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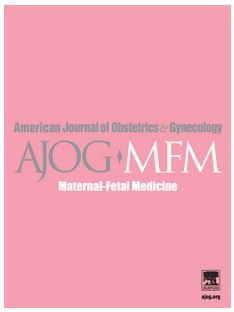

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Dexamethasone vs. betamethasone for preterm birth: a systematic review and network meta-analysis

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

Condensation

Corticosteroids are effective for most neonatal and child outcomes against placebo. The identified differences between dexamethasone and betamethasone are still inconclusive, warranting further research.

Short Title

Corticosteroids for preterm birth: a network meta-analysis

AJOG at a Glance

Why was this study conducted?

This study was conducted to further analyze the clinical advantages of two corticosteroids routinely used during preterm delivery, with the ultimate goal of determining if one is more advantageous over the other.

Key findings

- This network meta-analysis included recently published evidence that almost doubled the number of participants involved in the direct comparison between corticosteroids.
- This analysis showed no difference in neonatal death, neurodevelopmental disability, intraventricular hemorrhage, or birthweight, but also showed no statistically significant, but potentially important differences, in chorioamnionitis, fetal death, puerperal sepsis and respiratory distress syndrome.

What does this add to what is known?

These mixed results justify shared decision-making with patients and warrant further research to improve the certainty of most results in order to inform health policies regarding preterm birth.

Keywords: preterm birth, antenatal corticosteroids, dexamethasone, betamethasone, systematic review, network meta-analysis

ABSTRACT

OBJECTIVES

To evaluate the comparative clinical effectiveness and safety of dexamethasone versus betamethasone for preterm birth.

DATA SOURCES

The sources searched were MEDLINE, EMBASE, Cochrane Library, LILACS, Clinical Trials.gov, International Clinical Trials Registry Platform without language restrictions until October 2019, along with reference lists of included studies. Field experts were also contacted.

STUDY ELIGIBILITY CRITERIA

Randomized or quasi-randomized controlled trials comparing any corticosteroids against each other or against placebo at any dose for preterm birth were included in the study.

STUDY APPRAISAL AND SYNTHESIS METHODS

Three researchers independently selected, extracted data, and assessed the risk of bias of the included studies by using EROS and COVIDENCE software. Random-effects pairwise meta-analysis and Bayesian network meta-analysis were performed. The primary outcomes were chorioamnionitis, endometritis/puerperal sepsis, neonatal death, respiratory distress syndrome and neurodevelopmental disability.

RESULTS

Forty-five trials (11227 women, 11878 infants) were included in the study. No clinical or statistical difference was found between dexamethasone versus betamethasone in neonatal death (odds ratio [OR] 1.05; 95% Confidence Interval [CI] 0.62-1.84; moderate-certainty evidence), neurodevelopmental disability (OR 1.03; 95%CI 0.80-1.33; moderate -certainty evidence), intraventricular hemorrhage (OR 1.04 95%CI 0.56-1.78); low-certainty evidence), or birthweight (+5.29 gr; 95%CI -49.79 to 58.97; high-certainty evidence). No statistically significant

difference, but potentially clinically important effect, was found between dexamethasone and betamethasone in chorioamnionitis (OR 0.70; 95%CI 0.45-1.06; moderate-certainty evidence), fetal death (OR 0.81; 95%CI 0.24-2.41; low-certainty evidence), puerperal sepsis (OR 2.04; 95%CI 0.72-6.06; low-certainty evidence) and respiratory distress syndrome (OR 1.34; 95%CI 0.96-2.11; moderate-certainty evidence). Meta-regression, subgroup and sensitivity analysis did not reveal important changes regarding the main analysis.

CONCLUSIONS

Corticosteroids have proven effective for most neonatal and child relevant outcomes compared with placebo or no treatment for women at risk of preterm birth. No important difference was found on neonatal death, neurodevelopmental disability, intraventricular hemorrhage, and birthweight between corticosteroids, and no statistically significant but potentially important difference was found in chorioamnionitis, fetal death, endometritis/puerperal sepsis and respiratory distress syndrome. Further research is warranted to improve the certainty of evidence and inform health policies.

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 to 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 persists doubt 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) guideline[7] states that there is no conclusive evidence that would support a recommendation of one over the other. It should be noted 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.

Objectives

To evaluate the comparative clinical effectiveness and safety of dexamethasone versus betamethasone for preterm birth.

