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# Prenatal Origins of Neurological Development: A Critical Period for Fetus and Mother

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## Abstract

A rapidly accumulating literature indicates that the prenatal period must be taken into account if we are to understand development of the central nervous system (CNS) across the life span. Evidence now suggests that intrauterine signals influence brain structure and affect cognitive function and emotional and physiological stress regulation in the offspring. Furthermore, prenatal hormone exposures are critical for priming the maternal brain for the challenges of motherhood and have implications for the mother's brain structure and function that may last the rest of her lifetime. Just as the reciprocal nature of the parent–child relationship must be understood during the postnatal period, in order to understand the persisting influences of the intrauterine environment on neurodevelopment, the effects of the prenatal environment on both fetus and mother, as well as their reciprocal influences, must be appreciated. This is critical because the same hormones that program fetal development are those that shape the maternal brain and because prenatal bidirectional signaling may provide an adaptive function for both mother and fetus.

## Keywords

pregnancy, prenatal, central nervous system development, stress, maternal brain, fetal development

In Britain, at the turn of the last century, there was a noticeable decline in population. Birth rates were low and infant mortality was high. Moreover, two thirds of the young men who volunteered to fight in the South African war were rejected because of physical frailties. In an enlightened response, one county enlisted an “army” of midwives to interview and assist all women during and after pregnancy. This intervention was intended to improve the health of mothers and their children, but a secondary consequence was meticulous record keeping of pregnancy histories and birth outcomes (Barker, 1998). These early-life-history records, combined with national health records from later in life, formed the basis of the developmental origins of disease model, or the Barker hypothesis, which asserts that prenatal exposures to adversity have implications for poor physical health across the life span. There now is substantial evidence that adverse intrauterine exposures increase subsequent risk for a range of outcomes including hypertension, heart disease, diabetes, obesity, and polycystic ovary disease, as well as psychiatric illnesses such as schizophrenia, mood disorders, and suicide. We and others are taking a prospective, interdisciplinary approach to examine the consequences of intrauterine experience on fetal central nervous system (CNS) development. A parallel focus of our research program is the role of the prenatal period in CNS development of the mother. Accumulating evidence indicates

that pregnancy remodels the architecture of the maternal brain, an effect that persists across the life span and is conserved across species.

## Fetal Programming of CNS Development

Each developing organism plays an active role in its own construction (Denver, 1997). The human fetus has evolved mechanisms to acquire information about the environment and guide its development. The human placenta is both a sensory and effector organ that incorporates and transduces information from its maternal environment into the fetal-developmental program. The fetal–placental unit's detection of stress signals from the maternal environment (e.g., cortisol) “informs” the fetus that there may be a threat to survival. This information primes or advances the placental clock, resulting in earlier delivery (McLean et al., 1995) and escape from the hostile environment. Concurrently, the fetus adjusts its developmental trajectory, modifying its nervous system to ensure survival.

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Most existing human studies of prenatal influences on development rely on retrospective designs in which birth phenotype (i.e., being born early or small) is determined archivally and is used to predict adult health (the logic is that these birth phenotypes reflect adverse intrauterine experience). The obvious limitations with this approach are that the prenatal environment cannot be characterized accurately and that it cannot be separated from the deleterious effects of being born early or small. A critical next step that is currently being undertaken is the prospective study of variations in the prenatal environment and how these influence postnatal development. Among these prospective studies, the majority have consistently reported that adversity in utero predicts behavioral and emotional disturbances. In particular, elevated prenatal psychological and biological stress signals repeatedly have been linked to hypothalamic-pituitary-adrenal (HPA) axis function and fearful temperament and also to internalizing and externalizing behavioral problems in childhood and adolescence (Davis, Glynn, Waffarn, & Sandman, 2011; O'Connor et al., 2005; Talge, Neal, Glover, & Health, 2007; Van den Bergh & Marcoen, 2004).

Fewer studies have examined the effects of prenatal stress on human cognitive development. However, there is evidence that maternal cortisol and psychological distress during the prenatal period are associated with delayed cognitive development, at least through adolescence (Talge et al., 2007). The first study showing that a mother's elevated pregnancy-specific anxiety (i.e., anxiety about her pregnancy and the health of her fetus) early in her pregnancy was associated with reduced gray matter volumes in her 6- to 9-year-old children was recently published (Buss, Davis, Muftuler, Head, & Sandman, 2010). The affected regions were those associated with higher cognitive functions including reasoning, planning, attention, working and recall memory, language, and social and emotional processing.

