Use of Glucocorticoids for the Fetus and Preterm Infant

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KEYWORDS

• Glucocorticoids • HPA axis • Fetus • Newborn • BPD • Hypotension
• Brain development

KEY POINTS

- Glucocorticoids have positive short-term impact on preterm infant survival.
- The environment impacts glucocorticoids on brain development in the preterm infant.
- Fetal and preterm function of the HPA axis are immature, possibly linked also to thyroid hormone dysfunction.

Use of glucocorticoid (GC) treatment in the prenatal state and in the preterm infant has been evaluated for more than 40 years.[1] Many issues have been studied, including the following:

1. Historical use of GC therapy in the fetus and preterm infant.
2. Selection of which GCs have been used prenatally and postnatally.
3. Impact of GC treatment in the preterm infant. Are outcomes for the fetus and for postnatal development enhanced by use of GCs?
4. Role of GCs in the transition to postnatal life in full-term infants.

GC treatment in the fetus and preterm infant was demonstrated to be a highly successful therapeutic intervention resulting in decreasing occurrence of many consequences of preterm birth, at a time when ventilator dependence was a growing problem.[2] This outcome was based on giving GC 1 to 10 days before delivery, and not continuing to give the medication after birth. However, long-term negative effects were observed in subsequent studies of GC therapy, not necessarily predictable when use of dexamethasone began.[3]

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Early interest in using exogenous GC included studies published in 1969 in prematurely delivered sheep that demonstrated improved outcome with GC therapy.[4] Of note, mean weight of the adrenal gland was 19% lighter in neonates dying of respiratory distress syndrome (RDS) within 72 hours of delivery, compared with adrenal weight in neonates who died of other causes.[5] Overall, results from sheep and humans suggested a role for GC in successful transition of the preterm infant to postnatal life. Betamethasone used predelivery in a controlled study was associated with a decrease in RSD occurrence in their infants.[6] However, despite many studies since then, there are still unresolved issues.[7,8]

Postnatal effects of GC therapy were noted in 1976 when women were given a single dose of hydrocortisone, 100 mg.[9] Infants born less than 24 hours after steroid therapy had no improved outcome. If the steroids were given greater than 24 hours before delivery, incidence and mortality associated with RDS were lowered. In addition, there was no acceleration of delivery, a concern because of a prior observation of increased contractions with GC infusion in the fetal state. It is unclear how the steroid dosage was chosen for these mothers. Lack of clarification of the rationale for choice of GC medication, dose, and duration of treatment are common issues in the literature. Several other studies during the same time period examined whether steroid therapy decreased occurrence of RDS.[10–12]

One of the reasons that GC therapy was initiated historically was the recognition of a poorly functioning fetal hypothalamic-pituitary-adrenal (HPA) axis in preterm infants. The fetus and placenta work together in controlling HPA axis action during pregnancy. Also controlled tightly during pregnancy are the types and levels of thyroid hormone encountered by the fetus. Then, as delivery approaches, changes in thyroid and cortisol concentrations begin to prepare the fetus for postnatal life.

The HPA axis does not function well early on after preterm delivery, especially when "stressed" or elevated levels of GCs are needed for successful postnatal transition of the preterm infant.[13,14] Even at 2 weeks of postnatal age, the corticotropin-releasing hormone (CRH) stimulation test (testing function of the pituitary) does not yield normal results in infants born at less than 30 weeks gestational age.[15]

Many studies have addressed suppression of the HPA axis by prenatal and/or postnatal GC treatment. Some of the results may be related to developmental delay in function of the HPA axis in the preterm infant. Replacement/treatment with GCs seems to be necessary for improved outcome in the preterm infant.[16]

The pattern of cortisol secretion after delivery depends on gestational age at birth. Ill infants born at greater than 27 weeks gestational age have rising cortisol values from Day 2 to Day 6, contrasted with cortisol values decreasing in well infants of the same age. Of note, a rise in cortisol is expected as a normal response to the physiologic stress of illness. In contrast, cortisol values significantly declined from Day 2 to Day 6 in well and ill infants who were born at less than or equal to 27 weeks gestational age. The cortisol concentrations in the premature infant are significantly correlated with gestational age and with markers of illness.[17] Postnatal effects after the use of antenatal steroids included a potential altered heart rate response to stressors later in life.[18]

TYPES OF GLUCOCORTICOIDS USED PRENATALLY

Unlike the preterm infant where several GCs have been used, there are two GCs that have been used primarily in the fetus: dexamethasone and betamethasone, often used