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Art and Science, Clinics in Perinatology

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There is no controversy about the core conclusion that women at risk of preterm delivery prior to 32–34 wks 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 [1], the NIH Consensus Development Conference in 1994 [2], the second Consensus Conference to evaluate repeated courses of antenatal steroids in 2000 [3], and the practice recommendations of obstetric societies worldwide. Three recent meta-analyses by the Cochrane Collaboration on the benefits of antenatal steroids [4], the choice of steroid and dosing [5], and repeat doses of corticosteroids [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 will focus on those areas of uncertainty.

CURRENT STATE OF ANTENATAL STEROID USE

Current Practice

This therapy is based on the initial Liggins and Howie trial (1972) that used betamethasone as a one-to-one mixture of betamethasone phosphate and betamethasone acetate [7]. 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. The majority of 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® [4, 6]. The other corticosteroid that has been tested in clinical trials is dexamethasone phosphate [5]. As with any drug therapy, optimization of treatments requires 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

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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 over 6,000 patients, there remain multiple questions 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 as they have similar high affinities for the glucocorticoid receptor that regulates gene expression [8]. However, non-genomic 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 animals also demonstrate differences in the drugs. For example, Ozdenir, et al., reported that betamethasone promoted more lung maturation with less growth restriction in fetal mice than did dexamethasone [10]. 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], while Subtil, et al. did not detect differences in fetal heart rate responses to the two drugs [14]. Independent of the formulations, betamethasone and dexamethasone are not equivalent drugs.

Dose and Route

The initial 2-dose of 12 mg betamethasone treatment given at a 24h interval used by Liggins and Howie [7] has been accepted as the standard in most all trials that have used betamethasone acetate plus phosphate [4]. The dexamethasone 4-doses of 6 mg treatment at 12h 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 pro-drugs in that soluble betamethasone phosphate and dexamethasone phosphate are dephosphorylated rapidly (half-life <1h) by phosphatases to the active drugs [17]. The terminal half-life for the free corticosteroids in plasma is about 4h, 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 4–12 μm in the betamethasone acetate plus phosphate preparation is quite insoluble. The free betamethasone enters the plasma slowly after deacetylation and has a terminal half-life of about 14h [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 demonstrate 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 less effects on fetal growth [20–21]. Single IM doses of cortisol (fetal), dexamethasone (fetal), or betamethasone phosphate (maternal) do not induce lung maturation in sheep [17, 22–23]. In contrast, four doses of cortisol given to the fetus at 4h intervals or four doses of betamethasone phosphate given to the ewe do induce lung maturation [22]. These results demonstrate 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. But, both maternal and fetal plasma free betamethasone levels are very low following maternal treatment with betamethasone acetate [17]. Surprisingly, a single maternal dose of betamethasone acetate is as effective for fetal lung maturation as is the standard two-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 demonstrated in Fig. 2. A fetal IM injection with betamethasone acetate plus phosphate (0.5 mg/kg fetal weight) results in much higher fetal plasma betamethasone levels for 3h than does a maternal injection of 0.5 mg/kg maternal weight [19]. Nevertheless, the maternal treatment induces more fetal lung maturation than is achieved with the fetal treatment [24]. Furthermore, the higher direct fetal exposure to betamethasone does no cause fetal growth restriction while the maternal treatment does. These results demonstrate 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, et al. [25] 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 with no indication of added benefit for 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 vs. Dexamethasone

