Dexamethasone vs. betamethasone for preterm birth: a systematic review and network meta-analysis

Agustín Ciapponi[1], Karen Klein[1], Daniela Colaci[1], Fernando Althabe[2], J. M. Belizan[1], Allie Deegan[3], Areti Veroniki[4], and Iván Flórez[5,6]

[1]1. Instituto de Efectividad Clínica y Sanitaria (IECS-CONICET)
[2]World Health Organization
[3]New York University College of Global Public Health
[4]University of Ioannina
[5]University of Antioquia
[6]McMaster University Faculty of Health Sciences

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Abstract

Objective To compare the effectiveness and safety of dexamethasone versus betamethasone for preterm birth (registered in PROSPERO CRD42017078006). Search strategy We searched in MEDLINE, EMBASE, Cochrane Library, LILACS, Clinical Trials.gov, International Clinical Trials Registry Platform, reference lists and contacted field experts. Selection criteria, data collection and analysis Randomized controlled trials comparing any corticosteroids against each other or against placebo. Three researchers independently selected, extracted data and assessed the risk of bias of the included studies by using EROS and COVIDENCE software. We performed a pairwise meta-analysis and Bayesian network meta-analysis. Main results We included 45 trials (11227 women, 11878 infants). There was no important difference between corticosteroids in neonatal death (odds ratio[OR] 1.05; 95% confidence interval 0.62-1.84; moderate-certainty evidence[CE]), neurodevelopmental disability (OR 1.03; 0.80-1.33; moderate-CE), intraventricular haemorrhage (OR 1.04; 0.56-1.78); low-CE) and birthweight (+5.29 gr; -49.79 to 58.97; high-CE). Compared with betamethasone, dexamethasone may reduce chorioamnionitis (OR 0.70; 0.45-1.06; moderate-CE), foetal death (OR 0.81; 0.24-2.41; low-CE) while may increase puerperal sepsis (OR 2.04; 0.72-6.06; low-CE) and respiratory distress syndrome (OR 1.34; 0.96-2.11; moderate-CE), however, the confidence interval indicates both beneficial and detrimental effects. Conclusions We found no important difference on neonatal death, neurodevelopmental disability, intraventricular haemorrhage and birthweight between corticosteroids. Compared with betamethasone, dexamethasone may reduce chorioamnionitis and foetal death, but may increase endometritis/puerperal sepsis and respiratory distress syndrome. Further research is warranted to improve the certainty of evidence. Keywords preterm birth, antenatal corticosteroids, dexamethasone, betamethasone, systematic review, network meta-analysis

INTRODUCTION

Preterm birth (less than 37 weeks' gestation) accounts for around 11% of all live births worldwide, poses risks of adverse outcomes and can be attributed 35% of deaths among newborns.[1-3] Preterm birth represents a significant health burden worldwide, mainly in Low-to-Middle-Income Countries (LMICs).

Respiratory distress Syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal death, lifelong disability and poor quality of life. RDS affects up to half of babies born before 28 weeks and a third of babies born before 32 weeks.[4] Antenatal corticosteroids for preterm birth prevent RDS and neonatal mortality[5], however there still persist doubts about the applicability in LMICs[6] and there is no consensus regarding the type of corticosteroid to use; nor the dose, frequency, timing of use or the route

of administration. Currently, either betamethasone or dexamethasone are the recommended corticosteroid for clinical practice. The World Health Organization (WHO) guidelines[7] states that there is no conclusive evidence that would support a recommendation of one over the other. We acknowledged that dexamethasone has an advantage over betamethasone in terms of lower cost and wider availability, and it is currently listed on the WHO Essential Medicine List and in WHO's Managing complications in pregnancy and childbirth guide.[8]

Two Cochrane systematic reviews have synthesized the effects of corticosteroids. Brownfoot et al. 2013[9] and Roberts et al. 2017[10], which compared any corticosteroids for preterm birth against each other, or against placebo, respectively. Although Brownfoot et al.[9] focused on direct comparisons, authors also assessed indirect comparisons of corticosteroids with placebo for some outcomes based on Roberts 2006[11]. While the indirect estimates suggest no significant differences between corticosteroids for puerperal sepsis, a significant difference favoured betamethasone for chorioamnionitis.[11]

