Published in final edited form as:

Semin Perinatol. 2016 August ; 40(5): 291–297. doi:10.1053/j.semperi.2016.03.005.

What we have learned about antenatal corticosteroid regimens

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Abstract

Administration of antenatal corticosteroids has been standard of care for women between 24 and 34 weeks of gestation who are at risk for preterm delivery for more than 20 years longer in other parts of the world. Although the benefit of steroids in this population has been confirmed, there remain many questions including the frequency of dosing and whether it is possible to expand the gestational age criteria to women likely to deliver before 24 weeks or after 34 weeks. The MFMU Network has played a major role in answering some of these questions.

Keywords

Antenatal corticosteroids; Betamethasone; Preterm Birth; Respiratory distress

Introduction

Over the last half century there has been little success in the prevention of preterm birth. Despite this, there have been dramatic reductions in perinatal morbidity and mortality including both acute complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and patent ductus arteriosus (PDA), as well as long-term morbidities including cerebral palsy, visual and hearing impairment, learning disabilities, and behavioral issues. Arguably, the single prenatal therapy responsible for most of this improvement has been the antenatal administration of corticosteroids, which has been available since 1972 and used with regularity by obstetricians since the NICHD Consensus statement in 1994 confirming their value.¹ Despite the regular use of antenatal steroids following this statement there have been consistent questions about the appropriate dosing and risks of treatment.

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Historical perspective: The effect of antenatal corticosteroids on the developing lungs

Endogenous corticosteroids are essential to the normal process of fetal lung development. During late gestation, internally secreted corticosteroid levels increase leading to maturation of the fetal lung structure and inducing enzymes and proteins to facilitate postnatal function.² The antenatal administration of antenatal corticosteroids accelerate these processes,^{3,4} making the lungs more mature than they would be without treatment.⁴

The discovery of the beneficial effects of antenatal corticosteroids on fetal lung development was made serendipitously in the late 1960s, by Graham Liggins, who was evaluating the hypotheses that the fetus produces labor-inducing substances, one of these being steroid hormones. Using a sheep model where large doses of exogenous steroids were given in an attempt to induce labor, Liggins⁵ observed that the exposed preterm lambs had structurally more mature lungs than expected, were viable at an earlier gestational age, and had less severe respiratory distress.

Along with pediatrician Ross Howie, Liggins⁶ investigated this finding in human pregnancies and in 1972 published the results of a randomized controlled trial using antenatally administered betamethasone to improve fetal lung function. They found that two 12 mg injections of betamethasone given 24 h apart significantly reduced the incidence of RDS in preterm neonates, from 15.6% to 10.0%.⁶ These results were later confirmed by other studies, which also exhibited a substantial reduction in preterm infant mortality from 11.6% to 6.0%.⁷

Despite this dramatic improvement, for 2 decades relatively few preterm infants actually benefited from antenatal steroid treatment.⁸ Unwarranted fears about potential side effects and concerns about the quality of evidence caused many physicians to be hesitant to adopt antenatal steroid treatment into routine clinical practice.⁹ Because of this, the National Institutes of Health (NIH) held a consensus conference in 1994 to review the available evidence on the safety and efficacy of antenatal corticosteroids.¹⁰ Citing a meta-analysis of 15 randomized controlled trials, the NIH panel concluded that the use of antenatal corticosteroids significantly reduced neonatal mortality, RDS, and IVH with no proven short- or long-term risks to the infant.¹¹ This panel advised that antenatal corticosteroids should be administered to all women between 24 and 34 weeks of gestation who are at risk for preterm delivery. The American College of Obstetricians and Gynecologists (ACOG) endorsed the resulting NIH consensus statement.¹² As expected, the use of antenatal corticosteroids in the United States rose dramatically because of these published statements.¹³

The appropriate dosing regimen: Is there a need for repeat courses?

