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Review

Effects of antenatal glucocorticoids on the developing brain

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ABSTRACT

Glucocorticoids (GCs) regulate distinct physiological processes in the developing fetus, in particular accelerating organ maturation that enables the fetus to survive outside the womb. In preterm birth, the developing fetus does not receive sufficient exposure to endogenous GCs *in utero* for proper organ development predisposing the neonate to complications including intraventricular hemorrhage, respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC). Synthetic GCs (sGCs) have proven useful in the prevention of these complications since they are able to promote the rapid maturation of underdeveloped organs present in the fetus. While these drugs have proven to be clinically effective in the prevention of IVH, RDS and NEC, they may also trigger adverse developmental side effects. This review will examine the current clinical use of antenatal sGC therapy in preterm birth, their placental metabolism, and their effects on the developing brain.

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Contents

1. Clinical use of antenatal synthetic glucocorticoid therapy

Glucocorticoids (GCs) regulate distinct physiological processes in the developing fetus, in particular accelerating organ maturation that enables the fetus to survive outside the womb [1–4]. In preterm birth, the developing fetus does not receive sufficient exposure to endogenous GCs *in utero* for proper organ development predisposing the neonate to complications including intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC). Synthetic GCs (sGCs) have proven useful in the prevention of these complications since they are able to promote the rapid maturation of underdeveloped organs present in the fetus [1–4]. While these drugs have proven to be clinically effective in the prevention of IVH, RDS and NEC, they may also trigger adverse developmental side effects [5]. This review will examine the current clinical use of antenatal sGC therapy in preterm birth, their placental metabolism, and their effects on the developing brain.

Current clinical guidelines indicate that mothers at risk of premature delivery before 34 weeks of gestation are candidates for antenatal sGC therapy, as administration does not demonstrate significant reductions in morbidity or mortality after this time [1,4,6]. One exception to this recommendation is in the case of

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suspected pulmonary insufficiency [6]. Recommended treatment courses include two doses of 12 mg betamethasone administered intramuscularly 24 h apart or four doses of 6 mg dexamethasone administered intramuscularly every 12 h. This treatment is not standardized across the United States and treatment courses may be administered multiple times [6], despite recent evidence that suggests that multiple doses of antenatal sGC do not significantly improve clinical outcomes [7]. In fact, the Multiple Courses of antenatal corticosteroids for preterm birth study at 5 years of age (MACS-5 study) indicated that multiple courses of antenatal sGC may have an increased risk for neurodevelopmental and neuropsychiatric conditions at the age of five years providing evidence against the use of multiple courses [7].

While antenatal sGC therapy remains the standard of care in the antenatal prevention of IVH, RDS and NEC, enthusiasm for postnatal sGC therapy for treatment or prevention of bronchopulmonary dysplasia (BPD) has diminished due to a number of studies demonstrating negative effects on brain development in preterm infants without a significant long-term improvement in pulmonary health [8,9]. Specifically, postnatal sGC treatment has been found to increase the risk for cerebral palsy [8,10–13].

While detrimental side effects have been observed after multiple courses of antenatal sGC therapy and postnatal sGC therapy, it is widely accepted that single dose sGC therapy does not have significant side effects. However a 2014 review highlighted that even a single course of antenatal sGC can result in an 18% reduction in birth weight, a 9% decrease in head circumference, 6% decrease in body length, as well as placental abnormalities when compared with both preterm and term unexposed infant [14]. Additionally relevant are the particular outcomes based on the timing of sGC administration prior to delivery. While the maximal benefit occurs after 24 h but within 7 days of maternal administration, it is not yet clear if longer exposure *in utero* may add to or detract from detrimental neurodevelopmental effects [14].

The benefits of antenatal sGCs, if administered properly, provide significant improvements in infant health, as highlighted by two recent analyses [10,15]. In fact, a single course of antenatal sGC therapy improved most neurodevelopmental outcomes studied in infants born prior to 34 weeks gestation [10]. A large study recently published by the *Eunice Kennedy Shriver* NICHD Neonatal Research Network which examined very early gestation births revealed a significant reduction in death and neurodevelopmental disability at 23, 24 and 25 weeks gestation, but not prior to 23 weeks [16]. This evidence suggests that antenatal sGC therapy is most beneficial to the infant at the limits of viability. This NICHD study also found a significant reduction in death, IVH, periventricular leukomalacia (PVL) and NEC.

