The vulnerable developing brain

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During healthy pregnancy, appropriate levels of fetal nutrition and oxygenation are indispensable for the optimal growth and development of the fetal organs. In pregnancy complicated by decreased nutrient and oxygen delivery to the fetus, current dogma is that the growth and development of key organs, such as the brain, are "spared" at the expense of nonessential organs served by peripheral vascular beds, for instance the kidneys, pancreas, and skeletal muscle. The article by Antonow-Schlorke et al. in PNAS (1) challenges this concept and shows that the developing brain is more vulnerable than previously thought, even to moderate reductions in maternal nutrition during early pregnancy. The study is particularly relevant because it was undertaken in nonhuman primates rather than in rodents. In contrast to primates, including the human, in rodent species many stages of brain development continue to occur after birth.

The concept of fetal brain sparing in adverse pregnancy is based on overwhelming evidence obtained from epidemiological studies in humans and experimental studies in animals, which have revealed that malnourished or hypoxic pregnancy yields disproportionately growth-retarded offspring (2, 3). The "thrifty phenotype" baby has an increased head diameter to body length or weight ratio, with a reduced ponderal index, being thin for its length. In experimental animals, asymmetric intrauterine growth restriction is also represented by increased fetal brain weight relative to body weight or an increase in the fetal brain to liver weight ratio (4, 5).

The Physiology of the "Fetal Brain Sparing" Response

The physiology underlying the fetal brain-sparing effect in hypoxic pregnancy is well established and involves neural reflexes triggered by the carotid body and endocrine and local factors in the fetus, which ultimately constrict peripheral circulations and dilate essential vascular beds (6). Consequently, the fetal cardiac output is redistributed, shunting blood flow away from peripheral and toward essential vascular beds, such as those perfusing the brain. The fetal brain-sparing effect in hypoxic pregnancy is so innate that it is conserved across all species studied to date, from the reptilian and avian embryo to the mammalian fetus, including sheep and nonhuman and human primate.

In contrast to hypoxic pregnancy, the physiology promoting the thrifty fetal phenotype in undernourished pregnancy is less certain, although there are increasing reports suggesting that hypoglycemia may also be a powerful stimulus eliciting redistribution of blood flow in the fetus. For instance, an increase in basal femoral vascular resistance has been reported both in hypoglycemic (7) and undernourished (8) ovine pregnancies. In addition, it is known that the carotid body is sensitive to hypoglycemia (9), and studies have postulated a possible role for a carotid body-mediated reflex in the hemodynamic response to undernutrition in fetal sheep (10). It is also becoming increasingly apparent that changes in maternal body composition and diet not only affect fetal growth and development as a result of direct effects on substrate availability to the fetus, but also indirectly through changes in placental growth and function. Maternal undernutrition in experimental animals and human pregnancy has been associated with reduced placental size and reduced blood flow in uterine and umbilical circulation (11, 12). Therefore, a component of the asymmetric fetal growth restriction in undernourished pregnancy in humans and animals is due to a reduction in oxygen as well as nutrient delivery to the fetus.

Undernutrition in early pregnancy may render the immature fetal brain particularly susceptible to developmental problems.

Whichever the mechanisms mediating the fetal brain-sparing response to adverse pregnancy, what is abundantly clear is that these pathways must be mature enough to mediate the compensatory cardiovascular responses. For instance, it is known that the fetal chemoreflex and endocrine response to hypoxia mature in the last third of gestation, in parallel with the prepartum surge in fetal plasma cortisol (13). Consequently, exposure of the preterm fetus to synthetic glucocorticoid matures the brain-sparing response to term levels (14). Therefore, if the physiology underlying the fetal brain-sparing response to adverse challenges in pregnancy only matures toward the end of gestation, which mechanisms protect the developing brain from adverse challenges in early pregnancy? Although it is known that the immature fetal brain is more tolerant to hypoxia than the mature fetal brain (15), undernutrition in early pregnancy may render the immature fetal brain particularly susceptible to developmental problems.

Maternal Undernutrition and the Primate Fetal Brain

Antonow-Schlorke et al. report that moderate maternal undernutrition in early pregnancy in the baboon led to major disturbances in the architecture of the fetal subventricular zone, a major area for the birth of nerve cells before they migrate out to their final locations within the brain. This occurred in conjunction with delayed maturation of the brain cortical neuronal network. Mechanisms evaluated included neurotrophic factor suppression, cell proliferation and cell death imbalance, impaired glial maturation and neuronal process formation, down-regulation of gene ontological pathways, and up-regulated transcription of cerebral catabolism. Additional mechanisms mediating the effects of maternal undernutrition on fetal brain development may be secondary to well-known detrimental effects of excess glucocorticoid exposure on the developing central nervous system (16). The same group of investigators has reported that a similar level of maternal undernutrition led to significant elevations in circulating glucocorticoids in the baboon fetus (17).

Long-Term Consequences

These results are also important in the context of developmental programming of health and disease. This concept explains how adverse environmental influences during pregnancy, in particular fetal undernutrition, fetal hypoxia, and inappropriate glucocorticoid exposure, not only affect the growth and development of organs in the fetus but also lifelong susceptibility to diseases. Abundant evidence has linked the fetal thrifty phenotype with insulin resistance and indices of cardiovascular disease in adult life (18, 19). What has been comparatively ignored is the contribution of adverse conditions during

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See companion article on page 3011.

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pregnancy, such as moderate maternal undernutrition during early pregnancy, on the developmental programming of neurodegenerative diseases. Of related interest is a study that has linked inappropriate maternal nutrition with cognitive impairment in children (20) and preliminary reports associating adverse pregnancy with an increased prevalence of depression and schizophrenia in later life (21).

Reduction in nutrient delivery to the fetus is not only a problem of malnutrition during pregnancy in developing countries but also a consequence of maternal dieting, teenage pregnancy, or impaired placental perfusion in complicated pregnancies in developed societies. The study by Antonow-Schlorke et al. makes it clear that nutrient restriction during pregnancy should be avoided at all costs because the challenge has important consequences for the appropriate growth and development of the brain and implications for fetal programming of cognitive, behavioral, and neurophysiological deficits in later life. The study highlights a clear and growing need to investigate the impact of adverse intrauterine conditions, such as reductions in nutrient and oxygen delivery to the fetus, on the developmental programming of neurodegenerative diseases. Such studies should concentrate on providing insight into mechanisms underlying the association in order to identify plausible clinical intervention.

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