The NIH consensus panel of 1994 suggested that the optimal benefit of antenatal corticosteroid treatment was seen 24 h to 7 days after initiation of treatment and recommended further investigation to determine whether the beneficial effects diminish after 7 days and whether additional treatment is necessary for infants that remain in utero.¹⁰

Evaluation of the duration of the treatment effect using the data from studies on a single course of steroids proved problematic, because the majority of the patients who did not deliver within 7 days of initial treatment remained pregnant for a substantially longer period. For example, in Liggins and Howie's original studies, more than 70% of pregnancies that continued for more than 7 days after treatment also continued until 34 or more weeks' gestation. At this gestation both the treated and control groups had an incidence of RDS of less than 5% making it difficult to determine how long the effect of the initial course of antenatal steroids persisted.⁶

Despite the dearth of evidence regarding the utility of additional steroids, use of repeat courses became widespread. In a 1996 survey, 96% of United States MFM specialists indicated that they would give more than one course of antenatal corticosteroids.¹⁴ Similar surveys in Australia and the United Kingdom reported that 85% of Australian and 98% of British MFMs prescribed multiple courses of antenatal corticosteroids.^{15,16} In 2001, a second NIH steroid consensus panel concluded that there was insufficient scientific data from randomized trials regarding the safety and efficacy of repeat corticosteroids to recommend either for or against their use. They suggested limiting administration of repeat courses to patients enrolled in randomized trials only.¹⁷

MFMU Network randomized placebo-controlled trial of antenatal corticosteroid regimens

At the time of the second NIH steroid consensus panel, the MFMU Network had recently initiated a randomized clinical trial to determine whether weekly courses versus a single course of antenatal corticosteroids would improve neonatal outcome. This randomized, double-masked, placebo controlled, and multicenter clinical trial (BEARS—for beneficial effects of repeat steroids) was performed by 18 MFMU network centers. The study enrollment was limited to pregnant women with intact membranes between 23 weeks 0 days and 31 weeks 6 days, who had received a single full course of betamethasone or dexamethasone between 7 and 10 days earlier, and remained at high risk for spontaneous preterm birth. Study participants were randomized into weekly courses of betamethasone or placebo. Each course consisted of two injections 24 h apart of 12 mg of betamethasone or the equivalent volume of matching placebo.¹⁸ Initially the protocol included an unlimited number of weekly courses until birth or 33 weeks 6 days' gestation, whichever was sooner, consistent with routine clinical practice at the time. Because of emerging data in the literature,^{19–21} suggesting possible harmful effects of multiple courses, after the first 67 participants, the protocol was changed so that no patient could receive more than five total courses.

The primary outcome was a composite of (1) severe respiratory distress syndrome (RDS), (2) grade III or IV intraventricular hemorrhage, (3) periventricular leukomalacia, (4) chronic lung disease, or (5) stillbirth or neonatal death. As early research suggested that birth weight and head circumferences might be reduced by antenatal steroid exposure, these outcomes were evaluated as the major safety outcomes.^{19–21} With the planned sample size there was ample power to detect small but meaningful differences.

Recruitment began in March of 2000 and ended in April 2003, when the Data and Safety Monitoring Committee (DSMC) recommended termination at the second formal interim analysis. The committee cited a tendency toward decreased birth weight in the repeat steroid group. There was no signal of improvement in the primary outcome although a slight suggestion of benefit in some of the pulmonary parameters. The DSMC considered the safety data in the literature and also had concerns regarding the ongoing relevance of the question being studied, as the regimen of repeated steroids had been abandoned by many obstetricians since the start of recruitment. The recruitment rate was lower than expected and it was estimated that an additional 6 years would be needed to complete enrollment. Moreover, the observed primary outcome rate in the placebo group was less than expected, which would have required an even larger sample size to have adequate power. At that time all randomized patients were permitted to complete the study resulting in an overall sample size of 495 women (591 fetuses).

