Prenatal Maternal Stress: Neurological and Physiological Impacts on Offspring

Anna Humphreys

Abstract: A growing body of research indicates that high levels of prenatal maternal stress (PNMS) can have lasting negative impacts on offspring. This review examines current literature about the structural and physiological effects of gestational stress on the brain of the fetus. Specific focuses include the structure and function of the hypothalamic-pituitary-adrenal (HPA) axis and how it is affected by high levels of maternal stress and how glucocorticoids such as cortisol cross the placenta and developing blood-brain barrier, altering the formation of the brain and its synapses. In addition, protective factors to prenatal stress are reviewed, such as placental enzyme 11ß-hydroxysteroid dehydrogenase type 2 (11ß-HSD2). The postpartum and longitudinal effects of stress are also explored, linking prenatal hormones to postpartum health and behavior of offspring. The author concludes by exploring ways to reduce ante-and postpartum maternal stress by improving the preconceptive, prenatal, and maternal-infant care systems.

Keywords: prenatal maternal stress, prenatal development, embryonic brain development

A womb-like experience may not be as universally comfortable, soothing, and safe as the "folk" understanding of this environment implies. In spite of the physical layers of muscle and skin protecting it from the outside world, the fetus is highly sensitive to every nutrient ingested and hormone secreted by its mother. Some effects of maternal stress, such as prematurity and low birth weight, have been thoroughly tested (Rondo et al., 2003; Torche, 2011; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). For example, some studies have shown that children exposed to prenatal stress develop language later than a non-stressed control group (Talge, Neal, Glover, & Network, 2007). A growing body of research also indicates that prenatal influences contribute to the development of psychiatric disorders such as anxiety, depression and externalizing behavior problems (Davis, Glynn, Waffarn, & Sandman, 2011).

The lasting impact on the offspring's brain and behavior is still a developing field of study. In an attempt to deepen our understanding of the link between prenatal maternal stress (PNMS) and long-term offspring development, this review will explore contemporary research on the impact of prenatal stress on early brain development and the stress-response system. I will begin with an overview of the gestational physiological and structural developments that are pertinent to this subject, expand into the impacts of PNMS on the offspring's physiology, behavior, and epigenetic expression, and

Anna Humphreys is a certified doula, CD (DONA), educator of infant massage (CEIM), and Calm Birth meditation instructor in Ashland, Oregon. She is the co-director of Calm Birth, as well as the part-time assistant to Sandra Bardsley, President of APPPAH. She is currently a senior at Southern Oregon University, where she anticipates graduating summa cum laude in June of 2016 with her Bachelors of Science in Psychology and a Certificate in Non-Profit Management. Contact: annahumphreys@calmbirth.org

end with a brief discussion of the potential for preventing or alleviating these adverse effects.

Structural Development of the Brain

The blueprint of the brain begins forming almost as the zygote splits exponentially into cells that will become a living, breathing person. It forms from the inside-out and the bottom up, beginning with the hindbrain to regulate the autonomic nervous system, then forming the limbic system, and at last developing the cerebral cortex (Moscoso, 2009). This process is as complex and intricate as life itself. This review focuses on the basics of prenatal brain development in order to set up further exploration of how stress impacts it.

In the earliest stage of development, the entire embryo is a miniscule, flat disk with three layers of cells: the endoderm, which will become the lining of the internal organs; the mesoderm, which is the basis for bones and muscles; and the ectoderm, from which the nervous system and skin arise (Bear, Connors, & Paradiso, 2016). At about 17 days after conception, a groove in the neural plate folds in on itself, beginning a process called "folding." At 22 days post-conception, the walls move together and fuse dorsally, forming the "neural tube." From this tiny tube, the entire nervous system develops. As the folds come together, some ectoderm (the "neural crest") pinches off and spreads laterally to the neural tube. This section of the brain develops in conjunction with the mesoderm, forming the nerves that innervate the skeletal muscles (Bear, Connors, & Paradiso, 2015).

