Prenatal Exposure to Stress and Stress Hormones Influences Child Development

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Stress has significant consequences throughout the lifetime. However, when it occurs early in life, the implications may be particularly profound and long lasting. Evidence suggests that high levels of maternal stress during pregnancy are associated with alterations in the normal activity of the maternal hypothalamic-pituitary-adrenocortical (HPA) and placental axis. Increased activity of this system is related to shortened gestation and impaired fetal growth, factors that place infants at a greater risk for a wide variety of developmental problems. In addition to the implications for birth outcome, our findings suggest that prenatal exposure to stress and stress hormones directly influences development of the fetal central nervous system (CNS). Fetuses that are exposed to disregulated production of stress hormones display impaired learning. Elevated levels of stress or stress hormones during pregnancy are also associated with more difficult infant temperament and disruption of infant HPA axis activity. These data suggest that prenatal experiences can have lasting implications on development. Key words:

It has become increasingly evident that the origins of many illnesses begin in fetal life, and that prenatal events have beneficial and harmful effects on health (Gluckman & Hanson, 2004). The influential studies of Barker (1998) provide convincing support for the importance of human fetal experience in determining developmental patterns. The potential vulnerability of the fetus to extrinsic factors is most apparent when teratogenic drug or alcohol exposure causes congenital malformations. However, even more moderate influences, such as stress during pregnancy, have been shown to cause such malformations (Carmichael & Shaw, 2000; Hansen, Lou, & Olsen, 2000). A range of studies has implicated intrauterine glucocorticoid (GC) exposure as one of the key mediators of the effects of intrauterine deprivation (Butler, Schwartz, & McMillen, 2002). We will discuss the ways that relatively subtle changes in the maternal/fetal environment relating to prenatal exposure to maternal stress and stress hormones can have profound and permanent influences on fetal growth, the fetal central nervous system (CNS), and subsequent behavior.

PREGNATAL STRESS

Prenatal exposure to stress and stress hormones is a risk factor affecting human development. Fetal stress can be defined as any event that disturbs fetal homeostasis and alters the normal trajectory of development (National Children’s Study, 2004). Stress any time during development can have lasting consequences. However, the effects of stress may be most harmful when they occur during early development. Stress during the prenatal period may have the most serious consequences. During pregnancy, maternal stress threatens the fetal nervous system and shortens the length of gestation. Both of these consequences increase the risk that infants are born with cognitive, physical, and emotional problems.
Maternal stress during pregnancy and birth outcome

The most well-documented consequence of prenatal stress is prematurity, an important indicator of newborn health. Although many studies examining the effects of prenatal stress are limited by conceptual and methodological problems (for a discussion of these issues, see Lobel, 1994; Paarlberg, Vingerhoets, Passchier, Dekker, & Van Geijn, 1995), there is significant evidence that pregnant women reporting high levels of stress or anxiety and low levels of social support during pregnancy are more likely to deliver earlier and smaller infants (Copper et al., 1996; Dole et al., 2003; Feldman, Dunkel-Schetter, Sandman, & Wadhwa, 2000; Hedegaard, Henriksen, Secher, Hatch, & Sabroe, 1996; Misra, O’Campo, & Strobino, 2001; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). It is interesting to note that the effects of maternal stress during pregnancy on birth outcome are related to the timing of exposure. Evidence suggests that stress has more profound effects when it occurs earlier in pregnancy. Mothers who were exposed to the stress of an earthquake during their first trimester delivered earlier than those who were exposed during the third trimester (Glynn, Wadhwa, Dunkel-Schetter, & Sandman, 2001).

Most important, maternal stress indicates that these birth outcomes are independent of established obstetric and sociodemographic risk factors. Furthermore, the magnitude of the independent effect size of maternal psychosocial processes in pregnancy on prematurity related outcomes is comparable to that of most other established obstetric risk factors. These findings suggest that maternal psychosocial processes in pregnancy are important and warrant further consideration.

Maternal stress during pregnancy and postnatal development

In addition to the consequences for birth outcome, maternal psychological state during pregnancy influences fetal and infant development. Extensive animal studies have documented lifelong effects of exposure to stress during prenatal development (Chapillon, Patin, Roy, Vincent, & Caston, 2002; Schneider, 1992; Weinstock, 2001). Much less is known about the consequences of prenatal stress for human development. Furthermore, it is difficult to generalize human populations on the basis of animal models because of significant interspecies differences in reproductive physiology as well as the type and severity of stressors examined.

