Controversy: Antenatal Steroids

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• Prematurity • Respiratory distress syndrome • Corticosteroids • Neurodevelopmental outcomes

There is no controversy about the core conclusion that women at risk of preterm delivery before 32 to 34 weeks’ gestational age should be treated with antenatal steroids. This practice is supported by the initial comprehensive meta-analysis of Crowley, Chambers, and Keirse in 1990,\textsuperscript{1} the National Institutes of Health Consensus Development Conference in 1994,\textsuperscript{2} the second Consensus Conference to evaluate repeated courses of antenatal steroids in 2000,\textsuperscript{3} and the practice recommendations of obstetric societies worldwide. Three recent meta-analyses by the Cochrane Collaboration on the benefits of antenatal steroids,\textsuperscript{4} the choice of steroid and dosing,\textsuperscript{5} and repeat doses of corticosteroids\textsuperscript{6} comprehensively summarize the available clinical information to about 2007. However, there are many unanswered questions about which steroid and dose to use and about their use in selected populations. This review focuses on those areas of uncertainty.

CURRENT STATE OF ANTENATAL STEROID USE

Current Practice

This therapy is based on the initial Liggins and Howie\textsuperscript{7} trial (1972) that used betamethasone as a 1:1 mixture of betamethasone phosphate and betamethasone acetate. The choice of the corticosteroid was empiric and based on Liggins research with fetal sheep, the available information about maternal to fetal transfer of fluorinated corticosteroids, and preparations available at that time for clinical use. Most clinical trials of a single course of corticosteroids and virtually all trials of repeated treatments have used the betamethasone acetate plus phosphate formulation available as Celestone.\textsuperscript{4,6} The other corticosteroid that has been tested in clinical trials is dexamethasone phosphate.\textsuperscript{5} As with any drug therapy, optimization of treatments requires

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information about the drugs, the dose, the treatment intervals, and potential toxicity. There is minimal information for antenatal corticosteroids because the therapy was developed and tested by investigators without industry support and without the intent to have the treatment licensed. Despite a clear consensus that the use of antenatal corticosteroids is standard of care, there has been no review or approval by the Federal Drug Agency in the United States. Although clinical trials have included more than 6000 patients, multiple questions remain about all facets of the pharmacology of corticosteroids for this unique strategy to treat the pregnant woman to benefit the fetus.

**Differences Between Betamethasone and Dexamethasone**

The drugs are similar fluorinated corticosteroids with primarily glucocorticoid and minimal mineralocorticoid effects. The only structural difference is the isomeric position of a methyl group on position 16 of the ring structure. However, these drugs do have distinct activities. Betamethasone and dexamethasone have comparable potencies that are 25 times greater than cortisol for genomic effects because they have similar high affinities for the glucocorticoid receptor that regulates gene expression.8 However, nongenomic effects on ion channels for example are about 6-fold higher for dexamethasone than for betamethasone.9 The few direct comparisons of dexamethasone with betamethasone in developing annals also show differences in the drugs. For example, Ozdenir and colleagues,10 reported that betamethasone promoted more lung maturation with less growth restriction in fetal mice than did dexamethasone. Pregnant sheep developed labor more consistently with fetal infusions with betamethasone than with dexamethasone, and the fetal betamethasone treatment decreased maternal progesterone more than dexamethasone.11 Subtle differences in fetal responses to maternal treatments may also occur in humans. There are reports that betamethasone decreased fetal heart rate variability and changed fetal behavior more than did dexamethasone,12,13 although Subtil and colleagues14 did not detect differences in fetal heart rate responses to the 2 drugs. Independent of the formulations, betamethasone and dexamethasone are not equivalent drugs.

**Dose and Route**

The initial 2-dose 12-mg betamethasone treatment given at a 24-hour interval used by Liggins and Howie7 has been accepted as the standard in almost all trials that have used betamethasone acetate plus phosphate.4 The dexamethasone 4-dose 6-mg treatment at 12-hour intervals was modeled to achieve similar receptor occupancy.15 The Liggins and Howie trial continued beyond the initial publication with randomization to evaluate twice the dose of betamethasone, with no apparent added benefit.16 The dose and intervals for treatment have not been systematically evaluated in the human. The pharmacokinetics of these drugs are complex. These corticosteroids are prodrugs in that soluble betamethasone phosphate and dexamethasone phosphate are dephosphorylated rapidly (half-life <1 hour) by phosphatases to the active drugs.17 The terminal half-life for the free corticosteroids in plasma is about 4 hours, but receptor occupancy should persist for considerably longer.18 After an initial high plasma level in the mother, fetal plasma levels of betamethasone or dexamethasone are about 30% of maternal levels in both humans and sheep.15,19 In contrast, betamethasone acetate as a milled particle of 4 to 12 μm in the betamethasone acetate plus phosphate preparation is relatively insoluble. The free betamethasone enters the plasma slowly after deacetylation and has a terminal half-life of about 14 hours.18 Plasma free betamethasone levels in the pregnant ewe peak within minutes of injection with betamethasone phosphate and then decrease rapidly. In contrast,
betamethasone acetate yields peak betamethasone levels that are about one-tenth that achieved with betamethasone phosphate in the plasma of the ewe. Betamethasone levels are virtually undetectable in fetal blood after maternal treatment with betamethasone acetate.17

Recent experiments in sheep models show how little is known about how these treatments modulate fetal maturation. In fetal sheep models, lower maternal doses of betamethasone phosphate were as effective as the clinical dose for lung maturation with fewer effects on fetal growth.20,21 Single intramuscular (IM) doses of cortisol (fetal), dexamethasone (fetal), or betamethasone phosphate (maternal) do not induce lung maturation in sheep.17,22,23 In contrast, 4 doses of cortisol given to the fetus at 4-hour intervals or 4 doses of betamethasone phosphate given to the ewe do induce lung maturation.22 These results show the need for a sustained fetal exposure for the maturational response.

The assumption has been that the benefits and risks of antenatal corticosteroid therapy result from direct fetal exposures to the agent. The rationale for including the betamethasone acetate in the treatment was that prolonged fetal exposure would be achieved. However, both maternal and fetal plasma free betamethasone levels are low after maternal treatment with betamethasone acetate.17 A single maternal dose of betamethasone acetate is as effective for fetal lung maturation as is the standard 2-dose betamethasone acetate plus phosphate treatment in fetal sheep (Fig. 1). Therefore, very low fetal exposures to betamethasone can induce lung maturation. The implication is that betamethasone acetate alone might achieve the clinical goals with minimal fetal exposure to a corticosteroid. A preparation of betamethasone acetate is not available for clinical use.

Another twist to the relationships between fetal plasma levels of betamethasone and fetal effects is shown in Fig. 2. A fetal IM injection with betamethasone acetate plus phosphate (0.5 mg/kg fetal weight) results in higher fetal plasma betamethasone levels for 3 hours than does a maternal injection of 0.5 mg/kg maternal weight.19

Fig. 1. Fetal indicators of lung maturation after maternal treatments with saline (control), 1 dose of 0.25 mg/kg betamethasone acetate (0.25, Beta-Ac), 1 dose of 0.5 mg/kg Beta-Ac, 4 doses of 0.25 mg/kg betaphosphate (Beta-PO4) given at 12-hour intervals, or 2 doses of Celestone (0.5 mg/kg of a 1:1 mixture of Beta-Ac and Beta-PO4 given at a 24-hour interval). All fetuses were delivered prematurely 48 hours after the initial treatment. (A) Lung compliance measured by the lung gas volume at 40 cm H2O pressure increased for all treated groups relative to controls. (B) The mRNA for the surfactant protein (SP)-B also increased in the fetal lungs. *P<.05 versus controls. (Data from Jobe AH, et al. Betamethasone dose and formulation for induced lung maturation in fetal sheep. Am J Obstet Gynecol 2009; 201(6):611,e1–7.)
Nevertheless, the maternal treatment induces more fetal lung maturation than is achieved with the fetal treatment. Furthermore, the higher direct fetal exposure to betamethasone does not cause fetal growth restriction, whereas the maternal treatment does. These results show that lung maturation is not optimally induced by high fetal plasma levels of betamethasone. Maternal treatment resulting in lower fetal exposure to the corticosteroid induces more lung maturation.

A clinical trial also has identified another quirk of corticosteroid dosing for fetal lung maturation. Betamethasone and dexamethasone can be given orally. Egerman and colleagues randomized women to IM or oral dexamethasone at equivalent effective doses to test the hypothesis that oral treatment would be effective. The trial was stopped because of adverse outcomes in the oral dexamethasone arm of the trial (Table 1). The oral treatment was associated with large increases in newborn sepsis and intraventricular hemorrhage (IVH) with no indication of added benefit for
respiratory distress syndrome (RDS) or death outcomes. There is no good explanation for these adverse outcomes after oral treatment.