Simultaneously, primary vesicles develop at the end of the neural tube. These three swellings will become the forebrain, midbrain, and hindbrain. In the forebrain, the optic and telencephalic vesicles sprout off, leaving the diencephalon between the two hemispheres. Nestled deep within the forebrain, the diencephalon differentiates into the thalamus and hypothalamus, structures that will eventually be heavily involved in complex sensory processing and homeostatic regulation (Bear et al., 2015).

Between the gestational ages of eight and 16 weeks, migrating neurons form the subplate zone, anticipating connections from afferent neurons originating in the thalamus, basal forebrain, and brainstem. Once neurons reach their final destination, they branch and establish connections with other areas of the brain, enabling their behavioral functions to unfold. (Nussey & Whitehead, 2001). The hypothalamic-pituitary-adrenal (HPA) axis, which functions as a primary stress response, is formed by 20 weeks gestation (Nussey & Whitehead, 2001). The amygdala, which governs detection of and response to emotions, specifically fear, is fully formed at eight months gestation (Ulfig, Setzer, & Bohl, 2003). The HPA axis and amygdala/limbic system form the foundation of the developing baby's fear response system, which is a complex adaptation for coping with postnatal life (Talge, Neal, Glover, & Early Stress, etc., 2007).

The complex process of embryonic development is subject to both intrinsic influences that are based in the genetic code and specialize in form, symmetry, and extrinsic influences, which include prenatal environment. These dynamics will continue to influence development until death (Moscoso, 2009). The process of brain formation is artful and intricate, and each detail is contingent upon the ability of the maternal body to support the pregnancy and provide the nutrients and hormones necessary for the prenate. However, subtle differences in hormones secreted by the mother have been indicated in an ever growing body of research to have a measurable impact on the offspring's behavior and cognition (Buss, Entringer, Swanson, & Wadhwa, 2012; Davis et al., 2007; Davis, Glynn, Waffarn, & Sandman, 2011; Huang, 2014). In one example, Davis et al.'s 2007 study correlated elevated maternal cortisol at 30-32 weeks of gestation with greater infant negative reactivity, as reported by the mothers.

At each stage of development, the portion of the brain that is being formed is in a sensitive period particularly susceptible to the impact of environmental influences, and is exacerbated by the leakiness of the blood-brain barrier through early infancy (Saunder, Liddelow, & Dziegielewska, 2012). This makes the baby's central nervous system especially vulnerable to damage from toxins and imbalanced maternal hormones resulting from elevated stress (Saunder et al., 2012). These effects may impact brain structure and function throughout the lifespan.

Prenatal Maternal Stress

Maternal stress is not inherently harmful. In fact, cortisol levels naturally elevate during pregnancy, which is necessary to the development of several organs, including the central nervous system (Huang, 2014). Some prenatal anxiety is also necessary for preparing the child for a world in which he or she will inevitably encounter stress. However, healthy pressures of life are different from psychosocial stress, in which aversive or demanding conditions tax or exceed an individual's actual or perceived resources (Lazarus, 1966). This type of stress is a multi-faceted dilemma that affects the behavior, physiology, and development. Elevated maternal stress influences the immune and vascular systems, and is associated with mothers engaging in negative health-related behaviors, such as smoking, lack of exercise, and poor nutrition, which also negatively impact the offspring (Davis et al., 2011).

On a purely physiological level, PNMS can significantly elevate cortisol, and in some cases result in stress-related health issues which could impact the baby in a negative way (Davis et al., 2007). For example, prenatal maternal anxiety and depression have been correlated with an elevated incidence of extremely high blood pressure, at 140/100 or above (Kurki, Hiilesmaa, Raimo, Mattila, & Ylikorkala, 2000). This condition, called preeclampsia, has been linked with low birth weight (Ødegård, Vatten, Nilsen, Salvesen, & Austgulen, 2000). During a longitudinal study, 20-year-old individuals who had been born with very low birth weights (mean=1197 g) were found to have more chronic

conditions, such as neurosensory impairment and abnormal height, lower IQ's, and less instances of graduating high school as compared to a normal-birth-weight control group (Hack et al., 2002).

