

EDITORIAL

Antenatal corticosteroids before 24 weeks: is it time?

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The anticipated delivery and birth of a periviable neonate at 22–23 weeks' gestation presents several difficult issues for obstetricians, neonatologists and families alike. The decision to resuscitate infants at these gestational ages is challenging, and practice variability exists within and across neonatal intensive care and labor and delivery units.^{1–3} When challenged with these events, communication with parents is of the utmost importance. Antenatal counseling of families should provide essential information to aid in the decision making process. This discourse includes not only expected outcomes of infants at extremely early gestational ages but also detailed options including (or excluding) treatments and therapies that may impact survival and neurodevelopmental outcome.⁴

It is established that administration of antenatal corticosteroids to women who are likely to deliver before 34 weeks' gestation is beneficial. In a 2006 Cochrane review of 21 studies, respiratory distress syndrome, intraventricular hemorrhage (IVH), necrotizing enterocolitis and neonatal mortality were all reduced in infants exposed to maternal administration of antenatal corticosteroids.⁵ Consequently, treatment guidelines advise the use of antenatal corticosteroids in mothers with threatened preterm birth from 24 weeks' to 32–34 weeks' gestation. Of note, many of these studies lack data on infants born at <26–28 weeks' gestation.

Onland *et al.*,⁶ in a systematic review of randomized controlled trials, evaluated the effects of antenatal corticosteroids in infants born before 26 weeks' gestation. They found no evidence to 'support or refute the recommendation of administering antenatal corticosteroids' in instances of threatened preterm delivery before 26 weeks' gestation. However, in a large, retrospective cohort study of over 10 000 infants born at 23 US academic centers between 1993 and 2009, antenatal corticosteroids showed significant benefit down to 23 weeks' gestation.⁷ In infants born at 23 weeks whose mothers received antenatal corticosteroids, death, severe IVH (grade 3 or 4) or periventricular leukomalacia and necrotizing enterocolitis were significantly reduced. At 18–22 months follow-up of survivors, moderate to severe cerebral palsy, blindness and deafness were also all reduced.

In this month's issue of the *Journal of Perinatology*, Wei *et al.*⁸ provide more evidence of the efficacy of maternal administration of antenatal corticosteroids at these extremes of prematurity. They present data from the California Perinatal Quality Care Collaborative evaluating the association between antenatal corticosteroid administration and IVH rates in infants \leq 32 weeks' gestation (and < 1500 g birth weight). Over 7 years, between 2007 and 2013, a total of 39 956 infants were admitted to California Perinatal Quality Care Collaborative neonatal intensive care units. The authors excluded infants who were outborn as well as those with missing data on IVH and antenatal corticosteroid administration. Just over 87% of the mothers of the 25 979 infants included in the analysis received either a partial or full course of antenatal corticosteroids.

Of the infants analyzed, 76.3% had no IVH although 23.7 and 7.5% had any grade hemorrhage or a severe (grade 3 or 4) hemorrhage, respectively. A quarter of infants with severe IVH were not exposed to antenatal corticosteroids although only 11.4% of those without IVH were not exposed. When the authors adjusted for maternal socio-demographic and medical risk factors

and stratified by gestational age, they found that infants at 23 0/7–23 6/7 weeks' gestation were significantly less likely to have any IVH or severe IVH. Although severe IVH was not impacted in infants < 23 0/7 weeks, there was a decrease in any IVH. In addition, in-hospital mortality rates were lower across all gestational ages in infants whose mothers received antenatal corticosteroids.

There are several limitations to this current study, including the lack of imaging data on a large number of infants and a lack of corticosteroid timing and dosing administration information. Also missing are data on whether women did not receive antenatal corticosteroids because there was a contraindication (e.g., acute maternal illness or because they delivered too quickly). Outcomes for those babies could be worse, skewing the unfavorable results to the no corticosteroid group and improving those data in babies for whom delivery could be postponed for 24–48 h after corticosteroid administration, potentially allowing for a more stable delivery. Furthermore, the outcomes for babies at the earliest gestational ages, specifically mortality rates, are potentially biased. Providers may not have equipoise in delivery room resuscitation between those babies whose mothers did or did not receive antenatal corticosteroids.