Human studies have reported that indicators of maternal stress, including anxiety and depression, during pregnancy shape fetal behavioral patterns (DiPietro, Hilton, Hawkins, Costigan, & Pressman, 2002; Monk, Myers, Sloan, Ellman, & Fifer, 2003) and predict higher cortisol and norepinephrine and lower Brazelton scores in the newborn (Jones et al., 1998; Lundy et al., 1999). A small but growing literature is beginning to demonstrate that the consequences of prenatal maternal stress persist into the postpartum period (e.g., Luoma et al., 2001; O’Connor, Heron, Golding, Beveridge, & Glover, 2002; Van den Bergh, 1990). These studies, however, are often limited by their reliance on retrospective report of stress during pregnancy or parent report of child behavior, and thus may reflect differences in the ways that anxious mothers perceive their children.

Recently, several prospective studies have been performed in which infant behavior is assessed by an independent observer. These studies demonstrate that prenatal stress, assessed using both maternal anxiety and the occurrence of negative life events, influences both cognitive development and temperament. Pregnant women’s anxiety has been shown to predict their infants ability to pay attention as well as their cognitive and motor development (Brouwers, van Baar, & Pop, 2001; Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002). Consistent with these findings, Laplante et al. (2004) demonstrated that prenatal exposure to a natural disaster predicted impaired performance
Figure 1. Neuroendocrine interactions between the fetus, placenta, and mother. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropin hormone; and 11βHSD = 11β-hydroxysteroid dehydrogenase.

on measures of cognitive and language development. These studies suggest that exposure to prenatal maternal stress impairs cognitive development. We assessed the impact of prenatal maternal anxiety on direct observations of infant negative behavioral reactivity in response to challenge. Prenatal maternal anxiety was significantly related to infant behavioral reactivity. Most important, prenatal anxiety accounted for a significant portion of the variance after controlling for postnatal maternal anxiety (Davis, Snidman et al., 2004). These data illustrate that prenatal maternal anxiety exerts persisting influences on human development, using objective measures of infant behavior. However, none of these studies using objective laboratory measures followed the offspring beyond infancy. Longitudinal studies utilizing maternal and teacher report measures have shown persisting consequences of maternal anxiety during pregnancy for child behavior problems or negative emotionality (Martin, Noyes, Wisenbaker, & Huttunen, 1999; O’Connor et al., 2002; Van den Bergh & Marcocen, 2004). There is a need for further prospective longitudinal studies that use objective assessments of the child’s behavior to differentiate the effects of prenatal and postnatal maternal psychological states on development.

The hypothalamic-pituitary-adrenocortical axis

A primary pathway by which stress effects the fetus is the hypothalamic-pituitary-adrenocortical (HPA) axis (Welberg & Seckl, 2001). Glucocorticoids, cortisol in humans, are the end product of the HPA axis, one of the body’s major stress systems. Glucocorticoids are released into the general circulation and have effects on nearly every organ and tissue in the body (Munck, Guyre, & Holbrook, 1984). Hypothalamic-pituitary-adrenocortical axis activity is regulated by the release of hypothalamic corticotropin-releasing hormone (CRH). The CRH is a neuroactive peptide produced in the hypothalamus and in extrahypothalamic sites. The CRH released from the hypothalamus stimulates the biosynthesis and release of adrenocorticotropin hormone (ACTH) and β-endorphin (βE) from the anterior pituitary. The ACTH triggers GC production and release from the adrenal cortex. As shown in Figure 1, GCs regulate their own release by negative feedback actions at several levels of the axis (i.e., hypothalamus and
pituitary) and at extrahypothalamic sites (i.e., hippocampus and frontal cortex) (Jacobson & Sapolsky, 1991; Sanchez, Young, Plotsky, & Insel, 2000). In contrast, GCs increase HPA axis activity through stimulation of the amygdala (Schulkin, 1999).

