The Infant – Mother Connection and Implications for their Future Health

Part 2 – Adverse maternal influences on her unborn child

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ABSTRACT: Adverse childhood experiences are known to negatively affect the physical and emotional health of adults. Now scientific research shows that adverse childhood experiences can actually begin in utero as the unborn child is exposed to the chemical influences of maternal stress hormones. Mothers who experience anxiety, depression, or intimate partner violence while pregnant may unknowingly adversely impact the development of their unborn child. However, research has shown that early recognition and prenatal intervention can help mitigate these negative consequences. ACPeds encourages health care professionals to consider such research when caring for pregnant women and their infants after birth to assure the best health outcomes for all involved.

Introduction

Stress is defined by the American Psychological Association as "any uncomfortable emotional experience accompanied by predictable biochemical, physiological and behavioral changes." [1] The body's response to stress is designed to improve the chances for survival, so some stress can be beneficial – enhancing the immune system and memory, for example. However, if stress exists for a prolonged period of time, or is severe, and the individual lacks resources to overcome it, the stress response can be detrimental or "toxic", causing physiological damage.[2]

The term Adverse Childhood Experiences (ACEs) was introduced into the medical literature in 1998 when the American Journal of Preventive Medicine published an article by Felitti, et al, describing the relationship between abuse and household dysfunction experienced during childhood and later morbidity and mortality as adults.[3] ACEs include emotional, physical, and sexual abuse, as well as violence, substance abuse, mental illness, parental incarceration, and divorce occurring in the child's home, and can constitute toxic stress. As the number of ACEs reported increases, so does that individual's risk of experiencing adulthood cardiac disease, asthma, mental illness, stroke, diabetes, and lower educational attainment with lower income. Many states are now utilizing the Behavioral Risk Factor Surveillance System (BRFSS) to collect data on ACEs and have found almost two-thirds of adults reporting at least one ACE, while more than one in five report three or more ACEs.[4]

At the same time we are learning more about the unique interactions occurring between the pregnant mother and her unborn child. As scientific evidence accumulates demonstrating the impact of maternal physical and emotional well being on her unborn child, we may now consider the possibility that ACEs as toxic stress can begin in utero. This is emphasized in an article reviewing the in-utero neurological development of the child. The author states evidence is accumulating that "adverse intrauterine exposures increase subsequent risk for a range of outcomes including hypertension, heart

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A note on terminology: There are two medical terms for what we refer to in English as the *unborn baby* or *unborn child*: "*embryo*" refers to the baby during the first 8 weeks of his or her life (up to 10 weeks after the mother's last menstrual period), and "fetus" (Latin for "young one") refers to the baby during the remainder of his or her time in-utero (from when all the organs have formed until birth). Because most of the research referenced in this paper does not differentiate between embryos and fetuses, we have chosen to use the all-inclusive term of unborn child in most instances.

disease, diabetes, obesity, and polycystic ovary disease, as well as psychiatric illnesses such as schizophrenia, mood disorders, and suicide." [5] This concept has been referred to as "fetal origins hypothesis" – "that prenatal environmental exposures – including maternal psychological state-based alterations in *in utero* physiology – can have sustained effects across the lifespan." [6]

The Institute of Medicine (IOM) update "From Neurons to Neighborhoods" in 2012 highlights the importance of the prenatal environment, stating, "Development is a continuum from the prenatal to the postnatal periods, with a particular influence from maternal nutrition, stress, and health. " [7]

Since development occurs most rapidly between conception and early childhood, events impacting the child during this time take on greater significance. The IOM report emphasizes this: "From the time of conception to the first day of kindergarten, development proceeds at a pace exceeding that of any subsequent stage of life….What happens during the first months and years of life matters a lot…because it sets either a sturdy or fragile stage for what follows." [8]

This paper will discuss some of the many ways stressful maternal conditions impact her unborn child. Part 1 of this series discussed more positive prenatal impacts imparted by the birth mother and the way the unborn child impacts maternal physiology and brain development, while Part 3 will review the influence of positive parenting as a means of ameliorating adverse effects of ACEs.