While antenatal sGC therapy is indispensable in the prevention of IVH, RDS and NEC associated with preterm birth, it remains unclear as to the proper or optimal timing or dosage of these medications. Exposure to sGCs *in utero* at critical developmental stages can lead to alterations in the function of many organ systems that extend into adult life. The consequences of this altered "fetal organ programming" are poorly characterized in humans, but it is well documented in animal models that antenatal exposure to sGCs can alter the function of the adult hypothalamic-pituitary-adrenal (HPA) axis, glucose homeostasis, and the cardiovascular system [2,3,17,18]. In addition, the long-term effects of sGC exposure at different developmental stages of fetal growth are not well known. This is particularly true for infants whose *in utero* exposure is lengthened by failure to delivery prematurely. Of particular concern are the approximately 70% of pregnant women who are given sGC for threatened preterm labor but do not deliver within 7 days, the accepted time of maximal benefit [17]. While antenatal sGC therapy is administered routinely, there is growing evidence for incomplete benefit, particularly in certain subpopulations of infants, and for sex specific benefits, further expressing the need for individualized therapy in the clinical setting. Specifically, understudied variables that may affect the response to antenatal sGC therapy include birth weight, multiple gestation, race and sex.

2. Demographic variables in the response to antenatal sGC therapy

As previously discussed, antenatal sGC therapy is given to all mothers at risk of premature delivery before 34 weeks gestation. Interestingly, there is no difference in the dosage, timing or specific sGC used in antenatal sGC therapy despite variability in birth weight, multiple gestation, ethnicity, sex or specific genetic polymorphisms, even though significant differences have been observed in clinical outcomes [19–22]. With ideal administration of sGC, one recent study suggests that nearly 40% of infants still present with RDS in the neonatal period [23]. In order to improve clinical outcomes, it is essential to understand the variables that affect the response to antenatal sGC therapy. This section will outline a number of observations that highlight demographic variables, which need to be assessed in order to individualize and optimize antenatal sGC therapy.

A recent study looking at antenatal sGC therapy in infants with a birth weight of less than 1500 g (growth-restricted fetuses) demonstrated no significant short or long-term benefit between the exposed and unexposed infants. This suggests that antenatal sGC may not be beneficial for all populations of infants [19]. In fact, RDS risk was increased in lower gestational age infants, and this was independent of whether or not a completed course of antenatal sGC therapy was achieved, suggesting that these infants may be needlessly exposed to potent therapeutics. As mentioned previously, there is no significant benefit of antenatal sGC therapy if administered prior to 23 weeks gestation [16]. Because of the adverse developmental side effects, it is important to consider whether the benefits outweigh the risks in certain sub-populations of infants.

Multiple-gestation studies have been performed looking at benefit of single course of antenatal sGC therapy. They have consistently found that multiple-gestations respond as singletons, but one study suggested that this was only true if the duration of antenatal sGC therapy optimally occurred between 2 and 7 days after maternal administration [20]. In addition, very low birth weight multiple gestation infants exposed to ACS may respond as well as their singleton counterparts [24], but it is not clear if this applies to exposure out of the optimal window for delivery.

Differential outcomes in patients exposed to sGC *in utero* could result from individual genetic variations in steroid metabolism or pulmonary gene specific single nucleotide polymorphisms (SNPs). In small for gestational age infants, these SNPs have been associated with differences in the reduction in RDS [25]. Clinical data suggests that the effect of antenatal sGC therapy is limited in intrauterine growth restricted fetuses (IUGR) and that 'it remains unclear if ACS therapy is beneficial due to heterogeneous populations and treatment regimes' [26].

Studies evaluating the influence of maternal ethnicity have also been performed and have reported that maternal ethnicity is 'independently associated with neonatal respiratory outcomes' after exposure to antenatal sGC therapy [21]. Also, a recent report showed that when controlling for gestational age as well as size, Caucasian infants have significantly higher incidence of RDS than infants who were not Caucasian [27].

In addition to differences in outcome based on ethnicity, a number of studies report different clinical outcomes of antenatal sGC therapy based on fetal sex. One particular study examined VLBW infants and found that 'compared with girls, VLBW male newborns