Prenatal Foundations

Fetal Programming of Health and Development

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The transformation from a single-celled zygote to a human newborn is a dramatic process. During this 9-month period development proceeds at an incredible pace, particularly in the brain, that is unmatched at any stage of the lifespan. The astounding pace of human brain development renders it susceptible to a variety of influences. Brain development begins early in gestation and follows a carefully orchestrated series of events. During gestation *neurogenesis* (the birth of new neurons) proceeds at a rate of 250,000 cells per minute (Cowan, 1979). These new cells begin to communicate, and during the third trimester the rate of synapse formation (connections between neurons) accelerates to a rate of 40,000 synapses per minute (Bourgeois, Goldman-Rakic, & Rakic, 1994). The fetal period is a time of enormous neurological changes and thus experiences during this period can dramatically influence development.

Studies of prenatal development historically have focused on insults to the developing brain or exposure to teratogens (e.g., drugs or alcohol). There is an increasing recognition that prenatal development is not simply an unfolding of a genetically determined timetable that is disrupted only in the context of exposure to extreme insults, but rather that the prenatal environment plays a critical role in shaping the developing fetus and contributes to individual differences in development. Normative changes in the prenatal environment, including variations in the exposure to maternal hormones, alter the developmental trajectory and may, in a predictive fashion, adapt the fetus for the postnatal environment. This issue of *Zero to Three* will consider new research illustrating the importance of prenatal influences such as maternal stress and stress hormones that critically influence the developmental program and the influence these factors have on adaptation to the postnatal world.

What Is Fetal Programming?

The fetal programming or developmental origins of disease models posit that during periods of rapid development or change the organism is susceptible to environmental influences and that these influences exert persisting consequences for health and disease risk (D. J. Barker, 1998). It is becoming increasingly evident that experiences and exposures in the womb are associated with many of the conditions that contribute to disease burden worldwide. Understanding the origins of these diseases requires a comprehensive approach that considers not only genetic risk but also the role of the early environment.

The fetal programing hypothesis, dependent on the ability to study individuals across the entire lifespan, has an interesting origin. Empirical support for the fetal programing hypothesis exists, in part, because of an intervention established by the British government in the early 1900s. At the start of the

Abstract

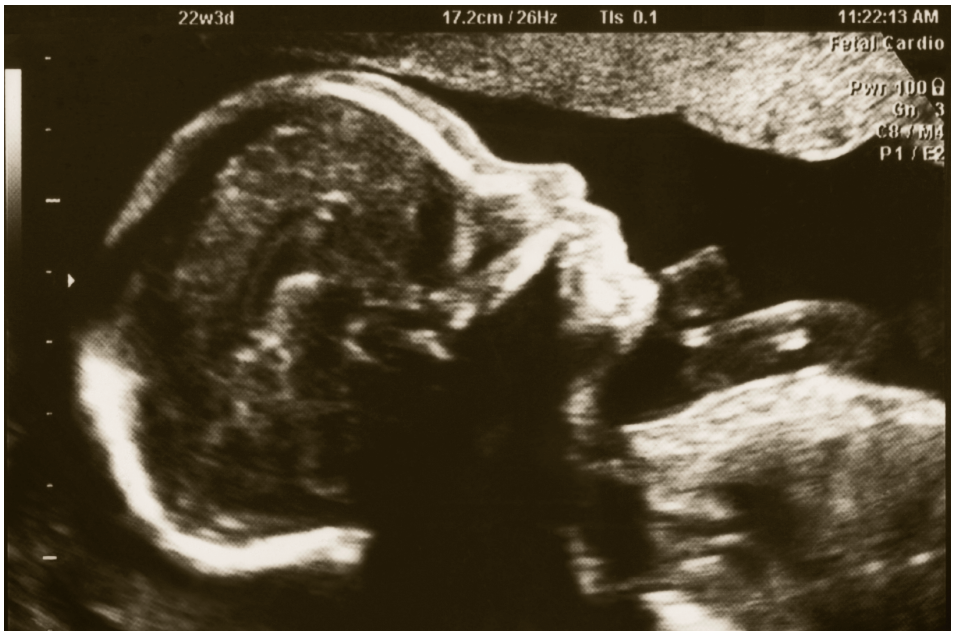
The fetal programming and developmental origins of disease models suggest that experiences that occur before birth can have consequences for physical and mental health that persist across the lifespan. Development is more rapid during the prenatal period as compared to any other stage of life. This introductory article considers evidence that fetal exposure to stress and stress hormones influences regulation of stress and emotion, cognitive functioning, and brain development during infancy and childhood. The authors consider implications for intervention and future research directions.