Methods

This systematic review and NMA is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for NMA.[15] The study protocol was registered in PROSPERO (CRD42017078006).

Eligibility criteria

To be eligible, studies had to be published or unpublished randomized controlled trials (RCT) or quasi-RCT that included women at risk of preterm birth, and comparing any corticosteroids against each other or against placebo regardless the dose or schedule (See **Table B.1** and **B.2** for the description of doses by study). The population was women with a singleton or multiple pregnancy expected to give birth preterm (before 37 weeks) as a result of either spontaneous preterm labor, preterm pre-labor rupture of membranes, medical indication for delivery or elective preterm birth.

The primary outcomes for the mother (defined by study authors) were chorioamnionitis and endometritis/puerperal sepsis, and for the fetus/neonate were neonatal death and RDS. The child relevant outcome was neurodevelopmental disability at follow-up (blindness, deafness, moderate/severe cerebral palsy, or development delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviation below population mean[16]), or other neurological disorders.

The secondary outcomes were: 1. maternal death; 2. perinatal death; 3. fetal death; 4. chronic lung disease (need for continuous supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age, whichever was later); 5. intraventricular hemorrhage (IVH) (diagnosed by ultrasound, diagnosed by autopsy); 6. mean birthweight (measured in grams); and 7. low birth weight.

Information sources and search strategy

A literature search strategy was established, developed by an experienced librarian, without language restriction. Considering the exhaustive strategic searches provided by the previous Cochrane reviews[9, 10], the evidence gathered by these reviews up to January 2013 was used (the oldest search date reported in Brownfoot 2013[9] was February 13, 2013) and searches were added from this point to 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 (See full search strategy in **Appendix A**). The reference lists of the included studies were also searched and field experts were contacted for additional evidence.

Study selection, data extraction assessment of risk of bias

Three authors (KK, DC and AC) independently screened titles and abstracts and reviewed the full-texts of the potentially eligible studies by using the Early Review Organizing Software (EROS)[17] and COVIDENCE[18]. Multiple publications of the same trial (or sample) were considered as unique studies and the larger sample sizes were selected. The same authors independently, and in duplicate, evaluated the risk of bias (RoB) domains of included studies using the Cochrane tool[19]. Data were extracted from each of the included studies and the information was entered into a data extraction form designed and piloted for this purpose. A summary RoB was classified as high risk for a study if at least one domain is classified as high risk, while a summary was low/moderate risk if there is no domain classified as high risk. Information was obtained regarding publication details; sources of support; trial methods, characteristics of participants; intervention, and comparators and outcomes.

Any disagreement at any of the aforementioned steps, was resolved by consensus. In the case that consensus could not be reached by two reviewers, a third author resolved the disagreements (IDF).

Data synthesis and statistical analysis

The statistical analyses were conducted in accordance with the guidelines developed by Cochrane[20].

A pairwise random-effects meta-analysis was performed for each available direct comparison. Treatment effects were estimated using odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, along with the 95% confidence intervals (CI). Heterogeneity was quantified for all the direct comparisons with the I^2 statistic, which expresses the percentage of variability that is due to true differences between studies rather than sampling error.[21] Values of I^2 between 30-60% were considered to be an indication of 'moderate'

heterogeneity. Anticipating clinical and statistical heterogeneity, a meta-analysis was carried out using a random-effects model to synthetize results. Subgroup tests were performed to determine differences by corticosteroid type. A $P< 0.05$ or an $I^2 > 30\%$ was considered suggestive of subgroup differences.

Bayesian random-effects NMA was also performed for each outcome to estimate the overall treatment effects, if the between-study homogeneity, transitivity, and coherence assumption across treatment comparisons were judged to be justifiable[22]. The network geometry and connectivity were explored using network diagrams, and results were presented in league tables and forest plots.

