# Need for caution before extending the use of antenatal corticosteroids beyond 34 weeks' gestation

The consequences of such exposure in infants born late-preterm or at term are not known and could be hazardous, data tell us. At a minimum, mid-term follow-up from the Antenatal Late Preterm Study should be available before any clinical practice changes are recommended.

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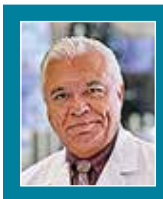
The results of the highly anticipated Antenatal Late Preterm Study recently have become available.[1] Data from this randomized controlled trial, conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, demonstrated that administration of betamethasone to women at risk for preterm delivery between 34 weeks 0 days and 36 weeks 6 days of gestation significantly reduces the rate of neonatal respiratory complications. It may represent the largest study of antenatal corticosteroids (ACS) to date, with 2,827 infants studied, and its results inevitably lead to the logical practical question: *Should ACS use be extended beyond the 34 weeks' gestation limit previously recommended by professional guidelines in the United States[2]?*

There are some issues that bear discussion before such a significant change in standard of care should be promoted.



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## Antenatal Late Preterm Study outcomes

The primary outcome in the study was a composite end point describing the need for respiratory support within 72 hours after birth. Based on a pilot study, the investigators had anticipated a 33% decrease in the rate of the primary outcome; however, the reduction was only 20% (relative risk [RR], 0.80; 95% confidence interval [CI], 0.66–0.97). Although the effect size was statistically significant, one could question the clinical relevance of such a small difference.

A 33% reduction effect, more consistent with the preliminary expectations, was noted in the prespecified secondary composite outcome of severe respiratory complications (RR, 0.67; 95% CI, 0.53–0.84). Occurrences included in the secondary composite outcome that also showed significant rate reductions were:

1. the use of continuous positive airway pressure (CPAP) or high-flow oxygen via nasal cannula for at least 12 hours (RR, 0.62; 95% CI, 0.48–0.80)
2. need for resuscitation at birth (RR, 0.78; 95% CI, 0.66–0.92)
3. surfactant use (RR, 0.59; 95% CI, 0.37–0.96)
4. transient tachypnea of the newborn (RR, 0.68; 95% CI, 0.53–0.87).

The reported reduction in bronchopulmonary dysplasia (RR, 0.22; 95% CI, 0.02–0.92) cannot plausibly be attributed to ACS. Randomized

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## Counseling your patient who asks if antenatal corticosteroids are right for her baby

Your patient's baby is between 34 weeks' and 36 weeks' 5 days' gestational age. As her physician, you should explain to your patient that the decision not to expose her baby to corticosteroids at this gestational age is based upon the following:

- Although corticosteroids have been shown to reduce the risk of the baby needing breathing support by 20%, they are associated with a 60% increase in risk for low blood sugar in the newborn (hypoglycemia). Hypoglycemia can place the baby at risk for seizures and even brain damage.
- There is an unknown safety profile for corticosteroid administration at this gestational age. The fetal brain is still developing during this period, and there is some information to suggest that corticosteroids could have an unfavorable effect on brain development.
- Corticosteroids are potent hormones and potentially can have undesired hormonal effects at this gestational age.
- If corticosteroids are given and the mother carries the baby to term (37 weeks or later) there are some studies that suggest the baby is at an increased risk for neurologic, cognitive, metabolic, and/or behavioral abnormalities in later life.

data aggregated by the Cochrane Database of Systematic Reviews[3] do not show improvement in chronic lung disease with ACS use. Moreover, the authors recognize that the assessment for bronchopulmonary dysplasia at only 28 days of life is only partially informative and that longer childhood follow-up is required to confirm the finding.

## We recommend caution before changing current practice

We propose prudence with ACS use after 34 weeks' gestation for the following reasons: the increased risk for neonatal hypoglycemia associated with ACS, the increased risk for ACS-related harm in term-born babies, and safety concerns with ACS in the late preterm period.

### Evidence shows an increased risk for neonatal hypoglycemia

The most profound effect modification observed in the study was an adverse effect—namely, a 60% increase in neonatal hypoglycemia with ACS administration (RR, 1.6; 95% CI, 1.37–1.87). The rate of neonatal hypoglycemia was 24% in the ACS group, compared with 15% in the placebo group.

Results of prior studies have demonstrated either no increased risk of hypoglycemia with ACS use[4–7] or a much smaller increase (from 4.2% to 5.7%).[8] The higher rate of neonatal hypoglycemia seen in this study suggests the possibility that the late preterm population may be more vulnerable to the negative impact of ACS on neonatal glucose/insulin homeostasis. Presumed mechanisms of action are either maternal hyperglycemia or fetal adrenal suppression or both, with potential for fetal adrenal suppression resulting from betamethasone exposure to affect long-term metabolic outcomes.[9]

Of note, women with pregestational diabetes were excluded from the study and, in routine practice, inclusion of such patients may further increase the risk of neonatal hypoglycemia.

There are few data on the prognostic significance of neonatal hypoglycemia in preterm infants, with the exception of a single study, the results of which show that it is associated with adverse neurodevelopment at 18 months of age.[10]

### Data reveal increased risk for harm in term-born babies

In spite of strict protocol specifications to increase the probability of delivery before 37 weeks' gestation, 16% of women in the trial delivered at term. Investigators of prior randomized studies of ACS, aimed at reducing the risks of prematurity, have reported a rate of term delivery of about one-third,[4,11] and in routine practice, administration of ACS after 34 weeks may be associated with even higher rates of term delivery.

