OBSTETRICS

Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations

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Over the past 40 years, the administration of synthetic antenatal corticosteroids as initially proposed by Liggins and Howie in 1972 has incontrovertibly demonstrated significant reductions in neonatal mortality and morbidity in preterm infants born before 34 weeks’ gestation. Multiple worldwide clinical trials have been well summarized in the meta-analyses by Crowley et al and in Cochrane Database reviews. These analyses, consensus statements, and practice guidelines have influenced changes in clinical practice for single and repeated courses of synthetic glucocorticoids (GCs) for women in preterm labor.

Dating back to the work of Levine, beginning in the 1950s, it has been known that the early environment has the potential to exert lasting consequences on the functioning of the hypothalamic-pituitary-adrenocortical (HPA) axis. Exposure to endogenous and exogenous GCs during pregnancy is one environmental influence that programs the development of the fetal HPA axis with long-term consequences. For this reason, exposure to excess GCs during gestation may have an adverse impact on stress responsive systems. This review will consider what is known about the effects of prenatal treatment with synthetic GCs on the functioning of the HPA axis.

The HPA axis

GCs (cortisol in humans), the end product of the HPA axis, are steroid hormones that are physiologically important for maintaining homeostasis. GCs exert a wide array of key metabolic, endocrine, and immune effects on most cells, perhaps more than any other biological ligand. Furthermore, GCs pass through the blood-brain barrier and with consequences for brain structure and function.

GCs serve as a major mediator of the stress response and promote survival in the face of threat. The cascade of events that produce changes in cortisol release by the adrenals begins with the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by cells in the paraventricular nuclei of the hypothalamus. CRH and AVP are released through capillary vessels to the anterior pituitary in which they stimulate the release of adrenocorticotropic (ACTH) hormone into circulation. ACTH stimulates the biosynthesis and release of cortisol from the adrenal cortex.

Because of the damaging effects of chronic exposure to elevated levels of cortisol, the HPA axis is protected by a negative feedback loop whereby cortisol binds to receptors in the pituitary and hypothalamus as well as the hippocampus and prefrontal cortex inhibiting or turning off the HPA axis response. In contrast to the inhibitory role of cortisol on hypothalamic CRH production, cortisol increases the production of CRH in brain regions such as the hypothalamus.
cluding the central nucleus of the amygdala, the activation of which plays a role not only in stimulating the HPA axis but also in stimulating increases in central norepinephrine and peripheral activation of the sympathetic nervous system. The activation of the HPA axis, including the release of GCs, involves a complex interaction of multiple central and peripheral stress response systems. The interaction between the HPA axis and the sympathetic nervous system has been critically reviewed by Kvetnansky et al.14 This review will focus on the primary consequences of GC treatment for the functioning of the HPA axis.

Changes in the maternal HPA axis during pregnancy

In the course of pregnancy, dramatic changes in the functioning of the maternal HPA axis are observed because the placenta expresses the genes for CRH (hCRHmRNA) and the precursor for ACTH and beta-endorphin (proopiomelanocortin). Placental CRH production increases dramatically over gestation and placental CRH plays a central role in the regulation of fetal maturation and the timing of parturition.15-17 In contrast to the negative feedback regulation of hypothalamic CRH, cortisol stimulates the expression of hCRHmRNA in the placenta, establishing a positive feedback loop that allows for the simultaneous increase of placental CRH, ACTH, and cortisol over the course of gestation.18 For example maternal cortisol increases 2- to 4-fold during pregnancy.19 This physiologic increase exerts broad influences on the developing fetus including maturation of the fetal lungs, the central nervous system (CNS), and other organ systems. GCs influence fetal brain development by changing neuronal migration, synapti
clasticity, and neurotransmitter activity.20 Because of the positive feedback between GCs and placental CRH, the effects of excess endogenous or synthetic GCs may be amplified with potentially negative consequences for the developing fetus. The consequences of prenatal treatment with synthetic GCs such as betamethasone and dexamethasone may be more profound as they cross the placenta more easily because they are not readily metabolized by the placental enzyme, 11β-hydroxysteroid dehydroge
nase type 2 (11β-HSD2), that protects the fetus from maternal cortisol (Figure).