Treatment effects were estimated using OR for dichotomous outcomes and MD for continuous outcomes, along with the 95% credible intervals (CrI). The study assessed the validity of the transitivity assumption by comparing the distribution of potential effect modifiers across treatment comparisons, including mean gestational age, mean Gross National Income (GNI), multiple/single corticosteroid doses, intact/ruptured membranes, country income classification, global RoB, and RoB in blinding. To check the assumption of coherence (also called network consistency) in the entire network, the design-by-treatment interaction model was used as described by Higgins and colleagues.[23] To evaluate the presence of local incoherence, the loop-specific approach was used.[24, 25]

A common-within network heterogeneity standard deviation ($\tau \sim N(0,1)$, $\tau>0$) was used given that many treatment comparisons were informed by a single study. After discarding the first 10,000 iterations, series of 100,000 burn-in simulations with thinning of 10 values were used. The model convergence was checked by visual inspection of the evaluation of the mixing of two chains. The assessment of statistical heterogeneity of the entire network was based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the NMA models. For dichotomous

outcomes, the magnitude of the heterogeneity variance was compared with the empirical distribution as derived by Turner.[26]

The prespecified subgroup analyses were gestational age at trial entry (24 to 28 weeks, 29 to 34 weeks, 35 to 37 weeks); intact vs ruptured membranes, and country income level: LMIC vs High-income countries (HIC), based on the World Bank Classification).[27] The study included sensitivity analysis for the overall quality of the studies (low/moderate versus high risk of overall bias) and for the use of placebo or mask treatment versus no treatment or unmasked intervention. A fixed-effect NMA (in a frequentist framework) was conducted for outcomes with rare events and fewer than five studies in the network, to see the impact on the results. A network meta-regression was performed based on Gestational age at entry, Country GNI per capita (current international $) based on the World Bank at the beginning of the study (https://data.worldbank.org/country) and the year of publication.

The study assessed small-study effects and publication bias that may affect the cumulative evidence through comparison adjusted funnel plots for the main eight outcomes and when at least 10 studies were available per outcome.[28] Treatments were ranked from best to worst using the Summary Under the Cumulative Ranking (SUCRA) curve and presented SUCRA values with their credible intervals[29, 30] across all outcome in a rank-heat plot.[31] All analyses were conducted in OpenBugs (version 3.2.3).[32] For secondary outcomes with scarce direct evidence, pairwise meta-analyses were performed using RevMan 5.3.[33] As a sensitivity analysis, a fixed-effect model was applied for pairwise meta-analysis to assess the robustness of the findings.

The confidence in the estimates for each reported outcome were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and specific criteria for NMA, such as potential intransitivity (based on the variables considered potential effect modifiers that were described in the subgroup analysis) and potential incoherence (based

on the statistical consistency assessment).[34, 35] Two authors (AC, IDF) independently graded the certainty of the evidence, and differences were resolved by consensus. The Cochrane recommendations were followed for reporting results according to the certainty of evidence and the magnitude of effect.[36] Additionally, a focus group was conducted to reflect patients' perspectives in the discussion (**Appendix C**).

Results

Study selection

The search identified 765 records, after removing duplicates, and ultimately included 45 RCTs[12-14, 37-78] involving 11,227 women and 11,878 infants (See **Figure 1Error! Reference source not found.**). Thirteen RCTs compared dexamethasone vs. betamethasone (2,903 women and 3,170 infants) and 32 trials 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 studies[21-27,30,33-38,40-43,45,46,49-53,55,57,58,60,61] included by Roberts 2017[10], this study included three additional studies[12-14] and identified four references from three ongoing trials[6, 79-81].

Study characteristics

The included trials had heterogeneity regarding settings, baseline population characteristics and intervention schemes (See in **Appendix B** in **Table B.2.1 Main characteristics of included studies** and in **Table B.2.2** the full description). 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).

The most common doses used were 24 mg of dexamethasone and 24 mg of betamethasone in different regimens (see the full description schemes in **Table B.2** and a descriptive summary in a footnote of the table).

Table B.3 describes the full characteristics of the ongoing studies[6, 79-81]. The ACTION-I[6] is a parallel, double-blind, placebo-controlled RCT of antenatal dexamethasone that will recruit 6018 women at risk of preterm birth in hospitals in low-resource countries. The RCT ACTWIN[79, 80] will compare betamethasone with placebo and will require 1616 neonates (808 twin pregnancies) from South Korea. The other ongoing RCT[81] will compare three arms, dexamethasone, betamethasone and placebo in 150 women at risk of preterm birth from Nigeria.

Table B.4 presents the reasons of excluded studies initially included by full-text[82-84].

Risk of bias assessment of included studies

RoB was considered low in 26 (58%) studies for random sequence generation, 17 (38%) for allocation concealment, 22 (49%) for blinding of participants and personnel, 15 (33%) for blinding of outcome assessment, 25 (56%) for incomplete outcome data, 31 (69%) for selective reporting, 16 (36%) for other bias and 21 (47%) for Global RoB (See **Appendix D: Risk of bias figures and tablesError! Reference source not found.**).

