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Malnutrition: an antecedent of diabetes?

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INTRODUCTION

Almost 25 years ago, Barker and associates published their first reports regarding the association between reduced fetal growth and a number of conditions occurring later in life. Notably, these investigators looked at the relationships between infant birth weight and future ischemic heart disease[1–3]. Two disparate observations led to the creation of the 'Barker hypothesis': first, the relationship between neonatal mortality and low birth weight; and second, the higher rates of mortality from heart disease in economically disadvantaged areas compared to more prosperous regions. At the basis of Barker's theory lies the assumption that malnourishment during intrauterine life can cause a series of adaptive changes in the fetus and the placenta, changes which bring about new metabolic regulation that becomes apparent in adult life.

Later, Barker and Hales put forward the 'thrifty phenotype' theory[4] concerning the association between low birth weight and the development of type 2 diabetes. This theory connects poor fetal and early life nutrition and growth (which causes irreversible changes in insulin and glucose metabolism – namely reduced insulin secretion and increased insulin resistance), with adult life obesity and physical inactivity, to explain the increased risk for type 2 diabetes. At the beginning of the 21st century, Bateson and Barker published their 'developmental plasticity theory'[5]. This theory presumes that the fetus responds to the nutritional condition of the mother as an adaptive mechanism preparing it to best fit environmental conditions later in life. When these environmental conditions change rapidly, the fetus who later becomes an adult is exposed to a different environment than the one he or she experienced *in utero*. This early preconditioning may become harmful or have a damaging effect on the specific risk to develop a specific disease(s).

The preceding commentary, although exceedingly brief, opens the discussion of a topic which is currently of great interest within the medical profession, that is, the epidemiological association between the intrauterine environment and adult onset diseases. The multiple theories that have been set forth to explain this improbable relationship all aim to explain how different phenotypes can be achieved with a given genotype. The integrated discipline trying to weld all of these theories together to form a new specialty is currently known as developmental origins of health and disease (DOHaD), and this chapter is written from this perspective.

IS BIRTH WEIGHT A RELIABLE INDICATOR FOR FETAL NUTRITIONAL STATUS?

Low birth weight obviously may serve as an indicator of a disrupted intrauterine environment. The growing fetus clearly is dependent upon a complex fetomaternal interaction. This

sophisticated interface relies on several components: maternal nutritional intake, uterine blood supply and placental transfer mechanisms, all of which depend on the maternal metabolic and cardiovascular condition.

If maternal nutrient supply is inadequate for fetal requirements, the fetus reacts by redirecting blood flow to the brain, adrenal gland and heart at the expense of other tissues, as well as by changing the secretion of several hormones such as insulin-like growth factor 1 (IGF-1), leptin, insulin and stress hormones[6,7]. The fetus may also redirect resources from tissues like muscle or bones towards the accumulation of fatty tissue. This may affect fetal body composition in a myriad of ways, some of them unexpected. For instance, fingertip ridge count (in particular that of the 5th finger) is low in those whose prenatal life may have been suboptimal as a result of the Dutch famine during World War II or who were exposed to the Dutch famine during prenatal life. This finding is now thought to be an indicator of the risk for diabetes in adulthood[8].

It is important to note that although birth weight is an easily measured variable and is readily available when conducting epidemiological studies, it is not a true diagnostic marker of maternal nutrition but rather an indirect indicator. Moreover, several other determinants also influencing birth weight are not related to the nutritional status of the mother, such as fetal gender or ethnic background. Furthermore, birth weight is an insensitive indicator of the timing, extent and duration of exposure to nutritional deprivation. Some randomized controlled studies even fail to find a significant effect of maternal dietary supplements (protein or caloric) on birth weight[9], whereas others demonstrate only a mild effect[10]. Under these circumstances, birth weight should be viewed as an insensitive substitute for other, more accurate, anthropomorphic (abdominal, head circumference, etc.) or metabolic variables which are currently unavailable in retrospective and epidemiologic studies.

