Fetal Programming: How Maternal Stress Impacts the Fetus

CONTENTS

> The layering effects of present stress upon past trauma such as ACEs only serve to magnify the enhanced activation of the stress management/ response system.

INTRODUCTION

A child's long term health and development is more profoundly shaped by influences in pregnancy than ever realized. Neuroscience substantiates the negative impact of stress across the life cycle beginning in utero. Prolonged elevation of stress hormones can alter the developing brain and central nervous system leading to abnormal development.[1] Given the increasing understanding of the impact of maternal stress on the fetus, efforts to promote mental health must begin in pregnancy.

From the point of conception, the fetus derives its nutrients, oxygen, internal and external homeostatic regulation from the placenta, and its physical safety from the maternal uterus. Consequently, the external environment and internal "well-being" of the mother have a direct impact on the developing fetus. Throughout pregnancy, fetal cellular and organ level growth and development occur at a rapid pace. Studies indicate that there are many factors which positively and negatively influence this process.

Greater understanding is emerging about maternal stress and its profound impact on the developing fetus. This type of stress "interweaves" itself into the fetus' genetic profile in the form of *fetal programming*.

FACTORS THAT CREATE MATERNAL STRESS

There are a number of prenatal factors and experiences that have been shown to have a direct effect on the mother and child both in the short and long term. The impact of early childhood stress, trauma, and other factors such as poor nutrition and environmental toxins on a person's lifelong health is well documented. Furthermore, when women experience these stress factors during pregnancy, the impact on the developing fetus can have deleterious effects on the lifelong health of the unborn child.

Environmental Stress Chronic poverty and economic hardship is associated with toxic stress. Compounding the stress of pregnancy with food insecurity, substandard housing, exposure to violence, and other environmental factors, can cause a chronic heightened stress response. Once initiated, the

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stress response produces abnormal levels of stress hormones, namely cortisol. When the stress hormones do not quickly equilibrate, the stress negatively affects both the mother and the fetus. The need for a woman to remain at a heightened sense of vigilance about basic needs such as housing, safety, and food access can either disrupt the stress response system or lead to chronically elevated stress hormones, which can be a physiologically toxic situation for the brain and body.

Substance Use As with environmental stress, it is well documented that maternal use of nicotine, alcohol, illicit, and some prescription drugs, can also have a major effect on fetal development and later increased risk for chronic diseases. The continued use of substances during pregnancy is often correlated with the mother's living situation and her attempt to alleviate the stress she is experiencing. It is important for obstetricians to know that maternal substance abuse, including smoking, rarely occurs in isolation of chronic stress and past adversity. Therefore, maternal substance abuse must be recognized and treated, but this should occur while appreciating the stress-related etiology.

Anxiety and Depression Maternal depression and anxiety affects as many as 1 in 5 women during pregnancy and have been shown to have both an independent effect on health risks in the children as well as an additive effect when combined with other forms of stress and substance abuse. Depression is known to disrupt the maternal HPA axis, which in turn may disrupt the development of the fetal HPA axis leading to an impaired ability to process and respond to stress, setting up a trajectory of poor development and health.

FETAL PROGRAMMING AND THE EFFECTS OF MATERNAL STRESS ON THE FETUS

What happens during fetal development in the maternal environment may be as important as genetic makeup in determining the health of an infant. Genes contain the full set of instructions that are fundamental to the life and survival of an individual. However, the external environment can leave an imprint on the genes directing which genetic instructions will be utilized.[2] One way to view the mechanisms for this imprinting is through the concept of fetal programming.

As reported in *Contemporary OB/GYN* (2013), the concept known as "fetal programming" has gained increased support through both human epidemiological studies and animal research.[3] Fetal programming occurs when utero conditions are altered by factors such as maternal nutrition, stress, or environmental toxins—all of which have the potential to alter organ structure or function. Although the actual genotype of the programmed infant does not change, modified gene expression may be a result of exposure-mediated epigenetic changes which can alter the expression of regulatory peptides and organ function.[4] It is these epigenetic mechanisms and fetal programming that can influence whether the fetus' genes are switched on or off (gene expression). It may be through epigenetic mechanisms that environmental factors like diet, stress, prenatal nutrition, or prenatal drug exposure leads to changes in gene expression from one cell to its daughter cells and, in some cases, from one generation to the next.[5] The significance of maternal physical health (body composition and diet) during pregnancy is profound.[6]

Poor nutrition is an example of a prenatal condition that can alter gene expression. If the mother has an inadequate diet, it signals the fetus that the future living conditions will be impoverished. As a result, the fetus adapts by changing its body size and metabolism to prepare for harsh conditions of food shortage after birth.[7] Should