Development of the fetal HPA axis

Liggins25 observed that the fetal HPA axis played a major role in the onset of labor, and its ablation resulted in the underdevelopment of the fetal lungs. Since then, a number of studies have shown that the fetal HPA axis is highly sensitive to excess levels of GC that could alter the regulation of HPA function.12,18,24,25 The fetal adrenal gland makes unique contributions to both the regulation of fetal development and the timing of parturition.

Morphologically, the fetal adrenal gland is comprised of 3 zones: the outer, definitive zone; a large, inner fetal zone; and an intermediate transitional zone. The fetal adrenals undergo rapid growth throughout gestation, and at term gestation, the fetal adrenals are significantly larger, relative to body weight, than the adult adrenals.26 The adrenal gland has steroidogenic enzymes as early as the seventh gestational week,27,28 and there is evidence for a functional stress re
sponse involving an increased production of cortisol in response to pain during the latter half of gestation.29

Animal and human data strongly sug
gest that GCs program the fetal HPA axis with consequences for postnatal functioning.18,30 This programming may occur in part through the alterations of brain regions that are both integral to the regulation of stress responses and vul
nerable to exposure to stress hormones. Vulnerable regions such as the hip
campus and amygdala undergo rapid development during fetal life. Both are identifiable between 6 and 8 gestational weeks, and by term the basic neuroanat
omical architecture of these regions is present.31 Cortisol has affinity to 2 receptors, mineralocorticoid receptors and gluco
corticoid receptors (GRs). Limited informa
tion exists regarding the time course of prenatal development of cortisol receptors in humans. However, data indicate that both receptors types are present in the human hippocampus by 24 gestational weeks.32

Animal data

Antenatal GC treatment has a broad range of effects on the fetus including regulation of growth, organ maturation, immune functioning, and the sympathetic nervous system. Alterations to the functioning of the HPA axis is a primary consequence of prenatal GC treatment that is observed in the offspring of a variety of species including rats, sheep, guinea pigs, and nonhu
man primates.30,33-39 Data indicate that these changes in the functioning of the HPA axis are associated with alterations of GR receptor number in regions including the prefrontal cortex, hippocampus, amygdala, and pituitary that are impor
tant for activation and negative feedback regulation of the HPA axis.40-42 The nature and the magnitude of these effects are determined by the type of steroid used (eg, betamethasone or dexamethasone), the number of doses, and the timing of exposure.35,43-45 Specifically, the binding affinity differs for be
tamethasone and dexamethasone (eg, dexamethasone has a greater affinity for GR receptors), and there is evidence that these steroids have differential conse
quences for offspring.30,35 In terms of dose, data indicate that exposure to mul
tiple doses is associated with more pro
found consequences.46,47 Finally, organ systems may be most vulnerable to the consequences of GC treatment during times of rapid development.48,49 Thus, the timing of treatment will likely deter
mine the nature and the magnitude of the effects.

In addition, the type of synthetic GC and dose also has differential effects on lung maturation and surfactant synthesis.20 Carefully conducted studies with sheep have further documented that the phenotypic changes to the HPA axis are additionally determined by the develop
mental stage at the time of assessment. For example, although increased HPA axis activity is observed in the young animal, suppression of HPA axis activity is observed as the animal matures.44,51

Exciting and important new work raises the possibility that prenatal expo
sure to synthetic GCs may alter repro
ductive functioning among female offspring and exert intergenerational effects on HPA axis functioning. Dunn et al have recently demonstrated that females exposed to betamethasone in utero require a greater number of ovulatory cycles for successful reproduction as compared with their unexposed counterparts. These data raise the possibility that intrauterine exposure to synthetic GCs may have consequences for fertility among female offspring. Intergenerational consequences of early life experiences for the functioning of the HPA axis have been observed. Potential mechanisms for these effects include altered functioning of endocrine and cardiovascular systems among prenatally exposed females as well as epigenetic changes.