Given the wealth of information, it is only possible to highlight the more significant ways the mother and child influence, affect, and impact each other's development. However, even these highlights clearly demonstrate the uniqueness of each mother-child interaction and argue for continuing this relationship post conception whenever possible. Even mothers who have experienced miscarriage or abortion, or who have given a child up for adoption have been impacted by their babies in ways that can affect these mothers for a life time – and likewise the living children carry with them life long maternal influences. This maternal-child bond is unique and powerful, and the College acknowledges and respects this special relationship which should generally be supported to promote optimal health for both individuals.

Physiologic Basis for Adverse Effects of Stress During Pregnancy on the Child

Although stress may induce positive changes in the individual, in this paper we will use stress as a synonym for distress – "an event or events that are interpreted as threatening to an individual and which elicit physiological and behavioral responses." [9]

The brain is responsible for determining the presence of stress as well as initiating the individual's response to that stress. The main pathway involved in the stress response is the hypothalamic-pituitary-adrenal axis, and it is through this mechanism that the adrenal gland is induced to produce the glucocorticoid known as the "stress hormone". The autonomic nervous system is also active during times of stress releasing epinephrine (adrenaline) which facilitates the "flight or fight" response. Other hormones and neurotransmitters are also involved.

One of the body systems greatly impacted by stress is the immune system. At times of increased acute stress, the immune system is activated to protect the individual from infection. Leukotrienes, prostaglandins, and cytokines work with the immune system, while cortisol is released to temper the potentially harmful effects of those inflammatory mediators. Normally the levels of cortisol and other stress hormones should decrease once the stress has disappeared. However, when individuals are under chronic stress, the levels of cortisol and other mediators do not decrease, leading to a prolonged poorly effective, if not harmful, immune-inflammatory response. Chronic inflammation is instrumental in the development of pathological entities such as atherosclerosis as well as chronic fatigue syndrome and a multitude of autoimmune disorders.

The brain not only determines whether or not stress exists, but is itself greatly affected and altered by the presence of chronic stress. The hippocampus is the area of the brain responsible for formation of memories and the cells in the

hippocampus have receptors for the stress hormones. When stress is short-lived, the higher levels of stress hormones, such as glucocorticoids and catecholamines, actually assist the formation of memories in the hippocampus, especially memories associated with strong emotions. However, when stress is chronic, these same stress hormones cause damage to hippocampal cells and impair cognitive function.[9] The chronic elevation of stress hormones and neurotransmitters in an individual's body damages other organs, including the heart, as well as endocrine glands. This has been postulated to be one of the mediating mechanisms leading to the long-term effects of ACEs such as hypertension and obesity.

It is with this background that we can now consider the effects of maternal physical and emotional well being on the unborn child who is in a critical period for neurodevelopment and is more vulnerable to exposures that adversely impact brain development.

Effects of Maternal Stress, Anxiety, and Depression During Pregnancy on the Child

There are several mechanisms by which it may be possible for maternal stress and anxiety to impact the unborn child. These include the hypothalamic-pituitary-adrenal (HPA) axis, as well as uterine artery resistance.[10] Researchers are evaluating additional mechanisms by which maternal stress may adversely influence fetal development, including changes in placental enzymes, genetic changes in Neuropeptide Y and alterations in the maternal vaginal microbiome.[11,12,13]

Maternal stress has been associated with many outcomes in the unborn child. In one study, maternal stress led to a more active fetus. Fifty-two healthy, pregnant women who were nonsmokers were assessed at 24, 30, and 36 weeks gestation using several scales that measured daily stress and pregnancy experiences. The mothers who identified their lives as more stressful had babies who were more active throughout the assessment period. The authors state, "Maternal stress can influence the fetus directly, through transport of neuropeptides, and indirectly, through alterations in maternal-fetal blood flow." [14]