Nevertheless, the clinician must treat with an available drug. Based on the above discussion, it should be clear that 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 two 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 analyses of the trials that compared each drug with placebo and then a comparison of the outcomes relative to the placebo controls (Table 2) [5]. The placebo-controlled trials were performed prior to 1990 and included primarily more mature infants, while the dexamethasone to betamethasone comparison trials were more recent. The indirect comparison identified less RDS with the 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, et al [26]. There has been a concern that maternal dexamethasone phosphate treatments may increase periventricular leucomalacia in the newborns because of sulfites used for preservative [27]. We think this is unlikely given the sulfite dose and volume of distribution in the mother. Infants are exposed to much higher amounts of sulfite from hyperalimentation and other drugs that they receive. The clinical experience of the NICHD neonatal research network for over 300 infants was an increase in death with antenatal dexamethasone treatment relative to betamethasone (odds ratio 1.66; confidence interval 1.07–2.57-check number) [28]. Another large recent series reported significantly less RDS and bronchopulmonary dysplasia for betamethasone than dexamethasone exposed infants [29]. Data for the generally favorable long-term outcomes are available only for betamethasone-exposed infants [4]. Despite the multiple trials, no definitive recommendation can be made in favor of one 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 wks to 32–34 wks gestation, there are minimal data from randomized trials for treatments with deliveries prior to 28 wks gestational age [4]. The irony is that preterm infants delivered at these very early gestational age 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 as the placebo controlled trials performed before 1990 enrolled few pregnancies with deliveries at <28 wks. A recent meta-analysis and systemic review of corticosteroid use prior to 26 wks gestation demonstrated no benefits [30]. The authors 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 will be very high and the corticosteroid treatment may not prevent RDS. For example, Garite et al. [31] 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 two avenues to the evaluation of the usefulness of antenatal corticosteroids for very preterm deliveries. Lung tissue from 12–24 wk human fetuses in explant culture will respond to corticosteroids with an increase in epithelial maturation and the appearance of lamellar bodies, the storage organelles for surfactant [32]. Fetal monkeys at early gestations respond to maternal corticosteroid treatments with lung maturation responses [33]. Thus, there is no biological reason to think 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 <26 wks in the United Kingdom and Ireland in 1995 were reported by Costeloe, et al. [34]. 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 wks gestation, the 25% who received a complete course of antenatal corticosteroids had an OR for death of 0.18, CI 0.06–0.54, relative to unexposed infants, although overall morbidity and mortality was very high [35]. A recent series from Japan also reports a decrease in RDS and IVH for infants exposed to antenatal corticosteroids that delivered at 24–25 wks. Death was decreased for infants delivered at 22–23 wks and at 24–25 wks relative to infants not exposed to antenatal corticosteroids [36]. 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 to date have only evaluated antenatal steroid use up to 24 and 34 weeks gestation. This upper gestational limit is relatively arbitrary and was chosen to include the sickest neonates in whom prematurity associated lung disease was a life threatening condition. Recently, it has been realized that there is a significant disease burden that continues beyond this gestational period. Since 3 of every 4 preterm births occur between 34 and 37 weeks gestation [37–46]. It is estimated that over 250,000 infants 34 weeks or greater are admitted to the 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 [47–48].

In understanding the potential benefit of antenatal steroid treatment in the late preterm period it should be remembered that not all respiratory distress is due to 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 [49–50]. As term approaches, lung fluid begins to be transferred from the lumen, across the apical membrane into the interstitium. This 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 [51]. Epithelial Na- channels (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 [52–53].

Preliminary data suggest that corticosteroids will 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 et al [54] 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 respiratory distress syndrome (surfactant deficiency) (7.5% vs 35.5%).

While the individual risk of a late preterm neonate requiring significant respiratory support is small, as a group it becomes substantial [37–46, 55]. 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 NHLBI have initiated a prospective randomized trial of antenatal steroids for pregnancies likely to deliver in this window and 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

While 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 [56] 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 [57]. Until recently, the majority of 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 [57–60].

Over the last decade a number of multicentered, prospective, randomized trials have been performed comparing a single course of treatment with retreatment at various intervals ranging from one to two weeks. These results have been summarized in a Cochrane review [6] which includes results for over 2000 women. In this analysis, treatment with repeat courses of corticosteroids is associated with a reduction in the overall occurrence of respiratory distress (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 lead to a reduction in 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, PVL and maternal infection. The authors conclude that the acute short-term pulmonary benefits for neonates support the use of repeat doses of antenatal corticosteroids.

While repeat courses of antenatal corticosteroids may improve neonatal pulmonary status, there are concerns that repetitive retreatment may be harmful. While the Cochrane review showed no overall reduction in birth weight of infants exposed to repeat steroids, the majority of fetuses had only one or two subsequent courses of treatment. However, in the US NICHD trial [61] 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 [62]. Placental size in the repeat group was also smaller [63].

