



Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

The practice of medicine continues to evolve, and individual circumstances will vary. This publication reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

Late preterm birth is defined as delivery between 34 weeks 0 days through 36 weeks 6 days of gestation and accounts for 70% of all preterm births.¹ Late preterm neonates are at risk for significant morbidities, including respiratory distress syndrome because pulmonary maturation continues through the late preterm period into early childhood.²

Although the use of antenatal corticosteroids prior to 34 weeks of gestation is standard practice for women at high risk for delivery in the next 7 days,³ such treatment has not been recommended for women during late preterm period birth because of the lack of supportive data from randomized controlled trials.

The purpose of this document is to review the findings of a recently conducted randomized controlled trial evaluating the use of antenatal corticosteroids in late preterm pregnancies and to provide guidance for implementation into clinical practice.

The Antenatal Late Preterm Steroids trial was conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network.⁴ This double-blind, placebo-controlled randomized controlled trial was conducted at 17 Maternal-Fetal Medicine Units centers across the United States from 2010 to 2015. Women with a singleton gestation at high risk for preterm delivery between 34 weeks 0 days through 36 weeks 5 days of gestation were eligible if they presented in preterm labor with a cervix that was at least 3 cm dilated or 75% effaced, if they had preterm premature rupture of the membranes, or if a planned delivery was scheduled in the late preterm period, with the indication at the discretion of the provider.

Women with obstetric or medical complications and anticipation for worsening status leading to a high likelihood for late preterm delivery between 24 hours and 7 days were eligible (eg, oligohydramnios, fetal growth restriction, or preeclampsia). Women were considered ineligible if they

were likely to deliver within 12 hours (eg, if they were deemed unstable, presented with active bleeding or non-reassuring status requiring delivery), had previously received a course of betamethasone, or had pregestational diabetes, chorioamnionitis, or any other contraindication to betamethasone.

The primary outcome of the study was a composite endpoint describing the need for respiratory support within 72 hours after birth and 1 or more of the following: the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 consecutive hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 continuous hours, extracorporeal membrane oxygenation, or mechanical ventilation.

The study involved treatment with either 2 doses of betamethasone (12 mg intramuscularly) 24 hours apart or a matching placebo. Tocolysis was not used as a part of the protocol, and clinical management decisions after study drug administration were at the discretion of the provider.

The most common indication for enrollment was preterm labor (28%), followed by delivery for gestational hypertension or preeclampsia (26%) and ruptured membranes (22%). There were no differences between groups in the time from randomization to delivery; approximately 60% of the women in the betamethasone group received 2 doses of study medication.

The study found a significant decrease in the primary outcome, which was the need for respiratory support within the first 72 hours (14.4% in the placebo group vs 11.6% in the betamethasone group; relative risk, 0.80, 95% confidence interval, 0.66–0.97, $P = .02$). There were also significant decreases in the rates of severe respiratory morbidity (a composite outcome of continuous positive airway pressure or high-flow nasal cannula for at least 12 continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 24 continuous hours, extracorporeal membrane oxygenation

or mechanical ventilation, stillbirth, or neonatal death within 72 hours after delivery), bronchopulmonary dysplasia, transient tachypnea of the newborn, the need for resuscitation at birth, and the need for postnatal surfactant.

There were no differences in maternal outcomes such as mode of delivery, clinical chorioamnionitis, or endometritis. With respect to the newborn, hypoglycemia (glucose <40 mg/dL) was increased with betamethasone (24.0% vs 14.9%; relative risk, 1.61, 95% confidence interval, 1.38–1.88); other adverse neonatal outcomes were not different between groups. The rates of hypoglycemia reported in the betamethasone group were similar to those expected in late preterm neonates.⁵

Antenatal Late Preterm Steroids is the largest randomized controlled trial to date (N = 2831 subjects) evaluating the benefits and harms of antenatal betamethasone in the late preterm period. Two small randomized controlled trials involving antenatal corticosteroids in late preterm pregnancies have been published,^{6,7} but the largest comparable study was the Antenatal Steroids for Term Elective Caesarean Section trial,⁸ which included 998 women who were to undergo scheduled cesarean delivery at term. Infants of women who received betamethasone had lower rates of NICU admission because of respiratory complications (relative risk, 0.46; 95% confidence interval, 0.2–0.93) as compared with controls.

The findings of the Antenatal Late Preterm Steroids study are consistent with multiple other randomized controlled trials of antenatal corticosteroids administered at <34 weeks of gestation.³ The rationale to implement the Antenatal Late Preterm Steroids protocol into clinical practice includes its relatively large sample size, the fact that it included a study cohort generalizable to the US population, and that it involved a methodologically rigorous study design and protocol that enhances its internal validity. Outcomes data from Antenatal Late Preterm Steroids are restricted at this time to the newborn period, and the lack of long-term information is a current limitation of this randomized controlled trial.