Human data

Less is known about the consequences of antenatal GC exposure in humans. Assessments of cord blood and amniotic fluid indicate acute suppression of endogenous fetal cortisol production and an acute increase in GC bioactivity in response to synthetic GCs. The suppression of endogenous fetal/neonatal cortisol production appears to persist into the immediate postnatal period. Several studies have shown that among preterm infants exposed to antenatal GCs, unstimulated (baseline) cortisol levels are suppressed for several days after treatment during the first postnatal week and then return to normal levels. The assessment of cortisol levels at a single time point during the day provides limited information regarding the functioning of the HPA axis. To better understand the influence of prenatal GC treatment on HPA axis functioning, it is necessary to use serial assessments to evaluate both responses to stressors and the circadian regulation.

Few studies have evaluated the consequences of intrauterine exposure to synthetic GCs on the ability of the HPA axis to respond to a challenge. As reviewed in the Table, the limited existing data, including studies from our own laboratory, suggest that prenatal GC treatment may have persisting effects on the HPA axis and regulation of stress responses. These studies indicate that although suppression of unstimulated/baseline levels of cortisol is present only during the first several days after treatment, the effects on HPA axis regulation persist. We have observed that prenatal treatment with a single course of betamethasone is associated with a suppression of the cortisol response to the painful stress of a heel-stick blood draw among preterm infants and that this effect persists for at least 4-6 weeks after birth. Similarly, in a study including a combined sample of term and preterm neonates, Schaffer et al documented a suppressed cortisol response to heel stick. These studies suggest that prenatal GC treatment has implications for HPA axis regulation that persist for at least 8 weeks after treatment, with some evidence for greater consequences associated with exposure to multiple courses.

One of the limitations of existing research is the focus on preterm infants who experience a range of acute medical complications and are exposed to multiple sources of stress as part of their care in neonatal intensive care units. Factors
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of GC; number of courses</th>
<th>GA wks at GC exposure</th>
<th>After GC days to birth</th>
<th>Maturity/GA at birth</th>
<th>Neonatal stress challenge</th>
<th>Behavioral response</th>
<th>Comment/Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al</td>
<td>Betamethasone × 1 course</td>
<td>N/A</td>
<td>Mean 8.3 d; range, 1–21 d</td>
<td>Preterm only 33-34</td>
<td>Blunted/no cortisol response among GC-treated infants compared with no-treatment comparison group</td>
<td>Similar to comparison group</td>
<td>HPA axis function altered</td>
</tr>
<tr>
<td>Davis et al</td>
<td>Betamethasone × 1 course</td>
<td>N/A</td>
<td>Mean 5.1 d; range, 1–9 d</td>
<td>Preterm only 28-30</td>
<td>Blunted cortisol response among GC-treated infants compared with no-treatment comparison group</td>
<td>Similar to comparison group</td>
<td>HPA axis function altered</td>
</tr>
<tr>
<td>Ashwood et al</td>
<td>Betamethasone × 1 course</td>
<td>23–31</td>
<td>Unknown</td>
<td>Preterm only &lt;32 and &gt;32</td>
<td>Blunted cortisol response in multiple-course group compared with single-course group. Greater blunting of cortisol response at earlier gestational exposure. Baseline cortisol lower in multiple-course group at d 7 compared with single course; baseline cortisol levels were similar in the 2 groups by d 14</td>
<td>Not studied</td>
<td>Acute differences in HPA axis function in infants exposed to multiple courses vs single course</td>
</tr>
<tr>
<td>Schaffer et al</td>
<td>Betamethasone × 1 course</td>
<td>29.4</td>
<td>Mean 60 d; &gt;34 wks</td>
<td>Term and preterm</td>
<td>Blunted cortisol and cortisone response among GC-treated infants compared with the no-treatment comparison group</td>
<td>Not studied</td>
<td>HPA axis function altered</td>
</tr>
<tr>
<td>Davis et al</td>
<td>Maternal psychosocial stress; exposed to elevated endogenous maternal cortisol in second and third trimesters</td>
<td>N/A</td>
<td>Term only 37-41</td>
<td>Larger cortisol response and slower recovery associated with elevated maternal endogenous cortisol levels</td>
<td>Slower recovery to baseline state</td>
<td>HPA axis function altered</td>
<td></td>
</tr>
<tr>
<td>Davis et al</td>
<td>Betamethasone × 1 course</td>
<td>29.5</td>
<td>Mean 60.5 d; range, 28–105 d</td>
<td>Term only 37-41</td>
<td>Larger cortisol response among the GC-treated infants compared with the no-treatment group; with greater response when GC exposure was at earlier GA</td>
<td>Similar to comparison group</td>
<td>HPA axis function altered</td>
</tr>
</tbody>
</table>