Consequences of GC release include energy mobilization and immunosuppression (Chrousos & Gold, 1992). Glucocorticoids easily pass through the blood–brain barrier (Zarrow, Philpott, & Denenberg, 1970), and there are receptors for GCs throughout the CNS (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Sanchez et al., 2000). Glucocorticoids play a role in the regulation of pregnancy. In primates, including humans, HPA axis functioning changes dramatically during pregnancy. In contrast to the negative control on hypothalamic CRH, GCs stimulate the expression of bCRHmRNA in the placenta (Schulkin, 1999). This allows for the simultaneous increase of CRH, ACTH, and cortisol in the maternal and fetal compartments over the course of gestation (King, Nicholson, & Smith, 2001).

**The hypothlalamic-pituitary-adrenocortical axis and birth outcome**

The maternal HPA axis is one mechanism that has been proposed to mediate the effects of maternal stress on birth outcome and the development of the fetus during pregnancy. It has been well documented that women who have high concentrations of placental CRH in their gestational stage are at significantly elevated risk for premature delivery (Erickson et al., 2001; Hobel, Dunkel-Schetter, Roesch, Castro, & Arora, 1999; Holzman, Jetton, Siler-Khodr, Fisher, & Rip, 2001; Inder et al., 2001; McLean et al., 1995; Moawad et al., 2002; Smith, Mesiano, & McGrath, 2003; Wadhwa et al., 2004). In addition to their role in the regulation of timing of delivery, HPA axis hormones including CRH and cortisol appear to directly impact fetal development (Challis et al., 2001; Hillhouse & Grammatopoulos, 2002; Smith, 2001). Glucocorticoids are essential for the regulation of intrauterine homeostasis, and differentiation and maturation of vital organ systems including the lungs, liver, and CNS (Mesiano & Jaffe, 1997; Rose, Schwartz, Green, & Kerr, 1998; Winter, 1998).

**Hypothlalamic-pituitary-adrenocortical axis and fetal and infant development**

There is increasing evidence that prenatal stress has persisting consequences for the development of the offspring. It has been proposed that the HPA-placental axis is a conduit for the effects of environmental stress on the fetus. Research with animals indicates that during prenatal development, the hormones of the HPA axis have programming effects on the developing CNS (Matthews, 2000; Welberg & Seckl, 2001). The influences of the intrauterine environment on the developing human fetal brain are poorly understood. This is because it is not feasible to perform experimental manipulations to examine the direct effects of HPA axis hormones on fetal and infant development. Observational studies have demonstrated that exposure to elevated levels of maternal HPA axis hormones during pregnancy impairs fetal learning (Sandman et al., 2003; Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999). These effects may persist to the postnatal period. Infants who were exposed to higher maternal cortisol (de Weerth, van Hees, & Buitelaar, 2003) and CRH (Davis et al., 2005) during pregnancy display more fussing and negative behavior when having a bath and display more difficult behavior as reported by their mothers.

**Summary**

Collectively, studies of human pregnancy indicate that exposure to prenatal maternal stress and HPA axis hormones has implications for fetal development that persist to the postpartum period. However, interpretation of these studies is limited for several reasons. First, most studies to date rely either on retrospective report of stress during pregnancy or on parent report of child behavior. Second, these studies rely on naturally occurring variations in maternal stress and stress hormones rather than on experimental
manipulations. This is problematic because the effects of stress cannot be separated from the consequences of other factors that might contribute to this association such as shared genes or child-rearing practices. Furthermore, women who experience greater levels of stress or anxiety during pregnancy are also more likely to have higher levels of postnatal stress and anxiety with implications for child rearing.

To determine the independent contribution of maternal stress for fetal and infant development, it is necessary to manipulate experiences during pregnancy. This technique has been implemented in animal research. One model for examining the consequences of prenatal stress for development involves the administration of stress hormones, such as GCs during pregnancy. Such manipulations have been performed with animals demonstrating lifelong consequences of prenatal exposure to GC treatment (Weinstock, 2001; Welberg, Seckl, & Holmes, 2001). Clearly, ethical limitations preclude the administration of GCs to women during pregnancy for experimental purposes. However, there are populations of women who are exposed to GCs during pregnancy for medical reasons. In these populations, we can directly evaluate the impact of GC exposure during pregnancy on development of the offspring.