The experimental literature does not support the currently used corticosteroids and treatment schedules as optimal for the indication of fetal maturation. The results in animal models suggest that prolonged, but very low fetal exposures to maternal corticosteroids should be evaluated to minimize fetal risks. Furthermore, fetal exposure to the corticosteroid may not be necessary. Perhaps placental responses to the corticosteroids signal the desired fetal effects.

**Clinical Outcomes with Betamethasone versus Dexamethasone**

Nevertheless, the clinician must treat with an available drug. Based on the earlier discussion, comparisons of the 2-dose betamethasone acetate plus phosphate treatment with the 4-dose dexamethasone phosphate treatment are not comparisons of equivalent fetal exposures to the same drug. There are 2 approaches to evaluating the relative benefits or risks of these drug treatments: a direct analysis of trials that randomized women to betamethasone or dexamethasone, or an indirect analysis of the trials that compared each drug with placebo and then a comparison of the outcomes relative to the placebo controls (Table 2). The placebo-controlled trials were performed before 1990 and included primarily more mature infants, whereas the dexamethasone to betamethasone comparison trials were more recent. The indirect comparison identified less RDS with betamethasone as the only significant difference. The direct comparison qualitatively favors dexamethasone for the outcome of severe IVH primarily because of the recent trial reported by Elimian and colleagues.

<table>
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<tr>
<th>Outcomes</th>
<th>Direct Comparison</th>
<th>Indirect Comparison</th>
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<tbody>
<tr>
<td>RDS</td>
<td>1.06 (0.88–1.28)</td>
<td>1.44 (1.14–1.78)</td>
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<tr>
<td>Severe IVH</td>
<td>0.40 (0.13–1.24)</td>
<td>0.47 (0.09–2.33)</td>
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<tr>
<td>Fetal/neonatal death</td>
<td>1.28 (0.46–3.52)</td>
<td>0.96 (0.71–1.30)</td>
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There has been a concern that maternal dexamethasone phosphate treatments may increase periventricular leukomalacia in newborns because of sulfites used for preservative. We believe this situation is unlikely given the sulfite dose and volume of distribution in the mother. Infants are exposed to higher amounts of sulfate from hyperalimentation and other drugs that they receive. The clinical experience of the National Institute of Child Health and Human Development (NICHD) neonatal research network for more than 300 infants was an increase in death with antenatal dexamethasone treatment relative to betamethasone (odds ratio [OR] 1.66; confidence interval [CI] 1.07–2.57). Another large recent series reported significantly less RDS and bronchopulmonary dysplasia for betamethasone-exposed than dexamethasone-exposed infants. Data for the generally favorable long-term outcomes are available only for betamethasone-exposed infants. Despite the multiple trials, no definitive recommendation can be made in favor of 1 drug treatment over the other.

**CLINICAL QUESTIONS**

**Efficacy at Very Early Gestational Ages**

Although treatment guidelines advise the use of antenatal corticosteroid for pregnancies at risk of preterm delivery from 24 weeks’ to 32 to 34 weeks’ gestation, there are minimal data from randomized trials for treatments with deliveries before 28 weeks’ gestational age. The irony is that preterm infants delivered at these very early gestational ages are most likely to benefit from the corticosteroid effects to decrease RDS, IVH, and death. These infants also are of most interest for contemporary perinatal care. The lack of information is historical in origin because the placebo-controlled trials performed before 1990 enrolled few pregnancies with deliveries at less than 28 weeks. A recent meta-analysis and systemic review of corticosteroid use before 26 weeks’ gestation reported no benefits. The investigators acknowledged that the trials and the meta-analysis were underpowered. We also suggest that there are other difficulties with accessing outcomes in these very early gestation outcomes. For diseases like RDS, the incidence is high and the corticosteroid treatment may not prevent RDS. For example, Garite and colleagues found no decrease in RDS, but a significant decrease in the severity of RDS. The care strategies and clinical outcomes also have changed since these trials were performed. New randomized placebo trials are unlikely to be performed to resolve this question.

The biology of corticosteroid effects on the developing fetus and recent clinical experiences are 2 avenues to the evaluation of the usefulness of antenatal corticosteroids for very preterm deliveries. Lung tissue from 12-week to 24-week human fetuses in explant culture responds to corticosteroids, with an increase in epithelial maturation and the appearance of lamellar bodies, the storage organelles for surfactant. Fetal monkeys at early gestations respond to maternal corticosteroid treatments with lung maturation. Thus, there is no biologic reason to believe that the fetal human lung would not respond to antenatal corticosteroids at even previable gestational ages.

Clinical experiences are prone to bias based on the decision to treat with corticosteroids. Nevertheless, the information does represent current practice and outcomes for these high-risk pregnancies. The outcomes for all infants born with gestational ages less than 26 weeks in the United Kingdom and Ireland in 1995 were reported by Costeoloe and colleagues. Antenatal corticosteroids were given to 65% of the women, and the exposed newborns had decreased death (OR 0.57, CI 0.37–0.85), and decreased severe IVH (OR 0.39, CI 0.22–0.77), but not a decrease in RDS. For a more recent cohort of 181 infants born at 23 weeks’ gestation, the 25% who received a complete course of antenatal corticosteroids had an OR for death of
0.18 and a CI 0.06 to 0.54, relative to unexposed infants, although overall morbidity and mortality were high. A recent series from Japan also reported a decrease in RDS and IVH for infants exposed to antenatal corticosteroids who were delivered at 24 to 25 weeks. Death was decreased for infants delivered at 22 to 23 weeks and at 24 to 25 weeks relative to infants not exposed to antenatal corticosteroids. Given the probable benefits, if the expectation is to care for a very preterm infant, then a single course of antenatal corticosteroids is indicated.

**Use in the Late Preterm Period**

Most studies have evaluated antenatal steroid use only up to 34 weeks’ gestation. This upper gestational limit is arbitrary and was chosen to include the sickest neonates in whom prematurity-associated lung disease was life threatening. Recently, it has been realized that there is a significant disease burden that continues beyond this gestational period, because 3 of every 4 preterm births occur between 34 and 37 weeks’ gestation. It is estimated that more than 250,000 infants born at 34 weeks or later are admitted to the neonatal intensive care unit (NICU) each year, many of these for respiratory distress. At 34 weeks nearly 50% of infants require intensive care, and this drops to 15% at 35 weeks and is still 8% at 36 weeks.

In understanding the potential benefit of antenatal steroid treatment in the late preterm period it should be remembered that not all respiratory distress is caused by surfactant deficiency and that antenatal steroids have multiple effects. One of the important steps in lung transition to air breathing is the removal of lung fluid. Through much of gestation, fetal lung development requires the active secretion of fluid into the alveolar spaces, which occurs via a chloride secretory mechanism. As term approaches, lung fluid begins to be transferred from the lumen, across the apical membrane into the interstitium. This process occurs through passive movement of Na from the lumen into the interstitium through Na-permeable ion channels followed by active extrusion of Na from the cell across the basolateral membrane into the serosal space. ENaC regulate the passive transfer of Na and are rate limiting in this process, which is maximally timed to occur in late gestation. Steroids play a key role in ENaC changes and thus in the absorption of fetal lung fluid.

Preliminary data suggest that corticosteroids have an effect on reducing respiratory morbidity in this population by both enhancing borderline surfactant production and by initiating lung fluid removal. In a retrospective cohort analysis, Ventolini and colleagues reported that infants born in the late preterm period who had previously received antenatal corticosteroids (from 24 to 34 weeks) had significantly reduced rates of overall respiratory distress (24.4% vs 81.3%) as well as a reduced rate of RDS (surfactant deficiency) (7.5% vs 35.5%).

Although the individual risk of a late preterm neonate requiring significant respiratory support is small, as a group it becomes substantial. In addition, the accrued medical costs and parental anxiety of mild respiratory difficulties, including transient tachypnea, cannot be ignored. To address this question, the members of the Maternal Fetal Medicine Units Network in collaboration with the National Heart, Lung, and Blood Institute have initiated a prospective randomized trial of antenatal steroids for pregnant women likely to deliver in this window and who have not received steroid treatment earlier. The trial will recruit approximately 2800 singleton and twin gestations and should be completed in 2014.

**Repeated or Rescue Courses**

Although treatment with a single course of antenatal corticosteroids has been clearly integrated into clinical care, controversy exists as to whether the beneficial effects are
time limited and whether retreatment is required. It is clear from animal and human studies that some of the effects of treatment such as surfactant production are reversible after approximately 7 to 10 days, but the impact of time on other beneficial effects as well as the overall clinical impact are less well described. Until recently, most clinical studies have suggested that the maximal effect of treatment does diminish over time, but all of these observational evaluations have been limited by multiple confounding factors.

