Fetal Programming [1]

By: Keller, Carrie Keywords: fetal origins hypothesis [2] thrifty phenotypes hypothesis [3] fetal adaptations [4] anxiety during pregnancy [5]

Fetal programming, or prenatal programming, is a concept that suggests certain events occurring during critical points of pregnancy [6] may cause permanent effects on the fetus [7] and the infant long after birth. The concept of fetal programming stemmed from the fetal origins hypothesis, also known as Barker's hypothesis, that David Barker proposed in 1995 at the University of Southampton in Southampton, England. The fetal origins hypothesis states that undernutrition in the womb [8] during middle to late pregnancy [6] causes improper fetal growth, which in turn, causes a predisposition to certain diseases in adulthood. In addition to nutritional impacts, researchers have studied the effects of fetal programming on many factors, such as maternal anxiety or violence during pregnancy [6]. Researchers proposing the concept of fetal programming established a new area of research into the developmental causes of disease, pointing towards the *in utero* environment and its critical role in healthy human development.

While most traits are passed down from parents to offspring genetically, researchers studying fetal programming investigate the possibility that the development of disease later in life may be caused in part by environmental factors during pregnancy [6] rather than genetic processes. Generally, an individual inherits traits from her parents through the passing on of genes [9], or units of heredity coding for specific traits. That genetic process explains why offspring have similar traits as their parents and describes how most traits are determined. However, an individual's environment also plays a significant role in the development of traits, as the development of nearly all diseases are determined by the way that an individual's genetics and environment interact.

Environmental factors fall under the category of epigenetics [10], which is when genes [9] are expressed differently without any change to the DNA sequence itself. For example, the coloring of Siamese cats' fur is temperature-sensitive. Since a cat's paws, nose, and tail are generally a cooler temperature than the rest of its body, a Siamese cat with temperature-sensitive fur has darker fur in those areas. While all areas of the cat's body carry the same genes [9] for fur color, those areas are darker due to temperature differences throughout the body. Researchers studying fetal programming suggested that the development of diseases may be the result of similar factors, pointing toward environmental rather than genetic effects. Specifically, fetal programming researchers look at the *in utero* environment, which is where a fetus [7] grows and develops within a pregnant woman's uterus [11]. Since pregnancy [6] is a critical period of development for many behavioral and developmental processes, researchers studying fetal programming demonstrate the significance of that early environment and its potential effects on later development.

Before Barker defined the fetal origins hypothesis in 1995, scientists attributed the importance of the *in utero* environment on later development in other ways. For example, research on the effects of a stressful *in utero* environment said to have resulted from poor maternal emotional health surfaced in the 1960s and early 1970s. Then, in 1981, Thomas Verny, a medical specialist who studied the diagnosis and treatment of certain mental illnesses, published *The Secret Life of the Unborn Child*, in which he developed the idea that a stressful in utero environment could have lasting impacts on a fetus's psychological, emotional, and physical development. Around that time, some scientists contended that fetuses could feel, perceive, and react to their environments while in the womb [8], typically during the later stages of development. However, as of 2020, there was not a clear consensus on a fetus's capacity to experience those things in a profound way.

In 1989, in "Weight In Infancy and Death From Ischemic Heart Disease," Barker and colleagues provided support that environmental influences may affect growth and development during early life and cause predisposition to certain diseases later in life. Specifically, Barker and colleagues looked at the correlation between birthweight and the eventual development of ischemic heart disease, a condition where not enough blood and oxygen reach the heart. In the article, the authors reported on an experiment during which they kept track of birthweights, weight at one year postpartum, and death by ischemic heart disease for nearly 6000 men throughout Hertfordshire, England. They stated that they recorded data only from men because men are more likely to die from ischemic heart disease and are more easily traceable since their last names do not change. They reported that the men who had had the lowest birth weights and lowest weights at one year postpartum experienced the highest death rates from ischemic heart disease.

However, in the same study, the authors pointed out that the known causes of ischemic heart disease at the time did not explain why the prevalence of the disease was highest among the lowest income groups throughout England. Since Barker and colleagues contended the lowest income groups would be less likely to afford proper nutrition for their growing offspring, they looked towards developmental and early growth delays as a cause for ischemic heart disease. Building on those findings, in 1990 Barker published another article further advancing the concept of fetal programming, titled "The Fetal and Infant Origins of Adult Disease." There, he noted that areas throughout England with high rates of infant mortality also had low neonatal birth weights and poorer overall health among pregnant women. Based on that finding, he suggested that the *in utero* environment was important to look at when studying the origins of disease.

