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What we have learned about antenatal corticosteroid regimens

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ARTICLE INFO

Keywords:
Antenatal corticosteroids
Betamethasone
Preterm Birth
Respiratory distress

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.

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.

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,

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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http://dx.doi.org/10.1053/j.semperi.2016.03.005
0146-0005/

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, Liggins[5] 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, Liggins[6] 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