Over the last decade several multicentered, prospective, randomized trials have been performed comparing a single course of treatment with retreatment at various intervals ranging from 1 to 2 weeks. These results have been summarized in a Cochrane review that includes results for more than 2000 women. In this analysis, treatment with repeat courses of corticosteroids is associated with a reduction in the overall occurrence of respiratory distress (relative risk [RR] 0.82, CI 0.72–0.93) and in the frequency of severe neonatal lung disease (RR 0.60, CI 0.48–0.75). In addition, repeat doses reduced overall serious infant morbidity (RR 0.79, CI 0.67–0.93). No significant differences were seen in other outcomes assessed, including chronic lung disease, perinatal mortality, IVH, periventricular leukomalacia, and maternal infection. The investigators conclude that the acute short-term pulmonary benefits for neonates support the use of repeat doses of antenatal corticosteroids.

Although repeat courses of antenatal corticosteroids may improve neonatal pulmonary status, there are concerns that repetitive retreatment may be harmful. Although the Cochrane review showed no overall reduction in birth weight of infants exposed to repeat steroids, most fetuses had only 1 or 2 subsequent courses of treatment. However, in the US NICHD trial in which undelivered pregnancies were all retreated weekly until 34 weeks’ gestation, 64% of infants had 4 or more repeat courses. In this subgroup receiving multiple exposures, there was a significant reduction in birth weight and an increase in small-for-gestational-age infants. Placental size in the repeat group was also smaller.

The ultimate evaluation of the efficacy and safety of repeat courses of antenatal steroids is the impact of treatment on the long-term health of the infant. The 3 largest multicentered national trials have now published their 2-year to 3-year follow-up. The results of these studies are reassuring, with no difference in weight, neurodevelopment outcome or other health parameters in the group receiving multiple courses. In the US study in particular, in which a large number of infants were exposed to more than 4 courses, there was no difference in any anthropometric or developmental parameters by 2 years of age. However, of some concern was the finding of cerebral palsy in 6 infants in the repeat corticosteroid group. All received 4 or more courses of corticosteroids, none had any perinatal complications, and 5 were born at 34 weeks or later in gestation. Only 1 child in the placebo group was diagnosed with cerebral palsy. Overall the number of cases of cerebral palsy was small, and these results did not reach statistical significance (RR 5.7, CI 0.7–46.7). However, the predominance of this finding in infants exposed to 4 or more courses suggests that caution should be advised in exposing the fetus to multiple courses of steroids and that routine prophylactic retreatment is inadvisable.

Ideally, antenatal steroid treatment should be given so that birth occurs more than 24 hours after the initial course and within 7 days. Obstetricians are limited in their ability to predict preterm delivery with such accuracy, with approximately 50% of patients given an initial course of antenatal corticosteroids remaining undelivered 7 to 10 days later. Women treated before 28 weeks’ gestation seem more likely to give birth more than 7 days later than those treated after 28 weeks.

To maximize the likelihood that every neonate has been treated during their ideal therapeutic window without requiring routine repetitive dosing, a rescue approach
has been suggested in which initial treatment is given when a substantial risk of preterm birth is suspected, and if delivery does not occur within 7 to 14 days, a single retreatment (rescue) course is administered when preterm birth seems imminent. The efficacy of this approach has recently been reported by Garite and colleagues,\textsuperscript{68} who randomized patients who remained at risk for preterm delivery 2 weeks or longer after their initial treatment to receive either a repeat course of betamethasone or a placebo when preterm delivery was highly likely. The group receiving an active drug rescue course had reduced composite morbidity (OR 0.65 [0.44–0.97]), a lower frequency of RDS (OR 0.64 [0.43–0.95]), and less need for postnatal surfactant treatment (OR 0.65 [0.43–0.98]). There was no reduction in bronchopulmonary dysplasia or the need for ventilator support. Birth weights and the frequency of intrauterine growth restriction were similar in both groups.

A few other observations from this study that may be of guidance to the clinician are noteworthy. In evaluating the timing and duration of the rescue effect, these investigators showed that the largest and most significant improvement in composite morbidity was seen in infants delivering between 2 and 7 days from the first dose of the rescue course. Although not a predesignated analysis, the investigators examined in which gestational ages the greatest efficacy of rescue treatment was seen. The reduction in composite morbidity was limited to babies born at less than 33 weeks, with no difference in outcome thereafter.

There is no consistent agreement among experts on the need and appropriateness of repeat administration of antenatal steroids. To address this inconsistency, a group of investigators representing each of the major trials of repeat and rescue dosing have recently been funded to perform an individual patient data meta-analysis to determine the efficacy and safety of various repeat dosing approaches. Led by Caroline Crowther of the University of Adelaide, this study should answer many of the remaining questions. In the meantime, it seems safe to administer a single rescue course if preterm birth at less than 33 weeks seems likely. The dose should be timed in an attempt to have delivery within 2 to 7 days from the first dose of the rescue course. Retreatment of infants beyond 33 weeks seems not to be effective or necessary.

**Twins**

The efficacy of antenatal corticosteroid use in twin gestations remains uncertain. The impact of antenatal corticosteroids in this clinical subcategory has never been evaluated in prospective trials of treated and untreated twins, so information is available only from cohort studies with multiple potential confounders or from subgroups of twins included within larger prospective trials of mostly singletons. This lack of information is unfortunate because twins and higher-order multiple gestations are an increasingly important contributor to preterm birth. The rate of twin births has increased 65% over the last 30 years and triplet gestations have increased more than 400%. Almost 60% of twins deliver at less than 37 completed weeks of gestation and more than 10% before 32 weeks.\textsuperscript{69}

Most studies have shown no significant benefit to antenatal corticosteroid administration in twins or if one is shown it seems to be less than that seen with singletons.\textsuperscript{70,71} A recent Cochrane meta-analysis performed by Roberts and Dalziel\textsuperscript{4} showed a nonsignificant reduction in the rate of RDS in twins after the administration of steroids (OR 0.85, 95% CI 0.60–1.20). Similarly, in one of the largest population based studies evaluating the impact of steroids in twins, Blickstein and colleagues\textsuperscript{71} reported that a complete course has a similar 40% to 50% reduction in RDS compared with no steroid treatment of both singletons and twins but that the effect is plurality dependent. Compared with treated singletons the OR for RDS in twins was 1.4 and in triplets it was 1.8.
There are several reasons that steroid treatment has not been confirmed to reduce RDS in twins. Initially it was speculated that the larger volume of distribution of women carrying twins and the larger fetal volume may result in reduced steroid exposure of the fetus. It has been shown that compared with women carrying a singleton, the half-life of betamethasone is shorter and the clearance greater in women carrying twins. However, most recently, Gyamfi and colleagues have measured both maternal and fetal (cord) betamethasone levels in both singleton and twin gestations and reported no difference. The cord betamethasone levels were higher in twins.

The most likely reason that twins have shown improvement after steroids is related to the small sample size of most studies, giving them insufficient power to confirm a difference. For example, the Cochrane analysis is based on only 4 studies with 167 twins and 157 controls. Confirming the 0.85 OR seen in this analysis would take a sample size of almost 4000 twin gestations.

From a practice standpoint it seems reasonable to treat women with twins who are at risk for preterm birth with a single course of antenatal steroids using the same dosing regimen as with singletons. One problem with this approach is predicting when to treat so that the maximum numbers of preterm infants are exposed and so that unnecessary treatment is minimized. To evaluate this approach, Murphy and colleagues compared 2 twin cohorts at risk for preterm birth. One group received prophylactic steroids every 2 weeks starting at 24 weeks, whereas the other group received a rescue course if preterm delivery appeared imminent. In this comparison, there was no significant benefit to routine treatment, with more than a 7.5-fold greater risk of unnecessary exposure. However, in the rescue group almost one-third of infants delivering preterm did not receive a complete course of treatment.

**Maternal Obesity**

Obesity is known to alter the maternal volume of distribution, raising the question of whether the dosing of antenatal steroids should be adjusted based on maternal body weight. Although obesity does not seem to alter drug absorption, tissue distribution and drug elimination may be changed.

Gyamfi and colleagues recently evaluated the impact of maternal obesity on both maternal and cord betamethasone levels. After controlling for the number of days since steroid treatment, number of courses, plurality, and gestational age there was no significant difference in maternal or cord betamethasone levels in obese patients.