In a study of 34 healthy women who underwent amniocentesis during their second trimester of pregnancy, compared to women without chronic stress, higher levels of corticotropin-releasing hormone (CRH) were found in the amniotic fluid of those women who had experienced chronic stress. (Though maternal cortisol decreases maternal CRH, it increases placental CRH, which may also rise due to other maternal stress hormones, such as epinephrine.)[15]

A possible outcome of maternal stress is a risk of having a low birth weight infant or a premature delivery. A meta-analysis of 29 studies in 2010 found that "Women with depression during pregnancy are at increased risk for PTB (preterm birth) and LBW (low birth weight infants), although the magnitude of the effect varies as a function of depression measurement, country location and US socioeconomic status." [16]

A prospective study of over 10,000 mothers and their children in the United Kingdom found that those children whose mothers had been exposed to the most stress at 18 weeks gestation were more likely to experience symptoms of hyperactivity and aggression.[17]

Depression during pregnancy is a specific source of maternal stress that has additional impacts on the unborn child. A study of 691 women in Korea found those who were depressed prenatally were more likely to give birth earlier than those who were not depressed.[18]

Due to the number of variables that must be evaluated, it is difficult to determine the long-term effects on children whose mothers experienced prenatal depression. However, there are a number of studies that suggest the possibility that exposure to prenatal depression can affect the mental health of older children.

Maternal depression is linked with changes in the infant's brain, specifically the amygdala, which is involved in regulating emotions. In one study of 24 infants who underwent both structural and resting-state functional MRIs at 6 months of age, those infants whose mothers experienced high prenatal depressive symptoms showed changes in the amygdala seen in

adolescents and adults with depressive disorders. The infants had greater functional connectivity between their amygdalas and the left temporal cortex and insula, - "regions that are important for processing fearful facial expressions of emotion."[19]

Maternal anxiety during pregnancy may also have an impact on the child's brain development. Thirty-five mothers were assessed for anxiety at 19 and again at 31 weeks gestation. When their children were later assessed at 6 – 9 years old, those whose mothers had been noted to be anxious when surveyed at 19 weeks gestation showed reduced brain grey matter on structural MRI scans. The decreased grey matter volume occurred in the prefrontal cortex, the premotor cortex, and the temporal lobe – areas associated with executive functions such as reasoning and planning.[20]

An interesting hypothesis is emerging that looks at adaptive responses of the unborn child when presented with an adverse environment. An infant, after birth, who experiences the same adversity as encountered in utero, may actually do better and thrive in the adverse environment, compared to an infant who experiences a mismatch between the intrauterine and extrauterine environment. For example, an infant who experienced maternal depression both in utero and as a young child may be better equipped to thrive than an infant whose mother was not depressed during pregnancy but develops depression after delivery. A study of 221 healthy pregnant women and their infants were followed for 12 months after delivery. Infants were divided into four groups depending upon whether the infant's mother had depression before delivery, after delivery, at both times, or neither. Infants in the two groups who experienced the same maternal environment, both before and after delivery, performed better on measures of development at 3 months and better in mental development at 12 months, than those infants whose mothers only developed depression after delivery or who were depressed before but not after delivery.[21]

Effect of Intimate Partner Violence (IPV) During Pregnancy on the Child

Another form of maternal stress during pregnancy occurs if the mother experiences IPV, and a review of IPV emphasized its negative effects on the mother-infant dyad. Negative effects on maternal health include insufficient or inconsistent prenatal care, poor nutrition, inadequate weight gain, substance use, increased prevalence of depression, physical injury, and even death. Adverse neonatal outcomes include low birth weight, preterm birth, small for gestational age delivery, and perinatal death.[22]

There is a direct relationship between a history of IPV and maternal depression. One thousand women who had never experienced depression were enrolled in a prospective study, and those women who suffered IPV were twice as likely to develop depression, and three times more likely to develop schizophrenia-like psychotic symptoms.[23]

