Review Article

ANTENATAL CORTICOSTEROIDS FOR FETAL MATURATION

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INTRODUCTION

Corticosteroid treatment of pregnant women at risk for preterm delivery enhances fetal lung maturity and improves neonatal outcomes(1). Despite convincing evidence of these effects, a consensus has not been reached about the indications for antenatal steroids, and the frequency with which they are used remains low in some countries(2). The use of antenatal corticosteroids for fetal maturation is a rare example of technology that yields substantial cost in addition to improving health. Because of these reasons, National Institutes of Health (NIH) Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes held in March 1994; reviewed the scientific basis for the use of corticosteroids (CS), short-term and long-term potential benefits of the medications, adverse effects for the infants and mother, dosage, timing and circumstances of administration, and associated therapy on treatment outcome (3).

In this article, we review the evidence supporting the benefits of CS, controversial issues concerning their use, and current practice recommendations.

FETAL LUNG MATURATION

Most infants destined to be delivered at term do not have mature lungs until about 36 weeks' gestation, but only about 50% of infants born at 30 weeks' of gestational age have respiratory distress syndrome (RDS). The decreased incidence of RDS needs to be interpreted within the context of maturational phenomena that occurs spontaneously in the preterm infant(4). After Liggins (1969) observed that fetal CS treatments resulted in early lung maturation in sheep, numerous clinical trials have documented that maternal CS treatments can decrease the incidence of RDS (5). In general, corticosteroids induce structural maturation of the lungs by increasing gas exchange surface area as is reflected by lung volume measurements and influence structural proteins, such as collagen (5). The meta-analysis by Crowley found that antenatal corticosteroids therapy between 24 and 34 weeks' gestation resulted in an overall approximately 50% in the odds of contracting neonatal RDS (6). A secondary analysis, stratified by the time interval between trial entry and delivery, indicates that babies delivered between 24 hours and 7 days after corticosteroid administration show a more marked benefit (typical odds ratio of RDS, 0.35;95% CI, 0.26-0.46). The odds ratios for RDS in infants delivered less than 24 hours (0.80; 95% CI, 0.56-1.15) or more than 7 days after trial entry (0.63; 95% CI, 0.38-1.07) suggest a trend towards a treatment effect that does not attain statistical significance (6). This data suggests that the beneficial effects of corticosteroids may be recognized within 24 hours of administration to

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the mother in preterm labor. These results are in contrast to earlier recommendations that a minimum of 48 hours was needed to observe a benefit from steroid use (7).

Corticosteroids not only reduce the incidence of RDS in infants exposed to the hormone before delivery, but also reduce the severity of respiratory distress syndrome . The study by Garite et al., which showed lower peak ventilatory pressures in betamethasone-treated compared with untreated infants in spite of similar rates of RDS, supports the hypothesis that betamethasone use can improve pulmonary function without necessarily reducing the overall rate of respiratory distress syndrome (8). Additional evidence for the respiratory benefit of betamethasone use seen by Maher et al., is the reduction in the number of days of mechanical ventilation for those infants born between 24 and 31 weeks gestation who received antenatal betamethasone therapy compared with those who did not (9).

Recent studies have demonstrated that there seems to be a synergistic response between antenatal steroids and surfactant use in the treatment of respiratory distress syndrome . Exogenous surfactant treatment also reduces the severity of RDS and increases the survival of very low birth weight infants (10, 11). Andrews et al., found that the outcomes of neonates who receive both corticosteroids and surfactant are improved compared with those neonates who receive only one of the treatments (12).

NONPULMONARY BENEFITS TO THE NEWBORN FROM PRENATAL STEROID TREATMENT

Intraventricular Hemorrhage:

One of the principal benefits of corticosteroids is the protective effect against intraventricular hemorrhage. Howie and Liggins reported that steroid treatment reduced the incidence of intraventricular hemorrhage (IVH) (13). In 1990 Crowley et al., while performing a meta-analysis of controlled trials evaluating the effect of corticosteroids before preterm delivery, noted that antenatal corticosteroid administration reduced the risk of neonatal intracranial hemorrhage in preterm neonates (1). Secondary analysis of recent trials evaluating the impact of neonatal corticosteroid administration on neonatal RDS has also revealed a reduction in the incidence of IVH (14).

Shankaran et al. recently evaluated prenatal and perinatal risk and protective factors for grade III and IV IVH in large cohort of singleton low birth weight infants (15). They found that a complete 24h course of corticosteroids was associated with an odds ratio of grade III-IV IVH of 0.39 and with a treatment course of <24h, the odds ratio was 0.78. Recently, Kari et al demonstrated that the incidence of IVH was 28% in the placebo compared with 10.4% in the steroid treatment group (14). Ment et al reported that corticosteroid use was associated with a 40% decrease in the incidence of IVH (16). Garite et al. performing a randomized, placebo-controlled trial of betamethasone for the prevention of RDS at 24 to 28 weeks' gestation noted a reduction in grades III and IV IVH in infants born to women who received antenatal steroid therapy (8).

Braks et al. using an animal model, showed that if steroids were administered before a hypoxic insult, the resulting cerebral infarct was smaller than that which occurred in untreated animals. Corticosteroids may also protect the brain of the preterm infant from hypoxic damage (17).