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 three largest multicentered national trials have now published their 2 to 3 year follow-up [62, 64–65]. The results of these studies are quite 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. Of some concern however was the finding of cerebral palsy in six infants in the repeat corticosteroid group. All received four or more courses of corticosteroids, none had any perinatal complications, and five were born at 34 weeks or later in gestation. Only one 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. Unfortunately, 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 7–10 days later

[66]. Women treated prior to 28 weeks gestation appear more likely to give birth more than seven days later than those treated after 28 weeks [67].

In order 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 demonstrated by Garite et al. [68] who randomized patients who remained at risk for preterm delivery two 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 BPD or the need for ventilator support. Birth weights and the frequency of IUGR 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, they demonstrated 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, they examined in which gestational ages the greatest efficacy of rescue treatment was seen. The reduction in composite morbidity was limited to babies born under 33 weeks with no difference in outcome thereafter.

At the present time there is no consistent agreement among experts on the need and appropriateness of repeat administration of antenatal steroids. To address this, a group of investigators representing each of the major trials of repeat and rescue dosing have recently been funded to do an individual patient data meta-analyses 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 mean time, it appears save to administer a single rescue course if preterm birth under 33 weeks seems highly 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 appears not to be effective nor necessary.

TWINS

The efficacy of antenatal corticosteroid use in twin gestations remains uncertain. Their impact in this clinical subcategory has never been evaluated in prospective trials of treated and untreated twins so that information is only available 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 since 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 over 400%. Almost 60% of twins deliver less than 37 completed weeks of gestation and over 10% before 32 weeks [69].

The majority of studies to date have shown no significant benefit to antenatal corticosteroid administration in twins or if one is demonstrated it appears to be less than that seen with singletons [70–71]. A recent Cochrane metaanalysis performed by Roberts and Dalziel showed a non significant reduction in the rate of RDS in twins after the administration of steroids (odds ratio, 0.85; 95% confidence interval, 0.60–1.20), [72]. Similarly, in one of the largest population based studies evaluating the impact of steroids in twins, Blickstein demonstrated that a complete course has a similar 40–50% reduction in RDS compared to

no steroid treatment for both singletons and twins but that the effect is plurality dependent. Compared to treated singletons the OR for RDS in twins was 1.4 and in triplets was 1.8 [71].

There are a number of 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. Indeed, it has been shown that compared to women carrying a singleton, the half life of betamethasone is shorter and the clearance greater in women carrying twins [73]. However, most recently, Gyamfi et al have measured both maternal and fetal (cord) betamethasone levels in both singleton and twin gestations and demonstrated no difference. The cord betamethasone levels were actually higher in twins [74].

The most likely reason that twins have not been demonstrated to show improvement following steroids is related to the relatively 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 odds ratio 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 while minimizing unnecessary treatment. To evaluate this, Murphy et al [75] compared two twin cohorts at risk for preterm birth. One group received prophylactic steroids every two 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 over a 7.5 fold greater risk of unnecessary exposure. However, in the rescue group almost a 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 appear to alter drug absorption, tissue distribution and drug elimination may be changed

Gyamfi et al [74] 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 C-section

Delivery by Cesarean section in the near term period without preceding labor increases the occurrence of fetal respiratory morbidity [39, 76]. Compared to infants delivered vaginally those delivered by pre labor C- section have a 2.3 to 6.8 fold increased risk of respiratory morbidities including transient tachypnea, surfactant deficiency and pulmonary hypertension. The risk of a NICU admission is doubled [49, 77–78]. 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 to deliveries in the 39th week [79]. Mechanical ventilation, newborn sepsis, hypoglycemia, admission to the neonatal ICU, 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 TTN decreased from 4.8% to 2.7%

Ideally, all pre labor Cesarean deliveries would only occur after 39 completed weeks of gestation but this is not always possible since obstetrical 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) [80] 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 non-significant reductions in all respiratory morbidities. While suggestive, the study was not blinded and did not utilize a placebo. In addition, respiratory distress was unconventionally defined as tachypnea (rate >60) with grunting, recession or nasal flaring. The authors hypothesized that corticosteroid treatment decreased respiratory complications by increasing ENaC expression and function thus allowing the lung to convert from active fluid secretion to sodium and fluid absorption. Since term infants, even after elective cesarean delivery, have a very low incidence of respiratory morbidity, the number needed to treat to prevent one case of RDS would be between 80 and 100 compared to 20 to 30 in the late preterm period and approximately 5 for infants under 32 weeks [81].