The final results of the study showed no difference in the primary outcome between repeat and single course steroids (Table). However, surfactant use, the need for mechanical ventilation, the need for pressure or volume support, and the occurrence of a pneumothorax were all significantly reduced in the repeat steroids group. Consistent with the DSMC's concern regarding fetal growth, there was a significant difference in birth weight analyzed as gestational age specific multiples of the median ($P = 0.01$). On subgroup analysis, however, the birth weight reduction appeared to be confined to those exposed to five or more total courses (entry course + four additional courses). Birth weight below the 10th percentile for gestational age was also significantly more common in the repeated steroids arm. There was no difference in the absolute or gestational age adjusted head circumferences, either overall or in the five or more course group.²² The results were similar when twins and singletons were analyzed separately. Overall the primary results of the trial were somewhat inconclusive as there was suggestion of both benefit and harm. However, it was concluded that that routine weekly repetition of steroids to all women at high risk for preterm birth, could not be justified and may be harmful.

A planned follow-up of the children at the age of 2–3 years was part of the trial. A total of 556 infants were available for follow-up. Of these, 486 underwent physical and neurologic examinations and 465 underwent Bayley testing between 24 and 36 months corrected age.²³ There were no significant differences in anthropometric measurements (height, weight, or head circumference below the 10th percentile) between the two groups. Being small for gestational age at birth (below the 10th percentile) was associated with a weight at follow-up that was below the 10th percentile and was consistent between the two groups. The clinical significance and mechanisms underlying the altered fetal growth seen at birth are unknown, but it is reassuring that long-term follow-up of these infants showed no residual effects.

The Bayley scores were similar in the two groups, as were the frequencies of scores that were less than 85 and those that were less than 70 for both the mental and the psychomotor scales. No significant difference in Bayley scores between children whose mothers had received more than four courses and those who had been exposed to fewer antenatal treatments was exhibited. There were also no significant differences between the groups in specific health outcomes, including seizures, pneumonia, and hospitalizations. Asthma was

reported less frequently in the repeat-treatment group, while systolic and diastolic blood pressures were similar in the two groups.

Worth noting was that cerebral palsy was diagnosed in six infants in the repeat-treatment group and only one infant in the placebo group. Five of the six children with cerebral palsy in the repeat-treatment group had been exposed to a total of five or more courses. Five of the six children with cerebral palsy in the repeat-treatment group were born at 34 weeks or more of gestation, an age at which this finding is rare. The one child with cerebral palsy in the placebo group was born at 33 weeks of gestation. This finding raises concern since neonatal studies also have demonstrated the potential vulnerability of the preterm brain to high doses of corticosteroids.^{24,25}

The cessation of BEARS was based on an interim analysis cohort of only 285 women—12% of the final sample size—and therefore was very likely to result in uncertainty. An early interim analysis may reveal a neutral effect or even a trend toward a negative effect suggesting that a positive effect demonstrated by the end of a trial is unlikely. However, the observed difference is a stochastic process and can change over the lifespan of a trial. It is useful to determine the conditional power to show a difference by treatment group given the observed data to date and calculated under the assumption that the trend in the data reverts to the alternative hypothesis until the end of the trial.²⁶ Because only 12% of the final sample size was included in the interim analysis cohort, there would still have been reasonable power to show a benefit.²⁷

The MFMU Network was not alone in evaluating repeat versus single dose steroids and there have been many trials with varying results and designs that can augment the information gained from the MFMU study.^{28–36} A systematic review originally published in 2003, was revised in 2015 to include 10 trials (4730 women and 5650 babies) Compared with BEARS, most other studies only repeated a course when preterm delivery appeared imminent. Thus, most patients received a limited number of courses. The meta-analysis showed that treatment with repeat dose(s), reduced the risk of the serious infant outcome (approximately equivalent to the primary outcome of BEARS) by 16% [relative risk (RR) = 0.84, 95% CI: 0.75–0.94], with a number needed to treat of 30, (95% CI: 19–79). Respiratory distress syndrome was also decreased in the repeat steroid group (RR = 0.83, 95% CI: 0.75–0.94). Treatment with repeat dose(s) of corticosteroid was associated with a reduction in mean birth weight of 76 g (95% CI: 34–118 g). However, outcomes that adjusted birth weight for gestational age did not differ between treatment groups. Treatment with repeat dose(s) of corticosteroids was also associated with a reduction in mean head circumference of 0.3 cm, (95% CI: 0.2–0.5 cm).

