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The proportions of term or late preterm births after exposure to early antenatal corticosteroids, and outcomes: systematic review and meta-analysis of 1.6 million infants

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BASED ON ARTICLE

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ABSTRACT

Objective: To systematically review the proportions of infants with early exposure to antenatal corticosteroids but born at term or late preterm, and short term and long term outcomes.

Design: Systematic review and meta-analyses.

Data sources: Eight databases searched from 1 January 2000 to 1 February 2023, reflecting recent perinatal care, and references of screened articles.

Eligibility criteria for selecting studies: Randomised controlled trials and population based cohort studies with data on infants with early exposure to antenatal corticosteroids (<34 weeks) but born at term (≥37 weeks), late preterm (34-36 weeks), or term/late preterm combined.

Data extraction and synthesis: Two reviewers independently screened titles, abstracts, and full text articles and assessed risk of bias (Cochrane risk of bias tool for randomised controlled trials and Newcastle-Ottawa scale for population based studies). Reviewers extracted data on populations, exposure to antenatal corticosteroids, and outcomes. The authors analysed randomised and cohort data separately, using random effects meta-analyses.

Main outcome measures: The primary outcome was the proportion of infants with early exposure to antenatal corticosteroids but born at term. Secondary outcomes included the proportions of infants born late preterm or term/late preterm combined after early exposure to antenatal corticosteroids and short term and long term outcomes versus non-exposure for the three gestational time points (term, late preterm, term/late preterm combined).

Results: Of 14 799 records, the reviewers screened 8815 non-duplicate titles and abstracts and assessed 713 full text articles. Seven randomised controlled trials and 10 population based cohort studies (1.6 million infants total) were included. In randomised controlled trials and population based data, ~40% of infants with early exposure to antenatal corticosteroids were born at term (low or very low certainty). Among children born at term, early exposure to antenatal corticosteroids versus no exposure was associated with increased risks of admission to neonatal intensive care (adjusted odds ratio 1.49, 95% confidence interval 1.19 to 1.86, one study, 5330 infants, very low certainty), intubation (unadjusted relative risk 2.59, 1.39 to 4.81, absolute effect 7 more per 1000, 95% confidence interval from 2 more to 16 more, one study, 8076 infants, very low certainty, one study, 8076 infants, very low certainty), reduced head circumference (adjusted mean difference -0.21, 95% confidence interval -0.29 to -0.13, one study, 183 325 infants, low certainty), and any long term neurodevelopmental or behavioural disorder in population based studies (eg, any neurodevelopmental or behavioural disorder in children born at term, adjusted hazard ratio 1.47, 95% confidence interval 1.36 to 1.60, one study, 641 487 children, low certainty).

Conclusions: About 40% of infants exposed to early antenatal corticosteroids were born at term, with associated adverse short term and long term outcomes (low or very low certainty), highlighting the need for caution when considering antenatal corticosteroids.

COMMENTARY

Antenatal steroids are given to mothers experiencing imminent preterm labor (before < 34 weeks + 6 days, or 34-36 weeks in the USA), regardless of the cause, delivery method, or number of fetuses. This is now the established medical practice and results in enhanced lung development in the fetus, reducing the risks of neonatal health issues and death. Nevertheless, in some cases, pregnancies progress and approach full term. The authors of this study aimed to investigate the effects of antenatal steroid exposure on infants born at or near term gestation.

This systematic review encompassed 7 randomized controlled trials (with a total of over 1,666,3450 participants) and 10 cohort studies based on population data (involving 4315 participants). The review spanned from January 2000 to February 2023 and covered 8 different databases. The researchers focused on the effects of antenatal steroid exposure before 34 weeks of gestation compared to no exposure or a placebo. They examined outcomes at different gestational stages: term (beyond 37 weeks), late preterm (34-36 weeks), and a combined group (over 34 weeks). The data were analyzed separately for randomized and nonrandomized studies, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was utilized for assessment.

The study revealed that 40 percent of infants, who had been exposed to antenatal steroids early on and reached term gestation, experienced heightened risks. These risks included a higher likelihood of being admitted to the neonatal intensive care unit, requiring intubation, needing treatment for hypoglycemia, having a smaller head circumference, and facing elevated long-term neurodevelopmental or cognitive risks.

The use of antenatal steroids seems to be double edged sword. In the short term, used in women at risk of preterm delivery (<34 weeks), it provides significant advantages to the fetus; however, prolonged exposure yields unfavourable outcomes. Both animal and human investigations indicate that steroids bring about changes in the structure and function of the heart, lungs, and brain, influencing metabolism. These effects are believed to stem from modifications in the hypothalamic-pituitary-adrenal axis, as well as their influence on the fetal transcriptome, thereby impacting developmental processes and programming. Furthermore, exposure to an additional surge of endogenous steroids contributes to these effects.

The study holds notable clinical implications. Initially, the application of antenatal steroids proves advantageous for infants born immediately after the steroid course. However, as pregnancies extend, the benefits become overshadowed by potential risks to the infant. Secondly, the liberal administration of antenatal steroids should be replaced by a more cautious approach, employing stringent criteria for identifying cases of 'threatened preterm delivery'. Thirdly, there exists a necessity for gathering data on the specific type of steroid used, the influence of fetal sex, and the steroid's role in fetuses with intrauterine growth restriction (IUGR), in order to facilitate informed decision-making. Lastly, the study underscores the importance of conducting long-term follow-up assessments for perinatal interventions. It is important to note that the study did not investigate the impact on mothers or explore the time interval between steroid administration and delivery.

IMPLICATIONS FOR PRACTICE

1. The administration of antenatal steroids to women at risk of threatened preterm delivery (< 34 weeks) yields substantial benefits for fetuses when delivered before <34 weeks.
2. When fetuses exposed to antenatal steroids progress to near-term or term gestation (as happens in 40%) experience noteworthy short-term and long-term adverse health challenges. Vigilant and prolonged monitoring is imperative for all such infants.
3. A cautious approach is recommended regarding the policy of unrestricted antenatal steroid use for impending preterm delivery. Clearly defined criteria for identifying 'threatened preterm delivery' and the development of predictive tools for preterm delivery are essential steps for optimizing the appropriate utilization of prenatal steroids.