It is not surprising, then, that IPV can also adversely affect the unborn child. In a study of 182 mothers, researchers found that gestational IPV can later manifest in the infants as increased startling to loud noises and bright lights, the avoidance of physical contact, nightmares, as well as having trouble experiencing enjoyment.[24]

Consistent with the findings by Grote, et al,[16] looking at maternal depression, in a review of 50 studies involving over 5 million women from 17 countries, researchers found that women who experienced IPV during pregnancy had an increased risk of preterm births and low birth weight infants, with the possibility of an increased risk of small for gestational age infants.[25]

The proposed mechanism by which IPV causes adverse effects on the unborn child is through the same HPA axis that is involved in the stress response. One study demonstrated that mothers affected by IPV have disruption of their diurnal cortisol rhythms, having higher-than-normal levels later in the day that may adversely affect the fetus.[26]

Maternal Exposures

Although there is much research evaluating the effects of maternal drug and chemical exposures on the developing unborn child, it is beyond the scope of this paper to enumerate all the adverse effects. However, it is important to note that commonly used drugs - alcohol, marijuana, and nicotine – all negatively influence in utero growth and development.

Fetal Alcohol Spectrum Disorders (FASD) demonstrate the strong relationship found between alcohol consumption during pregnancy and impact on the unborn child. Growth restriction, congenital anomalies and malformations, intellectual deficiency, attention deficit hyperactivity disorder, as well as increased risk of more subtle learning difficulties are all associated with even small amounts of alcohol ingestion.[27,28]

Marijuana also adversely impacts the developing child and has been shown to increase the risk that the child will be small for gestational age and require admission to neonatal intensive care units.[29]

Marijuana may also affect the developing brain by changing the endocannabinoid system resulting in impaired executive functioning skills such as increased impulsivity. Difficulties with problem solving and memory in offspring have also been associated with maternal marijuana use.[30,31]

Maternal cigarette smoking, including e-cigarettes, and even second-hand smoke may adversely affect the unborn child. The CDC reports that maternal smoking is associated with premature birth, birth defects (cleft lip and palate) and an increased risk of infant death.[32]

Drugs of abuse and many prescription medications can also potentially harm the unborn baby. For example, street drugs such as cocaine and methamphetamines can decrease placental blood flow, leading to intrauterine growth restriction, placental abruption, and preterm birth. Sedatives and opiates – both illicit as well as prescription -- can lead to severe newborn withdrawal symptoms. Other medications, especially some anticonvulsants, are well-known teratogens.[33,34,35,36]

Exposures to infectious agents including rubella, syphilis, cytomegalovirus, herpes simplex, toxoplasmosis, varicella, human immunodeficiency virus, malaria, group B streptococcus, and Zika virus can infect children prenatally and/or perinatally, causing congenital anomalies, neurological deficits, and other morbidities if not mortality.[37,38] The details of these adverse events are beyond the scope of this paper.

THE GOOD NEWS – The effects of prenatal stress on the child may be ameliorated by early intervention during pregnancy as well as postnatal parenting.

As Alhusen, et al, note, "Prenatal care presents a unique window of opportunity in which health care providers can foster trusting relationships with pregnant women, thereby increasing the likelihood of IPV detection and mitigating its related negative consequences to both mother and child." [22] The authors mention several possible interventions including prenatal screening, home visitation programs, and targeted psychobehavioral training.

The positive impact of sensitive, nurturing parenting will be addressed in a subsequent paper.

Conclusion

Toxic stress can begin in utero and can negatively affect the long-term physical and mental health of the child. However, research indicates that prenatal intervention as well as sensitive, nurturing parenting may ameliorate the effects of prenatal adversity. The College encourages health care professionals to consider this research when caring for pregnant women and infants to assure the best health outcomes for mothers and children – and ultimately for society.

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The American College of Pediatricians is a national association of licensed physicians and healthcare professionals who specialize in the care of infants, children, and adolescents. The mission of the College is to enable all children to reach their optimal physical and emotional health and well-being.

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