### **If Interested in the Role of Prenatal Experience, Study the Fetus**

Even more current work has begun to study the development of the fetus, because this approach allows the direct examination of intrauterine environment on the developing human, independent from birth phenotype and the effects of the postnatal environment. Fetal activity has been linked to maternal anxiety, depression, anger, and pregnancy-specific stress and also to maternal cortisol. However, assessment of the fetal response (usually heart rate or movement) to extrauterine stimuli (e.g., tones or vibroacoustic stimuli) across gestation provides a more sensitive assessment of the developing CNS. Elevations in placental corticotropin-releasing hormone (pCRH) are associated with diminished ability of the fetus to detect and respond to stimulation, and overexposure to maternal endogenous opiates with delayed ability to habituate to a repeated stimulus (Sandman, Davis, Buss, & Glynn, in press). The direct study of programming effects on the fetus repre-

sents an important approach for understanding prenatal influences, independent from postnatal influences.

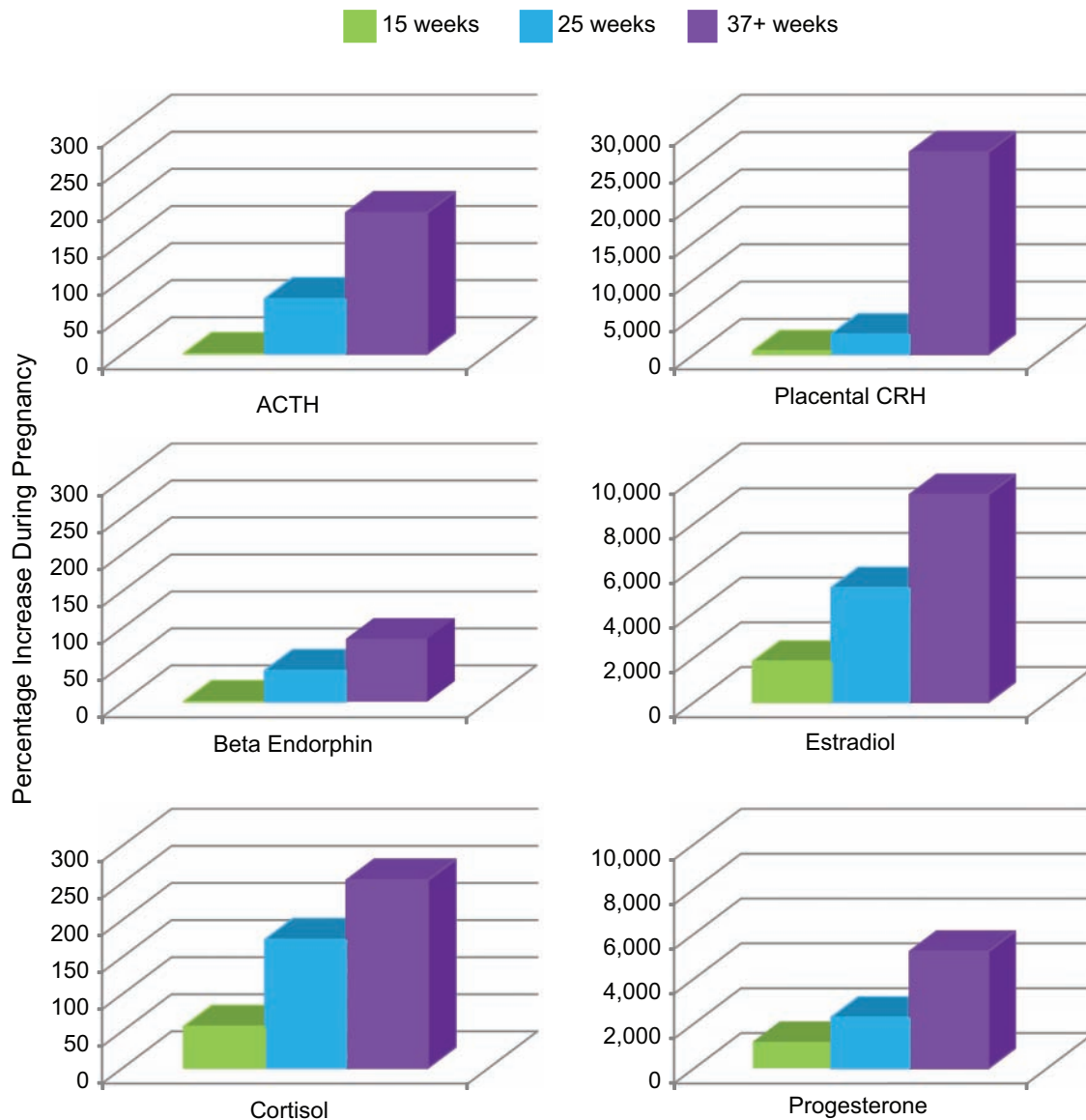
### **Beyond Fetal Programming: The Predictive Adaptive Response**