Follow-up data on preterm newborns who received a single course of antenatal corticosteroids do not suggest any increased risk for long-term adverse effects.^{9,10} Concern has been raised about the potential increased risks associated with neonatal hypoglycemia, but these should be minimized by the utilization of routine testing for all late preterm newborns, as advocated by the Committee on Fetus and Newborn of the American Academy of Pediatrics.¹¹

There is always the potential for unintended consequences with any change in clinical practice. The Antenatal Late Preterm Steroids protocol did not attempt to change clinical management of late preterm pregnancies other than to administer betamethasone. Greater than 80% of women in the trial delivered prior to 37 weeks of

gestation. Thus, in the absence of new data, the use of betamethasone administration in the late preterm period should not include an attempt to delay delivery such as with tocolysis or expectant management for pre-eclampsia with severe features or premature rupture of membranes.

Another important aspect of the Antenatal Late Preterm Steroids study was that preterm labor was strictly defined in that the cervix was required to be at least 3 cm dilated or 75% effaced. Utilization of similar criteria for preterm labor is recommended to decrease the potential risk of overtreatment of women who ultimately would deliver at term.

Outcomes for women in the late preterm period who were not included in the Antenatal Late Preterm Steroids study remain unknown (eg, women with multiple gestations, those who had previously been treated with betamethasone prior to 34 weeks of gestation, those with pregestational diabetes, or those with scheduled cesarean deliveries at or beyond 37 weeks of gestation).

Additional data are needed prior to the use of betamethasone in the late preterm period for these indications. For these reasons, institutions should utilize standard guidelines for the implementation of the Antenatal Late Preterm Steroids study into routine clinical practice.

SMFM recommendations

1. In women with a singleton pregnancy between 34 weeks 0 days and 36 weeks 6 days of gestation who are at high risk for preterm birth within the next 7 days (but before 37 weeks of gestation), we recommend treatment with betamethasone (2 doses of 12 mg intramuscularly 24 hours apart).
2. In women with preterm labor symptoms in the late preterm period, we recommend waiting for evidence of preterm labor, such as a cervical dilatation of at least 3 cm or effacement of at least 75%, before treatment with betamethasone.
3. In women with late preterm pregnancies receiving betamethasone, we recommend against the use of tocolysis in an attempt to delay delivery to complete the steroid course because it is unclear whether the benefits of betamethasone administration are outweighed by the risks of attempts to delay delivery.
4. In women with late preterm pregnancies with a potential medical indication for delivery, we recommend betamethasone not be given unless there is a definitive plan for late preterm delivery.
5. We recommend that institutions utilize standard guidelines for the assessment and management of neonatal hypoglycemia in late preterm newborns.
6. We recommend against implementation of the Antenatal Late Preterm Steroids protocol for conditions not studied in the randomized controlled trial unless performed as part of research or quality improvement. ■

REFERENCES

1. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. *Natl Vital Stat Rep* 2015;64:1-65.
2. Consortium on Safe Labor, Hibbard JU, Wilkins I, et al. Respiratory morbidity in late preterm births. *JAMA* 2010;304:419-25.
3. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Review. *Cochrane Database Syst Rev* 2006:CD004454.
4. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med* 2016.
5. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr* 2012;161:787-91.
6. Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. *BMJ* 2011;342:d1696.
7. Balci O, Ozdemir S, Mahmoud AS, Acar A, Colakoglu MC. The effect of antenatal steroids on fetal lung maturation between the 34th and 36th week of pregnancy. *Gynecol Obstet Invest* 2010;70:95-9.
8. Stutchfield P, Whitaker R, Russell I; Antenatal Steroids for Term Elective Caesarean Section Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ* 2005;331:662.
9. Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. *Obstet Gynecol* 2015;125:1385-96.
10. Dalziel SR, Lim VK, Lambert A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ* 2005;331:665.
11. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics* 2011;127:575-9.

All authors and Committee members have filed a conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication. Any conflicts have been resolved through a process approved by the Executive Board. The Society for Maternal-Fetal Medicine has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

This document has undergone an internal peer review through a multi-level committee process within the Society for Maternal Fetal Medicine (SMFM). This review involves critique and feedback from the SMFM Publications and Risk Management Committees and final approval by the SMFM Executive Committee. SMFM accepts sole responsibility for document content. SMFM publications do not undergo editorial and peer review by the American Journal of Obstetrics & Gynecology. The SMFM Publications Committee reviews publications every 18-24 months and issues updates as needed. Further details regarding SMFM Publications can be found at www.smfm.org/publications. All questions or comments regarding the document should be referred to the SMFM Publications committee at pubs@smfm.org.