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Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee members Yasser Y. El-Sayed, MD, Ann E.B. Borders, MD, MSc, MPH, and the Society for Maternal–Fetal Medicine's liaison member Cynthia Gyamfi-Bannerman, MD, MSc.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to reflect a limited focused change to clarify that, among specific populations, antenatal corticosteroids should be administered when a woman is at risk of preterm delivery within 7 days.

Antenatal Corticosteroid Therapy for Fetal Maturation

ABSTRACT: Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number. Administration of betamethasone may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported. Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are encouraged.

Recommendations

The American College of Obstetricians and Gynecologists makes the following recommendations:

- A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number.
- Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context.
- A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.
- Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended.
- A single repeat course of antenatal corticosteroids should be considered in women who are less

than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.

- Whether to administer a repeat or rescue course of corticosteroids with preterm prelabor rupture of membranes (PROM) is controversial, and there is insufficient evidence to make a recommendation for or against.
- Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported.
- Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are effective and should be encouraged.

Introduction

This Committee Opinion was developed to help guide the timing and frequency of corticosteroid administration under various clinical contexts before preterm birth. Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes (1–5). The administration of antenatal corticosteroids to the woman who is at risk of imminent preterm birth is strongly associated with decreased neonatal morbidity and mortality (6–10). Neonates whose mothers received antenatal corticosteroids have significantly lower severity, frequency, or both, of respiratory distress syndrome (relative risk [RR], 0.66; 95% confidence interval [CI], 0.59–0.73), intracranial hemorrhage (RR, 0.54; 95% CI, 0.43–0.69), necrotizing enterocolitis (RR, 0.46; 95% CI, 0.29–0.74), and death (RR, 0.69; 95% CI, 0.58–0.81), compared with neonates whose mothers did not receive antenatal corticosteroids (11, 12).

Routine Administration for Women at Risk of Imminent Preterm Birth

A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation, and may be considered for pregnant women starting at 23 0/7 weeks of gestation, who are at risk of preterm delivery within 7 days (1, 11, 13). A Cochrane meta-analysis reinforces the beneficial effect of this therapy regardless of membrane status and concludes that a single course of antenatal corticosteroids should be considered routine for all preterm deliveries (11, 12).

Betamethasone and dexamethasone are the most widely studied corticosteroids, and they generally have been preferred for antenatal treatment to accelerate fetal organ maturation. Both cross the placenta in their active form and have nearly identical biologic activity. Both lack mineralocorticoid activity and have relatively weak immunosuppressive activity with short-term use. Although betamethasone and dexamethasone differ only by a single methyl group, betamethasone has a longer half-life because of its decreased clearance and larger volume of distribution (14). *The Eunice Kennedy Shriver* National Institute of Child and Human Development (NICHD) 2000 Consensus Panel reviewed all available reports on the safety and efficacy of betamethasone and dexamethasone. It did not find significant scientific evidence to support a recommendation that betamethasone should be used preferentially instead of dexamethasone. Of the 10 trials included in a Cochrane review on this issue, there were no differences in perinatal death or alterations in biophysical activity, but there was a decreased incidence of intraventricular hemorrhage with dexamethasone treatment (15). Alternatively, an observational study reported less-frequent adverse neurological outcome at 18–22 months after betamethasone exposure (16). These inconsistent and limited data are not considered sufficient to recommend one corticosteroid regimen over the other.

Treatment should consist of either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone administered intramuscularly every 12 hours (11). Because treatment with corticosteroids for less than 24 hours is still associated with significant reduction in neonatal morbidity and mortality, a first dose of antenatal corticosteroids should be administered even if the ability to give the second dose is unlikely, based on the clinical scenario (11, 13). However, no additional benefit has been demonstrated for courses of antenatal corticosteroids with dosage intervals shorter than those outlined previously, often referred to as "accelerated dosing," even when delivery appears imminent (11). The benefit of corticosteroid administration is greatest at 2–7 days after the initial dose. Therefore, corticosteroids should not be administered unless there is substantial clinical concern for imminent preterm birth.

In the Setting of Periviability

Specific data on the use of corticosteroids in the periviable period are supported by a combination of laboratory data on the response of lung tissue and clinical observational studies (1, 2, 17, 18). Data from an NICHD Neonatal Research Network observational cohort revealed a reduction in death and neurodevelopmental impairment at 18–22 months for infants who had been exposed to antenatal corticosteroids and born at 23 0/7 weeks through 23 6/7 weeks of gestation (83.4% versus 90.5%), 24 0/7 weeks through 24 6/7 weeks of gestation (68.4% versus 80.3%), and 25 0/7 weeks through 25 6/7 weeks of gestation (52.7% versus 67.9%) (1, 2). At 22 0/7 weeks through 22 6/7 weeks of gestation, no significant difference in these outcomes was noted (90.2% versus 93.1%) (2). In this study, antenatal corticosteroid exposure also decreased incidence of death,

intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis in infants born between 23 0/7 weeks and 25 6/7 weeks of gestation (1). A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation, and may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days (1, 11, 13). Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context (1).