Recently, an alternative conceptual framework to the Barker Hypothesis has emerged. Instead of assuming that pathology is the only outcome of fetal exposure to adversity, the predictive adaptive response (PAR) model proposes that the developing organism makes adjustments based on the predicted postnatal environment. When the PAR does not match the environment (i.e., the prediction is inaccurate), the mismatch results in disease states. For example, the fetus exposed to an impoverished intrauterine environment will prepare for, and perhaps thrive in, a postnatal environment of nutritional scarcity. However, if that same fetus is instead born into an environment of nutritional abundance, its developmental adjustments may result in an increased risk for obesity, diabetes, and cardiovascular disease. There is persuasive support for the PAR model from studies examining a mismatch between prenatal and postnatal nutrient environments. More recently, an examination of consistency of another indicator of early life adversity, maternal depression, provides further support for the PAR model by demonstrating that congruous prenatal and postnatal environments confer an adaptive advantage in motor and mental development during an infant's first year of life, even when the environments are unfavorable (Sandman, Davis & Glynn, in press).

### **Maternal Programming**

In the life span of the human female, no other naturally occurring hormone exposures are more extreme than those experienced during the perinatal period (see Fig. 1). A substantial literature indicates that other, less extreme endocrine events, such as puberty and menopause, are associated with changes in human brain structure and function. In contrast, almost nothing is known about how the hormone exposures linked to reproductive experience influence the brain and behavior of human mothers. Rodent models have confirmed that reproduction produces neurological changes that persist throughout the life span and that these changes are not confined to those areas of the brain directly involved in maternal behaviors. For example, alterations have been observed also in brain regions associated with emotion (amygdala) and memory (hippocampus). Our studies have examined the influence of reproductive experience on the structure and function of women's brains—a process we term “maternal programming.”

The existence of hormonal control of onset and maintenance of maternal behavior in nonhuman species (largely rodents) is well established. What little is known about humans is largely consistent with this literature, suggesting that in humans, too, the hormone exposures of pregnancy prime the



**Fig. 1.** Endocrine changes across pregnancy. Graphs show percentage increase at 15 weeks, 25 weeks, and 37+ weeks for adrenocorticotropic hormone (ACTH) placental corticotrophin-releasing hormone (CRH), Beta endorphin, estradiol, cortisol, and progesterone.

maternal brain for the challenges of motherhood. Specifically, there are a small number of studies demonstrating that prenatal estrogen, cortisol, and oxytocin exposures influence the quality of early postpartum maternal care and the ability to respond to infant signals. Furthermore, new findings indicate that the early postpartum period is one in which gray matter volumes increase in brain regions implicated in maternal motivation and behavior and that mothers who have the most positive feelings toward their infants show the largest increases (Kim et al., 2010).

Species from rats to humans show a decline in physiological and behavioral responses to stress during pregnancy. Late in gestation, women exhibit a dampened cortisol response to HPA challenge and show decreased blood pressure, heart rate, and catecholamine responses to psychological and physical

challenges (de Weerth & Buitelaar, 2005). In parallel to these physiological changes, pregnant women also experience diminished psychological responses to stress (Glynn, Wadhwa, Dunkel Schetter, Chicz-DeMet, & Sandman, 2001). There is reason to believe that the down-regulation of stress responding during pregnancy serves an adaptive purpose, providing some protection for mother and fetus from the adverse effects of stress. It has been shown that early exposures to stress are more likely to result in preterm birth than are later exposures (Glynn et al., 2001), and women who do not show the normative, protective decrease in stress responding during pregnancy are at increased risk for preterm delivery (Glynn, Dunkel Schetter, Hobel, & Sandman, 2008).