Four of the trials included follow-up to early childhood. No statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths, survival free of any disability or major disability, disability, or serious outcome) or in the secondary outcome growth assessments. They concluded, similar to BEARS, that the available evidence reassuringly shows no significant harm in early childhood from repeat doses of antenatal corticosteroids.^{37,38} In addition to the systematic review, the Prenatal Repeat Corticosteroid International

Study Group (PRECISE) was formed to conduct an individual patient data meta-analysis of repeat corticosteroid trials that includes the BEARS trial data.³⁷ The final results have not been published yet.

Expanding the window for antenatal steroid use

In addition to the question of the need for repeat dosing, the MFMU and NICHD have been involved in understanding the appropriate gestational window for antenatal steroid use. At the time of the initial investigations by Liggins and Howie and the subsequent studies confirming the efficacy and safety of treatment, the most clinically relevant gestational ages for treatment were evaluated. Antenatal steroid treatment prior to 24–26 weeks was not considered because neonatal care at that time resulted in very few intact survivors. Investigation of the efficacy of treatment after 32–34 weeks was not appropriate until the short- and long-term safety was confirmed on the population at highest risk. This is no longer the case at either extreme.

Use in the periviable period

There are limited randomized trials to guide the use of antenatal steroids between 22 and 26 weeks gestation, but there are both in vitro studies and observational cohort evaluations to suggest that treatment would be beneficial.

Between 22 and 26 weeks gestation, the fetal lung is in the canalicular stage of development. The conducting airways are formed early in this stage and as a fetus approaches 22–24 weeks, epithelial differentiation occurs, in which the cells lining the subsequent alveoli become thinner and more epithelial in appearance. Concurrently, the capillaries move closer to the epithelial lining of the airways, beginning the subsequent air–blood barrier. Surfactant begins to appear in the type 2 alveolar cells and within the airway spaces and in vitro studies of lung cell cultures obtained from pregnancies at this stage and even earlier have demonstrated responsiveness to exogenous steroids.³⁹ In short, there is no biologic reason that steroids could not be beneficial at this stage of development and clinical observational studies confirm this.

The NICHD Neonatal Research Network prospectively evaluated the neonatal morbidity and mortality of 10,541 pregnancies delivered between 22 and 25 weeks gestation from 1993 to 2009. As part of this evaluation, they compared outcomes in steroid treated versus non-steroid treated infants.⁴⁰ Exposed neonates born in weeks 23, 24, and 25 were significantly less likely to die. The study also showed a significantly lower frequency of Grades 3 and 4 intraventricular hemorrhages from 23 through 25 weeks gestation in those exposed to antenatal steroids. There was no difference in chronic lung disease or bronchopulmonary dysplasia by exposure group. Subgroup analysis demonstrated that the apparent beneficial effect was significant in all subgroups except small for gestational age infants and mothers with hypertension and pre-eclampsia.⁴⁰ In the same publication 18–22 months follow-up of the infants born from 2003 to 2008 were included. The composite of death or neurodevelopmental impairment was lower in the steroid-exposed cohort as was moderate and severe cerebral palsy. Tyson et al.⁴¹ had previously reported on the 18–22 month

postnatal evaluation of the infants born between 1998 and 2003 from the same cohort. Again, there was a significantly lower rate of death or profound impairment in the steroid-exposed group.

Similarly, a large cohort study from the Neonatal Network of Japan reviewed 11,607 preterm births from 87 tertiary care centers. From those delivering in the periviable period they concluded that antenatal corticosteroids improved fetal survival and reduced the frequency of severe intraventricular hemorrhage. They found no improvement in respiratory distress syndrome or chronic lung disease.⁴²

This information suggests that antenatal corticosteroid administration has value in the periviable period. It could be offered when clinically appropriate. However, it is less certain if they should be utilized at 22 weeks or less.

