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Perinatal Programming of Obesity

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Introduction

Obesity is a growing threat worldwide, and the prevalence has risen dramatically over the last decade. Several studies have shown that early life exposures are important in promoting adult obesity (1–3). There are a number of critical periods during childhood that appear to influence the later development of obesity, that is the prenatal period, the adiposity rebound period around 5–7 years of age, and puberty (3). The period from conception to birth is a time of rapid growth, cellular replication and differentiation, and functional maturation of organ systems. These processes are very sensitive to alterations of the nutritional milieu. Programming describes the mechanisms whereby a stimulus or insult at a critical period of development has lasting or lifelong effects. This review summarizes both human and animal studies relating fetal exposures to later obesity.

Association between birth weight and later obesity

A number of epidemiological studies have shown that there is a direct relationship between birth weight and BMI in childhood and in adult life (4,5). In the U.S. Growing Up Today Study, a cohort study of over 14,000 adolescents, a 1-kg increment in birth weight in full term infants was associated with an approximately 50% increase in the risk of overweight at ages 9–14 year (6). When adjusted for maternal BMI, the increase in risk remained significantly elevated at 30%. A study of Danish military conscripts showed that even after controlling for birth length and maternal factors, BMI at ages 18–26 strongly correlated with birth weight (4). Both paternal and maternal adiposity are correlated with a higher birth weight of the offspring. However, the association is much stronger for the mother compared to the father (5, 7) suggesting that the intrauterine environment plays an important role in the later development of obesity.

Studies done in identical twins are conflicting. Allison et al. found that the correlation of intra-pair differences in birth weight with intra-pair differences in adult height were highly significant but were not correlated with adult BMI (8). These data suggest that the intra-uterine environmental influences on birth weight have a long lasting impact on adult height but not on adult relative weight. In contrast, in a study of female monozygotic twins, Loos et al found that a higher birth weight was positively correlated with adult BMI. Pairwise comparison showed that for every level of intrapair birth weight difference, the twin who was heavier at birth was taller and slightly heavier in adult life. When the birth weight

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difference between the twins exceeded 15%, the heavier twin had a higher BMI as an adult than the lighter twin (9).

While it is apparent from these studies that higher birth weight confers some additional risk for the later development of obesity, the mechanisms underlying this phenomenon are unclear. It is clear that a number of factors influence the development of childhood and adult obesity and birth weight as a proxy for the intrauterine environment may be one of the many. Carefully designed large longitudinal studies need to be performed.

Diabetes in Pregnancy

Substrate availability has profound effects on fetal hormones and on the hormonal and metabolic interactions between the fetus, placenta and mother. This is most apparent in the fetus of the mother with diabetes. Increased maternal concentrations of glucose and amino acids stimulate the fetal pancreas to secrete exaggerated amounts of insulin, and the fetal liver to produce higher levels of IGF's. Fetal hyperinsulinism stimulates the growth of fetal adipose tissue and of other insulin-responsive tissues, often leading to macrosomia. Thus, offspring of mothers with gestational diabetes often have higher birth weights and fat mass is increased relative to lean body mass (10). Infants of women with gestational diabetes mellitus, even when they are average weight for gestational age, have increased body fat compared with infants of women with normal glucose tolerance (10). This relative increase in adiposity predisposes the offspring of a diabetic pregnancy to the later development of obesity. A number of investigators have reported a significant increase in the rates of obesity in children, adolescents, and adults whose mothers had diabetes during pregnancy (6, 11–14). In those studies that controlled for maternal pre-pregnancy or pregnancy weight and BMI, the association between exposure to diabetes in pregnancy and later development of obesity remained significant, but was less robust (6, 13, 14). In a population of 324 children from Caucasian women with GDM, Schaefer-Graf et al. demonstrated that these children had consistently increased BMI at various time points up to 8 years of age compared with the average German population. Independent predictors of the children’s BMI were BMI at birth (or the fetal abdominal circumference), recent maternal BMI, and recent paternal BMI. Infants from GDM pregnancies born with normal weight still had a rate of 67% childhood overweight when both parents were obese in contrast to 19% overweight children when both parents had a BMI <30 kg/m2. (15).

In addition to increased adiposity at birth, altered appetite control may also play a role in the development of obesity in infants of diabetic mothers. Animal studies by Plagemann et al have shown that offspring of streptozotocin (STZ)-diabetic mother rats, a well-known animal model for insulin-deficient diabetes in pregnancy, display hyperphagia and overweight during later life. This was found to be associated with alterations of hypothalamic neurons expressing orexigenic neuropeptides such as neuropeptide Y (NPY) in the arcuate hypothalamic nucleus (ARC) (16).