20th century the British government was concerned about the declining health of the British population and the poor health of young men attempting to enlist in the army. An enlightened intervention was established. Ethel Margaret Burnside was named as the country's first "chief health visitor and lady inspector of midwives." She established a team of nurses to travel around the country to advise mothers on how to care for their infants. One extraordinary consequence of this intervention was that meticulous records were kept related to infant weight at birth and over the first postnatal year (D. Barker, 2003). More than 60 years later Dr. David Barker was able to link these birth records to death records. Using these data he made an astounding observation. A disproportionate number of deaths from coronary heart disease occurred among individuals with low birth weight (D. Barker, 2003). These data have since been replicated in numerous epidemiological studies. Size at birth is predictive of a variety of later health outcomes including heart disease, diabetes, and obesity as well as psychiatric dysfunction (D. J. Barker, 2002; Nathanielsz, 1999) illustrating the importance of considering fetal origins of later health and disease.

The Dutch Hunger Winter: An Example of Fetal Programming

Some of the most compelling evidence for fetal programming of adult disease comes from long-term follow-up studies of survivors of the Dutch "Hunger Winter." During the Nazi occupation of the Netherlands (winter 1944–1945) a severe famine was experienced in the western Netherlands resulting from a German embargo on rail transport and a severe winter. For approximately 9 months, a significant portion of the Dutch population was forced to subsist on less than 1,000 calories per day. During this time period many Dutch starved to death. The famine ended abruptly with the Allied liberation of the Netherlands in the spring of 1945. This tragedy has provided unique information about the consequences of nutritional deprivation during pregnancy. Because the famine was circumscribed in time and place it was possible to determine the long-term consequences for fetuses who were exposed in specific gestational intervals. The national registries in the Netherlands provided the opportunity for long-term and intergenerational assessment of the consequences of fetal exposure to this famine.

The findings from this large research literature indicate that although many of the immediate effects of maternal malnutrition on newborns (such as birth weight) were not strongly predictive of later outcomes, there were important latent effects. Adults who were exposed as fetuses to the famine exhibited



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significantly heightened risk for a variety of physical and mental health problems, including adult obesity, diabetes, heart disease, and schizophrenic disorders, compared to pregnancies not affected by the famine or same-sex sibling controls (Lumey et al., 2007; Lumey, Stein, & Susser, 2011). Many of these later outcomes are consistent with *adult metabolic disorder*, in which biological systems are functioning maladaptively to enhance cardiovascular risk. It appears that the period of early malnutrition caused biological adaptations to nutritional insufficiency in the fetus (such as decreased energy metabolism and growth rate) to prepare for a postnatal life of food scarcity. When children instead grew up in conditions of plentiful food, their physiological systems were unprepared for this, contributing to later health problems.

How Does Stress Physiology Change During Pregnancy?

Maternal stress, like nutrition, is another critical aspect of the prenatal environment that can have enduring consequences for child development. This is especially important because of changes in maternal stress physiology that occur during pregnancy.

Stressors are real or perceived threats to psychological or physical viability that are responded to by stressor-specific biological processes. A stressful event can trigger the "fight-or-flight" response, causing the release of hormones such as adrenaline and cortisol. These biological molecules orchestrate integrated responses that have evolved to increase survival in the immediate face of threat (Joels & Baram, 2009). Cortisol, the end product of the hypothalamic-pituitary-adrenocortical (HPA) axis exerts influences throughout the body including mobilizing energy and resources to support the fight or flight response. Cortisol crosses the blood-brain barrier and acts directly on the brain. Short-term increases in cortisol are necessary to manage stress or challenge. Chronic elevations in cortisol may exert deleterious effects and can impair the functioning of a number of brain systems. This may in particular be true during development. The HPA axis is one of the major stress responsive systems and has been proposed to play a central role in fetal programing. In response to stress signals a cascade of events is initiated resulting in the release of cortisol. In the nonpregnant state the HPA axis is contained by a negative feedback regulation. High levels of cortisol subsequently decrease HPA axis activity thereby "turning off" the stress response. This system changes drastically during pregnancy. The placenta (a fetal organ) produces hormones that change the regulation of this stress responsive system. Over the normal course of human pregnancy all of the HPA axis hormones (including corticotropin releasing hormone, CRH, and cortisol) increase dramatically. Cortisol levels in maternal circulation rise 2- to 5- fold. Levels of placental CRH increase 40-fold from the first to the third trimester, reaching levels only achieved centrally in the nonpregnant state during stress (Sandman et al., 2006). It is important to note that these increases are normative. These hormones play an important role in regulating pregnancy, maturing the fetus, and determining timing of delivery (Davis & Sandman, 2010).