Direct comparisons in Brownfoot 2013[9] showed that dexamethasone may have some benefits compared to betamethasone such as less intraventricular haemorrhage. Roberts 2017[10] suggested that dexamethasone may also be associated with a higher rate of chorioamnionitis. New additional published trials[12-14], that almost doubled the previous number of participants involved in direct comparisons, warranted a network meta-analysis (NMA), to urgently define this hot topic. Our aim was to assess the comparative clinical effectiveness and safety of dexamethasone versus betamethasone for women at risk of preterm birth.

METHODS

We reported the study according to the PRISMA extension statement for NMA.[15] The study protocol, registered in PROSPERO (CRD42017078006), contains method details.

Search strategy

We conducted a literature search strategy without language restriction. We updated the exhaustive searches of the previous Cochrane reviews[9,10]from the oldest search date reported in Brownfoot 2013[9](February 13, 2013) until October 2019, in PubMed MEDLINE, EMBASE, LILACS, Cochrane Library, Clinical Trials.gov and the International Clinical Trials Registry Platform (ICTRP) for ongoing trials search. The MeSH search terms included premature birth, betamethasone, dexamethasone and glucocorticoids (Full search strategy in **Appendix S1**). We also searched references of included studies and contacted experts for additional evidence.

Study selection and data collection

We included published or unpublished randomized controlled trials (RCT) or quasi-RCT that included women at risk of preterm birth (before 37 weeks), and comparing any corticosteroids against each other or against placebo regardless the dose or schedule.

The primary outcomes for the mother (however defined by study authors) were chorioamnionitis and endometritis/puerperal sepsis, for the foetus/neonate were neonatal death and RDS and for the child neurodevelopmental disability at two years follow-up (blindness, deafness, moderate/severe cerebral palsy, or development delay/intellectual impairment[16].

The secondary outcomes were: maternal death; perinatal death; foetal death; chronic lung disease; intraventricular haemorrhage; mean birthweight; and low birth weight.

Three authors (KK, DC, AC) independently screened titles and abstracts and reviewed the full-texts of the potentially eligible studies by using EROS[17] and COVIDENCE[18] software, and independently extracted data into a pre-piloted data extraction form including the RoB of using the Cochrane tool[6]. We classified a summary RoB for each study as high risk if at least one domain is classified as high risk and the others as low/moderate risk.

Data synthesis and statistical analysis

We conducted the statistical analyses in accordance with Cochrane guidelines.[19]

We estimated odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, along with their 95% confidence intervals (CI) trough pairwise meta-analysis for direct comparisons. Heterogeneity was quantified with the I^2statistic[20] (30-60% was considered 'moderate' heterogeneity). We used a random-effects model and tested subgroup differences ($P < 0.05$ or $\mathbf{I^2} > 30\%$).

We performed a Bayesian random-effects NMA to estimate treatment effects and 95% credible intervals (CrI), if the between-study homogeneity, transitivity and coherence assumption across treatment comparisons were judged to be justifiable.[21,22,23,24]We explored the network geometry and connectivity using network diagrams.

We assessed the statistical heterogeneity of the entire network by the heterogeneity variance (τ^2) considering the empirical distribution.[25]

Our prespecified subgroup analyses included gestational age at trial entry (24-28 , 29-34 , 35-37 weeks); intact vs ruptured membranes and country income level: LMIC vs HIC[26]. We performed sensitivity analysis by low-moderate overall quality of the studies and by using masked treatments. We performed network meta-regression based on gestational age at entry, GNI per capita and the year of publication.

We assessed small-study effects and publication bias,[27] We estimated SUCRA values with their CrIs[28,29]in a rank-heat plot.[30]NMA were conducted in OpenBugs (version 3.2.3)[31] and pairwise meta-analysis in RevMan 5.3.[32].

We assessed the confidence in the estimates by outcome using the GRADE approach and specific criteria for intransitivity (based on potential effect modifiers) and incoherence (based on the statistical consistency).[33,34]Two authors (AC, IDF) independently graded the certainty of the evidence (CE), and differences were resolved by consensus.