Circulatory Effects and Patent Ductus Arteriosus (PDA):

Corticosteroid treatment improves circulatory stability. The trial by Kari et al. demonstrated that mean arterial pressures were higher in corticosteriod exposed neonates (14) and Moise et al. reported that antenatal steroids reduce the need for blood pressure support in the preterm infant, and that the treated infants had more stable mean arterial blood pressures than untreated ones (18).

The overall frequency of PDA is reduced in low birth weight infants following prenatal maternal corticosteroid treatment. In neonates weighing less than 2 kg, Waffarin and associates noted reduction in the frequency of PDA from 44% to 6.5% with steroid treatment (19). Similarly Clyman and associates noted a reduction in PDA frequency from 34% to 18% in steroid-treated neonates weighing 500 to 1500 g(20). Clyman investigated a potential explanation for fewer

PDA using vascular rings from the PDA of lambs exposed to hydrocortisone in utero compared with those of control lambs. The rings were obtained from animals 48 hours after steroid treatment. PDA rings from the steroid-treated fetuses were three times less sensitive to prostagland E2 relaxation than those from control fetuses (21). However, a recent retrospective study by Andrews et al found that a partial course of corticosteroid was associated with a slight increase in the incidence of PDA (12).

Necrotizing Enterocolitis (NEC):

The risk of NEC is reduced following prenatal corticosteroid treatment. A prospective placebo-controlled trial confirmed these observations(22). In that trial, prenatal betamethasone reduced the frequency of NEC to 3.4% compared with 14.4% in the control group. The postnatal group in this study involved randomized treatment with dexamethasone or placebo for infants in the prenatal placebo treatment group. In this portion of the study, postnatal dexamethasone treatment reduced the frequency of NEC to 6.9% compared with 14.4%. Each of the steroid-exposed groups, both prenatally and postnatally, had significantly reduced frequencies of NEC compared with groups not treated with steroids (22).

Neonatal Mortality:

Antenatal maternal administration of corticosteroids was first shown to decrease the neonatal mortality rate in 1972 (13). This finding has since been confirmed, both in single and multiple center trials. In 1990 Crowley et al. used meta-analytic techniques to evaluate 12 randomized controlled trials. They showed that corticosteroid therapy significantly reduced the risk of neonatal mortality, with an odds ratio of 0.61 (0.49 to 0.78) (1). Atkinson et al found that steroid use was associated with a 50% reduction in the odds of neonatal death (23). Other studies also have reported similar results (24).

Studying the long term outcome of these infants is important. Goldenberg et al. have reported that infants who received antenatal steroids were less likely to be suffering from major neurologic handicap at 1 year of age when compared with an untreated group (25). In fact, long-term follow-up of the patients reported orginally by Liggins and Howie revealed greater gains in height and weight among females orginally exposed to betamethasone (13). In addition, no differences were found between male and female babies upon neurologic and ophtalmologic examination (13, 26).

Other Controversies:

The most controversial recommendation made by the National Institutes of Health (NIH) Consensus Conference concerned the use of corticosteroids in women with preterm premature rupture of membranes (PPROM) (3). The rationale for this recommendation was that even in pregnancies complicated by PPROM, the incidence of IVH is lower in neonates exposed to antenatal steroids when compared with nonexposed infants (23).

The meta-analysis by Ohlsson found that there was a significant decrease in the incidence of respiratory distress syndrome in infants exposed to antenatal steroids in pregnancies complicated by PPROM(27). The potential benefits of corticosteriods must be compared with the possible complications when used in pregnancies with PPROM. The Crowley meta-analysis did not find a significant increase in neonatal infection after corticosteroid treatment in pregnancies with PPROM (6).

The other question concerning corticosteroid use is related to repeat dosing of antenatal steroids if the mother remains pregnant 7 days after the first steroid treatment but is still at risk of having a preterm delivery. A recent retrospective review of patients who did or did not receive doses of corticosteroids found no difference in the incidence of RDS between the two groups (28). Also, Bradley et al. reported a case of neonatal Cushingoid Syndrome with hypothalamic-pituitary-adrenal axis suppression following maternal treatment with seven courses of betamethasone (29). For these reasons, until a prospective trial demonstrates the benefit of repeated dosing with corticosteroids, this strategy cannot be recommended.

CONCLUSION

For the 27 years since the first clinical reports of prenatal corticosteroid treatment to enhance fetal lung maturation, this treatment has been studied

in thousands of preterm newborns. Corticosteroids promote the maturation of all organ systems, stabilization of arterial blood pressure and acceleration of the maturation of neuronal cells and germinal matrix vessels may contribute to their protective effects as well as increased lung maturation and decreased severity of respiratory distress syndrome . No immediate or long-term adverse effects have been demonstrated for the newborn or fetus. With PROM, mothers may have an increased risk of endometritis without a clear increase in overall frequency of infection, at the same time steroids significantly decrease the frequency of respiratory distress syndrome in newborns.

Although numerous randomized controlled trials had shown corticosteroids to reduce neonatal morbidity and mortality, only about 20% of the mothers of preterm infants were treated with this hormone before delivery. The NIH Consensus Conference recommended that mothers at risk of preterm delivery between 24 and 34 weeks' gestation should receive corticosteroids unless delivery was imminent. The conference also recommended that women with PPROM between 24 and 32 weeks' receive corticosteroids to reduce the incidence of IVH. Hopefully, obstetricians will use corticosteroids more often in the management of preterm labor because this treatment may markedly improve the quality of survival for many premature newborns.

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