**Elective Cesarean Section**

Delivery by cesarean section in the near-term period without preceding labor increases the occurrence of fetal respiratory morbidity. Compared with infants delivered vaginally those delivered by prelabor cesarean section have a 2.3-fold to 6.8-fold increased risk of respiratory morbidities, including transient tachypnea, surfactant deficiency, and pulmonary hypertension. The risk of an NICU admission is doubled. Even after 37 weeks' gestation, the risk of morbidity is inversely related to gestational age. In a large series of women delivering by repeat cesarean delivery, births at 37 weeks and at 38 weeks were associated with an increased risk of adverse respiratory outcomes compared with deliveries in the 39th week. Mechanical ventilation, newborn sepsis, hypoglycemia, admission to the NICU, and hospitalization for 5 days or more were increased by a factor of 1.8 to 4.2 for births at 37 weeks and 1.3 to 2.1 for births at 38 weeks. The risk of any adverse outcome decreased from 15.3% to 8% from 37 to 39 completed weeks; the risk of RDS decreased from 3.7% to 0.9%, and transient tachypnea decreased from 4.8% to 2.7%.
Ideally, all prelabor cesarean deliveries would occur only after 39 completed weeks of gestation but this is not always possible because obstetric conditions of the mother or child may make a near-term delivery necessary. Whether administration of steroids in these cases is appropriate is uncertain, but a recent study suggests that it may be helpful. The Antenatal Steroids for Term Cesarean Section (ASTECS) trial addressed the value of antenatal corticosteroids in patients undergoing elective cesarean section at term. Candidates were randomized to a course of antenatal betamethasone or no treatment. The study enrolled 998 women, 503 of whom received active treatment. Corticosteroids significantly decreased the rate of admission to the special care nursery for respiratory distress (RR 0.46, CI 0.23–0.93), with nonsignificant reductions in all respiratory morbidities. Although suggestive, the study was not blinded and did not use a placebo. In addition, respiratory distress was unconventionally defined as tachypnea (rate >60 breaths per minute) with grunting, recession, or nasal flaring. The investigators hypothesized that corticosteroid treatment decreased respiratory complications by increasing epithelial Na channel (ENaC) expression and function, thus allowing the lung to convert from active fluid secretion to sodium and fluid absorption. Because term infants, even after elective cesarean delivery, have a low incidence of respiratory morbidity, the number needed to treat to prevent 1 case of RDS is between 80 and 100 compared with 20 and 30 in the late preterm period and approximately 5 for infants at less than 32 weeks.

Inflammation and Corticosteroids

There is not much controversy about corticosteroid treatment of women at risk of preterm delivery with ruptured membranes, although membrane rupture is a strong surrogate indicator for clinically silent chorioamnionitis. Clinical experience and a meta-analysis of the trial data support the benefits of antenatal corticoid treatments despite preterm rupture of membranes or a retrospective diagnosis of histologic chorioamnionitis. A problem for the analysis of current clinical series is that most women have received antenatal corticosteroids. For example, 87% of women from a consecutive series of 457 deliveries at less than 32 weeks’ gestation received corticosteroids, and the women not treated differed in the incidence of preeclampsia and type of preterm birth. Decisions about which women may benefit from antenatal corticosteroids in the future may depend on new information about how infection/inflammation affects the pregnancy and outcomes. For example, new information that much of the histologic chorioamnionitis is associated with nonculturable organisms detected by polymerase chain reaction analyses will change how the perinatal community thinks about and diagnoses antenatal infections. In experimental models with live Ureaplasma, the organism most frequently associated with histologic chorioamnionitis, the maturational effects on the fetal lung depend on the amount of inflammation and the chronicity of the infection, variables that are not considered clinically. Further, fetal inflammatory and immune modulatory responses to the combined exposures of antenatal corticosteroids and fetal inflammation are complex and depend on the timing and the order of the exposures. We know little about how the interactions of these responses may benefit or harm the fetus.

AN INTERNATIONAL PERSPECTIVE

Although antenatal corticosteroids are standard of care for pregnancies at risk of preterm delivery before 32 to 34 weeks worldwide, the use of antenatal corticosteroids in resource-poor environments is estimated to be only about 10% for women at risk. This low use has been recognized as a target to improve outcomes by the World Health
Organization. However, there are multiple unanswered questions about how to best improve outcomes for the approximately 30% of newborn deaths within the first month of life attributed to prematurity.\(^8\) The drug-related issues are substantial. Betamethasone acetate plus phosphate may be the drug of choice for the developed world, but the stability of this preparation has been poorly studied. The need to give repeated timed injections in low-resource environments is also a challenge. However, the largest challenge is the identification of the deliveries at risk in populations with no or minimal antenatal care or gestational dating and with a high incidence of fetal growth restriction. Furthermore, these populations with significant incidences of malaria, tuberculosis, and human immunodeficiency virus may be at risk if treated with corticosteroids. Even if treatments can be given effectively for home and low-level clinic deliveries, there is no benefit unless the care for the preterm infant is improved. Antenatal corticosteroids should be targeted for pregnancies at risk of delivering infants with birth weights of perhaps more than 1500 g, because the very preterm infants will likely not survive in these environments without risk of significant handicaps. However, the attack rates for antenatal corticosteroid responsive problems in these later gestational age infants remain essentially unstudied even in the developed world.\(^8\) The NICHD has started a trial to evaluate if antenatal corticosteroids can benefit these late-preterm deliveries. The use of antenatal corticosteroids in resource-poor environments is challenging and may not be effective or free from risk.

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Antenatal Corticosteroids in the Management of Preterm Birth: Are We Back Where We Started?

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KEYWORDS
- Corticosteroids  •  Preterm birth  •  Prematurity  
- Neonatal mortality  •  Respiratory distress

TRENDS IN PRETERM BIRTH

For nearly three decades, the preterm birth rate has been steadily increasing in the United States, rising by more than 30% during this time period. However, after peaking at 12.8% of all births in 2006, the preterm birth rate has declined for three consecutive years, to 12.18% in 2009. As preterm birth can result in serious long-term medical and developmental problems, with tremendous individual, family, and societal cost, this represents a most welcome trend. Meeting the Healthy People 2020 goal of an 11.4% rate of preterm birth may now be possible.

The reasons for this recent downturn in preterm birth are not entirely clear. The decrease has been demonstrated in both late preterm (34–36 completed weeks) deliveries and early preterm deliveries (<34 weeks). Preterm births for patients delivered by cesarean, induced vaginal birth, and noninduced vaginal birth have all declined, and the reduction in preterm birth is not explained by a change in the proportion of multiple births. These data suggest that efforts by the American Congress of Obstetricians and Gynecologists (ACOG) and other advocacy groups such as the March of Dimes have helped to decrease iatrogenic late preterm birth. In addition, interventions such as 17α-hydroxyprogesterone caproate for prevention of recurrent preterm birth and vaginal progesterone for prevention of preterm birth in women with a short cervix may be effectively reducing the rate of spontaneous preterm birth.

Even with the recent decline, preterm birth remains a critical public health issue in this country. Primary prevention of preterm birth remains the ultimate goal. However,
until a better understanding of the mechanisms underlying preterm birth leads to its effective and universal prevention, efforts to minimize the impact of preterm birth on neonatal morbidity and mortality are paramount. Antenatal corticosteroid treatment for fetuses born preterm remains one of the most important antenatal interventions in obstetric practice.

HISTORICAL PERSPECTIVE

The story of antenatal corticosteroids—the discovery of this therapy for fetal maturation, the adoption into clinical practice, and the evolution of corticosteroid administration in obstetrics—highlights several fascinating and universal truths about science and medicine. The first is that scientific breakthroughs are often happened upon incidentally. In the 1960s, the obstetrician Graham Liggins was investigating factors involved in the initiation of labor in a sheep model. His goal was to solve the problem of preterm labor by determining what controls labor at term. While testing his hypothesis that steroid hormones might trigger labor, he found that preterm lambs exposed to corticosteroids in utero had structurally more mature lungs, were viable at an earlier gestational age, and had less severe respiratory distress at birth than expected. The pediatrician Ross Howie helped Liggins appreciate the potential for this therapy to improve the lung function in premature infants. Liggins and Howie then designed and conducted a randomized controlled trial (RCT) on maternal administration of betamethasone. The results were published in a landmark article in 1972. Not only did this therapy reduce the incidence of respiratory distress syndrome (RDS) in preterm infants from 15.6% to 10.0%, but further analysis showed a reduction in neonatal mortality from 11.6% to 6.0%.