Synthesis of results

The composition of the networks and the direct, indirect, and NMA (mixed) effect estimations for the main eight outcomes of the comparison dexamethasone vs. betamethasone are presented in

Figure 2, **Figure 3** and **Table 1**. Also, Appendix E presents the direct comparison dexamethasone vs. betamethasone forest-plots, Appendix F summarizes the findings of the tables of corticosteroid vs. control, and **Appendix G** displays the pairwise meta-analysis forest-plots by type of corticosteroid against placebo. Since there were only three nodes for this network and the focus was on the comparison of dexamethasone vs. betamethasone, the ranking made less sense. However, the SUCRA values for the main outcomes are reported in **Appendix H**.

The analysis found no statistically significant differences for any outcome. Anyway, following Cochrane guideline[36], below highlights each central estimate as the most probable result, while describing the confidence intervals.

-Chorioamnionitis (6,698 patients, 15 studies)

Compared with placebo/no treatment (control), dexamethasone likely increases chorioamnionitis but on 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 also showed this disparity (P= 0.010, I^2 84.2%).

Since there was a serious incoherence between direct and indirect evidence (Ratio of OR [ROR] 3.18 [95%CI 1.26-8.02]), and the differences in the certainty of the evidence (direct and indirect: moderate) the direct evidence was considered to be the most reliable estimation for this outcome. Compared with betamethasone, dexamethasone likely reduces chorioamnionitis but on one side of the CrI could also be slightly detrimental: OR 0.70 (95%CrI 0.45-1.06), moderate-certainty evidence.

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

Dexamethasone may increase endometritis/puerperal sepsis and betamethasone likely has little or no effect against control: OR 1.93 (95%CI 0.8534.41) and 0.94 (95%CI 0.47-1.87), respectively. The test for subgroup differences by corticosteroid type suggest disparities (P 0.16, I^2 49.8%).

There was no report of direct evidence regarding this outcome. Indirect evidence suggests that compared with betamethasone, dexamethasone may increase endometritis/puerperal sepsis with respect to betamethasone, but on one side of the CrI could also be protective: OR 2.04 (95%CrI 0.72-6.06), low-certainty evidence.

-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. The test for subgroup differences by corticosteroid type shows no disparity (P 0.81, I^2 0%). There was found no incoherence between direct and indirect evidence ROR of 1.15 (95%CI 0.44-2.96), therefore the NMA evidence was considered to be the most reliable estimation. Compared with betamethasone, dexamethasone likely has no effect on neonatal death, but the CrI limits could also be compatible with beneficial or detrimental effect: OR 1.05 (95%CrI 0.62-1.84), moderate-certainty evidence.

-Fetal death (3857 patients, 13 studies)

Dexamethasone may reduce fetal death and betamethasone likely has 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.

The test for subgroup differences by corticosteroid type 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 fetal death, but the CrI limits could also be compatible with large beneficial or detrimental effect: OR 0.81 (95%CrI 0.24-2.41), low-certainty evidence.

-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. The test for subgroup differences by corticosteroid type suggest disparities (P 0.11, I^2 54.7%).

There was found no serious incoherence between direct and indirect evidence ROR of 1.14 (95%CI 0.71-2.75), therefore the NMA evidence was considered to be the most reliable estimation. Compared with betamethasone, dexamethasone likely increases RDS the CrI limits could also be compatible with a small protective effect: OR 1.38 (95%CrI 0.96-2.11), moderate-certainty evidence.

-Neurodevelopmental disability (2628 patients, 3 studies)

No direct evidence was found for betamethasone vs. placebo. Dexamethasone may reduce neurodevelopmental disability against control: OR 0.39 (95%CI 0.01-8.08)

Compared with betamethasone, dexamethasone likely has no effect on neurodevelopmental disability, but the CrI limits could also be compatible with large beneficial or detrimental effect: OR 1.14 (95%CrI 0.24-13.86). Two of the included studies had rare events, and a random-effects model adds extra variability to the already uncertain treatment effect estimates. Allowing for the same between-study variance across comparisons (τ^2=0.45 95% CrI (0.00, 4.88)) increased CrIs. A sensitivity analysis estimating the treatment effect for dexamethasone vs. betamethasone in a frequentist meta-analytic framework estimated τ^2=0.00, which was equivalent to a fixed-effect meta-analysis model. The frequentist analysis suggested more precise and reliable estimation an **OR 1.03** (95%CI 0.80-1.33), **moderate-certainty evidence**.

