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Nutrition and Stress and the Developing Fetus

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KEY POINTS

- Prenatal maternal nutrition and maternal stress have a major impact on the growth and development of the fetus.
- Specific macro- and micronutrient deficits impact on the normal growth and development of the fetus.
- Prenatal maternal nutrition and maternal stress have an impact on intrauterine growth and development, postnatal infant medical outcome, infant and child neurobehavioral and cognitive development, and programs for adult cardiac, metabolic and mental health function.
- The effect of prenatal maternal nutrition and maternal stress on the fetus may be explained, to a degree, by common underlying mechanisms.
- Disturbances in both the adult and fetal hypothalamic–pituitary–adrenal axis result from maternal nutritional deficits and stress.

1. INTRODUCTION

The most dramatic events in the growth and development of an infant occur before birth and result from the dynamic interplay of the fetus’s genetic potential and appropriate environmental stimuli, a process termed epigenetics (Kelly & Trasler, 2004). While this process may be viewed as a progressive unfolding and continuum, it now recognized that fetal life is characterized by “critical” or “sensitive” periods wherein exposure to specific environmental stimuli is required for the normal sequence of development of both anatomical structures and their subsequent functioning. Thus, the previously held concept that the fetus is safe from the vagaries of the maternal state and is functionally the equivalent of an obligatory parasite is no longer tenable. In particular, it is clear that the nutritional state of the mother, both quantitatively and qualitatively, has a major effect on fetal growth and development. This is best exemplified by the now understood role of folic acid in the development of the neural tube. Mothers who delivered infants with defects such as anencephaly and spina bifida were noted to have lower serum levels of folic acid. Conversely, women who took supplementary folic acid at the time of conception through the first trimester were substantially less likely, as compared to women who
did not take folic acid, to deliver a fetus with neural tube defects. The protective advantage of supplementary folic acid was even more dramatic in those mothers who had already delivered an infant with a neural tube defect. Such results clearly confirm the critical importance of timing and the interplay with genetic predisposition when discussing nutritional factors as related to development (American Academy of Pediatrics Committee on Genetics, 1999; Czeizel & Dudas, 1992).

No less important are the recent observations that the environment of the developing fetus during these sensitive periods of development may also “program” for ultimate function, way beyond infancy. The concept that in utero environmental factors act early in fetal life and can permanently imprint physiological systems is known as prenatal programming. The concern is that if at critical windows of time during intrauterine existence there is an absence of the proper stimulus or the presence of an adverse stimulus, individual tissues and/or whole organ systems can be inappropriately programmed with deleterious consequences for later life.

The biological purpose of early life programming is not known. The present understanding is that the prenatal plasticity of the physiological systems allows for the organism to tolerate a less than ideal intrauterine environment wherein suboptimal maternal nutrition, stress, and/or disease exists. This is accomplished by altering the setpoint of the organ systems and/or its tissue functions. Resetting, perhaps better termed downregulating, various biochemical or physiological processes in turn increases the offspring’s chance for survival under these adverse conditions. However, this survival advantage is at the price of a subsequent postnatal functional disadvantage in the now more optimal extrauterine environment (Lucas, 1998; Singhal, Wells, Cole, Fewtrell, & Lucas, 2003).

Human epidemiological and experimental animal studies have tested the nutritional programming hypothesis, and the consensus is that humans, like other species, have sensitive periods for nutrition in relation to later outcomes (Lucas, 1998). For example, impaired intrauterine growth caused by maternal suboptimal nutrition or placental insufficiency has been found to be associated with an increase incidence of cardiovascular and endocrine disease in adulthood (Barker, 1998). The fetal programming hypothesis has been tested experimentally in a number of species using a variety of techniques to impair fetal growth. The range and types of reported postnatal physiological disorders in these experimental animal models were similar to those seen in human populations. Several structural and functional mechanisms underlying these associations have been suggested, such as disproportionately large reductions in the growth of some fetal organs and tissues, impaired cellular development, or deficiency of and/or impaired hormonal regulation (Barker, 1998; Fowden & Forhead, 2004). Of particular interest are the experimental studies of intrauterine growth retardation (IUGR) that have demonstrated a reduction in cerebral cellularity and dendritic branching, particularly in the hippocampus and dentate gyrus (Mallard, Rees, Stringer, Cock, & Harding, 1998; Rees & Harding, 1988).

One of the most interesting findings of these animal models of induced IUGR is an altered functioning of the adult and fetal hypothalamic–pituitary–adrenal (HPA) axis (Economides, Nicolaides, & Campbell, 1991; Goland et al., 1993). Normally this axis mediates the release of glucocorticoids in response to diurnal cues and stress. Glucocorticoids, in turn, regulate their own secretion by negative feedback to the hypothalamus and the pituitary, inhibiting the synthesis and/or release of corticotropin-releasing hormone (CRH), arginine, vasopressin, and adrenocorticotropic hormone (ACTH), thus