Additionally, we conducted a focus group to reflect patients' perspectives in the discussion (**Appendix S3**).

RESULTS

We identified 765 records after removing duplicates, and we finally included 45 RCTs[12-14, 35-76] involving 11,227 women and 11,878 infants (**Figure 1**). Thirteen RCTs compared dexamethasone vs. betamethasone (2,903 women and 3,170 infants) and 32 compared corticosteroids vs. placebo/no treatment (8,324 women and 8,708 infants). In addition to the 12 trials[28,29,31,32,39,44,47,48,54,56,59,62]included by Brownfoot 2013[9] and the 30[21-27,30,33-38,40-43,45,46,49-53,55,57,58,60,61]included by Roberts 2017[10], we included three additional ones[12-14] (1,896 women and 2,059 infants) and we identified four ongoing trials[6,77-79].

Characteristics of included, excluded and ongoing studies

The included trials had heterogeneous characteristics and intervention schemes. The most common doses used were 24 mg of dexamethasone and betamethasone (**Appendix S2** : **Table S2.1** ,**S2.2**). The studies were published between 1972 and 2019. Sixteen studies were conducted in the USA, four in Iran, and two studies each were conducted in United Kingdom, the Netherlands, Finland, France, Israel and Brazil. Most studies were conducted in HICs (37), five in upper MICs and only three in lower MICs (median GNI per capita was 20,170 USD). The sample size varied from 18 to 2,831 women (median 118 women). Membranes were intact, ruptured and mixed (both intact and ruptured) in 7, 12 and 26 studies, respectively. Regarding the recruitment gestational age, 30 RCTs set 23-28 weeks as the lower limit and 33 studies set 34-37 weeks as the upper limit (median gestational age 30.44 weeks).

Table S2.3 describes the ongoing studies' characteristics,[6,77-79]and **Table S2.4** the reason of excluded studies initially included by full-text[80-82]).

Risk of bias assessment of included studies

Global RoB was considered low in 21 studies (47%), 58% for random sequence generation, 38% for allocation concealment, 49% for blinding of participants and personnel, 33% for blinding of outcome assessment, 56% for incomplete outcome data, 69% for selective reporting and 36% for other bias (**Appendix S4: Risk of bias figures and tables**).

NMA results: dexamethasone vs. betamethasone

The geometry of the treatment networkis presented in **Figure 2** , and the direct, indirect and NMA (mixed) effect estimations for the main eight outcomes of the comparison dexamethasone vs. betamethasone are presented in **Figure 3** and **Table 1** of Summary of finding. We also present in the **Appendix S5** the direct comparison forest-plots, in **Appendix S6** the summary of finding tables of each corticosteroid vs. control, in **Appendix S7** the pairwise meta-analysis forest-plots by type of corticosteroid against placebo and in **Appendix S8** the NMA outputs and SUCRA values.

-Chorioamnionitis (6,698 patients, 15 studies)

Compared with placebo/no treatment (control), dexamethasone probably increases chorioamnionitis but in one side of the confidence interval could also reduce it: OR 1.46 (95%CI 0.81-2.66). On the contrary betamethasone reduces chorioamnionitis: OR 0.63 (95%CI 0.41-0.95). The test for subgroup differences by corticosteroid type showed this disparity (P= 0.010, I^2 84.2%).

Compared with betamethasone, dexamethasone probably reduces chorioamnionitis but in one side of the CrI is slightly detrimental:**OR 0.70** (95%CrI 0.45-1.06), **moderate-CE** . We found serious incoherence between direct and indirect evidence (Ratio of OR [ROR] 3.18 [95%CI 1.26-8.02]).

-Endometritis/puerperal sepsis (4,030 patients, 10 studies)

Dexamethasone may increase endometritis/puerperal sepsis and betamethasone probably have little or no effect against control: OR 1.93 (95%CI 0.8534.41) and 0.94 (95%CI 0.47-1.87), respectively (Test for subgroup differences suggest disparities; P: 0.16, I^2 49.8%).