-Intraventricular hemorrhage (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. The test for subgroup differences by corticosteroid type shows no disparity (P 0.88, I^2 0%).

There was no serious incoherence found between direct and indirect evidence ROR of 1.54 (95%CI 0.57-4.16). The NMA evidence suggested that compared with betamethasone, dexamethasone may reduce IVH but the confidence interval limits could also be compatible with

beneficial or detrimental effect: OR 0.812 (95%CrI 0.420-1.427), low-certainty evidence. However, there was 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-analyzed infants), the unique marked effect favoring dexamethasone of the study Elimian 2007[48], and the incoherence that this study had generated particularly before the inclusion of the ASTEROID trial[12], a post-hoc sensitivity analysis was performed while excluding it and rerunning the analyses. Both the heterogeneity and the test for subgroup differences changed to an I^2 of 0%. The new estimation, still low-certainty evidence, OR 1.04 (95%CrI 0.56-1.78) was more consistent with the indirect evidence (ROR was reduced to 1.14 (95%CI 0.51-2.57) and therefore it was considered as the most reliable estimation.(See forest-plots in **Appendix E**).

-Mean birthweight (8645 patients, 23 studies)

Both dexamethasone and betamethasone have no effect on birthweight against control: MD -17.04g (95%CI -75.48; 41.41) and -9.74 g. (95%CI -43.11; 23.63), respectively. The test for subgroup differences by corticosteroid type shows no disparity (P 0.80, I^2 0%). No serious incoherence was found between direct and indirect evidence ROR of 1.15 (95%CI 0.44-2.96), and both direct and indirect evidence were considered as high certainty evidence, therefore the NMA evidence was considered to be the most reliable estimation. Dexamethasone has no effect mean birthweight: mean difference +5.29g (95%CrI -49.79, 58.97) high-certainty evidence.

-Other outcomes

Regarding corticosteroids vs. control, there was no direct evidence found about low birthweight and there may be no difference between betamethasone and control on maternal death: OR 0.98 (95%CI 0.06-15.90). Dexamethasone and betamethasone likely reduce perinatal death: OR 0.62 (95%CI 0.33-1.18) and 0.66 (95%CI 0.48-0.91), respectively. The test for subgroup differences

by corticosteroid type shows no disparity (P 0.86, I^2 0%). Dexamethasone may increase chronic lung disease and betamethasone may reduce this outcome, but the confidence interval limits could 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. The test for subgroup differences by corticosteroid type shows no disparity (P 0.47, I^2 0%).

There was no direct evidence found that compared dexamethasone vs. betamethasone with regard to maternal death, perinatal death, and scarce evidence was found about low birth weight and chronic lung disease (need for continuous supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age, whichever was later) and these were assessed only by pairwise meta-analysis.

One study (105 participants) assessed low birth weight and another study (1,489 participants) chronic lung disease. Compared with betamethasone, dexamethasone may reduce these outcomes, however the confidence interval limits could also be compatible with large beneficial or detrimental effect: OR 0.75 (95%CI 0.33-1.71, low-certainty evidence) and OR 0.92 (95%CI 0.62-1.37) respectively (See **Appendix E: Direct comparison dexamethasone vs. betamethasone forest-plots**).

The effect and the test for subgroup differences by corticosteroid type for the main eight outcomes of the comparison corticosteroid vs. placebo/no treatment by type of corticosteroid and related certainty of evidence is presented in Summary of finding tables in the **Appendix F**.

Appendix H presents several NMA outputs and **Appendix I** presents the meta-regression, subgroup and sensitivity analyses. Meta-regression for the four primary outcomes did not find statistically significant differences. The subgroup and sensitivity analysis did not reveal important changes regarding the main analysis. All the confidence interval limits were compatible with beneficial or detrimental effects. The ORs > 2.0 for dexamethasone compared to betamethasone

were: chorioamnionitis in studies only including women with ruptured membranes, for endometritis/puerperal sepsis in studies with multiple doses, with intact/ruptured membranes or only ruptured membranes, in HICs or adjusting by GNI per capita or for missing data; and for RDS in the subgroup of UMICs.