Up to 80% of women report impaired cognitive function during pregnancy. This observation is supported by empirical

investigations of memory function during pregnancy. A meta-analysis of the 17 studies published over the last decade indicated deficits in two components of memory during pregnancy that persist into the postpartum period: recall memory and the executive component of working memory (Henry & Rendell, 2007). The largest prospective study of human memory function during pregnancy was recently published, and for the first time, potential endocrine mechanisms (estradiol and cortisol) associated with impaired prenatal and postpartum memory function were identified (Glynn, 2010).

At present, essentially nothing is known about how reproduction alters the brain structure of women. However, it is extremely likely that the dramatic hormone exposures of pregnancy do result in permanent changes for several reasons. First, the massive fluctuations in estrogens dwarf those seen at any other time in development, and it is known that these hormones have effects on human brain structure and function. Second, adult neurogenesis is modulated by reproduction—for example, in rats, pregnancy enhances production of neuronal progenitors in the forebrain subventricular zone, stimulating the formation of new olfactory neurons (Shingo et al., 2003). Third, animal models demonstrate that changes in CNS structure associated with reproduction endure across the life span. Fourth, findings from animal models also indicate that the effects of pregnancy and parturition may be additive—with each successive litter, the effects of pregnancy on cognition and stress responding are amplified.

### How Might the Fetus Program the Mother?

It is becoming increasingly recognized that maternal signals shape the development of the fetus. However, it is not as widely acknowledged that this is only one side of a bidirectional relationship; specifically, fetal or placental signals may also shape the development of the maternal brain and behavior. It is possible that the fetus exerts these influences through endocrine, cellular, and behavioral routes. Corticotropin-releasing hormone (CRH) is a 41-amino-acid neuropeptide that is synthesized primarily in the paraventricular nucleus of the hypothalamus and has a major role in regulating pituitary-adrenal function and the physiological response to stress. During pregnancy the placenta also expresses the genes for CRH, and placental CRH (pCRH) increases across gestation, reaching levels in the maternal circulation observed only in the hypothalamic portal system (i.e., the blood vessels that carry regulatory hormones from the hypothalamus to the pituitary) during conditions of physiological stress. Little is known about the possible influences of pCRH on the maternal brain. In the nonpregnant state, CRH is believed to play a role in the etiology of depression. Because of the dramatic increase in pCRH during pregnancy and a demonstrated link between CRH and depression in the nonpregnant state, it is possible that pCRH exposures may present a risk for postpartum depression. To date, one report provides evidence consistent with this possibility (Yim et al., 2009) and more broadly

demonstrates that a fetal endocrine signal may affect neurological function in the mother.

Fetal behavior represents a second pathway through which the fetus might shape the mother. DiPietro and colleagues (DiPietro, Irizarry, Costigan, & Gurewitsch, 2004) applied time-series analysis to longitudinal data from mother–fetus pairs and found that, beginning at 20 weeks of gestation until term, fetal movement stimulated rises in maternal heart rate and skin conductance. Currently the pathway through which fetal movements might determine maternal sympathetic arousal is unknown. However, it is unlikely that this occurs through conscious perception of these movements. (At term, women detect as few as 16% of fetal movements.) Given that the influence does not operate through conscious channels, DiPietro et al. propose that the most likely local mechanism is through perturbations of the uterine wall. They further suggest that the sympathetic activation in response to the fetal movement signal may begin to prepare the woman for the new demands of motherhood by redirecting maternal resources away from competing but less relevant environmental demands. This finding raises the additional provocative question of whether the degree of prenatal synchrony between mother and fetus might set the stage for postnatal mother–infant interaction.

A third possible route, the cellular, involves what is called fetal microchimerism: Fetal cells cross the placenta and enter the maternal circulation. In humans, fetal cells have been detected in a range of maternal tissues years after delivery. Relevant to maternal programming are findings demonstrating the presence of fetal cells in the brains of pregnant mice (Tan et al., 2005). These fetal cells are capable of taking on a range of attributes including neuron-, astrocyte- and oligodendrocyte-like types (the latter two are glial cells that provide support and protection for neurons in the brain). Whether these fetal cells have any functional or physiological significance has yet to be demonstrated. However, the fetal cells were preferentially found in the region of the olfactory bulb, an area critical for offspring recognition. It is possible that pregnancy changes the attraction of specific brain areas for fetal cells.