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the environment prove to be as predicted, the infant/child is programmed for an improved ability to adapt to the conditions. However, if the environment is abundant with food, the child is placed at risk for later health conditions such as obesity, diabetes, and hypertension.[8]

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Epigenetic changes to fetal development can also result from maternal exposure to adverse experiences and stress.[9] Through epigenetics, stress can forge a direct path from the pregnant mother to the fetus, effecting modifications in genetic expression and ultimately establishing the foundation for adult chronic diseases. Fetal programming may explain the association between prenatal exposure to maternal stress and, altered fetal growth and development, influencing later pathophysiology. Adverse maternal experiences activate the stress system in the mother, through the Hypothalamic-Pituitary-Adrenal (HPA) axis. The stress-induced activation of the HPA axis passes through the placenta and can change placental function. This, in turn, can affect the HPA axis, or stress system, in the fetus.[10] These types of changes can increase the child's risk for later psychiatric, immune, inflammatory, cardiovascular, or metabolic disease. Changes in the fetal stress system that result from the maternal stress may make the infant predisposed to respond to stress poorly. Infants born with an altered stress system may have lifelong developmental and health problems such as poor academic achievement, substance abuse, mental health disorders, and other chronic medical conditions.[11]

In animal models, prenatal stress changes the way that glucocorticoids and sex hormones regulate neurogenesis in the developing brain. By modifying the fetal HPA axis, glucocorticoid receptors, pancreas, and renal system, stress in pregnancy can permanently disrupt the endocrine function in animal models creating a predisposition for diabetes, cardiovascular disease, and metabolic syndrome.[12] Changes in the "set points" for physiologic feedback loops (e.g. leptin, insulin, cortisol) alters the way individuals sense and respond in the future to dynamic changes in the environment. These changes have lifelong consequences.[13]

For example, in humans, there is compelling evidence that maternal stress in pregnancy can lead to Type 2 diabetes, hypertension, and metabolic syndrome in the child. The etiology of attention deficits, cognitive performance, anxiety, depression, autism, and schizophrenia is also thought to be related.

Thus, nutritional status, environmental toxins, and stress can have a profound impact on the development of the fetus and the child's later health status. This emerging information illustrates the need to monitor the expectant mother's exposure to serious stressors, be aware of past adverse experiences that could be a compounding factor and offer the necessary supports and interventions.

Screening for Stress

Women would benefit greatly from education early in the pregnancy about the biological effects of excessive stress to the unborn child and to the pregnancy.

Notably, the obstetrician is responsible for screening the mother and infant for numerous physical conditions and threats throughout the pregnancy. Included are screening questions for intimate partner violence and other immediate threats (stressors) to the mother's safety. Obstetricians should also consider routinely screening for trauma, depression, anxiety, substance abuse, and other sources of potential harm to the fetus.

> In the same manner in which the obstetrician understands the impact of maternal injuries, disease, and malnourishment, maternal stress should be viewed as a source of potential harm to the developing fetus.

Past experiences such as adverse childhood experiences can create higher vulnerabilities to stress for the expectant mother. Therefore, the obstetrician should also consider screening for prior adverse childhood experiences and exposure to trauma as well as current stressors. Screenings should be considered even when she appears to be functioning well. These prior events may not appear to play a direct role in the current pregnancy; however, lacking an awareness of past experiences may create a scenario of additional stressors.[14]

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The obstetrician could consider screening for stressors regularly and offering interventions and referrals as necessary. Although few screening tools directly address the pregnant patient within the OB practice, the following tools may be utilized:

- The ACE Questionnaire (Felitti et al)
- The Primary Care PTSD Screen
- The SPAN as a means to assess PTSD symptoms (Acronym for symptoms of Startle, Physiologic Arousal, Anger and emotional Numbness: Multihealth Systems Inc, North Tonawanda, NY).[15]

Women determined to be at risk based on screening should be referred for mental health or substance abuse services. Other community-based programs such as Healthy Families can help the mother prepare for motherhood. Self-care in the face of stress, including proper nutrition, sleep, exercise, and relaxation are also paramount to the health of the mother and child and should be encouraged.

THREE PRACTICES TO IMPLEMENT

1. Conduct screening and follow up assessment for all major sources of stress. The ACEs can be assessed along with brief, validated tools for detecting substance abuse, depression, and interpersonal violence.
2. Women at risk for any of these conditions, alone or in combination, should be flagged as a possible high-risk pregnancy and receive interventions to address her particular risk profile.
3. Refer women for treatment and / or help her to mobilize supports and resources to address any alterable risk factors.

CONCLUSION

Given the permanent effects of fetal programming, it is critical for obstetricians to pay close attention to trauma, depression, anxiety, malnutrition, and/or other behaviors during pregnancy as they have a direct effect on the physical health and well-being of the next generation.

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