The second point that the story of corticosteroids illustrates is that clinicians can be slow to adopt new therapies into clinical practice. Over the next few decades, additional studies corroborated the findings of Liggins and Howie. However, concerns about the quality of the evidence and fears about potential side effects made obstetric providers hesitant to use this therapy routinely for women at risk for preterm birth. In 1990, Crowley and colleagues published a meta-analysis of 12 RCTs of antenatal corticosteroids, demonstrating that this therapy significantly reduced RDS and other neonatal morbidities such as intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) as well as overall neonatal mortality. In 1994 the National Institutes of Health (NIH) held a consensus conference to review the safety and efficacy of antenatal corticosteroids. Based on the recent meta-analysis and other available evidence, the panel recommended that antenatal corticosteroids be administered to all women at risk for preterm birth between 24 and 34 weeks’ gestation. This recommendation and the endorsement by ACOG helped to increase the utilization of antenatal corticosteroids dramatically. Within a few years, 70% to 90% of women who delivered at less than 34 weeks had received a course of corticosteroids. In fact the logo for the Cochrane Collaboration features one of the forest plots from the Crowley meta-analysis because of the tremendous impact of this study on obstetric practice and outcomes for premature infants.

Subgroup analysis from the initial trial on antenatal corticosteroids suggested that effectiveness peaked between 2 and 7 days from the initial injection. This led to the phenomenon of mothers being considered “steroid complete” at 48 hours. Subsequent systematic reviews also suggested a waning of steroid effect at 7 days, prompting concern about the management of mothers who remained pregnant after 7 days but were still at high risk for preterm delivery and adverse neonatal outcomes. Hence the third conclusion in the history of corticosteroids: Clinicians can become overeager in the use of certain interventions before there are adequate supportive
The administration of repeat courses of corticosteroids to pregnant women at risk for preterm delivery quickly became common practice in the 1990s. In a 1995 survey of perinatologists, 96% of respondents reported willingness to administer more than one course, and more than half would give four or more repeat courses. The routine use of repeat corticosteroids became so widespread that the NIH reconvened a consensus conference in 2000, only 6 years after the conference to promote corticosteroid adoption, to address this issue. The panel recommended that repeat courses of corticosteroids be limited to patient participating in RCTs, because of the insufficient data on the safety and efficacy of this practice.

It is also interesting to note how arbitrary choices can insinuate themselves into standard clinical practice. The initial Liggins and Howie trial used betamethasone as a 1:1 mixture of betamethasone phosphate and betamethasone acetate (currently available as Celestone), as have nearly all subsequent trials. The two injection course of 12 mg given at a 24-hour interval was also empirically chosen by Liggins and Howie. Despite clear evidence of the effectiveness of this therapy, this dosage and this regimen have never been rigorously tested in clinical studies. In fact, this regimen has become such a standard practice that future clinical trials to test them will be difficult, or even impossible to conduct.

This article takes a critical look at the evidence for the efficacy and safety of antenatal corticosteroids that has accumulated over the past 40 years. The story of antenatal corticosteroids is ongoing, and there is much at stake as we continue to perfect the use of this vital therapy.

**EFFICACY OF ANTENATAL CORTICOSTEROID TREATMENT**

The most recent Cochrane review on antenatal corticosteroids for women at risk for preterm birth included 21 studies of 3885 patients and 4269 infants. The authors included all randomized comparisons of antenatal corticosteroid (betamethasone, dexamethasone, or hydrocortisone) administration to placebo or no treatment for women expected to deliver preterm. Treatment with a single course of antenatal corticosteroids decreased the risk of neonatal death by 31% (95% confidence interval [CI] 19%–42%, 3956 infants). The risk of RDS was reduced by 34% (95% CI 27%–41%, 4038 infants), IVH by 46% (95% CI 31%–57%, 2872 infants), NEC by 54% (95% CI 26%–71%, 1675 infants), and infection in the first 48 hours by 44% (95% CI 15%–62%, 1319 infants). Need for respiratory support and admission to the neonatal intensive care unit were also reduced by therapy.

In studies that examined long-term outcomes of antenatal corticosteroids, treatment was associated with a 51% reduction in developmental delay in childhood (95% CI 0–76%, 518 children) and a trend toward fewer children having cerebral palsy (relative risk [RR] 0.60, 95% CI 0.34–1.03, 904 children). The longest specified duration of follow-up in these studies was 6 years.

The authors concluded that a single course of antenatal corticosteroids should be considered routine for preterm delivery. In fact the weight of this evidence was so compelling that “There is no need for further trials of a single course of antenatal corticosteroids versus placebo in singleton pregnancies.”

**EFFICACY IN SPECIAL PATIENT POPULATIONS**

Though the efficacy of antenatal corticosteroids to improve outcomes after preterm birth may be established for singleton infants, there remain questions about efficacy in specific patient populations.
Multiple Gestations

Patients with multiple gestations are at significantly higher risk of delivering preterm. In 2008, 58.9% of twins were delivered preterm (<37 weeks’ gestation), with 11.6% of them born before 32 weeks. In contrast, only 10.6% of singletons were born preterm, with 1.6% born before 32 weeks. Triplet gestations and higher order multiples are at even higher risk. Patients with multiple gestations are more likely to be delivered preterm for a multitude of reasons, including higher rates of obstetric complications such as preterm labor and preterm rupture of membranes, and the increased incidence of maternal complications such as preeclampsia in these pregnancies.

In the most recent Cochrane review, antenatal corticosteroids were not effective in reducing the risk of RDS, IVH, or neonatal death for women with multiple pregnancies. In a much larger population-based study examining the incidence of RDS in singleton, twin and triplet gestations exposed to antenatal corticosteroids, Blickstein and colleagues demonstrated that plurality is an effect modifier. However, in this study a complete course of antenatal corticosteroids did reduce the risk of RDS compared to no steroid treatment in both twin and triplet pregnancies. Smaller, retrospective studies have been divided on the effectiveness of antenatal corticosteroids to reduce neonatal morbidity and mortality in preterm twin versus singleton pregnancies.

There may be physiologic reasons for the diminished effectiveness of antenatal corticosteroids in multiple gestations. Some authors have suggested that the larger volume of distribution in the maternal and fetal compartments in multiple gestations would have a dilutional effect on the concentrations of drugs reaching the fetuses. However, one study of the pharmacodynamics of betamethasone showed that the volume of distribution was actually the same between singleton and twin pregnancies. These investigators did demonstrate that twin pregnancies exhibited a shorter half-life and faster clearance of betamethasone, which they postulated was an effect of the two fetoplacental units accelerated metabolism of betamethasone, which could potentially decrease effectiveness. More recently Gyamfi and colleagues demonstrated that maternal and umbilical cord serum betamethasone concentrations at delivery did not differ between singleton and twin gestations, suggesting that any apparent decrease in effectiveness of steroids in twin pregnancies is not due to inadequate fetal drug levels. This analysis was restricted to patients receiving multiple courses of antenatal corticosteroids who delivered within 1 week of betamethasone administration.

The most current evidence does not confirm the efficacy of antenatal corticosteroids in multiple gestations. Yet guidelines uniformly advocate for corticosteroid administration in these pregnancies at risk for preterm birth because of the weight of the evidence in singleton gestations. The most likely reason that studies in multiple gestations have not demonstrated efficacy is the quality of the available data, which do not include large prospective trials comparing corticosteroid treatment versus no treatment. Only two prospective trials totaling 167 twins and 157 controls supplied the data for the Cochrane review. The remainder of the evidence comes from retrospective studies with multiple potential confounders. The Cochrane authors suggested that there may be additional unpublished data on twin pregnancies that may help clarify the benefit of treatment in this population, as further trials will be difficult to conduct.

Obese Women

The problem of obesity has reached epidemic proportions across developed nations and even across the globe. Obesity is an independent risk factor for many different

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adverse obstetric outcomes, although most studies have not found a strong association between obesity and spontaneous preterm delivery.\textsuperscript{24,25} Still, with the high prevalence of obesity, the need for administration of antenatal corticosteroids to an obese patient is a common occurrence in obstetric practice. Just as in multiple gestations, it has been hypothesized that obesity might influence the effectiveness of antenatal corticosteroids because of differences in tissue distribution and drug elimination. However, Hashima and colleagues found that body mass index (BMI) did not influence neonatal outcome in women receiving a single course of antenatal corticosteroids.\textsuperscript{26} In fact, in a study of maternal and cord serum betamethasone levels, there was no significant difference between obese and nonobese women (BMI ≥30 kg/m\textsuperscript{2} vs BMI ≤30 kg/m\textsuperscript{2}) after controlling for confounding factors.\textsuperscript{22} Therefore, despite theoretical concerns, there is no current evidence supporting an alternative antenatal corticosteroid regimen based upon maternal BMI. 

