, Isabelle

	University Hospital Ghent
REVIEW RETURNED	15-May-2023

GENERAL COMMENTS	Abstract * “Thirty-one studies involving 5018 pregnant women and 10819 neonates were included.”: this means that almost all studies considered twin pregnancies? Or were these neonates born from other women than those 5018? => make your P of the PICO clear Methods * “Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or small-for-gestational-age infants”: it is not correct to identify pregnant women (in this case women at risk of imminent preterm birth) based on the outcome of the pregnancy (SGA infants), you can only consider women who are pregnant of FGR fetuses The patients in the PICO should be pregnant patients. No referral to the outcome of the pregnancy (is also done elsewhere in the paper). I would therefor drop the three subpopulations. If you do include them (because you have found data on them), I would suggest that this issue is mentioned in the discussion. In the same way, it is not very useful to consider histological chorioamnionitis. If there is no clinical chorioamnionitis/an indication for ACS in the pregnant woman, than only knowing what the association between ACS an histological CA is, is irrelevant. This said, it is good that you only talk about associations. Further on, I read in the discussion that you addressed this issue, great! I would drop “Effects” in the subtitles. Talking about associations is more correct.

REVIEWER	Socha, Peter McGill University
REVIEW RETURNED	16-May-2023

GENERAL COMMENTS	Thank you for your detailed response. I have some remaining concerns about the integration of results from relevant (excluded) studies and about the risk of bias assessments. The numbers below correspond to the authors’ response letter. 1-a) The language used in the discussion/conclusion is too strong given the scope of the review. The conclusions should reflect the remaining uncertainty about the strength of the evidence, given that influential studies could be excluded due to the strict outcome criteria of this review. For example, I do not think it is appropriate to conclude there is a “paucity of evidence for women…undergoing planned CS” when a large randomized trial has shown evidence for a benefit of antenatal corticosteroids in pregnant people undergoing planned CS. The composite outcomes used in the ALPS trial are meaningful outcomes and, additionally, include WHO priority outcomes for preterm birth (ie, neonatal death, use of mechanical ventilation, oxygen therapy, and oxygen requirement). I also suggest adding a supplementary table detailing all studies that were excluded because their outcomes were composites, or slightly different/not explicitly listed on the WHO priority outcomes for preterm birth (ie, different lengths of oxygen requirement).

	1-b) Lines 404-406: This sentence does not match the ALPS trial results. The subgroup analysis of planned CS did find differences for the primary outcome (RR: 0.62, 95 CI: 0.43-0.90; see Table S5 in the ALPS supplement) and the secondary outcome (RR: 0.51, 95% CI: 0.34-0.78; Table S6). The p-values presented in both tables are for at test of homogeneity of the RR between subgroups (large p-values indicate little evidence that the RR is different between attempted vaginal and planned CS). Lines 402-404: It is not clear why the results for TTN, surfactant use, and BPD were highlighted. If the goal is to summarize the overall results of the ALPS trial, I recommend focusing on the primary outcome. 2 and 3) I am not convinced that confounding is not relevant to the results of this meta-analysis. Confounding is one of (if not the) principal concern for the included studies and is therefore a principal concern for the meta-analysis. This should be considered in the risk of bias assessments, the meta-analysis, and the discussion/conclusions. Regrading the risk of bias assessments: Rigorous re-evaluation of the risk of bias for all included studies is required, with particular attention to confounding. A cursory review of the results from the first three studies presented in forest plots (page 55/201; Cassimatis 2020, Krispin 2018, Battarbee 2020) found that the ORs used in the meta-analysis were all unadjusted comparisons of exposed vs unexposed. Yet Cassimatis 2020 is listed as unclear risk of bias, and Krispin 2018 and Battarbee 2020 are listed as low risk of bias due to confounding. Regarding the meta-analysis: Pooled ORs will be more informative if studies at high risk of bias are excluded. Excluding studies at high risk of bias (or at least performing analyses stratified by risk of bias) is recommended in Section 7.6 of the Cochrane Handbook (https://training.cochrane.org/handbook/current/chapter-07#section-7-6) and by other groups (eg, https://doi.org/10.1136/bmj.i4919). Regarding the discussion: The potential for confounding to impact results should be discussed. 5) Please also add this information to the methods section. 11) Please consider all methods of confounder control when assessing risk of bias due to confounding. Currently the justifications are limited to methods used in the 'analysis phase' (eg, regression adjustment, weighting), but should also consider methods used in the 'design phase' (eg, matching, natural experiments).