In addition to its physiological impact, stress affects the growth of highly vulnerable structures, such as the amygdala. This is the governor of the fear-response system, and can be highly useful in preparing an infant for a world in which he or she will be very likely to encounter stressful situations (Gerhardt, 2004). However, research indicates that if the amygdala is formed under exposure to abnormally high levels of cortisol, the fear-response system may be overactive (Davis et al., 2011). Development of the fetal nervous system can be influenced by cortisol that passes through the placenta, because this hormone easily crosses the blood-brain barrier and targets glucocorticoid (GC) receptors, which are present throughout the nervous system (Davis et al., 2011).

When a fetus vicariously experiences a heightened level of stress from its mother, its brain can become overwhelmed with cortisol. In response, the developing receptors, as well as the development *of* receptors, may shut down, particularly in the hypothalamus and hippocampus (Gerhardt, 2004). In the future, the offspring will have less ability to reuptake cortisol that is produced during a stress-response. Thus, the cortisol will remain floating in the brain, exacerbating high levels of stress that are very difficult to suppress (Gerhardt, 2004). The child will be subjected to a high baseline of stress, which compromises the natural ability to respond to or recover from truly stressful situations (Davis et al., 2011).

Programming

Programming is the process by which an event or environmental factor occurring during a sensitive developmental period has a longitudinal impact (Sandman & Glynn, 2009). Tissues and organs develop sequentially, and are sensitive to environmental issues at different stages of development. During these formative periods, psychosocial stress disturbances can alter the release of hormones such as 11ß-hydroxysteroid dehydrogenase type 2 (11ß-HSD2), cortisol, and corticotropin-releasing hormone (CRH), in addition to the hypothalamus-pituitary-adrenal (HPA) axis and limbic system, which may negatively alter the programming effect for the prenate (Davis et al., 2007).

11β-HSD2. Psychosocial stress increases maternal cortisol levels beyond what is required for normal embryonic development. This leaves the fetus less protected by the placenta due to the reduced expression and activity of the placental enzyme 11ß-HSD2, which is not equipped to process the heightened levels of cortisol (Huang, 2014). At normal levels, 11ß-HSD2 converts cortisol to its inactive form, cortisone. Although this enzyme protects the fetus from 80% to 90% of maternal cortisol, a small but significant amount passes through the placenta and the fetus's immature blood-brain barrier (Huang, 2014).

When maternal cortisol levels are elevated to a level far above the baseline, activity and expression of 11ß-HSD2 are reduced, leaving the fetus exposed and vulnerable. A disproportionate amount of cortisol is transferred through the placenta and into the prenate's developing body. Unfortunately, these high levels of cortisol can result in offspring having fewer placental enzymes than they would normally have to process the stress hormones (Gerhardt, 2004). This may be the contributing/causal factor discussed in the research findings that babies who were exposed to elevated maternal cortisol levels have higher baseline levels of cortisol, and are quicker to express fear and irritation and slower to recover from perceived stress (Davis et al., 2007).

Corticotropin-releasing hormone (CRH). CRH is a neuropeptide synthesized primarily in the paraventricular nucleus of the hypothalamus. It plays a major part in the regulation of physiological reactions to stress by influencing the pituitary-adrenal function (Sandman & Glynn, 2009).

During pregnancy, the placenta expresses the genes for CRH. Maternal cortisol quickly activates the synthesis of placental CRH (pCRH) from the fetus. Higher levels of cortisol increase this production. This rapid response can begin a domino effect on the health of the fetus, sometimes resulting in pre-term birth. Early delivery can have undesirable, long-lasting consequences for the infant, which may include sensory, motor, and neurological impairments (Sandman & Glynn, 2009).