GA, gestational age; GC, glucocorticoids; HPA, hypothalamic-pituitary-adrenocortical; N/A, not applicable.
such as preterm birth, acute respiratory illness, and exposure to painful medical procedures have been shown to affect the development of the HPA axis and thus may interfere with the ability to accurately identify and isolate the consequences of GC therapy.

To address this issue, we evaluated the cortisol response to the painful stress of a heel-stick blood draw among full-term infants treated with a single course of the GC betamethasone and a matched comparison group of infants born at term gestation. We found that prenatal treatment with the synthetic GC, betamethasone, was associated with a more pronounced cortisol response to the painful stress of the heel-stick procedure among healthy infants born at term gestation, despite no difference in baseline levels. Interestingly, this heightened cortisol response to the heel-stick procedure is similar to the one observed among term infants exposed to elevated levels of endogenous maternal cortisol during the third trimester. We found that prenatal treatment with the synthetic GC, betamethasone, was associated with a more pronounced cortisol response to the painful stress of the heel-stick procedure among healthy infants born at term gestation, despite no difference in baseline levels. Interestingly, this heightened cortisol response to the heel-stick procedure is similar to the one observed among term infants exposed to elevated levels of endogenous maternal cortisol during the third trimester. These data suggest a lasting influence of prenatal exposure to excess GCs that has persistent consequences for the functioning of the newborn HPA axis.

There is limited evidence regarding the long-term consequences of prenatal GC treatment for the functioning of the HPA axis. The 2 studies that evaluate the consequences of GC exposure for HPA axis functioning later in infancy yield conflicting results. This may be due to the inclusion of heterogeneous samples of preterm infants who were exposed to different types and doses of steroids at varying times during pregnancy and postpartum. To our knowledge, only 1 study has evaluated the consequences of antenatal GC treatment for adult HPA axis functioning. At 30 years of age, morning cortisol levels were 7% higher among individuals exposed to antenatal steroids as compared with the control group. This increase was not significant after consideration of factors including sex, birthweight, gestational age at birth, trial type, body mass index, and the use of oral contraceptives. The fact that a tendency for an effect on the HPA axis was observed in the presence of multiple confounding variables and with a limited evaluation of the HPA axis leaves open the possibility that prenatal GC treatment may exert long-term consequences on the functioning of the HPA axis in humans.

Based on the experimental animal data and human observations, it is evident that the HPA axis is particularly vulnerable to exposure to elevated levels of endogenous and exogenous GCs. Dysregulation of HPA axis functioning during infancy may put children at risk for physiological and behavioral problems throughout the life span. A parallel set of observations in a model of prenatal stress having programming effects and adverse outcomes on the fetal HPA axis and the hypothalamus-adrenal-gonadal axis is with the fetal alcohol spectrum disorder, which further confirms that the fetal HPA axis is susceptible to changes secondary to prenatal stress with long-term consequences.

The focus of this review is on the programming consequences of antenatal GC treatment. It is, however, noteworthy that other common antenatal therapies such as administration of beta 2 adrenergic agonists additionally exert developmental influences and may interact with the effects of GC treatment.