A number of guidelines prior to 2014 suggest the use of antenatal corticosteroids after 24 weeks' gestation. In 2014, a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) produced a recommendation for antenatal corticosteroids and newborn resuscitation for deliveries at 23 0/7 weeks or greater.⁹ A recommendation was also made to consider antenatal corticosteroids after 22 0/7 weeks if 'delivery at or later than 23 0/7 weeks is anticipated.' More recently, after acceptance of the manuscript by Wei *et al.*, ACOG revised their practice bulletin on the management of preterm labor by the addition of the following:

A single course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation and may be considered for pregnant women starting at 23 weeks of gestation, who are at risk of preterm delivery within 7 days.¹⁰

The different recommendations between ACOG and the Joint Workshop make it challenging for clinicians to determine how best to counsel families and manage threatened delivery at or before periviable gestational ages. In order to provide the best patient-centered care, prospective parents need clear information and clinicians require evidence of benefit and safety. To accomplish this, we suggest the following practices:

- Combine neonatal–obstetric counseling around periviability

In a small study involving simulated counseling of women with ruptured membranes at 23 weeks' gestation, obstetricians and neonatologists provided counseling that was complementary; however, both fields deferred questions about corticosteroid administration to the other specialty.¹¹ When parents' concerns go unanswered, the care team may appear 'disjointed or disconnected rather than practicing a 'team' approach to care.' Joint counseling will ensure team cohesiveness in recommendations and also minimize redundant or inconsistent information.

- Involve parents

Parents should be the center of any discussion about resuscitation at the perivable age. Having strict gestational age cutoffs is irrational as our knowledge of the precise dating of an individual fetus is, at best, a 'guesstimate' except in instances of *in vitro* fertilization. Also, ensuring the knowledge, understanding and acceptance by the parents of possible neonatal outcomes, and the contribution antenatal corticosteroids may provide to these outcomes are not to be discounted.

In addition, we urge the AAP and other professional organizations to include parents in the development of guidelines and clinical reports, especially regarding care practices surrounding the perivable infant. It should be noted that neither the AAP clinical report on counseling parents in the perivable period nor the Joint Workshop executive summary had parents on their working groups (although two neonatologists, recognized as experts in neonatal ethics, who have publically shared their personal NICU experience, were part of the Joint Workshop).^{4,9} As others have noted, clinical practice guidelines must be 'led by specialty societies but with a new model that integrates other stakeholders, including patients.'¹²

- Continue research on antenatal corticosteroids before 24 weeks

Current data suggest that antenatal corticosteroids provide benefit when offered from 23 weeks' gestation onward. However, most of this evidence comes from cohort studies, which may show unintended bias.¹³ Evidence for administration before 23 weeks is limited. In addition, as more mothers are treated with corticosteroids at these gestational ages but do not deliver within 1–2 weeks, more questions will arise regarding the timing and safety of repeated courses of corticosteroids. Follow-up studies of infants of mothers who received antenatal corticosteroids at a perivable gestational age and then received a subsequent course have not been performed; results of such investigations would add considerably to our understanding of antenatal corticosteroid safety and efficacy.

- Provide a coherent message

The study by Wei *et al.*⁸ supports previous findings that antenatal corticosteroids reduce death and IVH in infants born before 26 weeks' gestation. Together, these studies provide helpful information aiding the bedside clinician and parents in determining a reasonable course of action when faced with delivery before 24 weeks' gestation. The message to obstetric and neonatology providers and to parents needs to be clear: if resuscitation is to be offered at such early gestational ages as 22–23 weeks, then administration of antenatal corticosteroids might offer some advantages with low risk. Extrapolating from older gestational age data, buying a minimum of 48 h for the corticosteroids to achieve optimum effect seems worthwhile. Nonetheless, there may indeed be birth weight and/or size

limitations that impede resuscitation and stabilization in the best of hands. The perinatal team must take the opportunity to fully disclose such possibilities to families lest having anyone misconstrue antenatal corticosteroid administration as a panacea.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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