\textbf{Intrauterine Fetal Growth Restriction} 

The literature appears to be conflicting on the efficacy of antenatal corticosteroids for pregnancies complicated by fetal growth restriction. As with the patient populations previously discussed, there are no randomized studies specifically designed to determine the benefits and risks of antenatal corticosteroid treatment in this group and therefore the evidence consists of observational and retrospective trials with their inherent limitations. Largely because the first trial of Liggins and Howie suggested an increased risk of fetal death in pregnancies complicated by hypertension and fetal growth disorders, these patients have been excluded from most of the subsequent trials.\textsuperscript{5} 

One large population-based study of infants with intrauterine growth restriction (IUGR) demonstrated that the benefits of antenatal corticosteroids were similar to those seen in normally grown infants. This study included 1720 infants between 25 and 30 weeks’ gestation with outcomes reported in the Vermont Oxford Network database.\textsuperscript{27} The risks of RDS, IVH, and neonatal death were all significantly reduced by therapy. Among the outcomes evaluated, only necrotizing enterocolitis was not reduced in neonates with IUGR. Interestingly, there was a smaller reduction in the rate of RDS among IUGR infants (odds ratio [OR] 0.70) than normally grown infants (OR 0.50). This information seems to refute the premise that in utero “stress” causes the release of endogenous steroid hormones, which negates the effect of exogenous treatment, though the magnitude of the corticosteroid effect might be less in growth-restricted infants because of this phenomenon. Another case control study looked at long-term outcomes of preterm infants with growth restriction secondary to placental insufficiency.\textsuperscript{28} Of 124 infants born between 26 and 32 weeks’ gestation survival without disability or handicap at 2 years of age was higher in the corticosteroid group than in matched controls. Conversely, a recent systematic review of antenatal corticosteroid therapy for growth-restricted, preterm infants concluded that treatment has no effect on neonatal morbidity or mortality in this population.\textsuperscript{29} 

Not only is there a degree of uncertainty about efficacy of antenatal corticosteroids for growth-restricted fetuses, but also there is some concern about the safety of use in this population. IUGR is associated with alterations in cardiovascular function to maintain adequate blood flow to vital organs. Glucocorticoids are powerful regulators of vascular tone, and it is possible that this has a particularly detrimental effect on brain development and long-term function. In a compelling study using a sheep model, Miller and colleagues demonstrated that IUGR fetuses display significant carotid blood flow reperfusion in response to maternal betamethasone administration, which may lead to lipid peroxidation in the fetal brain, thereby contributing to an
increased incidence of cell death. There may also be adverse effects of corticosteroid administration on placental function and fetoplacental dynamics, which place these fetuses at risk for adverse neurological outcomes.

Several investigators have advocated for a RCT to examine whether treatment is truly beneficial for IUGR fetuses. This would appear to be particularly prudent given the concerns regarding short- and long-term safety in this population.

**Very Early Preterm**

Advances in neonatology and obstetric care in the last few decades have resulted in increased survival of extremely premature infants. Because of this, resuscitation of preterm infants before 24 weeks’ gestation has become increasingly common. The administration of antenatal corticosteroids at 23 weeks’ gestation and even earlier has become more frequent, without clear evidence to support the benefit in this population.

In a post hoc analysis, the Cochrane review evaluated outcomes of antenatal corticosteroid treatment versus placebo by gestational age at entry to the trial. Neonatal death was significantly reduced in corticosteroid-treated infants entering a trial, from 26 to 29 6/7 weeks (RR 0.67, 95% CI 0.45–0.99) but not from less than 26 weeks (RR 1.87, 95% CI 0.61–5.87). Similarly, RDS was reduced in all gestational ages with the exception of less than 26 weeks’ gestation. Unfortunately there are very few trials that included pregnancies less than 26 weeks’ gestation; only one study with fewer than 30 infants supplied the data for this group.

In 2011, Onland and colleagues published an updated systematic review of RCTs on the effects of antenatal corticosteroids given before 26 weeks’ gestation. Nine trials that together randomized 1118 subjects were included; publication dates ranged from 1980 to 2006. Although none of the existing trials actually reported the outcomes in this particular subgroup, metaregression and subgroup meta-analysis revealed no significant reduction of neonatal mortality or morbidity in the corticosteroid-treated group compared with the untreated group. Certainly these analyses may be underpowered to demonstrate effectiveness. It is also possible that antenatal corticosteroids can improve lung function only once adequate numbers of primitive alveoli and lamellar bodies have started to appear, which typically occurs in the saccular phase of lung development beginning at approximately 25 weeks’ gestation, though some in vitro studies would suggest a maturational effect can occur earlier in gestation.

However, if there is a beneficial effect of antenatal corticosteroids at very early gestational ages, it may be more evident in mortality rates and neurologic morbidity than in prevention of RDS. Evidence from the EPICure study, a prospective cohort study of all infants born at less than 26 weeks’ gestation in the United Kingdom and Ireland in 1995, showed that exposed newborns had decreased rates of death (OR 0.57, 95% CI 0.37–0.85) and severe IVH (OR 0.39, 95% CI 0.22–0.77), but not a decreased rate of RDS. A more recent retrospective cohort study of 181 infants born at 23 weeks’ gestation also showed that antenatal corticosteroids decreased the risk of death (OR 0.32, 95% CI 0.12–0.84) relative to unexposed infants. A retrospective series from Japan even demonstrated a decrease in mortality of infants born at 22 or 23 weeks’ gestation after exposure to corticosteroids.

Although the results of observational cohort studies and retrospective analyses are sensitive to various biases, at times they represent the best of our understanding of the evidence, particularly when randomized studies are unavailable. In a large prospective cohort of 4446 infants born at 22 to 25 weeks’ gestation published by Tyson and colleagues from the Neonatal Research Network of the National Institute of Child Health and Human Development, multivariable analyses showed that those
who received intensive care, were exposed to antenatal corticosteroids, were of female sex, and were from singleton pregnancies and of higher birth weight had reduced rates of death.\textsuperscript{37} In addition, among survivors the risk of death or impairment at 18 to 22 months corrected age was also reduced by corticosteroid exposure. Long-term data from the EPICure investigators also showed that antenatal corticosteroids were associated with an increased mental development index assessed at 2.5 and 6 years of age.\textsuperscript{38}

The decisions surrounding the “threshold of viability” are exceedingly difficult, on the part of patients, families, obstetricians, and neonatologists. Even with the most aggressive intervention, the neonatal mortality rate is high, as is the chance of adverse long-term neurodevelopmental outcome. Despite the lack of randomized data on efficacy in the very preterm period, the suggestion of benefit for these preterm infants seems sufficient to recommend its use.

\textit{Late Preterm}

Most studies to date have evaluated antenatal corticosteroid administration to patients at risk for preterm birth less than 34 0/7 weeks’ gestation. Certainly the risk of neonatal death in the late preterm period (34 0/7–36 6/7 weeks) is exceedingly low, and the risk of the major morbidities that antenatal corticosteroid use has been shown to decrease (RDS, IVH, NEC) are relatively rare. However, in deciding whether antenatal corticosteroid use is appropriate at a specific gestational age, the frequency of disease must be balanced by the total number of infants who may benefit. In fact, because nearly 75% of all preterm births occur in the late preterm period, the absolute number of infants being admitted to the neonatal intensive care unit for respiratory distress or a respiratory indication is significant.\textsuperscript{16}

Interestingly, the Cochrane review supports use of antenatal corticosteroids for women at risk of preterm birth up to 34 6/7 weeks’ gestation.\textsuperscript{15} This recommendation arose from the apparent decrease in the rate of RDS in the subgroup of infants receiving treatment between 33 and 34 6/7 weeks (RR 0.53, 95% CI 0.31–0.91). The Royal College of Obstetricians and Gynaecologists (RCOG) recommends that clinicians offer a single course of antenatal corticosteroids to women up to 34 6/7 weeks who are at risk of preterm birth.\textsuperscript{39}

It is obvious that if antenatal corticosteroids work to improve respiratory function, there is likely to be a continuum of benefit across the preterm, and potentially even the early term period. It has been hypothesized that corticosteroids may be effective at later gestational ages, not because of an increase in surfactant production from type II alveolar cells or acceleration in lung structural development reducing the incidence of classic RDS, but by increasing expression of epithelial sodium channels (ENaCs) that allow the alveoli to convert from active fluid secretion to sodium and fluid absorption with subsequent reduction of fetal lung fluid.\textsuperscript{21}

To answer this question formally, the Maternal Fetal Medicine Units Network is currently conducting a prospective, RCT of antenatal corticosteroids for patients at risk for late preterm birth. The trial is expected to be completed in 2014. It will be particularly interesting to see if antenatal corticosteroids confer an overall benefit in this population, or if the benefit is dependent on mode and circumstances of delivery such as cesarean versus vaginal delivery or indicated preterm birth versus spontaneous preterm birth. Multiple studies have suggested the potential benefit of antenatal corticosteroids to decrease respiratory morbidity even at term for patients delivered by elective cesarean.\textsuperscript{40–42}
SAFETY OF ANTENATAL CORTICOSTEROID TREATMENT

A single course of antenatal corticosteroids is not associated with any significant short-term fetal or neonatal adverse effects. Specifically, studies have shown no difference in the rate of fetal death in exposed versus unexposed. For the neonate, there is no impact of antenatal corticosteroids on birthweight, hypothalamic–pituitary axis function, or the incidence of proven infection while in the intensive care unit. Importantly, long-term follow-up of those enrolled in RCTs through early adulthood shows no apparent adverse neurologic or cognitive effects from a single course of treatment.

