Start offering antenatal corticosteroids to women delivering between 34 0/7 and 36 6/7 weeks of gestation to improve newborn outcomes

Consider 3 options for your practice. Offer antenatal corticosteroids to: 1) all women at high risk for late preterm delivery, or 2) women scheduled for a cesarean delivery for an obstetric indication between 34 0/7 and 36 6/7 weeks of gestation, or 3) women at high risk for late preterm delivery whose newborns are most likely to benefit from treatment, those women at 34 0/7 to 35 6/7 weeks of gestation.

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Antenatal corticosteroid treatment prior to preterm birth is the most important pharmacologic intervention available to obstetricians to improve newborn health. Antenatal corticosteroids reduce preterm newborn morbidity and mortality.[1] The American College of Obstetricians and Gynecologists (ACOG) recently has summarized updated recommendations for the use of antenatal steroid treatment.[2]

ACOG guidance includes:

- "A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation, including for those with ruptured membranes and multiple gestations." This guidance is supported by many high-quality trials and meta-analyses.[1]
- A single course of corticosteroids "may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days."
- "A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days and whose prior course of antenatal corticosteroids was administered more than 14 days previously." A repeat course of corticosteroids could be considered as early as 7 days from the prior dose.
- **No more than 2 courses of antenatal steroids should be administered.**

An important new ACOG recommendation is:

- **"A single course of betamethasone is recommended for pregnant women between 34 0/7 and 36 6/7 weeks of gestation at risk**

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Instant Poll

For mothers at 34 3/7 weeks of gestation who are at high risk for preterm delivery within 1 week, will you offer a single course of antenatal glucocorticoids in your practice?

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TABLE Newborn and maternal outcomes in the Antenatal Late Preterm Steroids trial[3]

Outcome	Treatment		Relative risk (95% confidence interval)	*P* value
	Betamethasone, % (n = 1,429)	Placebo, % (n = 1,402)		
Need for resuscitation at birth	14.5	18.7	0.78 (0.66–0.92)	.003
Severe respiratory complications	8.1	12.1	0.67 (0.53–0.84)	<.001
Transient tachypnea of the newborn	5.5	6.4	0.68 (0.53–0.87)	.002
Surfactant use	1.8	3.1	0.59 (0.37–0.96)	.03
Bronchopulmonary dysplasia	0.1	0.6	0.22 (0.02–0.92)	.04
Neonatal hypoglycemia	24.0	15.0	1.60 (1.37–1.87)	<.001
Neonatal sepsis	0.6	0.8	0.80 (0.33–1.93)	.62
Chorioamnionitis	1.4	2.3	0.61 (0.35–1.07)	.08
Postpartum endometritis	1.1	1.1	0.98 (0.49–1.95)	.96

of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids."

This recommendation is based, in part, on a high-quality, randomized trial including 2,831 women at high risk for preterm birth between 34 0/7 and 36 6/7 weeks of gestation who were randomly assigned to receive a course of betamethasone or placebo. The newborn and maternal outcomes observed in this study are summarized in the **TABLE**.[3]

A few points relevant to the Antenatal Late Preterm Steroids study bear emphasizing. The women enrolled in this trial were at high risk for preterm delivery based on preterm labor with a cervical dilation of ≥3 cm or 75% effacement, spontaneous rupture of the membranes, or a planned late preterm delivery by cesarean or induction. No tocolytics were administered to women in this study, and approximately 40% of the women delivered within 24 hours of entry into the trial and only received 1 dose of corticosteroid or placebo.

Women with multiple gestations, pregestational diabetes, or a prior course of corticosteroids were not included in the trial; therefore, this study cannot guide our clinical practice for these subgroups of women. Of note, betamethasone should not be administered to women in the late preterm who have chorioamnionitis.

The investigators calculated that 35 women would need to be treated to prevent one case of the primary outcome: a composite score of the use of respiratory support. Consequently, 34 fetuses who do not benefit from treatment are exposed *in utero* to betamethasone. Long-term follow-up of infants born to mothers participating in this study is currently underway.

A recent meta-analysis of 3 trials including 3,200 women at high risk for preterm delivery at 34 0/7 to 36 6/7 weeks of gestation reported that the corticosteroid administration reduced newborn risk for transient tachypnea of the newborn (relative risk [RR], 0.72; 95% confidence interval [CI], 0.56–0.92), severe respiratory distress syndrome (RR, 0.60; 95% CI, 0.33–0.94), and use of surfactant (RR, 0.61; 95% CI, 0.38–0.99).[4]

The recommendation to offer a single course of betamethasone for pregnant women between 34 0/7 and 36 6/7 weeks of gestation at risk for preterm birth has not been embraced enthusiastically by all obstetricians. Many experts have emphasized that the **known risks** of late preterm betamethasone, including neonatal hypoglycemia and the **unknown long-term risks** of treatment, including suboptimal neurodevelopmental, cardiovascular, and metabolic outcomes should dampen enthusiasm for embracing the new ACOG recommendation.[5] Experts also emphasize that late preterm newborns are less likely to benefit from antenatal corticosteroid treatment than babies born at less than 34 weeks. Hence, many late preterm newborns will be exposed to a potentially harmful intervention and have only a small chance of benefiting from the treatment.[6]

Many neonatologists believe that for the newborn, the benefits of maternal corticosteroid treatment outweigh the risks.[7–9] In a 30-year follow-up of 534 newborns participating in antenatal corticosteroid trials, treatment had no effect on body size, blood lipids, blood

pressure, plasma cortisol, prevalence of diabetes, lung function, history of cardiovascular disease, educational attainment, or socioeconomic status. Corticosteroid treatment was associated with increased insulin secretion in response to a glucose load.[10] In this study, the mothers received treatment at a median of 33 weeks of gestation and births occurred at a median of 35 weeks. Hence this study is relevant to the issue of late preterm corticosteroid treatment.

