EDITORIAL

Use of Antenatal Corticosteroids for Risk of Preterm Birth—Is Timing Everything?

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The administration of corticosteroids in women who are at risk for preterm birth is standard practice and considered "one of the most significant antenatal therapies available to improve newborn outcomes."[1] Antenatal corticosteroids accelerate fetal lung maturation and result in decreased perinatal death, neonatal death, and respiratory distress syndrome. Administration has also been demonstrated to reduce the risk of intraventricular hemorrhage and long-term developmental delays, although the level of evidence for these findings is lower.[2]

Related article

The timing of administration of antenatal corticosteroids has long been discussed and, along with dose and gestational age, defines the optimal medication delivery. Glucocorticoid signaling stimulates lung maturation through the promotion of mesenchymal tissue thinning by decreasing cell proliferation. This process reduces the distance between the alveolar capillary and alveolar space, improving gas exchange.[3] Glucocorticoids also promote surfactant production. Evidence in preclinical models and some human studies suggests that antenatal corticosteroids accelerate fetal organ maturation through mediation of functions and processes within cells, between cells, and across all of the organs of the body. In this way, antenatal corticosteroids inform in utero fetal organ development as well as stress and immune responses,[3] improving the short- and long-term outcomes for neonates whose developmental sequences may otherwise be interrupted by preterm birth. Cortisol levels continue to inform organogenesis after birth given that levels increase dramatically 5 to 6 weeks after delivery.[3] At 24 to 34 weeks' gestation, the optimal administration of antenatal corticosteroids is defined as a single course of corticosteroids administered between 24 hours and 7 days before delivery. For the risk of late-preterm birth, a single, carefully timed course of antenatal corticosteroids may also be administered. Administration of repeated antenatal corticosteroid courses is somewhat controversial, with as many detractors as there are proponents. Antenatal corticosteroids may sometimes be used before 24 weeks' gestation, depending on a family's decision and preferences, but is not recommended as standard of care.[1,4]

The advent of antenatal corticosteroids changed the landscape for those who were at risk for preterm birth; in the past, preterm birth often resulted in death or severe brain injury with lifetime consequences for the newborn. Although the risks of preterm birth remain for mothers and neonates, antenatal corticosteroids remain one of the greatest tools in the perinatal arsenal.

When preparing for birth before 34 weeks' gestation, neonatologists want to know whether the mother received corticosteroids and when they were administered. Timing matters. Neonatologists anticipate the likely care and ventilatory needs as well as overall infant outcome with the optimality of antenatal corticosteroid receipt in mind. In this issue of *JAMA Pediatrics*, Ninan et al[5] present a systematic review and meta-analysis that shifted the discussion of antenatal corticosteroid administration from the timing of receipt to the timing of delivery. This viewpoint is important to examine given that approximately 50% of children who receive antenatal corticosteroids before 34 weeks' gestation deliver at term.[4] Ninan et al[5] assessed long-term neurodevelopmental outcomes after antenatal corticosteroids based on the timing of birth rather than the timing of maternal administration. The authors found that children who were born preterm after antenatal corticosteroid administration had significantly lower adjusted odds of neurodevelopmental impairment. However, those children who were born at term after antenatal corticosteroid administration had significantly higher adjusted risks of neurodevelopmental impairment.[5]

Medical teams and families always hope and strive for a term birth despite preterm pregnancy complications. Yet term birth after antenatal corticosteroid administration may confer safety risks on long-term fetal development: courses of specific postnatal corticosteroids are known to adversely affect neurodevelopmental outcomes.[3] Therefore, it is possible that receipt of antenatal corticosteroids during a term pregnancy may itself disrupt a complex cascade of developmental gene activation and predispose children to worse development in early childhood. As we move forward, it will be important to ascertain whether birth timing remains important when considering the possibility that these children may have been exposed to multiple courses of antenatal corticosteroids; the number of courses was not available in nearly 60% of the studies included in the analysis.[5] Most long-term follow-up results in the meta-analysis occurred around the age of 2 years, using variable assessment tools and outcomes to identify neurodevelopmental status; it is unclear whether these findings would remain applicable in school-aged children.[6,7] In addition, randomized follow-up data were scarce, as the authors noted.[5] Many of the original randomized clinical trials that reported the benefit of antenatal corticosteroids were conducted before 2000 after 28 weeks' gestation in well-resourced settings; repeating the trials before 34 weeks' gestation was believed to be unethical given the favorable findings.[8] However, in light of the substantial changes in perinatal care (eg, maternal magnesium, tocolytics, and antibiotics; changes in neo-

natal ventilation and nutritional strategies; and routine resuscitation of fetuses <24 weeks' gestation[8]) that have occurred since these seminal studies were performed and the importance of ensuring equity in care, it may be time to reassess the benefits of antenatal corticosteroids—keeping in mind the administration and delivery timing, as well as current care strategies—in contemporary patient cohorts from variably resourced environments.

Although criticisms abound regarding the lack of evidence on the effectiveness of most neonatal medications, meta-analyses of existing research can help move the field forward, especially if they report unfavorable results or safety concerns. Far from being useless, these reports can impel neonatal researchers to develop new medication approaches and design innovative trial methodologies. Neonatal science is still an emerging field compared with the millenia of trial and error in adult medicine. Future studies of antenatal corticosteroid management will likely be challenging but critically important in charting an appropriate course forward. As obstetrical and neonatal-perinatal care continue to evolve and improve, findings such as those presented by Ninan et al[5] should generate new hypotheses and hope. Such reports confirm that the developing child is not simply a small adult and should not be treated as such.

ARTICLE INFORMATION

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Published Online: April 11, 2022. doi:10.1001/jamapediatrics.2022.0480

Conflict of Interest Disclosures: Dr Maitre reported receiving nonfinancial support from SmallTalk Equity outside the submitted work. No other disclosures were reported.

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