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Antenatal Corticosteroids in the Management of Preterm Birth: Are we back where we started?

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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.[1] 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.[2] 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 downtrend in preterm birth are not entirely clear. The decrease has been demonstrated in both late preterm (34 to 36 completed weeks) deliveries and early preterm deliveries (less than 34 weeks).[2] Preterm births for patients delivered by cesarean, induced vaginal birth and non-induced vaginal birth have all declined.[3] And the reduction in preterm birth is not explained by a change in the proportion of multiple births.[3] This data suggests that efforts by the American Congress of Obstetricians and Gynecologists (ACOG) and other advocacy groups like the March of Dimes have helped to decrease iatrogenic late preterm birth. In addition, interventions such as 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth and vaginal progesterone for prevention of preterm

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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 being 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.[4] 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 on maternal administration of betamethasone. The results were published in a landmark article in 1972.[5] 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%.[6]

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 obstetrical providers hesitant to use this therapy routinely for women at risk for preterm birth.[7,8] In 1990, Crowley and colleagues published a meta-analysis of 12 randomized controlled trials 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.[9] 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.[10] This recommendation and the endorsement by ACOG helped to increase the utilization of antenatal corticosteroids dramatically.[11] Within a few years, 70–90% of women who delivered less than 34 weeks had received a course of corticosteroids.[12] 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 obstetrical practice and outcomes for premature infants.

Subgroup analysis from the initial trial on antenatal corticosteroids suggested that effectiveness peaked between two and seven days from the initial injection.[5] 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 seven 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 is adequate supportive data. 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 over half would give four or more repeat courses.[13] The routine use of repeat corticosteroids became so widespread that the NIH reconvened a consensus conference in 2000, only six years after the conference to promote corticosteroid adoption, to address this issue.[14] The panel recommended that repeat courses of corticosteroids be limited to patient participating in randomized clinical trials, 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.[5] The two injection course of 12milligrams (mg) given at a 24-hour interval was also empirically chosen by Liggins and Howie.[5] 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 review will take 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.[15] 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 towards fewer children having cerebral palsy (RR 0.60, 95% CI 0.34–1.03, 904 children). The longest specified duration of follow-up in these studies was six 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 "[t]here is no need for further trials of a single course of antenatal corticosteroids versus placebo in singleton pregnancies".[15]

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 (less than 37 weeks gestation), with 11.6% of them being born before 32 weeks.[16] In contrast, only 10.6% of singletons were born preterm, with 1.6% born before 32 weeks.[16] 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 obstetrical 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.[15] 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.[17] 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.[18,19]

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. [20] However, one study of the pharmacodynamics of betamethasone showed that the volume of distribution was actually the same between singleton and twin pregnancies.[21] 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.[22] This analysis was restricted to patients receiving multiple courses of antenatal corticosteroids who delivered within one 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 does 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.[23] Obesity is an independent risk factor for many different adverse obstetric outcomes, although most studies have not found a strong association between obesity and spontaneous preterm delivery.[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 obstetrical 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.[26] In fact, in a study of maternal and cord serum betamethasone levels, there was no significant difference between obese and non-obese women (BMI $\geq$ 30kg/m^2 vs. BMI $\leq$30kg/m^2) after controlling for confounding factors.[22] Therefore, despite theoretical concerns, there is no current evidence supporting an alternative antenatal corticosteroid regimen based upon maternal BMI.

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.[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.[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 (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.[28] Of 124 infants born between 26 and 32 weeks gestation survival without disability or handicap at two years of age was higher in the corticosteroid group than 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.[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. Intrauterine growth restriction 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 by Miller and colleagues using a sheep model, these investigators 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. [30] 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. [31]

Several investigators have advocated for a randomized controlled trial to examine whether treatment is truly beneficial for IUGR fetuses.[29, 31] 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 obstetrical 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.[15] 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 less than 30 infants supplied the data for this group.

Earlier this year, Onland and colleagues published an updated systematic review of randomized controlled trials on the effects of antenatal corticosteroids given before 26 weeks gestation.[32] Nine trials which 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 group compared with no treatment. Certainly these analyses may be underpowered to demonstrate effectiveness. It is also possible that antenatal corticosteroids can only improve lung function 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.[33]

However, if there is a beneficial effect of antenatal corticosteroids at very early gestational ages, it may be more evident in mortality rates and neurological 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.[34] 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.[35] A retrospective series from Japan even demonstrated a decrease in mortality of infants born at 22 or 23 weeks gestation after exposure to corticosteroids.[36]

While 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, were from singleton pregnancies and of higher birth weight had reduced rates of death.[37] In addition, among survivors the risk of death or impairment at 18–22 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.[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.