It is important to note that the safety of corticosteroids administered in the periviable period has not been confirmed and there are clear animal data suggesting that exposure has an effect on fetal growth, including brain growth.⁴³ Although long-term (age: 5–7 years) follow-up of humans exposed to a single course of corticosteroids is reassuring, the number treated at very early gestational ages is limited. Follow-up studies have only been performed in neonates that delivered between 22 and 26 weeks gestation and not those who remain in utero after exposure.

Less than 20% of pregnancies delivering between 22 and 25 weeks gestation were treated with antenatal corticosteroids in 1993. Periviable corticosteroid treatment increased dramatically after the NICHD special emphasis panel of 1994. By 1996, approximately 80% of infants delivering between 24 and 25 weeks had been treated and this rate has remained stable. This includes 80% of infants delivering between 24 and 25 weeks, 60% of infants delivering at 23 weeks, and 10% delivering at 22 weeks.⁴⁰

Use of antenatal corticosteroids in the late preterm period

In the mid 2000s, the neonatal complications related to late preterm delivery became the topic of an NICHD workshop entitled, “Optimizing care and outcome for late-preterm (near-term) infants.”⁴⁴ Prior to this time it was conventionally believed that infants born from 34 to 36 weeks gestation had a rate of complications similar to that of term infants.⁴⁵ This workshop reviewed emerging literature to show that late-preterm infants had significantly higher morbidities, particularly respiratory morbidities, compared with infants born at term (37 weeks or greater). The workshop concluded that research on improving outcomes for late-preterm infants was necessary, including assessing whether antenatal corticosteroids would improve outcomes in this group.

MFMU investigators designed a trial to specifically answer whether antenatal corticosteroids would be beneficial in this group (clinical trials #NCT01222247). Antenatal corticosteroids to improve fetal lung maturity had not previously been used for pregnancies at risk for late preterm delivery (34 weeks 0 days–36 weeks 6 days of gestation), mainly because the question had not been adequately answered in a clinical trial setting. Liggins and Howie⁶ found a decrease in respiratory distress syndrome in infants treated with

betamethasone after 32 weeks in their 1972 trial, but due to the small numbers in that group, the finding was not statistically significant. Every subsequent trial only included women at 34 weeks gestation or earlier.⁴⁶

The most notable respiratory morbidities in late-preterm infants include respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN), particularly as pulmonary maturation continues through the late preterm period into early childhood.^{47,48} Because approximately 70% of all preterm deliveries are late preterm, this significantly impacts public health care resources.⁴⁹

The Antenatal Late Preterm Steroids (ALPS) trial was a double-blind, placebo-controlled randomized clinical trial conducted at 17 MFMU centers across the United States from 2010 to 2015.⁵⁰ Investigators evaluated the use of antenatal betamethasone for pregnancies at high risk for delivery in the late preterm period, between 34 weeks 0 days and 36 weeks 6 days of gestation. Women with a singleton pregnancy at 34 weeks 0 day to 36 weeks 5 days of gestation and a high probability of delivery in the late preterm period (which extends to 36 weeks 6 days) were eligible for enrollment. High probability of delivery was defined as either preterm labor with intact membranes and at least 3 cm dilation or 75% cervical effacement, or spontaneous rupture of the membranes. If neither of these criteria applied, a high probability was defined as expected preterm delivery for any other indication either through induction or cesarean section between 24 h and 7 days after the planned randomization, as determined by the obstetrical provider. Women were considered ineligible if they were likely to deliver within 12 h, had previously received a course of betamethasone, had pre-gestational diabetes, chorioamnionitis, or any other contraindication to betamethasone. Eligible and consenting women were randomized to receive 2 doses 24 h apart of 12 mg betamethasone or an identical placebo. Tocolysis was not employed as a part of this trial. The management of the patient after administration was left to the discretion of the provider.