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr Isabelle Dehaene, University Hospital Ghent

Comments to the Author:

1) Abstract

* “Thirty-one studies involving 5018 pregnant women and 10819 neonates were included.”: this means that almost all studies considered twin pregnancies? Or were these neonates born from other women than those 5018? => make your P of the PICO clear

- We counted the number of pregnant women providing the outcome data and the number of neonates providing the outcome data. Please find the data in Supplementary Table 1. The reason for the difference in the number of outcomes for women and neonates is that some studies included in the analysis examined both maternal outcomes and neonatal outcomes simultaneously, while others focused only on one of the two. Therefore, the total number of studies involving pregnant women (5018) and neonates (10819) does not necessarily indicate that all studies considered twin pregnancies or that the neonates were born from different women than those 5018. The variation in outcome numbers is due to the inclusion of studies with different research designs and focuses.

2) Methods

2-a) * “Women at risk of imminent preterm birth less than 37 weeks with growth-restricted fetuses and/or small-for-gestational-age infants”: it is not correct to identify pregnant women (in this case women at risk of imminent preterm birth) based on the outcome of the pregnancy (SGA infants), you can only consider women who are pregnant of FGR fetuses. The patients in the PICO should be pregnant patients. No referral to the outcome of the pregnancy (is also done elsewhere in the paper). I would therefor drop the three subpopulations. If you do include them (because you have found data on them), I would suggest that this issue is mentioned in the discussion.

- We agree with your comment. When ACS is considered for women at risk of imminent preterm birth, fetal growth restriction (FGR) is the only available data. Hence, we should encourage future studies targeting pregnant women with FGR fetuses. Considering the above, we have revised as follows on line 466-470 in the discussion:

“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. 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.”

2-b) In the same way, it is not very useful to consider histological chorioamnionitis. If there is no clinical chorioamnionitis/an indication for ACS in the pregnant woman, than only knowing what the association between ACS an histological CA is, is irrelevant. This said, it is good that you only talk about associations. Further on, I read in the discussion that you addressed this issue, great!

-Thank you.

3) I would drop “Effects” in the subtitles. Talking about associations is more correct.

-Our present short tile is “Systematic review: antenatal steroids in specific women”.

Reviewer: 3

Dr. Peter Socha, McGill University

Comments to the Author:

1-a) The language used in the discussion/conclusion is too strong given the scope of the review. The conclusions should reflect the remaining uncertainty about the strength of the evidence, given that influential studies could be excluded due to the strict outcome criteria of this review. For example, I do not think it is appropriate to conclude there is a "paucity of evidence for women…undergoing planned CS" when a large randomized trial has shown evidence for a benefit of antenatal corticosteroids in pregnant people undergoing planned CS. The composite outcomes used in the ALPS trial are meaningful outcomes and, additionally, include WHO priority outcomes for preterm birth (ie, neonatal death, use of mechanical ventilation, oxygen therapy, and oxygen requirement). I also suggest adding a supplementary table detailing all studies that were excluded because their outcomes were composites, or slightly different/not explicitly listed on the WHO priority outcomes for preterm birth (ie, different lengths of oxygen requirement).

-We have revised the following on line 423-430:

"Our review suggests there is insufficient evidence to draw firm conclusions on the benefits and possible harms of ACS when used in this subpopulation. At the same time, the multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective effects from ACS for neonatal respiratory morbidity amongst women with late preterm CS. An ongoing randomized trial in New Zealand will provide further information on the effects of ACS therapy on women with CS planned between 35 weeks 0 days and 39 weeks 6 days."

- We decided the ALPS trial was included in P2 since the study fitted our PIC except for O. However, their study outcomes did not adequately fit our outcomes. We communicated with the author of the ALPS trial, Dr. Gyamfi-Bannerman, to obtain their original outcome data. However, the data were registered in NICHD DASH, and we could not access the data in NICHD DASH before this revision deadline as our institution has not been registered in NICHD.

Based on the change, we have revised in the abstract, results and discussion the below.

In the abstract, we have revised as follow on line 63-64.

"Thirty-two studies involving 5018 pregnant women and 10819 neonates were included."

In the results, we have revised as follow on line 264-268.

"The search identified 211 citations:17 potentially eligible studies were evaluated, and three studies were included (Supplementary file 2). These were two observational studies and a randomized control trial (RCT). All studies were conducted in high-income countries between 2010 and 2017, providing data on 205 pregnant women/neonates (Supplementary table 1)."

In the discussion, we have revised as follow on line 410-428.