PRENATAL EXPOSURE TO GLUCOCORTICOIDS

Antenatal treatment with synthetic glucocorticoids

It is the current recommendation that a single course of antenatal GCs should be administered to women who go into labor before 34 weeks’ gestation (NIH Consensus Development Conference, 1995). Synthetic GCs readily pass through the placenta (Albiston, Obeyesekere, Smith, & Krozowski, 1994; Brown et al., 1996). They are not oxidized by 11β-hydroxysteroid dehydrogenase into an inactive form (cortisone) as is maternal cortisol (Kajantie et al., 2003; King, Smith, & Nicholson, 2001). Furthermore, synthetic GCs have a greater affinity for naturally occurring receptors than cortisol (Ballard & Ballard, 1995). Synthetic GCs are administered to enhance lung maturation (Crowley, 2000). Such treatment acutely changes the fetal lung structure, resulting in improved lung compliance and better gas exchange. Prenatal GC treatment has been shown to significantly reduce the incidence of respiratory distress and intraventricular hemorrhage among infants born before 34 weeks’ gestation (Crowley, 2000). Evaluation of the offspring of women who received GC treatment during their pregnancy is a method that can be used to determine the consequences of prenatal GC exposure for development.

Prenatal glucocorticoid exposure and growth

Although prenatal GC treatment has positive effects on lung functioning, it also appears to have a negative influence on growth. For decades, it has been observed that GC therapy during pregnancy reduces birth weight in animal models, including non-human primates (Ikegami et al., 1997; Moss, Nitsos, Harding, & Newnham, 2003; Moss et al., 2001; Nyirenda, Lindsay, Kenyon, Burchell, & Seckl, 1998; Reinisch, Simon, & Karwo, 1978). Such effects are most powerful in the latter stages of pregnancy (Nyirenda et al., 1998), presumably reflecting the catabolic actions of GCs that are most manifest during the phases of maximum fetal somatic growth. Several recent large clinical studies have provided evidence that antenatal GCs in addition play a role in restricting human fetal growth (Bloom, Sheffield, McIntire, & Leveno, 2001; French, Hagan, Evans, Godfrey, & Newnham, 1999; Thorp, Jones, Knox, & Clark, 2002). In a large cohort study, French et al. (1999) observed that increasing numbers of antenatal GC courses were associated with a significant reduction in birth weight of 9% and a reduction in head circumference of 4%. In a second study of 14,000 infants from 100 neonatal intensive care units in North America, it was found that antenatal GC treatment was
independently associated with a reduction in both birth weight and head circumference (Thorp et al., 2002). The reduction in head circumference after controlling for birth weight suggests that antenatal GCs reduce brain growth more than somatic growth. Furthermore, relatively small reductions in head circumference are associated with more significant reductions in intracranial volume (French et al., 1999).

The suppression of growth by antenatal GC treatment does not appear to persist. It has been shown that there is “catch up” growth in childhood. Several studies found no effect of prenatal GC treatment on height, weight, and head circumference at 3 to 4 years of age (French et al., 1999; Hasbargen, Reber, Versmold, & Schulze, 2001), while others found that children exposed to antenatal GCs were taller and heavier at ages 6 and 14 than controls (Doyle, Ford, Rickards et al., 2000; MacArthur, Howie, Dezoete, & Elkins, 1982). These data parallel the sheep model, which demonstrates that the growth restriction that accompanies GC exposure is followed by catch-up growth (Moss et al., 2001). Even though catch-up growth occurs, being born small has lasting implications on health later in life. Large epidemiological studies have demonstrated that decreased birth weight is associated with increased risk of adult cardiovascular and metabolic disorders, including hypertension, hyperlipidemia, Type 2 diabetes, and death from ischemic heart disease (Barker, 1998; Godfrey, & Barker, 2000).

It has been proposed that GCs play a role in fetal programming. The association between low-birth weight and adult disease may, in part, be mediated by overexposure to GCs during the prenatal period (Welberg & Seckl, 2001). This hypothesis is supported by evidence from animal studies illustrating that antenatal GC exposure can have lifelong effects on blood pressure (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993; Dodic, May, Wintour, & Coghlan, 1998), insulin resistance (Nyirenda, Welberg, & Seckl, 2001), HPA axis function (Welberg & Seckl, 2001), and the CNS (Bakker, van Bel, & Heijnen, 2001; Matthews, 2000).