This is important because recent evidence shows an unfavorable impact of ACS exposure in term-born children.[12] The 5-year follow-up of the largest randomized trial in which multiple ACS courses were used noted that babies born at term had a 4-fold increased odds ratio for neurosensory disability.[11] There was no dose–response interaction, with the same adverse odds ratio after 1 or 4 additional ACS courses. This observation was consistent with a previously reported Swedish national cohort, pointing to an unfavorable impact of even a single course of ACS in term-born children, with a greater likelihood of harm than benefit.[13]

In a UK follow-up of children aged 8 to 15 years who were enrolled in an RCT of ACS before cesarean delivery at term, low academic achievement was significantly more common in the group whose mothers had received ACS.[14] In another study of

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## When might glucocorticoid therapy be considered for women with threatened preterm delivery between 34 weeks to 36 weeks 5 days?

If a pregnant woman previously has delivered a baby beyond 34 weeks who developed a need for respiratory support, and the woman was again at risk for a late preterm delivery, it may be reasonable to offer her corticosteroids with full informed consent.

This is the only scenario in which we feel antenatal corticosteroids could be used in a fetus aged 34 weeks to 36 weeks 5 days. In the setting of a scheduled cesarean delivery between 34 weeks and 35 weeks, the concerns relative to term delivery after corticosteroid exposure may not apply, but the concerns in relation to the administration of corticosteroid in the late preterm period—which is a time of possibly increased neurohormonal and neurologic vulnerability—still apply. With regard to the risk of neonatal hypoglycemia, one might argue that close neonatal monitoring of babies so exposed may ensure that any associated neonatal hypoglycemia does not go unnoticed or untreated. However, the prognostic significance of even short periods of neonatal hypoglycemia has not been established.

304 children born at term after exposure to a single course of ACS, investigators noted significantly increased cortisol reactivity to acute psychological stress at ages 6 to 11 years in the ACS-exposed patients, compared with 212 babies of women with threatened preterm labor who did not receive ACS and 372 babies from uncomplicated term pregnancies.[15]

The relevance of such study findings extends beyond childhood given the fact that elevated hypothalamic-pituitary-adrenal (HPA) axis reactivity has been linked to the pathogenesis of metabolic syndrome and depression in adult life.[16] As recently as 2015, investigators of a randomized trial of ACS in 6 low- and middle-income countries highlighted their concern regarding "potentially harmful use of antenatal corticosteroids for infants not delivered preterm."[17]

### There are safety concerns with ACS in the late preterm period

The effects of ACS are more pleiotropic than those reflected in a lower incidence of respiratory difficulties. Knowledge of the overall consequences of ACS exposure in infants born late-preterm or at term is still limited. The close-to-term fetus exposed to exogenous corticosteroids is also exposed to the physiologic endogenous surge of cortisol known to occur in the maternal circulation in late pregnancy, which reaches levels 3 times higher than those seen in nonpregnant women.[18] Although placental 11 beta-hydroxysteroid dehydrogenase type 2 plays a protective role by allowing no more than 10% to 20% of maternal corticosteroids to cross the placenta, fetal overexposure from concomitant exogenous maternal corticosteroid administration remains a theoretical concern close to term. This is especially worrisome if there is a gestational age–related increase in the sensitivity to corticosteroid-induced in utero fetal programming. It has been reported that fetal overexposure to corticosteroids in late pregnancy can permanently increase the activity of the HPA-axis, with likely consequences in adult life.[19]

Another concern relates to oligodendrocytes development. Although the neuronal division process in humans usually is completed by 24 weeks' gestation, the most rapid growth for oligodendrocytes occurs between 34 and 36 weeks' gestation; these are the cells responsible for the synthesis of myelin. Overexposure to corticosteroids at this vulnerable time in the late preterm fetus potentially may have unanticipated negative neurologic consequences.[20]

## Where should future studies focus?

There is clear neonatal benefit from a single course of ACS given to women who will deliver before 34 weeks' gestation. It is widely accepted, based on the evidence provided by the 30-year follow-up of the cohort of 534 participants from the Auckland trial (the longest follow-up for any pregnancy trial), that administration of ACS at less than 34 weeks' gestation is not associated with any obvious major developmental risk.[21–23]

However, the reassurances provided by the Auckland cohort should be neither directly extrapolated to the administration of ACS in the late preterm period nor applied to term-born babies exposed to ACS, for the simple reason that these subgroups never have been analyzed separately. The risk:benefit ratio of ACS use in the late-preterm period is as yet unknown, and in term-born babies the ratio may be unfavorable.

### Follow-up studies are needed

We consider that there is a vital need for long-term follow-up studies. The focus of research on the effects of ACS no longer is on the immediate neonatal outcomes and now is on safety and the long-term outcomes of this exposure.

## Bottom line

We regard the large, high-quality study conducted by the NICHD MFMU Network[1] as an opportunity to answer current concerns. It is hoped that the resources necessary for in-depth follow-up of the children involved in this study will be provided to the investigators and to the NICHD. It is only with such follow-up that mid- and long-term adverse effects can be assessed. We believe that, at a minimum, mid-term follow-up data should be available before it is wise to make any definitive recommendations for a sweeping change in clinical practice.


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