Comment

Principal 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. As expected, there was found no effect on birthweight considering the short timeframe between the intervention and delivery.

A not statistically significant effect was found suggesting 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%. Likely, there are no differences in neonatal death and neurodevelopmental disability and may be no difference in IVH and in birthweight. Except for neurodevelopmental disability and birthweight, these effects were imprecise.

Strengths and limitations

Among the strengths of this work, it is worth mentioning that Cochrane guidelines[20] were followed, as well as the PRISMA-NMA extension[15] (**Appendix J**), and the study protocol was registered in advance. This work is the most updated and complete systematic review assessing clinical effectiveness and safety of corticosteroids for preterm birth. The exhaustive search strategy used in this study, included clinical trials registries and contacted experts for additional

relevant evidence. Although the strategy did not hand-search conference proceedings, it is unlikely that the search strategy missed RCTs not included in biomedical databases nor the trials registries.

This NMA added two small trials[13, 14] and one large, good quality trial that compared dexamethasone directly with betamethasone[12] to the body of evidence. The NMA also 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 the results.

The certainty of the evidence was assessed by the GRADE-NMA approach[34, 35], 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.[23, 25]

The results of the NMA were mostly coherent, except for chorioamnionitis which 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[38, 39, 43, 49, 51, 53, 54, 57-59, 62, 67, 69, 71, 74], while the direct evidence was 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[34], the direct evidence was considered the most reliable estimation of 23 fewer cases (43 fewer or 5 more) per 1000 women treated with dexamethasone.

In general, the included trials were heterogeneous in terms of clinical settings, baseline population characteristics, and intervention schemes and doses. Studies conducted in a range of 50 years and healthcare advances were included, specifically in neonatology, adding an extra-source of heterogeneity that could partially explain the contradictory direction of effect for some

outcomes, but the effect modifiers nor RoB did not provide a solid explanation of the effects. The mixed beneficial or detrimental effect of different outcomes warranted the decision to explore the patients' perspectives about the analyses' findings comparing corticosteroids through a focus group (**Appendix C).** Briefly, women failed to make a decision about which corticosteroids they would choose because the trade-off between risk and benefits were very complex. The women agreed that it would be a decision that they would share or delegate to a professional with whom they established a bond of trust. It is noteworthy that the health risk for women had more importance for those participants who already had children, since they considered the family impact of their own health.

The evidence shows limitations, regarding its generalizability to lower-resource countries, since only three[14, 44, 49] out of the 45 included RCTs (only 5.5% of the included infants) were from lower-MICs and none from LICs. Trials have been largely conducted in tertiary hospitals and recruited highly selected populations.[85] 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.[86] However, no important differences were found by country income classification nor by GNI per capita. Hopefully, the ongoing ACTION study in five low-resource countries will answer this question regarding the effects of dexamethasone on 6018 women at risk of preterm birth.[6] An additional placebo-controlled ongoing RCT to be conducted in Nigeria, will include separate arms for each corticosteroid, allowing a direct comparison in a low-resource setting. The placebo-controlled ongoing RCT ACTWIN[79, 80] will evaluate the effect of betamethasone on 808 twin pregnancies in South Korea. This body of evidence will increase the precision of estimations in a future update of our network meta-analysis. However, future studies are needed to explore the differential effect of doses, because the multiple schemes used across the included studies precluded this

455 analysis. Additionally, many studies used a combination of betamethasone phosphate and acetate
456 to maximize the drug's efficiency. Both formulations have different
457 pharmacokinetic/pharmacodynamic characteristics[87], but only Subtil 2003[75] compared acetate
458 and phosphate versus phosphate alone as a third arm (finding no difference in fetal heart rate), so
459 this study was not able to assess the differential effect of both schemes.
460
461