Clinical considerations
The initial choice and dose of synthetic GCs for accelerating fetal lung maturation was not subject to formal evaluation and Food and Drug Administration (FDA) approval for prenatal use. However, based on multiple clinical trials and wide clinical experience, the current standard of practice is to administer either a single course of betamethasone or dexamethasone (i.e., 2 doses of beta-methasone 12 mg intramuscularly at 24 hour intervals or 4 doses of 6 mg of dexamethasone intramuscularly at 12 hour intervals) to women in preterm labor between 24 and 34 weeks’ gestation.

There is also evidence that incomplete or partial treatment with these formulations does provide some benefit in terms of decreasing morbidity. Although the effects of antenatal corticosteroids on lung maturation appear to be dose dependent, the biological effects and the optimal dose of antenatal GCs is unknown and under investigation, especially with respect to the long-term effects on other organ systems, particularly the CNS and neurodevelopmental outcomes.

Detailed studies in sheep suggest that comparable acceleration of fetal lung maturation (biochemical and functional) could be achieved with a single dose of maternal betamethasone acetate as compared with the conventional clinical 2 dose regimen. As suggested by Jobe et al., the hypothesis that low fetal exposure to betamethasone following maternal beta-acetate treatment might decrease risks of adverse neurodevelopmental and growth effects remains to be tested.

The practice of repeated courses of antenatal corticosteroids has been widely used for more than 25 years with the intent of maximizing maturation of the lungs and decreasing the incidence of acute lung disease in premature infants. Follow-up studies have shown a decrease in the incidence and severity of lung disease along with decreases in fetal growth and head circumference. More recently, the National Institutes of Health in its second consensus conference in 2000 and the American College of Obstetricians and Gynecologists concluded that the repeat course of antenatal corticosteroids, including rescue therapy, should be reserved for women enrolled in clinical trials. The majority of the metaanalyses of clinical trials comparing the standard single course regimen of antenatal GCs to repeated doses up to 34 weeks’ gestation also suggest caution in recommending the repeated course regimens.

The latest updated systematic review by Crowther et al. comparing a single dose to repeated doses of synthetic GC betamethasone from 10 randomized clinical trials between 2001 and 2010 in 4730 mothers and their 5700 infants found a significant reduction in the risk of respiratory distress syndrome and serious neonatal morbidity. Long term, 2- to 3-year follow-up of infant outcomes among 4170 of these infants showed no difference in major neurosensory disabilities as well as in secondary outcomes in cerebral palsy, blindness, and deaf-
ness. The authors concluded that a repeated-dose regimen in these trials “showed no evidence of harm or benefit” as compared with the standard single course of antenatal GC and recommended consideration of repeated doses of antenatal GC as was used in these clinical trial protocols for women at risk of preterm delivery.

Of note, however, is that in one of the studies included in this review, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Network Study Group\(^5\) reported a higher number of infants with cerebral palsy in a subgroup of infants exposed to either the single course or the placebo group. Although the difference in their 2 groups was not statistically significant, appropriate concern and caution was raised regarding the routine repeated courses of GCs. These clinical observations (along with those in animal literature) of repeated exposure of the fetus to synthetic GCs raises the possibility that the long-term effects on brain development and outcomes are not yet fully appreciated.

The randomized studies to date have reported primarily on major neurosensory disabilities and overall neurodevelopmental outcomes. There is a need for detailed evaluations of the more subtle CNS effects of GC exposure such as those mediated through effects on the HPA axis, the pituitary-gonadal axis, and other specialized pathways in the brain. The need to evaluate these subtle changes is substantiated by a recent report by Sandman et al\(^6\) documenting the lasting influence on prenatal exposure to naturally occurring stress hormones for HPA axis functioning, cognitive and emotional regulation, and brain development.

An alternate approach being studied to reduce and minimize the potential risks of multiple courses of antenatal corticosteroids is to limit repeated exposures, with the administration of a single retreatment (rescue) course following the standard initial course, when preterm delivery seemed imminent before 33 weeks’ gestation.\(^7\) This rescue dosing strategy appears to have the same benefits as multiple courses of steroids in terms of overall postnatal morbidity, decrease in respiratory distress syndrome, and postnatal surfactant use.