**Prenatal glucocorticoid exposure and endocrine and behavioral responses to stress**

The HPA axis is a primary target for GC programming. In the rodent, fetal exposure to GCs leads to lifelong alterations in regulation of the HPA system. Antenatal GC treatment results in elevated baseline plasma corticosterone (Welberg, Seckl, & Holmes, 2001) and a larger corticosterone response to stress in rodents (Muneoka et al., 1997). Similarly, in sheep, exposure to GCs alters HPA responsiveness in the offspring at up to 1 year of age (Sloboda, Moss, Gurin, Newnham, & Challis, 2002). Only one study has assessed the long-term effects of prenatal exposure to GCs on HPA axis functioning in nonhuman primates. Pregnant rhesus monkeys were given a synthetic GC treatment, which was modeled after the regimen that is currently given to pregnant women. Their offspring had elevated basal and stress-induced cortisol secretion at 10 months of age (Uno et al., 1994).

Despite significant evidence from the animal literature that prenatal exposure to GCs has a persisting influence on the HPA axis, there have been few studies of this phenomenon with humans. In human infants, baseline cortisol levels are suppressed for 2 to 7 days after prenatal GC treatment and subsequently return to normal levels (Ballard, Gluckman, Liggens, Kaplan, & Grumbach, 1980; Dorr et al., 1989; Kauppila, Koivisto, Pukka, & Tuimala, 1978; Parker, Atkinson, Owen, & Andrews, 1996; Wittekind, Arnold, Leslie, Luttrell, & Jones, 1993). The effect of antenatal GC treatment on HPA axis reactivity and regulation in response to stress, however, appears to persist beyond the neonatal period. The cortisol response to the CRH stimulation test was suppressed in infants who received antenatal GC treatment (Ng et al., 2002). Furthermore, we demonstrated that a single course of GC treatment suppressed the cortisol response to a painful stressor (Davis, Townsend et al., 2004). To date, there are no
published studies examining long-term effects of antenatal GC treatment on HPA functioning in children.

In addition to direct influences on the HPA axis, GC exposure impacts the development of systems involved in the regulation of behavioral stress responses. In animal models, manipulations that alter GC exposure, such as prenatal stress, lead to increased behavioral indicators of fear or anxiety in response to challenges, such as novelty (Schneider, 1992; Ward, Johnson, Salm, & Birkle, 2000; Weinstock, 2001). Furthermore, administration of GCs to rats for all 3 weeks of gestation or only in the last week increases fear behavior as indexed by reduced ambulation and rearing in the open field in adult offspring (Welberg et al., 2001). Late gestation administration of GCs in addition decreases exploration on an elevated plus maze and reduces mobility during a forced-swim test (Welberg et al., 2001). These data suggest that fetal GC exposure may program increased behavioral stress reactivity and reduced coping in aversive situations.

Similar to animal models, there is evidence that prenatal GC exposure increases behavioral responses to challenge in children. Trautman, Meyer-Bahlburg, Postelnek, and New (1995) assessed a group of children exposed to GC treatment in early pregnancy because they were at risk of congenital adrenal hyperplasia, but did not go on to develop this disorder. These children showed increased shyness, emotionality, and internalizing behavior problems (Trautman et al., 1995). These data are consistent with studies showing that acute GC administration increases self-reported negative emotions in adults (Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999) and children (Bender, Lerner, & Kollasch, 1988). In conjunction, these studies suggest that prenatal GC exposure plays a role in the development of behavioral signs of distress and increased negative affectivity in response to challenge.

Prenatal glucocorticoid exposure and cognition

There is significant evidence from work with adult animals demonstrating that acute exposure to GCs causes impairments on memory and executive function tasks (de Quervain, Roozendaal, & McGaugh, 1998; Lyons, Lopez, Yang, & Schatzberg, 2000; Wolf, 2003). Furthermore, early exposure to manipulations such as prenatal stress, which are likely to influence HPA axis functioning, has been associated with cognitive deficits (Welberg & Seckl, 2001). Consistent with these studies, prenatal exposure of rats to GCs led to poorer performance as adults on a spatial memory task thought to involve the hippocampus (Brabham et al., 2000). These studies suggest that one likely consequence of prenatal exposure to GCs is cognitive impairments.