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Consideration of the prenatal and the postnatal environment is essential to understanding the role early experiences play in shaping mental health.

These stress responsive systems are an important mechanism by which information about the external environment is communicated to the fetus. For example, in a high stress environment the fetus may restrict its growth to preserve resources and to increase the chances of survival. The fetus and the fetal brain are "under construction." The signals the fetus receives in the womb influence the progression of development. It is interesting that these very early stress signals appear to exert lasting influences on brain and behavior throughout the lifespan.

Does Fetal Exposure to Maternal Stress Signals Influence Development?

The fetal programing hypothesis has contributed to the generation of a compelling set of studies indicating the critical importance of fetal experiences for health and development across the lifespan. Size at birth (except in extreme circumstances) does not directly cause later health outcomes. Rather small size at birth indicates that perturbations occurred during the prenatal period affecting the development of biological systems influencing later health. Research by Davis and colleagues and studies presented in this issue prospectively evaluate processes that influence fetal development and the implications for postnatal development. These studies demonstrate that fetal exposure to stress signals exerts lasting consequences on physical and mental health.

As discussed in this issue, prenatal stress leads to shortened gestation or premature birth (birth at less than 37 gestational weeks; Dunkel Schetter & Glynn, 2011). Preterm birth occurs in 12% of live births in the U.S. (March of Dimes, n.d.) and is the most significant challenge facing maternal child health (March of Dimes). Shortened gestation, even among full term infants, has detrimental consequences (Davis, Buss, et al., 2011; Spong, 2013). Research presented here and in this issue illustrates that stress related processes that influence birth outcome also affect the developing fetal brain.

Fetal Programing of Emotional and Stress Regulation

A consistent research finding is that fetal exposure to maternal stress signals is associated with increased stress and emotional reactivity in the offspring. For example, babies who were exposed to high maternal cortisol as fetuses produced a larger cortisol response to the stress of a heel-stick blood draw that they received in the hospital after birth (Davis, Glynn, Waffarn, & Sandman, 2011). These data suggest that fetal exposure to maternal stress may affect the development of fetal stress systems (e.g., the HPA axis). This increased stress reactivity that researchers observe in newborns may suggest that these babies will continue to be more reactive to challenges they experience. In fact, fetuses who experience higher maternal stress in the womb are more fearful and more reactive to novelty as infants and young children (Blair, Glynn, Sandman, & Davis, 2011; Davis et al., 2007; Davis et al., 2004). Further, these children are at an increased risk for affective problems such as depression or anxiety during preadolescence and adolescence (Davis & Sandman, 2012; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). Recent research illustrates that exposure to elevated levels of stress hormones (e.g., cortisol) influences brain development. Further, these studies suggest that the changes to the brain may be responsible for observed increases in child stress and emotional reactivity (Buss et al., 2012; Davis, Sandman, Buss, Wing, & Head, 2013). This set of studies illustrates the role prenatal experiences play in shaping postnatal responses to experiences and associated outcomes.

Fetal Programing of Cognitive Development

The influence that fetal exposure to maternal stress signals has on cognitive and motor development is less clear. There is evidence that maternal self-report of elevated stress and anxiety as well as exposure to traumatic life events, such as severe ice storms, during pregnancy are associated with delayed infant and child cognitive, language, and neuromotor development (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; LaPlante et al., 2004). However, not all studies have demonstrated such associations, and there is evidence that modest elevations in stress during late gestation may actually increase cognitive maturation (Davis & Sandman, 2010; DiPietro, Novak, Costigan, Atela, & Ruesing, 2006).