There have been no reports of serious maternal complications linked to antenatal corticosteroid treatment. The Cochrane review did not demonstrate any statistically significant difference in the rate of chorioamnionitis (RR 0.91, 95% CI 0.70–1.18) or puerperal sepsis (RR 1.35, 95% CI 0.93–1.95) in treated versus untreated patients. Patients with pregestational or gestational diabetes will frequently experience an increase in hyperglycemia and those on medical treatment may require temporary adjustments in their regimens. For patients with poor glycemic control, inpatient observation during antenatal corticosteroid treatment may be required. Of note, patients with diabetes have universally been excluded from RCTs on antenatal corticosteroids, so the benefit of corticosteroid treatment has been extrapolated from the non-diabetic population.

There are no specific contraindications to a single course of antenatal corticosteroids. However, there is concern that the immunosuppressive effect would exacerbate systemic infection or activate latent disease. Active tuberculosis has been suggested as a potential contraindication for antenatal corticosteroid treatment, although there is no evidence upon which this is based. Clearly this will not be as common a problem in developed countries as it will be in developing countries where antenatal corticosteroid administration is still a rare practice. Close monitoring of the safety of corticosteroid treatment in developing countries as the use increases is critical.

Preterm Premature Rupture of Membranes

Data from the Cochrane review demonstrates reductions in neonatal death, RDS, IVH, and NEC in the subgroup of infants whose mothers received antenatal corticosteroids for preterm premature rupture of membranes (PPROM). There is no increase in maternal or neonatal infection in this setting. However, concern remains about use of corticosteroids in this population because of the increased risk of chorioamnionitis and the strong association between clinical chorioamnionitis and cystic periventricular leukomalacia as well as cerebral palsy. A recent meta-analysis of observational studies demonstrated that antenatal corticosteroids were effective in reducing neonatal mortality and morbidity (to include severe IVH and periventricular leukomalacia) in the setting of both histologic and clinical chorioamnionitis. However, because of lingering concern about the preterm delivery in the setting of chorioamnionitis largely stemming from a trial of weekly antenatal corticosteroids, ACOG still does not fully endorse corticosteroid administration after 32 weeks’ gestation. Close monitoring of the safety of corticosteroid treatment in developing countries as the use increases is critical.
antenatal corticosteroids for patients with PPROM up to 32 to 34 weeks in the absence of overt infection.

**CHOICE OF ANTENATAL CORTICOSTEROID**

Both betamethasone and dexamethasone have demonstrated efficacy in the promotion of fetal maturity. Betamethasone (given as a combination of betamethasone sodium phosphate and betamethasone acetate) is administered as two doses of 12 mg given intramuscularly, 24 hours apart. Dexamethasone sodium phosphate is administered as four doses of 6 mg given intramuscularly, 12 hours apart. These agents are structurally similar, fluorinated compounds with minimal mineralocorticoid activity and weak immunosuppressive activity with short-term administration. However, a betamethasone suspension (Celestone Soluspan) frequently used in this country has a longer half-life because of the prolonged absorption of the betamethasone acetate component. In addition, although they have comparable genomic potencies because of similar high affinities for the glucocorticoid receptor, the nongenomic effects of dexamethasone appear to be significantly stronger. The bottom line is that these are different drugs, and it should come as no great surprise if they have different effects.

In a subgroup analysis of antenatal corticosteroids versus placebo or no treatment by type of corticosteroid, Roberts and Dalziel found that betamethasone treatment resulted in a greater reduction in RDS than dexamethasone treatment (RR 0.56, 95% CI 0.68–0.93). There were no other statistically significant differences between groups, except that dexamethasone significantly increased the incidence of puerperal sepsis. This indirect comparison would seem to favor betamethasone administration. However, a subsequent Cochrane review summarized the evidence from trials, which directly compared these two agents. This analysis demonstrated that dexamethasone decreased the risk of IVH compared with betamethasone (RR 0.44, 95% CI 0.21–0.92). No difference was seen for any other outcomes evaluated, including severe IVH.

In a large historical cohort study from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Registry, Lee and colleagues reported on the outcomes of very low birthweight infants (401–1500 g) exposed to betamethasone, dexamethasone, or no corticosteroid treatment. Beta-methasone was associated with a significantly reduced risk for neonatal death. In addition, there were trends of decreased risk for other adverse neonatal outcomes with exposure to betamethasone over dexamethasone. These authors concluded that “it may be in the best interests of neonates to receive betamethasone rather than dexamethasone when available.”

Yet in a recent RCT comparing betamethasone to dexamethasone there was no difference seen in neonatal mortality, RDS, NEC or sepsis. However, neonates exposed to betamethasone had a significantly higher rate of IVH (17% vs 5.7%). It would appear that the randomized data tends to favor dexamethasone over betamethasone because of this reduction in IVH. However, the conclusions are clearly inconsistent across the range of studies. Importantly, there are no long-term outcome data on safety or efficacy for those treated with dexamethasone as there is with betamethasone. Additional RCTs are necessary to determine the preferable agent as well as to establish the optimal treatment regimen. According to ACOG guidelines, both betamethasone and dexamethasone are acceptable for promotion of fetal maturity in women at risk for preterm delivery.
TIMING OF EFFECTIVENESS

After reviewing the available evidence, the 1994 NIH consensus panel concluded that the optimal benefit of antenatal corticosteroids was seen at 24 hours to 7 days after initiation of treatment. The panel recommended that further studies were necessary to determine whether the beneficial effects diminished after 7 days and whether retreatment at some time point would be necessary.

In the subgroup analysis of antenatal corticosteroids versus placebo or no treatment by entry to delivery interval, the Cochrane analysis demonstrated a reduction in the risk of RDS in treated infants born before 48 hours (RR 0.63, 95% CI 0.43–0.93) and between 1 and 7 days after treatment (RR 0.46, 95% CI 0.35–0.60) but not those born before 24 hours or after 7 days. Curiously, neonatal death was reduced in treated infants born before 24 hours (RR 0.53, 95% CI 0.29–0.96) and before 48 hours (RR 0.49, 95% CI 0.30–0.81) but not those born between 1 and 7 days after treatment or after 7 days. IVH was reduced in those born before 48 hours but not in any other time period studied.

Additional studies have attempted to clarify the duration of corticosteroid effectiveness. Vermillion and colleagues published a retrospective analysis of neonates treated with antenatal corticosteroids who were delivered between 28 and 34 weeks’ gestation. They found no difference between those delivered 8 to 14 days after treatment compared to those delivered within 7 days. Peaceman and colleagues also found no difference in outcomes of those delivered more than 7 days after treatment compared to those delivered within 7 days, in a study of 197 neonates whose mothers received a complete single course of antenatal corticosteroids.

Even if there is some decline in the effectiveness of antenatal corticosteroids over time, it is likely that this decline is not static across all gestational ages or birthweights. There may be a relationship between the specific gestational age at administration and the gestational age at delivery. Ring and colleagues reported on the outcomes of 357 singleton pregnancies delivered between 26 and 34 weeks after completing a single course of antenatal corticosteroids. Neonatal outcomes were compared between those exposed within 14 days of delivery and those exposed after 14 days. Outcomes among treatment groups were stratified by gestational age at delivery (<28 weeks, ≥28 weeks). A steroid-to-delivery interval of more than 14 days was associated with an increased need for ventilatory support and surfactant use, particularly for those delivered beyond 28 weeks.

In an intriguing article published in 2007, Simon Gates and Peter Brocklehurst criticized the subgroup analyses published in the systematic reviews on antenatal corticosteroids that led to the conclusion that effectiveness declines after 7 days. They cited four ways in which the data—and therefore the conclusion—could be unsound. The first problem listed was the arbitrary choice of 24 hours and 7 days as the cutoff points for the subgroups, which the first clinical trial and most subsequent trials have analyzed. Unfortunately, this means that all infants born at term will be in the more than 7 days subgroup; because of a lower incidence of adverse outcomes in these patients it is unlikely that a statistically significant difference would be found. This does not equate to a complete lack of treatment effectiveness at 8 days, although that has been a frequent conclusion. Gates and Brocklehurst also pointed out that statistical tests of interaction should be used to assess subgroup differences, not tests of statistical significance, because subgroups with fewer trials are less likely to give significant results even if their effects are the same. Finally, subgroup analyses classified by variables that arise after randomization have a high risk of producing
misleading results because of bias. Differences in effectiveness of the intervention may arise because of differences in the subgroup.