There was no report of direct evidence regarding this outcome. Indirect evidence suggest that compared with betamethasone, dexamethasone may increase endometritis/puerperal sepsis, but in one side of the CrI is protective: **OR 2.04** (95%CrI 0.72-6.06), **low-CE** .

-Neonatal Death (8697 patients, 23 studies)

Both dexamethasone and betamethasone reduce neonatal death against control: OR 0.60 (95%CI 0.37-0.94) and OR 0.57 (95%CI 0.39-0.80), respectively (Test for subgroup differences shows no disparity; P: 0.81, I^2 0%). We found no incoherence; ROR 1.15 (95%CI 0.44-2.96), therefore we considered the NMA evidence the most reliable estimation. Compared with betamethasone, dexamethasone probably has no effect on neonatal death, but the CrI is compatible with beneficial or detrimental effect:**OR 1.05** (95%CrI 0.62-1.84), **moderate-CE** .

-Foetal death (3857 patients, 13 studies)

Dexamethasone may reduce foetal death and betamethasone probably have little or no effect against control: OR 0.86 (95%CI 0.32-2.16) and 1.05 (95%CI 0.58-2.15), respectively (Test for subgroup differences shows no disparity; P: 0.70, I^2 0%). There was no report of direct evidence regarding this outcome. Indirect evidence suggest that compared with betamethasone, dexamethasone may reduce foetal death, but the CrI limits is compatible with large beneficial or detrimental effect: **OR 0.81** (95%CrI 0.24-2.41), **low-CE** .

-Respiratory distress Syndrome (9784 patients, 30 studies)

Both dexamethasone and betamethasone may reduce neonatal death against control: OR 0.64 (95%CI 0.47-0.90) and 0.47 (95%CI 0.35-0.60), respectively (Test for subgroup differences suggest disparities; P: 0.11, I^2 54.7%).

We found no serious incoherence; ROR 1.14 (95%CI 0.71-2.75), therefore we considered the NMA evidence the most reliable estimation. Compared with betamethasone, dexamethasone probably increases RDS but the CrI is compatible with a small protective effect: **OR 1.38** (95%CrI 0.96-2.11), **moderate-CE** .

- Neurodevelopmental disability (2628 patients, 3 studies)

We did not find direct evidence for betamethasone vs. placebo. Dexamethasone may reduce neurodevelopmental disability against control: OR 0.39 (95%CI 0.01-8.08).

Compared with betamethasone, dexamethasone probably has no effect on neurodevelopmental disability, but the CrI is compatible with large beneficial or detrimental effect: OR 1.14 (95%CrI 0.24-13.86). Two of the included studies had rare events. The frequentist analysis suggested more precise and reliable estimation an **OR 1.03** (95%CI 0.80-1.33), **moderate-CE** .

-Intraventricular haemorrhage (IVH) (7449 patients, 17 studies)

Both dexamethasone and betamethasone reduce IVH: OR 0.473 (95%CI 0.281-0.738) and 0.381 (95%CI 0.191-0.668), respectively (Test for subgroup differences shows no disparity; P: 0.88, I^2 0%).

We found no serious incoherence; ROR 1.54 (95%CI 0.57-4.16). The NMA evidence suggested that compared with betamethasone, dexamethasone may reduce IVH but the CrI is compatible with beneficial or detrimental effect: OR 0.812 (95%CrI 0.420-1.427), low-CE. However, we found mild heterogeneity (I^2 31%) and important subgroup differences by corticosteroid type (I^2 63.5%).

Considering the very high risk of attrition bias (43% of non-analysed infants), the unique marked effect favouring dexamethasone of the study Elimian 2007[46] and the incoherence that this study had generated, we performed a post-hoc sensitivity analysis excluding it. Both the heterogeneity and subgroup differences changed to an I^2 of 0%. The new estimation, still**low-CE** , **OR 1.04** (95%CrI 0.56-1.78) was more consistent with the indirect evidence (ROR 1.14 (95%CI 0.51-2.57) and therefore we considered it as the most reliable estimation (forest-plots in **Appendix S5**).