Balancing risks and benefits is complex. Balancing immediate benefits against long-term risks is most challenging. Regarding antenatal steroid use there are many unknowns, including optimal dose, drug formulation, and timing from treatment to delivery. In addition we need more high-quality data delineating the long-term effects of antenatal corticosteroids on childhood and adult health.

Consider these 3 options for your practice

As noted, the Antenatal Late Preterm Steroids trial investigators are pursuing long-term follow-up of the children born after maternal treatment with antenatal glucocorticoids. Both ACOG and the Society for Maternal-Fetal Medicine (SMFM)[11] recommend administration of antenatal glucocorticoids to women at high risk for late preterm delivery. However, since some experts are concerned that a great number of babies born late preterm will have been exposed to glucocorticoids, whose long-term risks are not well known, with only a few babies having a modest short-term benefit, 3 options could be considered for your clinical practice.

Option 1

Follow the ACOG and SMFM suggestion that all women with a high risk of late preterm birth be offered antenatal corticosteroids. Counsel the mother and family about the potential risks and benefits and involve them in the decision.

Two alternative options are to limit antenatal corticosteroid treatment to subgroups of late preterm babies most likely to benefit from treatment, those born by cesarean delivery and those born at the earliest gestational ages.

Option 2

Limit the use of antenatal corticosteroids in the late preterm to women who are scheduled for a cesarean delivery for an obstetric indication between 34 0/7 weeks and 36 6/7 weeks of gestation. This approach greatly reduces the number of babies born in the late preterm that will be exposed to antenatal corticosteroids and focuses the treatment on a subset of babies who are

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certain to be born preterm and most likely to benefit.

Option 3

Limit the use of antenatal corticosteroids to women at high risk for preterm birth whose newborns are most likely to benefit from treatment—women at 34 0/7 to 35 6/7 weeks of gestation. Neonates born in the 34th or 35th week of gestation are at higher risk for morbidity than those born in the 36th week of gestation and are likely to derive the greatest benefit from antenatal corticosteroid treatment.[3,12]

My advice

Yogi Berra advised, "It is tough to make predictions, especially about the future." Although ACOG and SMFM have recommended administration of glucocorticoids to women at high risk for late preterm birth, many experts caution that until the long-term effects of antenatal corticosteroids are better characterized we should limit the use of corticosteroids in the late preterm.[5,6,13] My prediction is that long-term follow-up studies will not document significant adverse effects of one course of late preterm antenatal glucocorticoid treatment on children. My advice is to start offering antenatal corticosteroids to some women at high risk for late preterm delivery.

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References

1. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006;CD004454.
2. American College of Obstetricians and Gynecologists' Committee on Obstetrics Practice; Society for Maternal–Fetal Medicine. Committee Opinion No. 677: Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2016;128(4):e187–e194.
3. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; NICHD Maternal-Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14):1311–1320.
4. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ. 2016;355:i5044.
5. Kamath-Rayne BD, Rozance PJ, Goldenberg RL, Jobe AH. Antenatal corticosteroids beyond 34 weeks gestation: What do we do now? Am J Obstet Gynecol. 2016;215(4):423–430.
6. Vidaeff AC, Belfort MA, Steer PJ. Antenatal corticosteroids: a time for more careful scrutiny of the indications? BJOG. 2016;123(7):1067–1069.
7. Dalziel SR, Lim VK, Lambert A, McCarthy D, 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(7518):665.
8. Dalziel SR, Rea HH, Walker NK, et al. Long term effects of antenatal betamethasone on lung function: 30 year follow up of a randomised controlled trial. Thorax. 2006;61(8):678–683.
9. McKinlay CJ, Cutfield WS, Battin MR, Dalziel SR, Crowther CA, Harding JE; ACTORDS Study Group. Cardiovascular risk factors in children after repeat doses of antenatal glucocorticoids: an RCT. Pediatrics. 2015;135(2):e405–e415.
10. Dalziel SR, Walker NK, Parag V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet. 2005;365(9474):1856–1862.
11. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Implementation of the use of antenatal corticosteroids in the later preterm birth period in women at risk for preterm delivery. Am J Obstet Gynecol. 2016;215(2):B13–B15.
12. Bastek JA, Langmuir H, Kondapalli LA, Pare E, Adamczak JE, Srinivas SK. Antenatal corticosteroids for late-preterm infants: a decision-analytic and economic analysis. ISRN Obstet Gynecol. 2012;2012:491595.
13. Nowik CM, Davies GA, Smith GN. We should proceed with caution when it comes to antenatal corticosteroids after 34 weeks. J Obstet Gynaecol Can. 2018;39(1):49–51.