It is possible that exposure to moderate elevations in stress signals does not negatively affect cognitive development. Alternatively, it may be that it is essential to consider the type of stress experienced by the mother and the timing of exposure. Given the rapid pace of fetal brain development, different brain systems may be susceptible at different times during pregnancy. Thus, it is important to consider the time during pregnancy when the fetal exposure to maternal stress occurred. With respect to consideration of type of stress, it is possible that self-report measures of general psychological distress may not adequately characterize stress that is unique during pregnancy. Evidence is emerging that measures of pregnancy-specific stress may be particularly potent predictors of child outcomes. Examples of pregnancy specific stress include: "I am fearful regarding the health of my baby," or "I am concerned or worried about losing my baby." Pregnancy-specific stress has been associated with fetal behavior and with infant and child cognitive and motor development (Buss, Davis, Hobel, & Sandman, 2011; Davis & Sandman, 2010). Recent evidence further demonstrates that pregnancy-specific stress is associated with child brain development (Buss, Davis, Muftuler, Head, & Sandman, 2010). Gestational exposure to pregnancy-specific stress is associated with decreased grey

matter volume in cortical regions involved in a variety of cognitive functions. For example, prefrontal cortical areas involved in executive functions such as planning, attention, and working memory as well as medial temporal lobe structures involved in memory were reduced in children born to women with high pregnancy-specific stress. It is important to note that these associations are not explained by actual medical risk associated with pregnancy and birth outcome.

Does Fetal Stress Exposure Affect Boys and Girls Differently?

As early as conception there are sex-specific developmental trajectories, and males and females respond differently to stress. It is well known that in response to early adversity males are at an increased risk for morbidity and mortality as compared to females. Males are at a greater risk for fetal demise, stillbirth, preterm delivery, infant mortality, and extreme developmental impairments (Challis, Newnham, Petraglia, Yeganegi, & Bocking, 2013; Hunt & Hassold, 2002). Because of the profound effects of adversity on male survival it is often thought that females are relatively immune to the effects of early adversity. It is likely, however, that the sex-specific adaptive strategy seen in females is associated with different and more subtle developmental costs. It is plausible that a viability–vulnerability trade off exists (Sandman, Glynn, & Davis, 2013). Data suggest a female vulnerability that is associated with increased risk for anxiety and affective problems. These outcomes contrast to the more extreme developmental impairments observed when males are exposed to early adversity.

Are These Developmental Changes Adaptive?

There is a strong tendency to consider stress exposure as negative and leading to maladaptive outcomes. However, stress signals may provide important information to the fetus about the world that it will be born into. These signals may help the fetus to adapt to the environment, increasing its chances of survival. The environment that is "optimal" for a given individual may be determined not only by an individual's genetic predisposition, but also by the prenatal environment as it foreshadows the quality of the postnatal environment in which the child will live.

Across species, prenatal signals shape developmental trajectories. The impact of adaptations to these signals for survival and disease risk are determined by the degree to which these changes benefit functioning in a given environment. Certain tadpole species alter their size and shape on the basis of the presence of dragonfly larvae, a predator, in their rearing environment (Van Buskirk & Relyea, 1998). After metamorphosis into a toad, these alterations are protective from predation by dragonflies, but maladaptive in an environment without dragonflies. The human fetus similarly incorporates signals from the maternal host environment into its developmental trajectory. It is plausible that stress signals provide important information to the fetus about the nature of postnatal conditions, increasing its ability to adapt to its environment. In the human, maternal stress accelerates development of systems necessary for survival (e.g., lungs) in the face of shortened gestation (Dunkel Schetter, 2009; Glynn, Dunkel Schetter, Hobel, & Sandman, 2008). This type of adaptation can be an advantage if the fetus is born preterm. Thus, the long-term health consequences of fetal changes in response to maternal prenatal signals may depend on the postnatal world.

The predictive adaptive response model developed by Gluckman and Hanson (2004) illustrated the importance of the match between the prenatal and the postnatal environment. Fetuses who experience nutritional deprivation exhibit metabolic changes that improve their ability to survive in a postnatal environment in which food is scarce. In contrast, fetuses who are deprived of nutrition and then born into an environment where food is plentiful are at risk for a range of health problems including obesity, heart disease, and metabolic syndrome, as was observed in the Dutch Hunger Winter victims. In other words, fetuses who experience nutritional deprivation in the womb are healthier if they experience a postnatal environment with similar food scarcity. These counterintuitive findings suggest that the consequences of the postnatal environment are determined, in part, by prenatal maternal signals. The same postnatal environment may have opposing effects depending the quality of prenatal maternal signals. Highly consistent with nutritional models, a study illustrated that consistency in maternal emotional state similarly predicts enhanced infant cognitive functioning (Sandman, Davis, & Glynn, 2012). One exciting avenue for future research is the idea that consideration of the prenatal and the postnatal environment is essential to understanding the role early experiences play in shaping mental health.