In 1992, in their paper "Type 2 Diabetes Mellitus: The Thrifty Phenotype Hypothesis," Barker and Nicholas Hales furthered the concept of fetal programing with the thrifty phenotype hypothesis. The thrifty phenotype hypothesis states that reduced fetal growth in the womb [8] is strongly associated with the development of a number of chronic conditions later in life. At the time, Hales worked at Cambridge University [12] in Cambridge, England, studying diabetes. Together, Barker and Hales studied the potential relationship between the causes and effects of type 2 diabetes and poor fetal and early postnatal nutrition. Type 2 diabetes is a chronic condition that inhibits the body from metabolizing sugar properly due to either resistance to or a lack of insulin, which is a hormone [13] that regulates the movement of sugar as a source of energy into cells. Since most cells that produce insulin later in life are produced during gestation [14], Hales and Barker hypothesized that fetal undernutrition in utero could be related to the development of type 2 diabetes. Thus, they pointed towards fetal origins for the development of the disease.

In 1995, Barker directly proposed the fetal origins hypothesis in "Fetal Origins of Coronary Heart Disease." Many researchers who have since studied fetal programming cite that specific paper outlining Barker's hypothesis. At the time of the paper's publication, animal studies had shown fetal undernutrition during pregnancy [6] to cause permanent biological changes for those animals after birth and later in life. Also at that time, as described in Barker's 1989 article, studies in humans [15] had shown that individuals with lower birth weights were more likely to develop certain diseases later in life, particularly heart disease. In addition, eventual heart disease diagnoses were more common among fetuses that were abnormally small in comparison to the placenta [16], which is an organ developed during pregnancy [6] in the womb [8] that helps nourish the fetus [7]. In conjunction with the animal studies revealing the permanent effects of fetal programming, those human associations gave rise to Barker's hypothesis.

In 2001, Barker and Keith Godfrey expanded on the ideas outlined in Barker's previous articles with "Fetal Programming and Adult Health," in which they attempted to describe the processes underlying fetal programming. In the article, the authors stated that fetal programming may be the result of fetal adaptation to the *in utero* environment, particularly maternal nutrition. However, while the biological adaptations made in response to the stressful in utero

environment may have been useful in the womb [8], their permanent effects on the fetus [7] may cause predisposition to disease later in life. For example, Barker and Godfrey described a potential mechanism explaining the association between low birth weights and the later development of hypertension, or abnormally high blood pressure. They explained that a low birthweight, which they theorized was caused by undernutrition in the womb [8], may cause a child to grow at an accelerated rate later in childhood in an effort to theoretically catch up with peers. Since blood pressure rises with age and growth, the authors propose that the accelerated growth spurt could potentially cause elevated blood pressure throughout the individual's life. Through that process, low birthweight would program for hypertension.

Many researchers have further studied the effects of fetal programming and attempted to identify the exact mechanisms underlying the process. For example, in 2009, researchers led by John Henderson at the University of Bristol in Bristol, England, reported an association between maternal anxiety during pregnancy [6] and the later development of asthma in their offspring. In 2011, other researchers led by Sarah McMahon at Rutgers University in New Brunswick, New Jersey, studied the effects of violence during pregnancy [6] on childhood development. The authors proposed that, when exposed to violence *in utero*, the offspring had poorer overall health, more difficult temperament, and increased likelihood of depression.

Other researchers have proposed mechanisms describing how fetal programming works. For example, researchers Amanda Drake and Brian Walker from the University of Edinburgh [17] in Edinburgh, Scotland, described the process of fetal programming as a cycle that persists throughout generations due to a persisting stressful *in utero* environment caused by the permanently programed effects. Another researcher working at the Imperial College in London, England, Vivette Glover, described fetal programming as evolutionary and stated that its effects may have actually been useful in primitive times. She asserts that that is because the stressful in utero environment may have served to prepare the fetus [7] for the environment in which the fetus [7] would be born. For example, she claimed that the development of anxiety, which is increased by exposure to prenatal stress, may have been useful for sensing and avoiding threats during primitive times, making fetal programming evolutionarily advantageous.

Nonetheless, according to researcher David A. Leon, some scientists were initially skeptical of some of the first fetal programming hypotheses, but researchers have progressively expanded and supported those hypotheses through both animal and human studies. Some scientists have argued that in studying the lifelong effects of fetal programming, researchers should consider postnatal factors as well, such as events that occur during early childhood. Other scientists have stressed that while some researchers have thoroughly established associations between low birth weight and the development of chronic diseases, it remains unknown if those relationships are causal. Those scientists state that too little is known about the role of maternal nutrition during pregnancy [6] to suggest fetal programming interventions. However, as of 2020, researchers have shown that events occurring during pregnancy [6] may have significant effects for lifelong health and provided insights into the mechanisms involved. Economists have even endorsed and provided further evidence for the fetal origins hypothesis, studying fetal programming effects related to education level and income.

The concept of fetal programing has established an entirely new area of research into the developmental causes of disease. The resulting fetal programming research has revealed the significance of the *in utero* environment and the lasting health effects that events occurring during pregnancy [6] may have on a developing fetus [7]. By indicating those factors in the study of disease development, the concept of fetal programming has encouraged research on preventative programming practices to promote healthier pregnancies and children.

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