HPA Axis. One of the most important effects of prenatal GC exposure is programming the fear-response system, including the limbic system and HPA axis (Davis et al., 2007). GC plays the important role of priming the fear-response system, and prenatal maternal GC release can augment existing baseline levels during development. When PNMS is at a high level, the elevated GCs can alter the neuroplasticity and behavior of the HPA axis, which may result in detrimental effects to the psychological well-being of the offspring (Huang, 2014). The structure and function of the hippocampus is vulnerable to the effects of GCs: animal experiments have indicated that elevated GC levels can result in offspring with smaller hippocampal volume (Davis & Sandman, 2010). In fact, the influence of PNMS on the developing fetal HPA axis has been proposed by Davis et al. as one mechanism that underlies fetal programming of adult health outcomes, such as vulnerability to disease and obesity, as well as psychological dysfunction, including behavioral inhibition and anxiety (Davis et al., 2011).

Cortisol. Cortisol is a key element of the maternal-fetal stress feedback loop. The cortisol that is not synthesized into cortisone by the placental 11ß-HSD2 passes through the fetus's highly permeable blood-brain barrier and targets GC receptors that are present throughout the central nervous system (Davis et al., 2011). Thus, an overabundance of maternal cortisol production impacts the fetus's entire nervous system. During this fragile time in which

the developmental blueprint is being formed, these effects can have deleterious lifelong impacts, including a greater propensity toward seizure disorders (Huang, 2014).

Early exposure to maternal cortisol may affect infant behavioral regulation. Cortisol influences the development of the connectivity between the brainstem, limbic, and cortical brain regions during the eight to 16 weeks gestational time period (Davis et al., 2011). The mother's cortisol may affect the development of the HPA axis, which includes alterations to cortisol receptor development. Therefore, individuals exposed to PNMS may not be able to respond to or recover from stressors in the environment appropriately. This is an effect that may last well into adulthood (Davis et al., 2011).

Epigenetic Imprint

Although physiological and behavioral impacts are apparent from exposure to PNMS, growing evidence indicates that high levels of PNMS can interact with both pre- and post-natal development in the progeny. In a study on maternal stress influencing microRNA (miRNA) regulation in rats, PNMS appeared to disrupt the expression of genes that are crucial to brain development and plasticity (Zucchi et al., 2013).

The epigenetic imprint on PNMS in humans is ethically impossible to study in a randomized controlled trial. However, researchers in Quebec used a stress-inducing natural disaster to their advantage when an ice storm hit in 1998. Cao-Lei et al. (2014) began a longitudinal study with women who were pregnant at the time of the storm, which left much of the city without power for days in the dead of winter. Objective and subjective stresses were measured from the pregnant women. When the offspring were eight years old, the researchers took samples of saliva, and then took blood samples when the children were 13 years old. Methylation levels of 1675 cytosine-guanine (CG) components were found to have significant alterations from PNMS, and significant CG signatures in 22 chromosomes, indicating that PNMS triggered a large signature alteration in the genome (Cao-Lei et al., 2014).

Prenatal exposure to maternal depression is also related to epigenetic changes, according to recent studies that correlated prenatal maternal affect with the risk for neurobehavioral disturbances in the offspring. One such study focused on the methylenetetrahydro-folate reductase C677T (MTHFR C677T) enzyme, which is associated with depression and changes in DNA methylation. Greater depressed mood during pregnancy was associated with affected DNA methylation patterns, indicating that maternal depression may contribute to developmental programming of the epigenetic expression in the progeny (Devlin, Brain, Austin, & Oberlander, 2010).

Lasting Impacts

Even before the challenges of modern societal stressors, individuals who were exposed to higher levels of prenatal cortisol displayed significantly different behavior than their counterparts whose mothers experienced less stress during pregnancy, according to a study on the effects of maternal cortisol at the end of pregnancy (de Weerth, van Hees, & Buitelar, 2003). One of the primary consequences of gestational GC exposure may be a more fearful, inhibitory response to new circumstances or stimuli, such as loud sounds and sudden noises (Davis et al., 2007).