In the human infant, birth weight and infant adiposity is positively correlated with leptin levels. Both cord blood and plasma concentrations are increased in infants of diabetic mothers (17, 18). In a study of a cohort consisting of 64 mothers, 33 GDM and 31 controls together with their 9-year-old offspring, an elevated child leptin was highly correlated with elevated maternal leptin only in GDM mothers (19). It is conceivable that programming of leptin regulatory pathways may be another causal mechanism linking obesity to exposure to diabetes in pregnancy.

Low Birth weight and Central Adiposity

A large number of studies have linked low birth weight to the later development of central adiposity (20–26). The landmark cohort study of 300,000 men by Ravelli and colleagues showed that exposure to the Dutch famine of 1944–45 during the first half of pregnancy resulted in low birth weight and was associated with significantly higher obesity rates at age 19 (22). Subsequent studies have demonstrated a relationship between low birth weight and the later development of the metabolic syndrome in populations through out the world (23–26). The associations with low birth weight and increased risk of coronary heart disease, stroke, and type 2 diabetes remain strong even after adjusting for lifestyle factors such as smoking, physical activity, occupation, income, dietary habits, and childhood socio-economic status (26).

The mechanisms underlying the association between low birth weight and the later development of obesity are unclear. Maternal malnutrition in the rat during pregnancy and lactation results in fetal growth retardation. In some studies, offspring develop insulin resistance, glucose intolerance, and obesity (27). These animals have increased adipocyte sensitivity to insulin that is accompanied by increased levels of insulin receptors in adipocytes (27). Increased food intake has also been shown to occur in offspring of maternal rats fed a hypocaloric diet during pregnancy (28).

A key adaptation enabling the fetus to survive in a limited energy environment may be the reprogramming of mitochondrial function. However, these alterations in mitochondrial function can have deleterious effects, especially if nutritional abundance is superimposed on the background of intrauterine growth retardation. Reduced oxidative enzyme activity in muscle, including smaller mitochondria and reduced electron transport chain (ETC) activity, has been found in obese men and women (29). Lower oxidative capacity has also been related to risk for weight gain (30).

We have developed a model of uteroplacental insufficiency (IUGR) in the rat that induces fetal growth retardation and eventually leads to the development of diabetes and obesity in the offspring (31). Intrauterine growth retardation is induced by bilateral uterine artery ligation during the latter third of gestation. Offspring are stunted at birth, however fat mass is increased as early as 2 weeks of life. These animals are also hyperphagic in the juvenile period which is accompanied by increased hypothalamic NPY levels (32). Energy expenditure is decreased and is associated with altered mitochondrial function (33–35). IUGR animals exhibit marked insulin resistance early in life (prior to the onset of hyperglycemia), characterized by blunted whole body glucose disposal in response to insulin and impaired insulin suppression of hepatic glucose output (36). Basal hepatic glucose production is also increased (36). Oxidation rates of pyruvate, glutamate, succinate, and α-ketoglutarate are significantly blunted in isolated hepatic mitochondria from IUGR pups (prior to the onset of diabetes) (33). Mitochondria in muscle of IUGR young adult rats, prior to the onset of hyperglycemia, exhibit significantly decreased rates of state 3 oxygen consumption with pyruvate, glutamate, α-ketoglutarate and succinate (35). Decreased pyruvate oxidation in IUGR mitochondria is associated with decreased ATP production, decreased pyruvate dehydrogenase activity and increased expression of pyruvate dehydrogenase kinase 4 (PDK4). Such a defect in IUGR mitochondria leads to a chronic reduction in the supply of ATP available from oxidative phosphorylation. Impaired ATP synthesis in muscle compromises energy-dependent GLUT4 recruitment to the cell surface, glucose transport and glycogen synthesis, which contributes to insulin resistance and hyperglycemia of type 2 diabetes (35).

We hypothesize that the relative energy deprivation caused by uteroplacental insufficiency programs the balance between energy intake and energy utilization resulting in the development of obesity.

In conclusion, a number of human and animal studies demonstrate that the intrauterine environment plays a critical role in programming body composition. Both excess and reduced nutrient availability during fetal development can lead to the later development of obesity. It will be critically important to determine how interventions can prevent the vicious cycle of obesity and its consequences.

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