Without knowing the exact time course of effectiveness, it is difficult to know if and when repeat or rescue courses of antenatal corticosteroids are necessary. This clinical dilemma is further complicated by the difficulty in predicting who will have a preterm delivery and when that delivery will occur. In a recent study in Ireland, the ratio of women given a complete course of corticosteroids to the number who actually delivered before 34 weeks’ gestation was 4:1. Analysis by indication for preterm birth revealed this ratio to be 15:1 in suspected preterm labor, 8:1 in antepartum hemorrhage, and 2:1 in both PPROM and medically indicated preterm birth. McLaughlin and colleagues also looked at the accuracy of physicians in timing the administration of antenatal corticosteroids. Overall, women treated before 28 weeks’ gestation were more likely to give birth more than 7 days later than those treated after 28 weeks. It is difficult to say if those data reflect a quicker tendency by physicians to treat patients at risk of preterm birth at earlier gestations for fear of adverse neonatal outcomes, or an actual difference in likelihood to deliver between these groups. Women who received antenatal corticosteroids because of placenta previa, multiple gestation, or cervical incompetence were more likely to remain pregnant in this study, while those with hypertension or idiopathic preterm labor had a higher rate of delivery within 7 days.

**TIMING OF ADMINISTRATION**

**Multiple Courses**

Over the last decade, a number of multicenter, prospective trials comparing a single course of antenatal corticosteroid treatment to multiple courses have been published. The results of 10 RCTs, involving 4730 women and 5650 neonates, have been summarized recently in a Cochrane review. Treatment of women who remained at risk of preterm birth 7 or more days after an initial course of antenatal corticosteroids with repeat dose(s) compared with no repeat treatment reduced the risk of infant respiratory distress syndrome (RR 0.83, 95% CI 0.75–0.91). In addition, serious infant morbidity was reduced by repeat dose(s) (RR 0.84, 95% CI 0.75–0.94). Serious infant morbidity was variously defined by the trialists but generally included a composite of death, RDS, severe IVH, PVL, and NEC. Treatment with repeat dose(s) was associated with a reduction in mean birthweight (mean difference –75.79 g, 95% CI –117.63 to 33.96).

Four of the trials included in the Cochrane analysis reported data from early childhood follow-up. No statistically significant differences were seen for children in the repeat corticosteroid group as compared to controls. Outcomes examined included death to early childhood follow-up, survival free of any disability, survival free of any major disability, and composite serious outcome at childhood follow-up. The authors concluded that short-term benefits support the use of repeat dose(s) of antenatal corticosteroids for women who have received an initial course and remain at risk for preterm birth 7 or more days later. However, they noted that although limited evidence from early childhood shows no evidence of harm, there is no proof of long-term benefit either. In addition, there are no data on overall health, neurodevelopment, and cardiovascular and metabolic function later in childhood or in adulthood after exposure to repeat dose(s).

Although overall there was no difference in outcomes assessed in early childhood across the studies, in the MFMU Network trial six children were diagnosed with cerebral palsy in the repeat corticosteroid group whereas only one child was diagnosed with cerebral palsy in the control group. All had received four or more
courses of antenatal corticosteroids, five were born at 34 or more weeks of gestation, and none of the pregnancies had obvious perinatal complications. Though this difference did not reach statistical significance, the striking nature of this finding would suggest caution in prescribing multiple courses of antenatal corticosteroids.

**Rescue Course**

One strategy, which seems to have come into wide clinical use, again with a paucity of supporting data, is to administer a “rescue” course of antenatal corticosteroids. Patients who have received an initial course of antenatal corticosteroids but do not deliver within 7 to 14 days may receive one repeat corticosteroid course known as the “rescue” course. Of course, given the limitations in the data on the timing of effectiveness of corticosteroids, it is not clear if it is appropriate to give this rescue course after 7 days, 14 days, or longer. It is also not clear if this interval should change depending on the timing of the initial course or if the rescue course should be given routinely or only if preterm birth is again deemed “imminent.” It seems obvious that the same issues with timing the rescue course will arise as with the initial one.

However, there is increasing data that the rescue approach might be both effective and safe. Vermillion and colleagues published a retrospective cohort study of 152 women at risk for preterm delivery who received a corticosteroid course before 28 weeks. Outcomes were compared for women readmitted for preterm labor after 28 weeks who received a single rescue dose of corticosteroid versus those who did not. Rescue corticosteroid administration was significantly associated with a reduction in frequency of RDS as well as mean days on the ventilator. Multiple logistic regression confirmed that the rescue dose was independently associated with a reduction in the rate of RDS. More recently, Garite and colleagues published the results of a randomized trial with a rescue approach. Patients with singleton or twin pregnancies less than 33 weeks, who had received a single course of antenatal corticosteroids before 30 weeks and were at risk for preterm delivery in the next week, were enrolled. Patients were randomized to a single rescue course of betamethasone or placebo. The treatment group had reduced composite morbidity (OR 0.65, 95% CI 0.44–0.97) as well as a reduced frequency of RDS (OR 0.64, 95% CI 0.43–0.95). Treatment did not decrease mean birthweight or impact the rate of IUGR.

**GUIDELINES BY MAJOR SOCIETIES**

In February of 2011, ACOG published a new Committee Opinion on antenatal corticosteroid therapy for fetal maturation. The College reaffirmed its support for administration of a single course of antenatal corticosteroids to pregnant women between 24 and 34 weeks’ gestation at risk of preterm delivery within 7 days. They do not recommend administering antenatal corticosteroids before 24 weeks’ gestation because of sparse evidence in this population. Also, in a departure from earlier publications, ACOG supports a single rescue course of antenatal corticosteroids under the following circumstances: if the antecedent treatment was given more than 2 weeks prior, if the gestational age is less than 32 6/7 weeks, and if the patient is deemed likely to give birth within the next week (rather than a scheduled administration).

The most recent RCOG guidelines differ from those of ACOG in a few interesting ways. The Royal College supports administration of a single course of antenatal corticosteroids between 24 0/7 weeks and 34 6/7 weeks, the upper limit arising from the Cochrane data presented earlier. However, they state that antenatal corticosteroids can be considered for women between 23 0/7 weeks and 23 6/7 weeks who are at risk of preterm birth, as long as this decision is “made at a senior level taking all clinical aspects into consideration.” In addition, the RCOG recommends that
Antenatal corticosteroids should be given to all patients for whom an elective cesarean is planned prior to 38 6/7 weeks, largely based on the results of one randomized trial of betamethasone versus no treatment that decreased the rate of admission for RDS. In the RCOG guideline, rescue corticosteroids “should only be considered with caution in those pregnancies where the first course was given at less than 26 0/7 weeks of gestation and another obstetric indication arises later in pregnancy.”

Although each of these guidelines appear reasonable, it is clear from the data already presented that these recommendations stem from varying interpretations of the data rather than comprehensively studied protocols.

FUTURE RESEARCH

Throughout this article the limitations in the current evidence on the safety and efficacy of antenatal corticosteroids have been highlighted. Although the evidence for benefit of a single course of antenatal corticosteroids for women at risk of preterm birth between 24 and 34 weeks is clear, questions remain about the best dose, best corticosteroid, length of effectiveness, as well as need for and timing of repeat corticosteroids. There are limitations in the evidence for all of the specific patient populations mentioned. Additional RCTs would be welcome. But even without regard to the time and expense required for randomized studies, because of the routine use of antenatal corticosteroids in these populations already, such trials will be exceedingly difficult to conduct.

To address some of these questions without new trials, a group of investigators representing each of the major trials of repeat dosing have been funded to conduct an individual patient data meta-analysis. Led by Caroline Crowther of the University of Adelaide, the primary goal of this study is to determine the efficacy and safety of various repeat dosing approaches. Hopefully this will be able to answer other outstanding questions regarding corticosteroids in lieu of additional studies.

SUMMARY

Though the preterm birth rate in the United States has finally begun to decline, preterm birth remains a critical public health problem. The administration of antenatal corticosteroids to improve outcomes after preterm birth is one of the most important interventions in obstetrics. This article summarizes the evidence for antenatal corticosteroid efficacy and safety that has accumulated since Graham Liggins and Ross Howie first introduced this therapy. Although antenatal corticosteroids have proven effective for singleton pregnancies at risk for preterm birth between 26 and 34 weeks’ gestation, questions remain about the utility in specific patient populations such as multiple gestations, very early preterm gestations, and pregnancies complicated by IUGR. In addition, there is still uncertainty about the length of corticosteroid effectiveness and the need for repeat or rescue courses. Though a significant amount of data has accumulated on antenatal corticosteroids over the past 40 years, more information is still needed to refine the use of this therapy and improve outcomes for these at-risk patients.

REFERENCES


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