-Mean birthweight (8645 patients, 23 studies)

Both dexamethasone and betamethasone have no effect on birthweight against control: MD -17.04gr (95%CI -75.48; 41.41) and -9.74 gr. (95%CI -43.11; 23.63), respectively (Test for subgroup differences shows no disparity; P: 0.80, I^2 0%). We found no serious incoherence; ROR 1.15 (95%CI 0.44-2.96) and both direct and indirect evidence were considered as high certainty evidence, therefore we considered the NMA evidence the most reliable estimation. Dexamethasone has no effect mean birthweight:**mean difference + 5.29gr** (95%CrI -49.79, 58.97) **high-CE** .

-Other outcomes

We did not find direct evidence about low birthweight. May be no difference between betamethasone vs. control on maternal death: OR 0.98 (95%CI 0.06-15.90). Dexamethasone and betamethasone probably reduce perinatal death: OR 0.62 (95%CI 0.33-1.18) and 0.66 (95%CI 0.48-0.91), respectively (Test for subgroup differences shows no disparity; P: 0.86, I^2 0%). Dexamethasone may increase chronic lung disease and betamethasone may reduce this outcome, but the 95%CI is also be compatible with large beneficial or detrimental effect: OR 1.30 (95%CI 0.57-2.96) and 0.75 (95%CI 0.22-2.62), respectively (Test for subgroup differences shows no disparity; P: 0.47, I^2 0%).

We did not find direct evidence regarding maternal death, perinatal death, and we found scarce evidence about low birth weight and chronic lung disease and they were assessed only by pairwise meta-analysis. Compared with betamethasone, dexamethasone may reduce these outcomes, however the 95%CI is compatible with large beneficial or detrimental effect: OR 0.75 (95%CI 0.33-1.71, low-CE) and OR 0.92 (95%CI 0.62-1.37) respectively (forest-plots in **Appendix S5**).

Meta-regression did not find statistically significant differences. The subgroup and sensitivity analysis did not reveal important changes regarding the main analysis. All the 95%CI were compatible with beneficial or

detrimental effects (**Appendix S9**).

DISCUSSION

Main Findings

Both corticosteroids have proven effective for women at risk of preterm birth on most neonatal and child relevant outcomes compared with placebo or no treatment.

We found that compared with betamethasone, dexamethasone may reduce the rates of chorioamnionitis around 30% and foetal death 20%, but may increase puerperal sepsis 100% and respiratory distress syndrome 40%. Probably, there are no difference in neonatal death and neurodevelopmental disability and may have no difference in IVH and in birthweight. Except for neurodevelopmental disability, and birthweight these effects were imprecise.

Strengths and limitations

Among the strengths of our work we can mention that we followed the Cochrane guidelines Cochrane[19], the PRISMA-NMA extension[15]for reporting and we registered the study protocol in advance. Our work is the most updated and complete systematic review assessing clinical effectiveness and safety of corticosteroids. Our exhaustive search strategy, included clinical trials registries and contacted experts for additional relevant evidence. Although we did not hand-search conference proceedings it is unlikely that our search strategy missed RCTs not included in biomedical databases nor the trials registers.

This NMA added two small trials[13,14]and one of large good quality trial that compared directly dexamethasone with betamethasone[12] to the body of evidence. It provided new indirect estimations and increased the precision of the estimations, still low for most outcomes, by combining direct and indirect evidence. The prespecified meta-regression, subgroup and sensitivity analyses reinforced the robustness of our results.

We assessed the certainty of the evidence by the GRADE-NMA approach[33,34], the validity of the transitivity assumption by comparing the distribution of potential effect modifiers across comparisons and the coherence assumption by the design-by-treatment interaction model and loop-specific approaches.[22,24]

The results of the NMA were mostly coherent, except for chorioamnionitis, may be due to differences between populations included in indirect and direct evidence, and differences in RoB. The indirect evidence came mostly from mothers with ruptured membranes[36,37,41,47,49,51,52,55-57,60,65,67,69,72]while the direct evidence from a mix of mothers with intact and ruptured membranes[12]. However, meta-regression, subgroup and sensitivity analyses did not explain this incoherence. Therefore, for chorioamnionitis, following the GRADE approach[33], we considered the direct evidence the most reliable estimation of 23 fewer cases (43 fewer or 5 more) per 1000 women treated with dexamethasone.