462 **Comparison with existing literature**

463 The new evidence provided by this study does not seem to contradict previous studies.
464 Antenatal corticosteroids administered to women who are at risk of preterm birth have shown to
465 reduce neonatal morbidity and mortality[10] and are cost-effective[88], thus, they are routinely
466 recommended worldwide.[7, 89, 90]. The pairwise meta-analyses results of both corticosteroids
467 against placebo agree with the results of the last Cochrane review by Roberts et al 2017,[10]. The
468 two additional studies found[13, 14] for this study only slightly improved the precision of the
469 results for RDS and birthweight outcomes.
470 The second Cochrane review, by Brownfoot,[9] compared both corticosteroids and different
471 regimes against each other, but authors could not consider recent evidence. The inclusion of the
472 new trial ASTEROID[12], almost doubled the number of included women and provided
473 information for the main outcomes, except puerperal sepsis, fetal death, and chronic lung disease.
474 Besides, this recent evidence improved the precision of the previous estimates for neurosensory
475 disability, where this study found no important difference between corticosteroids, while for
476 chorioamnionitis it was found that dexamethasone may have a beneficial effect.
477 The potential beneficial effect of dexamethasone on IVH, suggested by very low-certainty direct
478 evidence, was reduced with the inclusion of the ASTEROID trial[12] and completely disappeared

when excluding Elimian 2007.[48] This post-hoc sensitivity analysis was key mainly due to the very high risk of attrition bias of this study and provided more consistent results with the indirect evidence. Additionally, systematic reviews and meta-analyses found an increased risk of neurodevelopmental impairment in children with Periventricular/Intraventricular Hemorrhage (PIVH)[91], mainly driven by cerebral palsy[92]. Since there was found to be no differential effect of dexamethasone on neurosensory disability, it would be unlikely a potential favorable effect on IVH. Additionally, even if a reduction in IVH was true, the observed absence of differences on long-term disability for the quality of life of survivors is more important.[93]

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

This NMA improved the precision and certainty of most previous estimations. The study identified a very recent NMA that evaluated antenatal maternal administration dexamethasone and betamethasone but also of ambroxol.[94] Authors reported that compared with placebo, all interventions demonstrated better efficacy in terms of preventing RDS and neonatal death, and no significant difference in the assessment of the incidence of bronchopulmonary dysplasia. Authors also suggest that ambroxol seems to have the potential 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 systematic review showing insufficient evidence to support or refute the practice of giving ambroxol to women at risk of preterm birth.[95] Additionally, ambroxol is not even mentioned in relevant guidelines for the management of preterm birth.[7, 89]

Unlike this study and the previous systematic review, the authors included studies with repeated exposure to antenatal corticosteroids and due to the search date, relevant recent trials could not be included. The largest and most recent trial[12] reported that children exposed to dexamethasone

were less likely to be hypertensive at age 2 years than those exposed to betamethasone adjusted OR 0.78 (95%CI 0.64-0.95), but there was incomplete outcome data and the clinical significance of this finding is still uncertain. There was also observed to be a higher use of the caesarean section with betamethasone, but it was not sustained in an adjusted post-hoc analyses.

A wise choice between dexamethasone and betamethasone should consider all factors besides evidence, including local availability, costs and cost-utility.[96, 97] A full course of betamethasone costs around US$35 while dexamethasone costs $1 (3% of the cost of betamethasone).[97] The cost-effectiveness of the administration of betamethasone in the late-preterm period is controversial and it should be based in the best estimation of effectiveness instead of individual trials.[98, 99] 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.[100] Hopefully, the findings of this study contribute to an informed decision-making process and to improve maternal and new-born care.

Conclusions and Implications

This comprehensive NMA showed that corticosteroids were mostly effective for neonatal and child relevant outcomes compared with placebo or no treatment. There was no clinical or statistical difference between corticosteroids on neonatal death, neurodevelopmental disability, intraventricular hemorrhage, or birthweight, but both corticosteroids have different effects on the remaining outcomes. No statistically significant difference, but potentially clinically important effect, was found between dexamethasone and betamethasone. Low to moderate-certainty evidence suggest, considering the central estimations, that dexamethasone may reduce chorioamnionitis, and fetal death, but may increase puerperal sepsis, respiratory distress

528 syndrome. However, the 95%CI indicates both beneficial and detrimental effects against
529 betamethasone for these outcomes. The opposing direction of these outcomes does not allow for
530 derivation of recommendations about what corticosteroid should be used. A few very large, well-
531 designed RCTs are warranted to improve the certainty of this evidence. Ideally, these trials
532 should represent low resource countries and, also, address the best schemes for administration in
533 different subgroups. Individual participant data meta-analysis could help to answer these
534 questions. In the meantime, monitoring short-term and long-term health outcomes, including
535 neurodevelopmental disability will be important to obtain real life data.
536 Since there is no robust evidence on which corticosteroid should be prescribed, decisions should
537 be based on availability, costs, opportunity, and facilities. Shared decision-making would help
538 patients to make their choices when facing this scenario.
539
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541 KK, DC, AD and AC collected and abstracted the data; IDF, AAV undertook the statistical
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The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Table 1. Summary of finding: dexamethasone vs. betamethasone