The timing during which exposure to PNMS occurs impacts neural and behavioral development. Early pregnancy is one of the key developmental periods, as the zygote folds in on itself and begins following the blueprint for development. Stress during this period is associated with lower scores on infant behavioral assessment examinations (Davis et al., 2011). Another sensitive period is 30 to 32 weeks, during which higher maternal cortisol during this brief period correlates with more negative infant reactivity (Davis et al., 2007).

In addition to timing, the magnitude and quality of stressors is important. Children of women who experienced six or more self-reported stressful life events during pregnancy, regardless of the timing, were at about four times greater risk of developing mental health problems later in life (Robinson, 2012). In another study, high CRH levels during gestation were correlated with decreased physical and neuromuscular maturity, which has been associated with impaired brain development and motor development abnormalities (Sandman, 2009).

Longitudinally, evidence points to an association between high levels of prenatal maternal cortisol and fearful and reactive behaviors of offspring (Davis et al., 2011). Babies who were exposed to high levels of stress in utero tend to be more reactive after birth, show more behavioral inhibition and anxiety during infancy, toddlerhood, and childhood, and display a slower rate of recovery from stress responses (Davis et al., 2011). They are also more likely as toddlers and children to have greater physiological arousal to challenges, to display anxiety or fear in new situations, to have higher stress reactivity and poorer emotional and attentional regulation (Davis, 2011). Further, studies comparing the cortisol levels on the day of a vaccination and the first day of school found that children who had been exposed to high levels of maternal stress showed that they had higher levels of cortisol in the faces of these stressors than children in a control group, which indicates that fetal development of the HPA axis is influenced by PNMS (Davis et al., 2011).

Conclusions and Future Orientation

More longitudinal research is needed on this topic, because associations between prenatal psychosocial stress and HPA axis regulation in offspring may

emerge later in development. (Davis et al., 2011). In addition, many aspects of the timing and hormone balance are very subtle, and studies in the future may be able to target these aspects more meticulously.

Although an extraordinary amount of development and programming occurs during gestation, an infant's brain is still very malleable after birth. Positive patterns in early life, especially in the first year, can heal trauma and enable a baby to develop the cortisol receptors and relax into a less-stressed state, from which it will develop accordingly (Gerhardt, 2004). Social supports, a nurturing home environment, and bonding techniques such as parent-infant massage can help mothers and their partners adjust to parenthood with less stress. This will have a direct and positive impact on babies exposed to high prenatal levels of stress hormones (McClure, 2000). Even if an individual did not receive this care during infancy, many therapists are becoming aware of the impact of prenatal trauma, and emerging therapeutic methods are targeting these early wounds for patients of all ages (Chamberlain, 2013).

Non-pharmacological prenatal stress-reduction techniques are also gaining solid footing in the obstetrical and psychological fields. Classes in yoga for pregnancy are popular in many areas of the world, and information about how to have a healthy pregnancy and birth is widely accessible. Studies on the positive effects of prenatal meditation on the mothers and offspring have yielded promising results. In one such study, a group of pregnant women were taught several meditation techniques. Umbilical cord blood cortisol levels were measured after birth, and the results showed that the babies in the intervention group had higher cord blood cortisol than those in the control group (Chan, 2014). This indicates a healthy stress-response system for these infants: the stress of childbirth elicits a cortisol surge that prepares a fetus for life outside the womb. At five months of age, the infants were assessed using a Carey Infant Temperament Questionnaire, and were measured to have "better" temperament (Chan, 2014). The physiological and behavioral findings of this study indicate that prenatal meditation may have a positive, lasting impact on the infant, though further longitudinal research is needed. Fortunately, maternal-infant healthcare has become more of a priority for Amnesty International and the United Nations in recent years, and the body of research into alternative methods for preconceptive mental health care is expanding rapidly.

Research about the deleterious impact of prenatal maternal stress is not meant to discourage, stress, or impart guilt upon the parents and children of today. Instead, this knowledge may inspire parents, healthcare workers, and scientists alike to explore new methods of prenatal or even preconceptive care, in which the psychological health of the mother is attended to and stress-reduction techniques are incorporated into daily life. The evolution and implementation of preventative prenatal healthcare may result in healthier future generations.

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