The most common indication for enrollment was preterm labor, followed by delivery expected for gestational hypertension or pre-eclampsia. The primary outcome was a composite end point describing the need for respiratory support within 72 h after birth. There was a significant decrease in the primary outcome in the betamethasone group compared with placebo (RR = 0.80; 95% CI: 0.66–0.97). A larger decrease was demonstrated for severe respiratory complications (a composite outcome of CPAP or high-flow nasal cannula for at least 12 continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, ECMO or mechanical ventilation, stillbirth, or neonatal death within 72 h after delivery), from 12.1% in the placebo group to 8.1% in the betamethasone group (RR = 0.67, 95% CI: 0.53–0.84, $P < 0.001$). There were also significant decreases in the rates of transient tachypnea of the newborn (TTN), bronchopulmonary dysplasia (BPD), a composite of respiratory distress syndrome, TTN and RDS, and the need for postnatal surfactant. Infants exposed to betamethasone were less likely to require immediate postnatal resuscitation. Prolonged neonatal intensive care/special care nursery stays were also decreased in the betamethasone group. There was no difference in proven neonatal sepsis, chorioamnionitis, or endometritis. Hypoglycemia was more common in the infants exposed to betamethasone 24.0% versus

14.9% (RR = 1.61, 95% CI: 1.38–1.88). However, there were no reported adverse events related to hypoglycemia, which was not associated with an increased length of hospital stay. Infants with hypoglycemia were discharged on average 2 days earlier than those without hypoglycemia that suggests that the condition was self-limited. Moreover, the rates of hypoglycemia were similar to what is reported in the general population of late preterm infants.⁵¹

While the results of this trial were published online by the New England Journal of Medicine in February, 2016,⁵⁰ the findings have already changed clinical practice. The American College of Obstetrician and Gynecologist and the Society for Maternal-Fetal Medicine both have planned updates and statements, respectively, which will incorporate the use of antenatal corticosteroids in the late preterm group. The impact of this trial's findings is yet to be understood, and a long-term follow-up study is planned.

The future

The value of antenatal steroid administration to prevent neonatal respiratory morbidity, death, IVH, and possibly necrotizing enterocolitis is unquestionable. Their use in pregnancies likely to deliver between 22 and 37 weeks gestation is strongly recommended. There still remain unanswered questions about the use of steroids, which will require further study. These include investigation of the most appropriate dosing regimens for specific maternal and fetal conditions such as twins, pre-eclampsia or fetal growth restriction. Likewise, future studies are needed to determine whether the use of treatment could be expanded even further to include their use prior to near term prelabor cesarean sections.

Acknowledgments

The work described was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), USA, the National Heart, Lung, and Blood Institute (NHLBI), USA, and the National Center for Advancing Translational Sciences (NCATS), USA [HD21410, HD21414, HD27860, HD27861, HD27869, HD27905, HD27915, HD27917, HD34116, HD34122, HD34136, HD34208, HD40485, HD40500, HD40512, HD40544, HD40545, HD40560, HD53097, HD53118, HD68268, HD68258, HD68282, HD36801, HL098554, HL098354, UL1 TR000040 and M01-RR-000080]. Comments and views of the authors do not necessarily represent views of the NIH.

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Table –

Selected outcomes by treatment group from the MEMU Network repeat versus single course trial.

	Repeat	Placebo	Relative risk (95% CI)	P value
Primary outcome	20 (8.0)	22 (9.1)	0.88 (0.49-1.57)	
RDS	24 (9.6)	32 (13.2)	0.73 (0.44-1.20)	0.21
On ventilator support	36 (14.4)	60 (24.8)	0.58 (0.40-0.84)	0.004
Use of surfactant	29 (11.6)	46 (19.0)	0.61 (0.40-0.94)	0.02
Any CPAP	44 (17.6)	60 (24.8)	0.71 (0.50-1.00)	0.05
BPD	16 (6.4)	26 (10.7)	0.60 (0.33-1.08)	0.08
Pneumothorax	1 (0.40)	7 (2.9)	0.14 (0.01-0.85)	0.03
PDA	7 (2.8)	14 (5.8)	0.48 (0.20-1.18)	0.10