Outcome	Direct evidence		Indirect evidence		NMA evidence		Absolute effects for NMA estimate		
	OR# (95%CrI)	Certainty*	OR# (95%CrI)	Certainty*	OR# (95%CrI)	Certainty	Risk with control±	Risk with beta±	Difference (95%CI)
Chorioamnionitis	**0.695** (0.451-1.055)	⊕⊕⊕ [1] **MODERATE**	**2.321** (1.152-4.943)	⊕⊕⊕ [1] **MODERATE**	**0.149** (0.003-0.878)	⊕⊕ [2] **LOW**	59 per 1000	82 per 1000	**23 fewer per 1000** (43 fewer or 5 more)
Endometritis/puerperal sepsis	-	-	**2.043** (0.715-6.058)	⊕⊕ [1,3] **LOW**	**2.043** (0.715-6.058)	⊕⊕ [1] **LOW**	-	-	**73 more per 1000** (22 fewer or 270 more)
Neonatal death	**0.941** (0.550-1.646)	⊕⊕⊕ [1] **MODERATE**	**1.078** (0.629-1.848)	⊕ [1,4] **VERY LOW**	**1.053** (0.619-1.836)	⊕⊕⊕ [1] **MODERATE**	270 per 1000	32 per 1000	**2 more per 1000** (12 fewer or 25 more)
Fetal death	-	-	**0.812** (0.241-2.406)	⊕⊕ [1,3] **LOW**	**0.812** (0.241-2.406)	⊕⊕ [1] **LOW**	-	-	**6 fewer per 1000** (24 fewer or 42 more)
Respiratory distress Syndrome	**1.040** (0.818-1.323)	⊕⊕⊕ [1] **MODERATE**	1.449 (0.990-2.128)	⊕ [1,4] **VERY LOW**	**1.377** (0.959-2.114)	⊕⊕⊕ [1] **MODERATE**	326 per 1000	260 per 1000	**66 more per 1000** (8 fewer or 166 more)
Neurodevelopmental disability	**1.031** (0.799-1.329)	⊕⊕⊕ [5] **MODERATE**	-	-	-	-	295 per 1000	289 per 1000	**6 more per 1000** (44 fewer or 62 more)
Intraventricular hemorrhage	**0.706** (0.297-1.581)	⊕ [1,6] **VERY LOW**	**1.128** (0.509-2.497)	⊕⊕ [1,3] **LOW**	**1.036** (0.555-1.783)	⊕⊕ [7] **LOW**	53 per 1000	52 per 1000	**2 more per 1000** (22 fewer or 37 more)
Mean birthweight (grams)	**MD +17.81** (-62.98; 98.18)	⊕⊕⊕⊕ **HIGH**	**MD -0.008** (-0.072; 0.056)	⊕⊕⊕⊕ **HIGH**	**MD +5.29** (-49.79, 58.97)	⊕⊕⊕⊕ **HIGH**	-	-	**+ 5.29 gr.** (-49.79, or +58.97 gr.)

GRADE Working Group grades of evidence
High certainty: Very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The shadowed cells are more reliable estimations that were used to calculate the absolute differences presented in the last column.
MD for mean birthweight
Presented here is the certainty of evidence considering imprecision, but this domain was omitted to directly assess imprecision for the NMA estimation.[35]
Estimated from direct comparisons and if not available from most similar outcome (i.e. for endometritis, the risks of chorioamnionitis were used)
CI: Confidence Interval, CrI: Credible Interval

Downgraded one level due to serious imprecision
Downgraded two levels, due to very serious incoherence
The lowest certainty of evidence (MODERATE) come from the dexamethasone vs. control, hence the final indirect assessment in the absence of intransitivity was MODERATE
The lowest certainty of evidence (LOW) come from the dexamethasone vs. control, hence the final indirect assessment in the absence of intransitivity was LOW.
Downgraded one levels, due to serious imprecision.
Downgraded two levels due to very serious methodological limitations (high risk of attrition bias)
Both direct and indirect evidence showed MODERATE certainty of evidence without considering imprecision and was downgraded one level due to serious imprecision for the NMA estimation.

858 **FIGURES**