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The research on fetal programming urges special attention devoted to nutritional assistance and stress reduction for the mother.

Implications

The evidence for fetal programming is clear. Despite the research challenges in identifying relations between environmental impacts on the developing fetus and later health and development, there is a general consensus that such consequences may be of tremendous importance.

There are also significant implications of this work, especially for those who are involved in supporting the health of pregnant women and their children. Several contributors to this issue discuss these implications. One implication is the need for access to regular prenatal care for all mothers. Regular prenatal care is important for providing guidance to women concerning their pregnancies. This includes attention to diet, avoidance of behavioral teratogens (e.g., smoking, drinking, and illicit drug use) and environmental

teratogens (e.g., mercury in fish), information concerning the typical course of pregnancy, and assistance in reducing undue stress on the mother. But prenatal care is inconsistently available to women in the United States and throughout the world because of sociodemographic barriers to access. One of the promising features of the Affordable Care Act is the incorporation of prenatal care into health care coverage that is designed to be more affordable and widely accessible.

In particular, the research on fetal programming urges special attention devoted to nutritional assistance and stress reduction for the mother. Unfortunately, women in economic distress are more likely to experience difficulty in both aspects, warranting greater attention to efforts to provide support to them through community programs. The Nurse Family Partnership approach to home visitation has been successful in promoting more positive child development, maternal health, and parenting outcomes. One reason may be that it begins prenatally, when parents are more receptive to guidance from a skilled professional and when the information and support provided by the home visitor may be helpful in improving the conditions of prenatal care for the developing fetus (Olds, Sadler, & Kitzman, 2007).

The significance of maternal stress for prenatal and early childhood development also is important for obstetric and pediatric professionals to understand because of the potential long-term—but preventable—consequences for children. A newborn who is temperamentally irritable and reactive may be exhibiting a genetic propensity, but it also may reflect a prenatal environment of chronic exposure to elevated maternal stress hormones. Enlisting the support of other family members, particularly the father, in reducing avoidable sources of maternal stress can be one way of supporting healthy fetal growth.

More broadly, the research on fetal programming provides new understanding of some of the biological processes contributing to the intergenerational transmission of risk in families. In addition to the ecological and family conditions that can cause young children in "risky families" (Repetti, Taylor, & Seeman, 2002) to develop emotional and behavioral problems, researchers now understand how family conditions can lead to biological changes in children, beginning prenatally, that contribute to their poorer emotional self-regulation, increased reactivity to stress, impaired learning and cognitive skills, and risks to health and mental health (Thompson, in press). The fetal programming research indicates that these family risk factors begin prenatally through their influences on maternal stress and other factors that affect the prenatal environment.

Remaining Questions and Future Research Directions

The studies reviewed here provide important prospective evidence for fetal programming. They suggest that the fetus' exposure to maternal stress and stress hormones influences its development and has lasting consequences for brain and behavior. The adaptive significance of these associations is yet to be determined and requires long-term follow-up evaluating the interaction between the prenatal and the postnatal environment. In some situations, fetal influences may better prepare the child for life after birth; in other situations, it may simply undermine healthy postnatal development. A number of potentially significant questions remain. For example, researchers know very little about the intergenerational consequences of fetal exposures. Compelling animal data as well as emerging human research indicate that fetal conditions in the womb have consequences for future generations. Thus, understanding fetal programing of health and development may have both generational and intergenerational implications. In addition, although clear evidence exists for sex-specific susceptibility to disease outcomes that originate early in life such as depression, autism, and heart disease, researchers know very little about the sex-specific consequences of fetal exposure to stress and stress hormones. Finally, and perhaps most important, few studies have identified effective avenues for intervention. It is unfortunate that few interventions target maternal stress or mental health during the prenatal period. This period of life may represent a prime opportunity for interventions that benefit both mother and child. The fetal programming literature illustrates the importance of the fetal period for shaping health and development across the lifespan and argues for the need for increased attention to this period of life.

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