In the Setting of Preterm Prelabor Rupture of Membranes

The use of antenatal corticosteroid administration after preterm PROM has been evaluated in a number of clinical trials and has been shown to reduce neonatal mortality, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (6, 12, 19, 20). Current data suggest that antenatal corticosteroids are not associated with increased risks of maternal or neonatal infection regardless of gestational age. A single course of corticosteroids is recommended for pregnant women with ruptured membranes between 24 0/7 weeks and 33 6/7 weeks of gestation. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation (as discussed in the In the Setting of Periviability section) who are at risk of preterm delivery within 7 days, irrespective of membrane rupture status (1, 11, 13). Whether to administer a repeat or rescue course of corticosteroids with preterm PROM is controversial, and there is insufficient evidence to make a recommendation for or against (see Single Rescue Course).

In the Setting of Multiple Gestation

A Cochrane review concluded that although antenatal corticosteroids are beneficial in singleton gestations, further research is required to demonstrate an improvement in outcomes for multifetal gestations (21, 12). More recently, a well-designed retrospective cohort study concluded that administration of a complete course of antenatal corticosteroids 1–7 days before birth in twin pregnancies is associated with a clinically significant decrease in neonatal mortality, short-term respiratory morbidity, and severe neurological injury that is similar in magnitude to that observed among singletons (22). Based on the improved outcomes reported in singleton gestations and limited but more recent data on multifetal gestations, unless a contraindication exists, one course of antenatal corticosteroids should be administered to all patients who are between 24 0/7 weeks and 33 6/7 weeks of gestation and at risk of delivery within 7 days, irrespective of fetal number (21, 23). In the absence of data, it is reasonable to extend this so that antenatal corticosteroids may be administered for pregnant women starting at 23 0/7 weeks (as discussed in the periviability section), regardless of fetal number.

In the Setting of Imminent Late Preterm Birth

Recent data also suggest that betamethasone can be beneficial in pregnant women at high risk of late preterm birth, between 34 0/7 weeks and 36 6/7 weeks of gestation who have not received a prior course of antenatal corticosteroids. The Maternal Fetal Medicine Units (MFMU) Network Antenatal Late Preterm Steroids trial (24) was a double-blind, placebo-controlled, randomized clinical trial designed to evaluate the use of antenatal betamethasone for pregnant women at high risk of delivery in the late preterm period. Women were identified to be at high risk if they presented in preterm labor, had preterm PROM, or if they had a planned delivery in the late preterm period, with the indication at the discretion of the obstetrician–gynecologist or other health care provider. Tocolysis was not employed as a part of this trial, and delivery was not delayed for obstetric or medical indications. The study found that the administration of betamethasone led to a significant decrease in the primary outcome, which was the need for respiratory support. A larger decrease was demonstrated for severe respiratory complications, from 12.1% in the placebo group to 8.1% in the betamethasone group (RR, 0.67; 95% CI, 0.53–0.84; $P<.001$). There were also significant decreases in the rates of transient tachypnea of the newborn; bronchopulmonary dysplasia; a composite of respiratory distress syndrome (RDS), transient tachypnea of the newborn and RDS; and the need for postnatal surfactant. Infants exposed to betamethasone were less likely to require immediate postnatal resuscitation. There was no increase in proven neonatal sepsis, chorioamnionitis, or endometritis with late preterm betamethasone. Hypoglycemia was more common in the infants exposed to betamethasone 24.0% versus 14.9% (RR, 1.61; 95% CI, 1.38–1.88); however, there were no reported adverse events related to hypoglycemia, which was not associated with an increased length of hospital stay. The rates of hypoglycemia found in the trial are similar to what is reported in the general population of late preterm infants (25). Although not studied in this trial, long-term adverse outcomes of prolonged and persistent neonatal hypoglycemia have been described (26, 27). In order to reduce this risk and achieve the benefits of betamethasone therapy for fetal maturity in late preterm pregnancies, the American Academy of Pediatrics' guidelines should be followed when employing this therapy (27). The American Academy of Pediatrics recommends the monitoring of neonatal blood sugars for late preterm infants because late preterm birth is a known risk factor for hypoglycemia. A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of

preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids (24, 28).