We included studies conducted in a range of 50 years and healthcare advances, specifically in neonatology, could be an extra-source of heterogeneity that could partially explain the contradictory direction of effect for some outcomes, but the effect modifiers or RoB did not provide a solid explanation of the effects. The contradictory beneficial or detrimental effect of different outcomes warranted our decision to explore the patients' perspectives about our findings comparing corticosteroids trough a focus group (**Appendix 3).** Briefly, women failed to make a decision about which corticosteroids they would choose because the trade-off between risk and benefits were very complex for them. They agreed that it would be a decision that they would share or delegate to a professional with whom they established a bond of trust.

The evidence shows limitations, regarding its generalizability to lower-resource countries, since only three[14,42,47](7%) out of the included RCTs were from lower-MICs and none from LICs. Trials have been largely conducted in tertiary hospitals and recruited highly selected populations.[83] Concerns about safety and efficacy in low-resource settings were supported by the adverse findings in neonatal deaths and maternal infection of ACT, a community-based, cluster-RCT conducted in six LMICs.[84] However we did not find important differences by income country classification and by GNI per capita. Hopefully, the ongoing ACTION study could answer this question.[6]

Interpretation

Antenatal corticosteroids for preterm birth have shown to reduce neonatal morbidity and mortality[10] are cost-effective[85], and are routinely recommended worldwide.[7,86,87]The Cochrane review,[10]and our review are aligned with these studies and recommendations.

The other Cochrane review,[9] comparing both corticosteroids, did not include recent evidence. The new trial ASTEROID[12], almost doubled the number of included women under direct comparisons, provided information for our main outcomes, improved the precision for neurosensory disability estimates, and unlike that it was believed it found that dexamethasone may have a beneficial effect on chorioamnionitis.

The potential beneficial effect of dexamethasone on IVH suggested by very low-CE, was reduced with the inclusion of the ASTEROID trial[12] and completely disappeared when excluding Elimian 2007.[46] This post-hoc sensitivity analysis, based on the very high risk of attrition bias of this study, provided more consistent results with the indirect evidence. Additionally, a meta-analyses found an increased risk of neurodevelopmental impairment in children with periventricular/intraventricular haemorrhage[88], mainly driven by cerebral palsy[89]. Since we did not find a differential effect of dexamethasone on neurosensory disability it would be unlikely a favourable effect on IVH. Additionally, even if a reduction in IVH was true, it is more important the observed absence of differences on long-term disability for the quality of life of survivors.[90]

Roberts 2006[11] assessed indirect estimations favouring betamethasone for chorioamnionitis. This was consistent with our indirect estimation but opposite to the ASTEROID trial[12] findings that were considered the most reliable estimation for this outcome.

Our NMA improved the precision and certainty of most previous estimations. We identified a another NMA that evaluated antenatal maternal administration dexamethasone, betamethasone and ambroxol to prevent RDS.[91] Compared with placebo, all interventions reduced RDS and neonatal death, but no significant difference in the incidence of bronchopulmonary dysplasia. They also suggest that ambroxol seems to be the most effective treatment for reducing the incidence of RDS and neonatal death based on its SUCRA values. This conclusion was not consistent with a Cochrane review[92] or the relevant preterm birth management guidelines.[7,86]

A wise choice should consider all factors besides evidence, including local availability, costs and cost-utility.[93,94]A full course of betamethasone costs around US$35 while dexamethasone $1 (3% of the cost of betamethasone).[94] The cost-effectiveness of the administration of betamethasone based in individual trials is controversial, and it should be based in the best estimation of effectiveness.[95,96]Mainly LMICs still have significant challenges to provide safe and effective antenatal corticosteroid use, including ensuring accurate gestational age determination, establishing clear treatment guidelines, strengthening provider capacity, incorporating corticosteroid in national essential medicines lists, and monitoring use and outcomes.[97]