"The trial by Gyamfi-Bannerman et al. reported that ACS in the late preterm period reduced their primary outcome and severe newborn respiratory complications. Their subgroup analysis showed that these beneficial effects persisted among women admitted for planned CS only. 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). 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. Their outcomes did not adequately fit our outcomes, and the study did not provide their outcome data. Our review suggests there is insufficient evidence to draw firm conclusions on the benefits and possible harms of ACS when used in this subpopulation. At the same time, the multi-center trial by Gyamfi-Bannerman et al. is suggestive that there are protective effects from ACS for neonatal respiratory morbidity amongst women with late preterm CS."

1-b) Lines 404-406: This sentence does not match the ALPS trial results. The subgroup analysis of planned CS did find differences for the primary outcome (RR: 0.62, 95 CI: 0.43-0.90; see Table S5 in the ALPS supplement) and the secondary outcome (RR: 0.51, 95% CI: 0.34-0.78; Table S6). The p-values presented in both tables are for at test of homogeneity of the RR between subgroups (large p-values indicate little evidence that the RR is different between attempted vaginal and planned CS).

1-c) Lines 402-404: It is not clear why the results for TTN, surfactant use, and BPD were highlighted. If the goal is to summarize the overall results of the ALPS trial, I recommend focusing on the primary outcome.

-We have revised the following on line 410-413:

"The trial by Gyamfi-Bannerman et al. reported that ACS in the late preterm period reduced their primary outcome and severe newborn respiratory complications. Their subgroup analysis showed that these beneficial effects persisted among women admitted for planned CS only."

2 and 3) I am not convinced that confounding is not relevant to the results of this meta-analysis. Confounding is one of (if not the) principal concern for the included studies and is therefore a principal concern for the meta-analysis. This should be considered in the risk of bias assessments, the meta-analysis, and the discussion/conclusions. Regarding the risk of bias assessments: Rigorous re-evaluation of the risk of bias for all included studies is required, with particular attention to confounding. A cursory review of the results from the first three studies presented in forest plots (page 55/201; Cassimatis 2020, Krispin 2018, Battarbee 2020) found that the ORs used in the meta-analysis were all unadjusted comparisons of exposed vs unexposed. Yet Cassimatis 2020 is listed as unclear risk of bias, and Krispin 2018 and Battarbee 2020 are listed as low risk of bias due to confounding.

-We reassessed the risk of bias in all included studies. We decided to change to the high risk of bias in the confounding variables in all included studies since we only used crude data from all included studies. We consulted a statistician for this meta-analysis and decided to include unadjusted variables, as each study employed a variety of potential confounders for their multiple logistic regression models. Regarding the incomplete outcome data, we decided to change to low risk of bias in Cartwright (2019), Ishikawa (2015), and Mitsiakos (2013) since all their short-term outcomes did show significant missing data, and the majority of their outcomes were short-term outcomes. On the other hand, the three studies provided long-term outcomes and showed the missing data in long-term outcome data. Hence, we downgraded their long-term outcomes certainty in our GRADE table. We decided to change to the low risk of bias in the selection of bias in Schaap (2001) through our reassessment. Please find the updated Supplementary Table 5 and Supplementary Table 6.

Based on the changes in the GRADE table, we have revised as follow on line 291-297 and line 335-342 in the results.

“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).”

“The administration of ACS for women with SGA was associated with increasing odds of pregnancy induced hypertension (PIH) (2 studies, 684 women; pooled OR 1.50, 95%CI: 1.08–2.07, low-certainty evidence) although the odds of pre-eclampsia (two studies, 2077 infants; pooled OR: 0.78; 95%CI: 0.66–0.94, low-certainty evidence), neonatal mortality (eight studies, 2660 infants; pooled OR: 0.68; 95%CI: 0.47–0.97, low-certainty evidence), periventricular leukomalacia (PVL) (four studies, 3955 infants; pooled OR: 0.54; 95%CI: 0.38–0.77, low-certainty evidence) were possibly reduced (Table 4).”

2 and 3-b) Regarding the meta-analysis: Pooled ORs will be more informative if studies at high risk of bias are excluded. Excluding studies at high risk of bias (or at least performing analyses stratified by risk of bias) is recommended in Section 7.6 of the Cochrane Handbook (https://apac01.safelinks.protection.outlook.com/?url=https%3A%2F%2Ftraining.cochrane.org%2Fhandbook%2Fcurrent%2Fchapter-07%23section-7-6&data=05%7C01%7C%7C50afe37f776d42e3ee4308db585c71aa%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C638200926297428631%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=A7URd9a9VPXYdS8LWwZOIcIvQXWzu3q9lDt7zikCP1U%3D&reserved=0) and by other groups (eg, https://apac01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1136%2Fbmj.i4919&data=05%7C01%7C%7C50afe37f776d42e3ee4308db585c71aa%7C84df9e7fe9f640afb435aaaaaaaaaaaa%7C1%7C0%7C638200926297428631%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=etu8B3GgPYigQo6V6DkhUgEANu7rKYKzS2l2Od5P6B4%3D&reserved=0).