There are important considerations specific to the administration of late preterm corticosteroids that should be noted and are derived from the methodology used by the trial. Late preterm administration of antenatal corticosteroids is not indicated in women diagnosed with clinical chorioamnionitis (intrauterine infection) (28). Furthermore, tocolysis should not be used in an attempt to delay delivery in order to administer antenatal corticosteroids in the late preterm period, nor should an indicated late preterm delivery (such as for preeclampsia with severe features) be postponed for corticosteroid administration (28).

Groups not studied by the Antenatal Late Preterm Steroids trial include women with multiple gestations, women with pregestational diabetes, women who previously had received a course of corticosteroids, and women who gave birth by cesarean at term. Whether or not late preterm corticosteroids provide benefit in these populations is unknown.

Evidence Against Serial Courses

Because of concerns for maternal and fetal harm, and the balance of risk and benefits, planned multiple courses are not recommended. In a randomized trial of single versus serial courses of antenatal corticosteroids, a reduction in birth weight and an increase in the number of infants who were small for gestational age were found, especially after four courses of corticosteroids (29). Although not consistent, six studies found decreased birth weight and head circumference with repeat courses (29–35) and three studies did not (36–38). The NICHD 2000 Consensus Panel concluded that studies regarding the possible benefits and risks of repeat courses of antenatal corticosteroids are limited because of their study design and "methodologic inconsistencies." The NICHD 2000 Consensus Panel noted that, although there is a suggestion of possible benefit from repeated courses (especially in the reduction and severity of respiratory distress), there also are animal and human data that suggest deleterious effects on the fetus regarding cerebral myelination, lung growth, and function of the hypothalamic–pituitary–adrenal axis. Follow-up of children at 2 years of age who were exposed to repeat courses of antenatal corticosteroids showed no significant difference in physical or neurocognitive measures in two studies (39, 40), and the same outcome was found in younger children in a third study (41). Although not statistically significant, the relative risk of cerebral palsy in infants exposed to serial courses of antenatal corticosteroids (RR, 5.7; 95% confidence interval, 0.7–46.7; P=.12) in one study is of concern and warrants further study (39). Maternal effects include increased risk of infection and suppression of the hypothalamic–pituitary–adrenal axis (31, 42). Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended (11).

Single Rescue Course

Although the initial data (43) suggested the benefit of corticosteroids may decrease after 7 days, the duration of corticosteroid benefit remains controversial (44). A multicenter randomized trial of a single rescue course was performed in 437 patients without preterm PROM who had completed a single course of antenatal corticosteroids before 30 0/7 weeks of gestation and at least 14 days before inclusion, and were judged to have a recurring threat of preterm birth within 7 days before 33 0/7 weeks of gestation (45). The investigators found a significant reduction in respiratory distress syndrome, the need for surfactant, and composite morbidity for those giving birth before 34 0/7 weeks of gestation and for the overall cohort. No increase in newborn complications or intrauterine growth restriction was identified, although the power to evaluate these individual outcomes was low. There was no difference in bronchopulmonary dysplasia, and long-term outcome developmental data are not available for these patients. The 2015 Crowther Cochrane meta-analysis (10 trials, 4,733 women and 5,700 infants) included trials with a repeat course of corticosteroids as early as 7 days from initial course. The results of the meta-analysis showed reduction in RDS and there was noted an associated small reduction in size at birth, but no significant adverse outcomes. Therefore, a single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously (45). Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario, given the Cochrane meta-analysis results (11, 46). Whether to administer a rescue course of corticosteroids with PROM is controversial, and there is insufficient evidence to make a recommendation for or against (6, 47).

Long-Term Outcomes, Risks, and Additional Considerations

The concern that corticosteroids may have the potential to adversely affect neurodevelopmental outcomes is largely based on animal data and from studies of multiple course corticosteroids (39). The MFMU study of repeat course corticosteroids suggested that four or more courses may be associated with the development of cerebral palsy (39). However, numerous studies have shown no evidence of long-term harm (and in fact showed improved survival and neurodevelopmental outcomes with long-term pulmonary and other benefits), particularly as it relates to a single course of corticosteroids administered at less than 34 0/7 weeks of gestation (48, 12). A follow-up to a trial of antenatal corticosteroids at term (greater than 37 0/7 weeks of gestation) showed a difference in subjective teacher evaluation of a child's quartile of ability, with