CONCLUSION

This comprehensive NMA confirmed that corticosteroids were mostly effective for neonatal and child relevant outcomes compared with placebo or no treatment. There was no important difference between corticosteroids on neonatal death, neurodevelopmental disability, IVH and birthweight. Low to moderate-CE suggest that dexamethasone may reduce chorioamnionitis, and foetal death but may increase puerperal sepsis and RDS. However, the 95%CI indicates both beneficial and detrimental effects for these outcomes. The opposing direction of these outcomes does not allow to derive recommendations about what corticosteroid should be used and large well designed RCTs are warranted to improve the certainty of evidence. Ideally, they should represent low resource settings and also evaluate the best schemes of administration. Individual participant data meta-analysis could help to answer these questions. In the meantime, monitoring short-term and long-term health outcomes, including neurodevelopmental disability will be important.

Since there is no robust evidence on which corticosteroid should be prescribed, decisions should be based on availability, costs, opportunity, and facilities. Shared decision-making would help patients to take their choices when facing this scenario.

Disclosure of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an

interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contribution to authorship

JB, FA and AC conceived the study; AC, FA, JB, IDF, AAV designed the study;

KK, DC, AD and AC collected and abstracted the data; IDF, AAV undertook the statistical

analysis; AC, FA, JB, IDF, AAV, KK, AD, DC drafted the manuscript; all authors had full access to all the data, including statistical reports and tables; all authors analysed and interpreted the data; all authors critically revised the manuscript for important intellectual content; AC is the guarantor.

Details of ethics approval

Not applicable.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 : Search Strategy

Appendix S2 : Characteristics of included, ongoing and excluded studies

Table S2.1 Main characteristics of population and setting of included studies**Table S2.2** Characteristics of included studies**Table S2.3** Characteristics of ongoing studies**Table S2.4** Characteristics excluded studies

Appendix S3 : Focus group: patients' perspectives

Appendix S4 : Risk of bias figures and tables

Figure S4.1: Risk of bias graph by risk of bias item (% across all included studies)**Figure S4.2:** Risk of bias summary by risk of bias item for each included study

Table S4.1 Support for judgement of included studies by risk of bias item

Appendix S5 : Pairwise meta-analysis results for direct comparison dexamethasone vs. betamethasone forest-plots

Appendix S6 : Summary of finding tables of corticosteroid vs. placebo/no treatment

Table S6.1 Summary of finding table: dexamethasone vs. control**Table S6.2** Summary of finding table: betamethasone vs. control

Appendix S7 : Pairwise meta-analysis results for direct comparison corticosteroids vs. placebo/no treatment forest-plots by type of corticosteroid