Human studies aimed at establishing the long-term consequences of prenatal GC treatment on cognition have yielded mixed results. Existing research is complicated by the fact that the children studied were born preterm, and were therefore already at risk for developmental delays. Despite these limitations, there is evidence for a persisting influence of prenatal GC treatment on cognition. In a group of 6-year-old children, antenatal GC exposure was associated with reduced visual closure and visual memory (MacArthur et al., 1982). In addition, 2-year-olds exposed to multiple courses of GCs had an increased risk of neurodevelopmental delays (Spinillo et al., 2004). Other studies, however, have demonstrated that prenatal GC treatment has either no effect on cognition (Collaborative Group on Antenatal Steroid Therapy, 1984; Dessens, Smolders-de Haas, & Koppe, 2000) or a beneficial effect for IQ (Arad et al., 2002; Doyle, Ford, Davis, & Callanan, 2000). These studies assessed a heterogeneous population of infants born at 23 to 32 weeks of gestation and included infants who were very ill, and infants with abnormal cranial ultrasounds in the neonatal period. These factors may obscure primary effects of GC treatment. A second limitation of existing studies is that they assess only general intelligence and not specific functions that are particularly likely to be impaired by elevated GCs. There are a number of studies with adults demonstrating that exposure to elevated levels of GCs
impairs memory (Lupien et al., 2002; Monk & Nelson, 2002; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994) and executive functions (Lupien, Gillin, & Hauger, 1999; Young, Sahakian, Robbins, & Cowen, 1999). Future studies are needed that assess the targeted effect of GCs on these cognitive functions as well as general effects on IQ.

**Prenatal glucocorticoid exposure and brain structure**

Glucocorticoid receptors are widely distributed throughout the brain including the pituitary gland, hypothalamus, hippocampus, amygdala, and prefrontal cortex (PFC) (Diorio, Viau, & Meaney, 1993; Jacobson & Sapolsky, 1991; Sanchez et al., 2000). Glucocorticoids exert a range of effects on the developing CNS (Korte et al., 1996; Meaney et al., 1996; Weinstock, 2001; Welberg & Seckl, 2001), and antenatal exposure to elevated GCs has adverse effects on brain development. In the sheep, antenatal GC treatment leads to acute changes in neuronal activity (Antonow-Schlorke et al., 2001; Schwab et al., 2001) and decreased brain weight, with repeated doses having a more profound effect (Huang et al., 1999). Postnatal brain cell proliferation is decreased in the rodent hippocampus by a dose of GCs that is similar to the one used in clinical practice (Scheepens, van de Waarenburg, van den Hove, & Blanco, 2003). In addition, manipulations during the prenatal and perinatal periods that are likely to lead to elevations of GCs are associated with an increase in amygdalar volume (Salm et al., 2004) and a decrease in PFC GC receptors (Shanks, Larocque, & Meaney, 1995).

Primate studies provide further evidence for a persisting influence of GC treatment on the brain. A single course of GC treatment decreased expression of neuronal cytoskeletal proteins and of the presynaptic marker synaptophysin (Antonow-Schlorke, Schwab, Li, & Nathanielsz, 2003), proteins that are necessary for brain development and neuronal functioning. The hippocampus may be specifically targeted by GCs. In two studies, pregnant primates were given a dose of GCs in the early third trimester that was designed to parallel the course and timing of treatment given in clinical practice. Neural degeneration was seen in the hippocampus of the offspring at birth. Repeating this course four times significantly exaggerated this effect (Uno et al., 1990). In the second study, the offspring showed a 30% reduction in hippocampal volume at 20 months of age compared with controls with no difference in overall brain volume (Uno et al., 1994). These data, indicating that prenatal GC treatment causes irreversible damage to the hippocampus, are consistent with a primate study demonstrating that prenatal stress leads to a reduction in hippocampal volume and a decrease in neurogenesis in the dentate gyrus (Coe, Lulbach, & Schneider, 2002). In summary, these data illustrate that GCs are powerful regulators of neural differentiation and maturation in the primate brain; therefore administration of antenatal GCs used therapeutically in human pregnancy has the potential to alter brain structures.