more children assessed at less than 25% for performance (17.7% versus 8.5%, *P*=.03) among those randomized to the corticosteroids but, at the same time, showed no difference in objective neurocognitive outcomes after assessing five neurocognitive dimensions (49). This single signal does not lead us to caution against corticosteroid use, particularly as it refers to term exposure, but continued surveillance of long-term outcomes should be supported. The only data available about long-term neurocognitive outcomes after late preterm administration of antenatal corticosteroids versus placebo come from the initial corticosteroids study (43), where patients at risk of preterm delivery were randomized from 24 0/7 weeks to 35 6/7 weeks of gestation. The 30-year neurodevelopmental follow-up of this cohort were exposed to corticosteroids from 30.9–34.6 weeks of gestation and delivered at a median of 35 weeks of gestation (range 33.4–38.0 weeks of gestation). A total of 34% (n=66) of the cohort delivered at term (50). Cognitive functioning as measured by the Weschler scales, working memory and attention, and other neurocognitive assessments were not different between exposure groups. The MFMU Antenatal Late Preterm Steroids study has not yet obtained long-term outcome data but doing so would add significantly to limited available literature. A final additional consideration regarding corticosteroid risks is that in the context of maternal critical care, antenatal corticosteroids are not contraindicated, even in the setting of sepsis (1, 51).

Optimizing Administration of Antenatal Corticosteroids

Perinatal Quality Collaboratives, such as the Ohio Perinatal Quality Collaborative, California Perinatal Quality Care Collaborative, and the March of Dimes Big 5 State Perinatal Collaborative have worked to improve use of antenatal corticosteroids through a focus on the identification of missed opportunities and use of quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration. Implementation of preterm labor assessment toolkits, standardized order sets for women at risk of early delivery, timely availability of medication in settings where pregnant women are cared for, maternal transfer protocols that indicate corticosteroids should be given before transport, and appropriate documentation of first course and rescue course antenatal corticosteroids in inpatient and outpatient health records, have been among the proposed strategies to improve appropriate and timely antenatal corticosteroid use. One study reported qualitative focus group data describing conditions that enable delivery of antenatal corticosteroids with high reliability at hospitals that participated in the Ohio Perinatal Quality Collaborative antenatal corticosteroid project (52). Six major themes supporting reliable implementation of antenatal corticosteroids were described, including 1) presence of a high reliability culture, 2) processes that emphasize high reliability, 3) timely and efficient administration process, 4) involvement of multiple disciplines, 5) evidence of benefit supports antenatal corticosteroid use, and 6) benefit is recognized at all levels of the care team. Participating obstetrician–gynecologists or other health care providers and staff described that these key processes and supports were needed to ensure appropriate and timely delivery of antenatal corticosteroids with high reliability (52).

The March of Dimes Big 5 State Perinatal Collaborative (California, Florida, Illinois, New York, Texas) has developed tools to improve timely administration of antenatal corticosteroids. A collaborative of 54 hospitals from across the Big 5 States has been convened to pilot the new resources to standardize the identification of eligible patients and to improve the appropriate timing of corticosteroid therapy. The Ohio Perinatal Quality Collaborative reported that antenatal corticosteroid rates increase and are maintained at high levels when hospitals are aware that antenatal corticosteroid use is monitored, and missed opportunities are identified and reviewed. The collaborative worked with Ohio vital records to add antenatal corticosteroid administration to the Ohio birth certificate registry. Monitoring hospital rates provided incentive for hospitals to improve appropriate administration and documentation. The California Perinatal Quality Care Collaborative's Antenatal Steroids Initiative included 1998 baseline data collection, dissemination of recommended interventions using member-developed educational materials, and presentations to obstetrician–gynecologists and other health care providers in participating hospitals. The antenatal corticosteroid administration rate increased from 76% of 1,524 infants at baseline to 86% of 1,475 infants postinitiative (*P*<.001), and 23 of 25 participating hospitals exceeded the baseline lower-quartile cutoff point of 69% (53). This work by state and regional collaboratives demonstrates that quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are effective and should be encouraged. Therefore, the administration of antenatal corticosteroids should be monitored and missed opportunities reviewed.

Overuse of antenatal corticosteroids was recently addressed at the Society for Maternal–Fetal Medicine conference in 2016. The Workshop on Quality Measures for High Risk Pregnancies discussed antenatal corticosteroids, among other measures. The optimal therapeutic window for delivery after corticosteroid administration is 2–7 days, yet one study suggests only 20–40% of women assessed at their institution for preterm labor delivered in that window (54). In the Ohio Perinatal Quality Collaborative, 45% of women delivered in a 2–14 day window after receiving corticosteroids (55). In view of this, it is critical to have ongoing development of strategies that encourage timely corticosteroid administration to women at risk of preterm delivery within 7 days and avoid overuse of corticosteroids for low risk women. Collecting measures that track antenatal corticosteroids

use for infants born before 34 weeks of gestation and timing of corticosteroids in relation to delivery will support quality improvement efforts to optimize appropriate and timely antenatal corticosteroid administration.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/AntenatalCorticosteroids.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's web site, or the content of the resource. The resources may change without notice.

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