Appendix S8 : Network meta-analysis outputs

Appendix S9 : Meta-regression, subgroup and sensitivity analysis

Appendix S10 : PRISMA NMA Checklist

Table/Figure Caption List

Table 1. Summary of finding table: dexamethasone vs. betamethasone

Figure 1. Study flowchart

Figure 2. Network composition by outcome

Figure 3. Network and direct forest plot for dexamethasone vs. betamethasone

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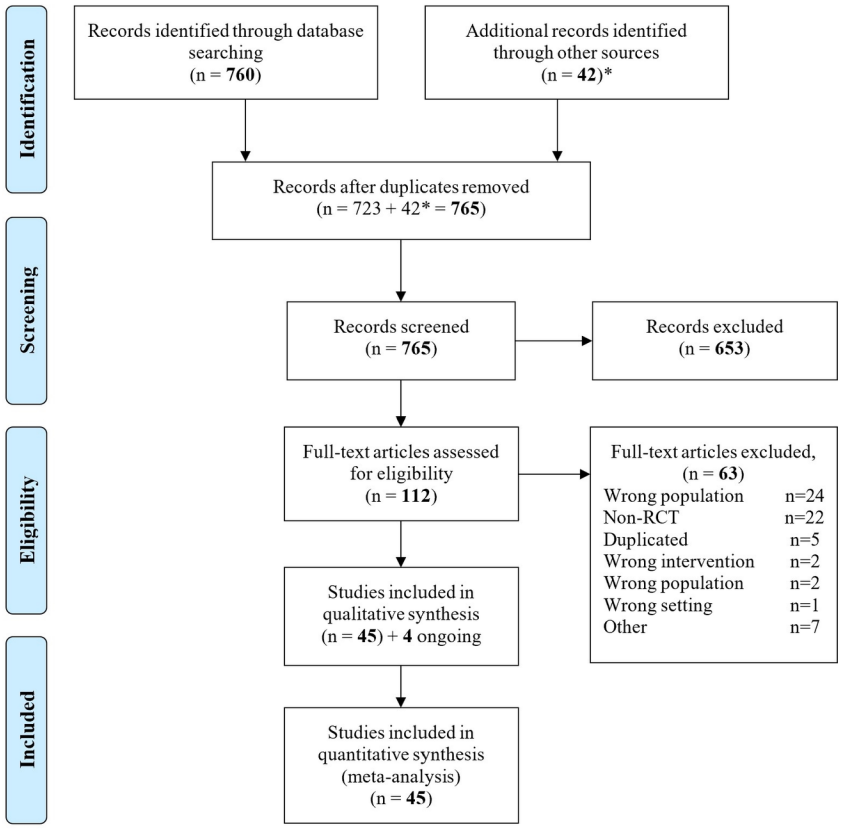
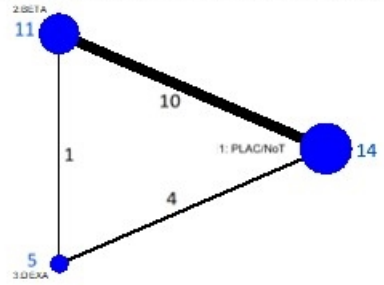
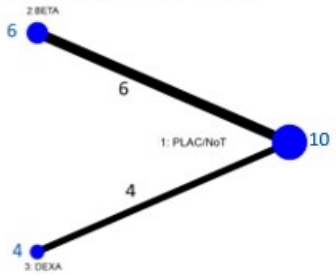
`Table 1. Summary of finding table. dexamethasone vs. betamethasone.docx` available at https://authorea.com/users/333502/articles/460561-dexamethasone-vs-betamethasone-for-preterm-birth-a-systematic-review-and-network-meta-analysis



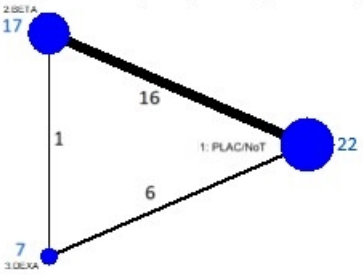
Chorioamnionitis: (6698 patients, 15 studies)



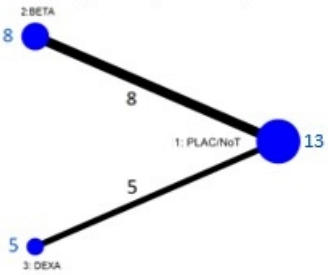
Endometritis (4030 patients, 10 studies)



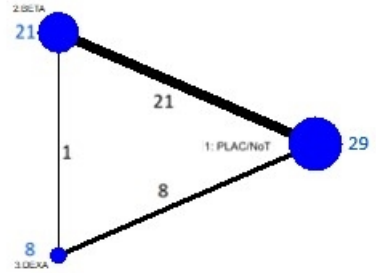
Neonatal Death (8697 patients, 23 studies)



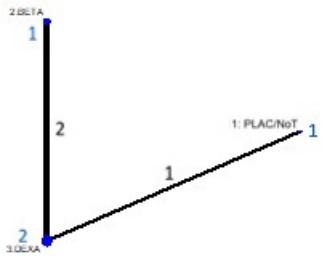
Fetal death (3857 patients, 13 studies)



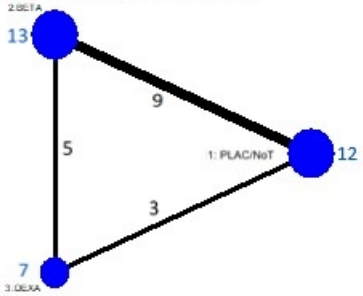
RDS (9784 patients, 30 studies)



Neurodevelop. disability (2628 patients, 3 studies)



IVH (7449 patients, 17 studies)



Mean birthweight (8645 patients, 23 studies)