Several magnetic resonance imaging studies have demonstrated structural differences in the brain of premature infants (Abernethy, Cooke, & Foulder-Hughes, 2004; Peterson et al., 2000). Two studies of the human neonate suggest that prenatal GC exposure has additional consequences for the brain. Cerebral cortical gray matter brain volume was reduced in premature infants treated with antenatal GCs as compared with untreated infants (Murphy et al., 2001). In addition, among 10 near term infants exposed to multiple doses of antenatal GCs, it was found that complexity of cortical folding and brain surface area were reduced as compared with controls (Modi et al., 2001). Although these studies are limited by their small sample size, they are consistent with the animal data. To date, the persisting influence of prenatal GCs on the brain has not been examined. Animal models and studies with adult humans indicate that the hippocampus, amygdala, and PFC are the most vulnerable to prenatal GCs (Salm et al., 2004; Sanchez et al., 2000). On the basis of these data, future studies should assess...
whole brain volume as well as volume of the hippocampus, amygdala, and PFC in children exposed prenatal GCs

SUMMARY AND CONCLUSIONS

Accumulating data support the argument that prenatal stress has profound and lifelong consequences for health and well-being. It has been suggested that the hormones of the HPA axis including GCs mediate these effects. Examination of the impact of pharmacological administration of GCs is one method that can be used to evaluate the influence of stress hormones on fetal development. Prenatal GC therapy is a commonly used treatment in obstetric practice. Glucocorticoid therapy improves lung functioning and increases survival among premature infants born at less than 34 weeks’ gestation. However, exposure to a pharmacological dose of GCs has risks for development that are similar to those of exposure to maternal stress during pregnancy. Both exposure to prenatal maternal stress (Feldman et al., 2000) and prenatal GC treatment reduce birth weight in human infants (Bloom et al., 2001; French et al., 1999). Data are beginning to emerge indicating persisting consequences of both prenatal stress and GC treatment for other aspects of development including endocrine and behavioral responses to stress, cognition, and the brain. These studies illustrate the importance of considering the pivotal role that the prenatal environment plays in shaping health and development, and demonstrate both the requirement for carefully assessing prenatal history when evaluating children and the need for prospective longitudinal studies that examine the persisting effects of prenatal exposure to stress and stress hormones for child development.

REFERENCES


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Butler, T. G., Schwartz, J., & McMillen, I. C. (2002). Dif-

tive development and temperament in infants. Neuro-

Butler, T. G., Schwartz, J., & McMillen, I. C. (2002). Differ-
cential effects of the early and late intrauterine en-
vironment on corticotrophic cell development. The Journal of Clinical Investigation, 110(6), 785–791.


al hypothalamic-pituitary-adrenal (HPA) axis, parturi-
tion and postnatal health. Molecular and Cellular Endo-

Chapillon, P., Patin, V., Roy, V., Vincent, A., & Caston, J. (2002). Effects of pre- and postnatal stimulation on de-
velopmental, emotional, and cognitive aspects in ro-


Coce, C. L., Luftach, G. R., & Schneider, M. L. (2002). Pre-
natal disturbance alters the size of the corpus callo-
sum in young monkeys. Developmental Psychobiol-

Collaborative Group on Antenatal Steroid Therapy. (1984). Effects of antenatal dexamethasone adminis-


Crowley, P. (2000). Prophylactic corticosteroids for preterm birth. Cochrane Database of Systematic Re-

tal maternal anxiety and depression predict negative behavioral reactivity in infancy. Infancy, 6(3), 319–331.

fects of prenatal corticosteroid exposure on regulation of stress physiology in healthy premature infants. Psy-
choneuroendocrinology, 29, 1028–1036.


teroid treatment. Pediatrics, 105(6), 77–84.

Diorio, D., Vieu, V., & Meaney, M. J. (1993). The role of the medial prefrontal cortex (cingulate gyrus) in the regu-


ticoid leads to hypertensive offspring in sheep. Clinical Science, 94, 149–155.


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O’Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children’s behavioural/emotional problems at 4 years: Report from the Avon Longitudinal study of Parents and


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