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 to 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 that 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.[16]

Interestingly, the Cochrane review supports use of antenatal corticosteroids for women at risk of preterm birth up to 34 6/7 weeks gestation.[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.[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 (ENaC) which allow the alveoli to convert from active fluid secretion to sodium and fluid absorption with subsequent reduction of fetal lung fluid.

To formally answer this question, the Maternal Fetal Medicine Units Network is currently conducting a prospective, randomized trial 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.[40,41,42]

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.[15] 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.[15] Importantly, long-term follow-up of

those enrolled in randomized controlled trials through early adulthood show no apparent adverse neurological or cognitive effects from a single course of treatment.[43,44]

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.[15] 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 randomized controlled trials 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.[45] 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).[15] 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.[46] 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.[47,48]

Certainly the etiology of periventricular leukomalacia and cerebral palsy after preterm birth is an active area of investigation. Infection and inflammation are believed to be important pathophysiologic factors. At this time we can certainly recommend that delivery not be delayed in the setting of clinical chorioamnionitis for administration of antenatal corticosteroids. But the evidence overall supports administration of antenatal corticosteroids for patients with PPROM up to 32–34 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 12mg given intramuscularly, 24 hours apart. Dexamethasone sodium phosphate is administered as four doses of 6mg 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 non-genomic effects of dexamethasone appear to be significantly stronger.[49] 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).[15] 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. [50] This analysis demonstrated that dexamethasone decreased the risk of IVH compared with betamethasone (RR 0.44, 95%CI 0.21–0.92). There was no difference 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 (401–1500g) exposed to betamethasone, dexamethasone or no corticosteroid treatment.[51] Betamethasone was associated with a significantly reduced risk for neonatal death. Additionally, 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”.[51]

Yet in a recent randomized controlled trial comparing betamethasone to dexamethasone there was no difference seen in neonatal mortality, RDS, NEC or sepsis.[52] 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 is no long-term outcome data on safety or efficacy for those treated with dexamethasone as there is with betamethasone. Additional randomized controlled trials 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 seven days after initiation of treatment. The panel recommended that further studies were necessary to determine whether the beneficial effects diminished after seven 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 one and seven days after treatment (RR 0.46, 95%CI 0.35–0.60) but not those born before 24 hours or after seven days.[15] 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 one and seven days after treatment or after seven 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.[53] This study found no difference between those delivered 8–14 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.[54]

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.[55] 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 which led to the conclusion that effectiveness declines after seven days.[56] 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 seven days as the cutoff points for the subgroups, which the first clinical trial and most subsequent trials have analyzed. Unfortunately, this means that all babies born at term will be in the more than seven 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 out of Ireland, the ratio of women given a complete course of corticosteroids to the number who actually delivered before 34 weeks gestation was 4:1.[57] 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.[58] Overall, women treated before 28 weeks gestation were more likely to give birth more than seven days later than those treated after 28 weeks. It is difficult to say if that data reflects 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 seven 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.[59,60,61] The results of ten randomized controlled trials, involving 4730 women and 5650 neonates have been summarized recent in a Cochrane review.[62] Treatment of women who remained at risk of preterm birth seven 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 −75.79g, 95%CI −117.63–33.96).

Four of the trials included in the Cochrane analysis reported data from early childhood follow-up. There were no statistically significant differences 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 seven or more days later. However, they noted that while limited evidence from early childhood shows no evidence of harm, there is no proof of long-term benefit either. In addition, there is no data on overall health, neurodevelopment, 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 while 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.[63] 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.[64] Patients with singleton or twin pregnancies less than 33 weeks, who had received a single course of antenatal corticosteroids prior to 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 this year, ACOG published a new Committee Opinion on antenatal corticosteroid therapy for fetal maturation.[65] 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. And 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 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.”[39] 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 which decreased the rate of admission for RDS.[66] 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.”[39]

While 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 we have highlighted limitations in the current evidence on the safety and efficacy of antenatal corticosteroids. While 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 randomized controlled trials 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.

In order 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 review summarizes the evidence for antenatal corticosteroid efficacy and safety that has accumulated since Graham Liggins and Ross Howie first introduced this therapy. While 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 intrauterine growth restriction. In addition, there is still uncertainty about the length of corticosteroid effectiveness and the need for repeat or rescue courses. Though there has been a significant amount of data accumulated on antenatal corticosteroids over the past forty years, we still need more information to refine the use of this therapy and improve outcomes for these at risk patients.

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