Current thinking on the choices of synthetic GC, the use of repeated or rescue dosing, and the use of antenatal corticosteroids for decreasing respiratory morbidity in the late preterm infant has recently been critically evaluated and summarized.\(^8\) The broadest clinical experience for single and repeat courses of antenatal corticosteroids is based largely on the use of currently formulated combined doses of betamethasone phosphate and betamethasone acetate. Although many of the observational cohort studies seem to indicate that treatment with betamethasone has better outcomes and less adverse effects than dexamethasone,\(^8,9\) these data are not conclusive.\(^8,9\)

A few clinical strategies currently being investigated have emerged, which, when used in conjunction, show promise for the improved diagnosis and management of preterm labor. These include the use of biological markers such as fetal fibronectin\(^9,94\) and the measurement of cervical length by transvaginal ultrasound\(^95\) for identifying women who are at risk for preterm labor and preterm delivery. Also of note is the recent FDA approval in 2011 of progesterone supplementation for the prevention of preterm birth. The evidence for the effectiveness of this treatment has been extensively reviewed by Norwitz and Caughey.\(^96\)

A recent report\(^97\) also suggests a promising clinical strategy of using transvaginal ultrasound for identifying mothers at risk for preterm labor and the use of progesterone therapy to prevent preterm delivery. These emerging clinical strategies, if confirmed, are likely to assist the clinician in being more selective in the choice of patients who are candidates for one or more courses of antenatal corticosteroids.

Unanswered questions and future directions

Because the early clinical diagnosis of preterm labor is difficult and subjective and the laboratory indicators of early preterm labor are imprecise, there are a number of mothers who receive antenatal GCs for preterm labor who deliver beyond 37 weeks’ gestation. The potential risks of antenatal GC exposure to these infants born at term needs to be evaluated in the context of clear and substantial benefit to preterm infants. The risk or benefit of GC exposure to this group of infants is unknown, and longitudinal follow-up studies for this subgroup of infants are clearly needed.

Other clinical studies that would help us better evaluate the potential risks and consequences of antenatal GC exposure are ones that would adequately evaluate sexually dimorphic responses to antenatal GC.\(^40,52\) Furthermore, new evidence indicates that the long-term programming effect on the HPA axis in females must include evaluation of the stage of the reproductive cycle.\(^35\) Separately, animal data\(^34,51\) and observational human studies\(^62,65\) indicate that the phenotype associated with exposure to antenatal GC treatment varies based on the developmental stage at the time of assessment of the HPA axis.

These findings bring up the need for prospective longitudinal studies to evaluate HPA axis function at multiple time points. Furthermore, comprehensive assessment of HPA axis function including responses to stress and circadian regulation in the human are needed to fully characterize the consequences of prenatal GCs on this system.

Summary and conclusions

Based on the available animal data and ongoing clinical studies, exposure to single and repeated courses of synthetic GCs causes dysregulation of the fetal and neonatal HPA axis. Animal studies indicate that these HPA axis changes persist into adulthood and represent a programming effect that is transgenerational and sex specific. This altered (dysregulated) state of the HPA activity appears to be a function of timing of the exposure (gestational age) and is dose dependent.

Although the short-term outcomes and benefits of exposure to single and repeated doses of synthetic GCs in humans have been largely reassuring, there is reason for caution in extrapolating these findings for the long term in humans based on the reported adverse long-term
and permanent changes on the HPA axis in multiple animal models and in select short-term clinical outcomes. The long-term clinical outcomes for the human with regard to subtle neurodevelopmental outcomes, the response to stress, learning, cognition behavior, and the risk for adult-onset diseases are presently unknown. More precise diagnosis and management of preterm labor and the careful selection of candidates for repeat courses of antenatal corticosteroids would potentially decrease the risk of long-term adverse outcomes in this group of infants. Careful and systematic longitudinal follow-up of those infants exposed to single and repeated doses of antenatal GCs in present and future studies are also of vital importance in determining the risks and benefits of this important clinical intervention.

REFERENCES


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