### Emerging Moderating Variables: Fetal Sex and Timing of Exposures

#### *Fetal sex*

The concept that the sex of the fetus is important in understanding neurological development is by no means novel. However, there are some issues that are unique to the prenatal period that deserve consideration. First, fetal sex is an additional factor that has the potential to alter the prenatal endocrine milieu. For example, levels of human chorionic gonadotropin (hCG; a hormone produced by the embryo and later by placental cells) differ depending on fetal sex. Second, there are sex differences in the structure and function of the placenta, including placental cytokine expression, insulin-like growth factor pathways, and glucocorticoid receptor

expression and function that may play a central role in fetal development. Furthermore, Clifton (2010) has posited that sex-specific differences in adaptation to adversity exist. Specifically, female fetuses make multiple adaptations in placental gene and protein expression in response to intrauterine adversity to ensure survival in the event of possible additional prenatal adversity. In contrast, males “take a minimalist approach” when faced with a similar hostile prenatal environment and do not adjust their developmental trajectories—a strategy that places the male fetus at risk if additional adversity is encountered. A third consideration is that fetal sex moderates trajectories of fetal CNS development—there is some evidence that female fetuses exhibit more precocious CNS development (Sandman, Davis, et al., in press).

### **The importance of timing**

The effects of timing stress exposure during gestation are determined by multiple factors. First, it is established that timing of such exposure will have different effects on the fetus depending on the timetable of development of organ systems. Second, the maternal–fetal endocrine milieu and the regulation of maternal–fetal endocrine exposures are highly dynamic (Fig. 1). Third, as we discussed, women become progressively less sensitive to perturbations in their environments, and so, as gestation advances, exposure to adversity stress may be less likely to shape CNS development. Taken together, these timing-dependent vulnerabilities in both mother and fetus are consistent with findings suggesting that the same signal may exert influences at certain gestational periods but not at others. For example, pregnancy-specific anxiety early in gestation, but not later, influences gray matter volumes in children (Buss et al., 2010). Or in the case of the mother, only estrogen levels early in gestation are predictive of the decline in maternal memory function during pregnancy (Glynn, 2010). The timetable of maternal and fetal vulnerabilities also may explain how the same signal can have opposite effects depending upon the timing of exposure. For example, early elevations in maternal cortisol have been linked to lower levels of toddler mental development, whereas late elevations predict enhanced mental development (Davis & Sandman, 2010).

### **Conclusions**

The fetal programming “movement” has had a significant impact on medicine and basic science. Despite the fact that this area of research is in its embryonic stage, the findings have created a paradigm shift. It now is essential to consider fetal experience in order to fully understand human development. Like early-life brain development, the reconstruction of the maternal brain may similarly represent a critical period for CNS development. The vast majority of women give birth to at least one child. As a result, a significant proportion of the adult population has its neurological abilities and functions distinctly altered by the transient state of pregnancy, and yet

the extent, persistence, and consequences of these alterations are largely unknown. Elucidation of the role of the prenatal period in the development of both mother and child cannot be achieved by a single level of analysis, because multiple inter-related pathways (biological, environmental, psychosocial, and genetic) are implicated in these processes. Progress will be greatest with collaborations between basic, social, and epidemiological scientists and with the application of prospective, multilevel, longitudinal approaches.

In addition to increasing understanding of the contribution of the prenatal period to CNS development, investigations of prenatal influences have potential to make intervention possible, improving maternal and child health. For clinical syndromes such as phenylketonuria, Down syndrome, and others, there are standard prenatal tests available to provide information and guide treatment. In the next 5 to 10 years, a more comprehensive understanding of the factors influencing “normal” fetal neurological development will emerge. For example, we may identify factors that impair child outcomes and also those that optimize them. Similarly, it is possible that the early identification of women at risk for postpartum depression or compromised maternal care could be achieved. With comprehensive characterization of maternal and fetal programming, specific and successful interventions could be realized.

### **Suggested Readings**

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- Clifton, V.L. (2010). (See References). A provocative new review describing the sexual dimorphism of the placenta and its implications.
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- Gluckman, P.D., & Hanson, M.A. (2004). Living with the past: Evolution, development, and patterns of disease. *Science*, 305, 1733–1736. This paper provides a full discussion of the predictive adaptive response.
- Kinsley, C.H., & Lambert, K.G. (2006). The maternal brain. *Scientific American*, 294, 72–79. A comprehensive, accessible review of evidence for the neural plasticity associated with pregnancy and reproduction derived from animal models.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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