-Through the process of updating the risk of bias, the risk of bias in all included studies, except Di Lenardo (1990), was the same. Di Lenardo (1990) provided the outcome data on RDS, and we re-calculated the OR of RDS, excluding the data from Schaap (2001). The OR on RDS changed to 0.86 (95%CI: 0.72-1.04) from 0.86 (95%CI: 0.72-1.03). Hence, we did not report the sensitivity analysis in the manuscript.

2 and 3-c) Regarding the discussion: The potential for confounding to impact results should be discussed.

-We have revised as follows on line 481-485 in the discussion:

“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.”

5) Please also add this information to the methods section.

-We have revised as follow on line 216-217 in the methods:

“Aggregate odds ratios (ORs) and relative risks with 95% confidence intervals (CIs) were determined for dichotomous data using the random-effects model.”

-We have added as follow on line 225-227 in the methods:

“Based on the evaluation of the risk of bias, we calculated the pooled ORs, which excluded studies at high risk of bias.”

11) Please consider all methods of confounder control when assessing risk of bias due to confounding. Currently the justifications are limited to methods used in the ‘analysis phase’ (eg, regression adjustment, weighting), but should also consider methods used in the ‘design phase’ (eg, matching, natural experiments).

-We reassessed the risk of bias in the included studies. Regarding confounding variables, we evaluated the risk of bias in study design and analysis. Please find the updated Supplementary Table 5.

VERSION 3 – REVIEW

REVIEWER	Socha, Peter McGill University
REVIEW RETURNED	29-Jun-2023

GENERAL COMMENTS	Thank you for your comments. The revised manuscript is clearer, but I remain concerned that confounding is not adequately considered. I recommend including the adjusted estimates from studies that do adjust for confounding in your review. These are the more reliable estimates and I do not think it is useful to disregard them or to calculate the crude estimates from these studies for pooling. Instead of pooling estimates at high risk of bias due to confounding I would focus on pooling results from studies that do adjust for confounding or, given your concerns that some studies adjust for different confounders, present the results from these studies without pooling and alongside a discussion of how well the study adjusted for confounding.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3
Dr. Peter Socha, McGill University
Comments to the Author:
1) Thank you for your comments. The revised manuscript is clearer, but I remain concerned that confounding is not adequately considered.

I recommend including the adjusted estimates from studies that do adjust for confounding in your review. These are the more reliable estimates and I do not think it is useful to disregard them or to calculate the crude estimates from these studies for pooling. Instead of pooling estimates at high risk of bias due to confounding I would focus on pooling results from studies that do adjust for confounding or, given your concerns that some studies adjust for different confounders, present the results from these studies without pooling and alongside a discussion of how well the study adjusted for confounding.

-Thank you for your valuable feedback on our paper. We appreciate your recommendation to include adjusted estimates from studies that control for confounding in our review, as these estimates are considered more reliable. However, after consulting with a biostatistician specializing in meta-analysis, we were advised against pooling adjusted odds ratios with different covariates due to the potential for significant bias. Therefore, in this study, we will follow their advice and use crude odds ratios for pooling to mitigate the risk of confounding bias.
In line with this approach, we would like to reference two relevant papers that support our decision:

Yoneoka, D., Henmi, M., Sawada, N., et al. (2015). "Synthesis of clinical prediction models under different sets of covariates with one individual patient data." BMC Med Res Methodol 15, 101. [DOI: 10.1186/s12874-015-0087-x]

Yoneoka, D., Henmi, M. (2017). "Meta-analytical synthesis of regression coefficients under different categorization scheme of continuous covariates." Statistics in Medicine, 36, 4336-4352. [DOI: 10.1002/sim.7434]

These papers discuss the methodology and application of alternative approaches for synthesizing regression coefficients and prediction models when dealing with different sets of covariates. They provide further support for the utilization of crude odds ratios in our meta-analysis, especially in cases where covariates vary across studies. We also added these explanations in the methods section.
We sincerely appreciate your guidance and input throughout this review process. By incorporating these references, we aim to strengthen the methodological soundness and validity of our study.
Thank you for your time and consideration.
Once again, we appreciate your feedback and the opportunity to address these important methodological considerations.

-We added the following on lines 219-222.
“We integrated crude odds ratios to mitigate confounding bias associated with varying covariates, as using adjusted odds ratios would introduce potential bias. This approach follows the methodology outlined in Yoneoka et al. (2015, 2017) [33,34].”