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 [82–83]. A problem for the analysis of current clinical series is that the majority of women have received antenatal corticosteroids. For example, 87% of women from a consecutive series of 457 deliveries at <32 wks gestation received corticosteroids, and the women not treated differed in the incidence of preeclampsia and type of preterm birth [84]. Decisions about which women may benefit from antenatal corticosteroids in the future may depend on new information about how infection/inflammation impacts the pregnancy and outcomes. For example, new information that much of the histologic chorioamnionitis is associated with nonculturable organisms detected by PCR analyses will change how the perinatal community thinks about and diagnoses antenatal infections [85]. 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 [86]. Further, fetal inflammatory and immune modulatory responses to the combined exposures of antenatal corticosteroids and fetal inflammation are complex and certainly depend on the timing and the order of the exposures [87]. We know very 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 prior to 32–34 wks worldwide, the use of antenatal corticosteroids in resource poor environments is estimated to be only about 10% for women at risk [88]. 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 [89]. 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 HIV may be at risk if treated with corticosteroids. Even if treatments can be given effectively for home and low level clinic deliveries, there will be no benefit unless the care for the preterm is improved. Antenatal corticosteroids should be targeted for pregnancies at risk of delivering infants with birth weights of perhaps >1500 g, as the very preterm infants will likely not survive without risk of significant handicaps in these environments. However, the attack rates for antenatal corticosteroid responsive problems in these later gestational age infants remain essentially unstudied even in the developed world [90]. The NICHD has started a trial to evaluate if antenatal corticosteroids can benefit these late-preterm deliveries. In summary, the use of antenatal corticosteroids in resource poor environments is challenging and may not be effective or free from risk.

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Fig. 1.

Fetal indicators of lung maturation following maternal treatments with saline (control), one dose of 0.25 mg/kg betamethasone acetate (0.25 – Beta-Ac), one dose of 0.5 mg/kg Beta-Ac, 4 doses of 0.25 mg/kg Beta phosphate (-PO₄) given at 12h intervals, or 2 doses of Celestone (0.5 mg/kg of a 1 to 1 mixture of Beta Ac and Beta-PO₄ given at a 24h interval). All fetuses were delivered prematurely 48h after the initial treatment. **A)** Lung compliance measured by the lung gas volume at 40 cmH₂O 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<0.05 vs. controls Data from Jobe, et. al. (17).

Fig. 2. Plasma levels of betamethasone (Beta), birth weights, and lung gas volumes. **A)** Beta levels in fetal plasma after maternal treatments with 0.5 mg/kg Beta acetate plus phosphate (maternal) or after fetal treatment with the same dose based on estimated fetal weight (fetal). **B)** One or 3 weekly fetal treatments with this dose did not decrease birth weight while maternal treatments decreased birth weight. **C)** Lung gas volume measured at 40 cmH₂O pressure as a measure of lung maturation increased more with maternal than fetal treatments. Data from Berry, et al (Frame A) (19) and Jobe, et al. (Frames B and C) (24). * $p < 0.05$ vs. control, ^t $p < 0.05$ – 3 doses maternal vs. 3 doses fetal

Table 1

A Comparison of Outcomes for Women Randomized to 6 mg Dex every 12h $\times$ 4 - IM or 8 mg Dex every 12h $\times$ 4*

	Oral	IM	P
N	99	84	-
RDS (%)	34.3	29.8	0.53
Newborn Sepsis (%)	10.1	1.2	0.01
Intraventricular Hemorrhage	10.1	2.4	0.04
Necrotizing Enterocolitis	1.2	5.1	0.13
Neonatal Death	7.1	4.8	0.55

Data extracted from Eggerman, et al., AJObGyn, 1998 (Ref. 25)

Table 2

Dexamethasone vs. Betamethasone Risk Ratio (95% Confidence Incidence)

Outcomes	Direct Comparison ¹	Indirect Comparison ²
RDS	1.06 (0.88–1.28)	1.44 (1.14–1.78)
Severe IVH	0.40 (0.13–1.24)	0.47 (0.09–2.33)
Feta/Neonatal Death	1.28 (0.46–3.52)	0.96 (0.71–1.30)

¹Data from Barefoot, Crowther, and Middleton (5)²Data from Roberts and Dalziel (Ref. 4)