EVIDENCE FOR FETAL PROGRAMMING

The pivotal role of the maternal nutritional condition on intrauterine growth and development as well as on perinatal mortality has been recognized for decades and thoroughly investigated, as noted above. The Dutch famine studies (referring to the famine occurring during the winter of 1944–45 while World War II consumed Europe) described the association between maternal malnutrition (mainly during first and second trimester of pregnancy) and low birth weight[11]. These studies also demonstrated congruity between low birth weight and the occurrence of cardiovascular morbidity and mortality later on[12].

Barker[13] first described the relationship between infants with low birth weight and risk of cardiovascular and metabolic diseases (diabetes and osteoporosis) in adult life. This relationship strongly implies that maternal malnutrition is related to longstanding or even permanent changes in the phenotype of the offspring, since such changes would of necessity have to occur during critical periods of early development. This process is currently referred to as fetal programming.

Recent studies indicate that the deprivation of certain elements, such as vitamin B12 and folate[14,15] may be associated with increased adiposity and insulin resistance in offspring. In a similar sense, over-exposure to harmful substances such as cigarettes, nicotine and alcohol, as well as intrauterine stress, may also cause fetal growth restriction and thus may influence prenatal and childhood outcome. The Pune Maternal Nutrition Study (PMNS)[14,15] was a prospective observational study conducted near Pune, India. The mean birth weight of about 700 infants included in the cohort study was only 2.7 kg, and although the newborns were extremely short and thin,

the babies were relatively adipose. The Indian babies were small in all body measurements, the smallest being abdominal circumference (standard deviation (SD) score −2.38, 95% CI −2.48 to −2.29) and mid-arm circumference (SD −1.82, 95% CI −1.89 to −1.75), while the most preserved measurement was the subscapular skinfold thickness (SD −0.53, 95% CI −0.61 to −0.46). This indicates that small Indian babies have small abdominal viscera and low muscle mass, but preserve body fat[15].

It has also been shown that maternal plasma levels of several nutrients and fuel materials (glucose, cholesterol and triglycerides) correlated with neonatal birth size and adiposity, and that low maternal intake of B12 but high folate correlated with insulin resistance in the offspring[14]. These data all demonstrate that adaptive changes are possible in the fetus during nutritional deficit – redirecting resources towards accumulation of fatty tissue which may provide fuel for brain growth and/or immune function. Such findings highlight the fact that birth weight provides only a crude summary of fetal growth and fails to describe potentially important differences in the development of specific tissues.

EPIGENETIC PROCESSES

The embryo inherits a given set of genes from both parents. It draws upon its genetic milieu for continued development and growth. However, the intrauterine environment in which the embryo/fetus develops is much more than a mere receptacle that contains the fetus until it has sufficiently developed for independent life. It is an interactive vessel that may dictate the expression of the genes, and may create permanent changes in their function and therefore alter the development of the fetus' bodily systems[6,7]. Epigenetics is 'the study of heritable changes other than those in the DNA sequence'[16] – or in other words, epigenetics studies the process by which a given genotype evolves into specific individual phenotypes. This should be distinguished from changes occurring to the DNA sequence such as mutations or polymorphisms which are genetic in nature.

After establishing the epidemiologic relationship between maternal malnutrition and later risk for cardiovascular and metabolic morbidity in offspring, one should try to look into the assumed mechanism by which this change occurs. There are several suggested methods by which genes are modified in the epigenetic process: DNA methylation, histone modification (acetylation) and microRNAs. These epigenetic mechanisms may help to illustrate how cell differentiation (i.e. how cells with the same genotype differentiate into different tissues) occurs.

Methylation of cytosine in the promotor region of a gene causes silencing of gene expression. Folate and B12 are important methyl donors. Animal models have demonstrated that maternal diet during pregnancy may influence the degree of methylation of specific fetal genes[17,18], affecting fetal and placental development. An experimental mouse model[17,19] showed that when pregnant mice were fed with a diet supplemented with methyl donors there was an increase in the coat-color gene methylation, and that a soy-rich diet caused increased methylation and reduced obesity in offspring. This means that the offspring, although sharing the same coat-color genes as its parents, had a distinctively different phenotype than its ancestors. There is some indication from plants that epigenetic changes can also be passed between generations of a species[20].

The growing fetus shows a remarkable ability to assume different sizes and discrete functional abilities within a given genotype. This trait has been referred to as 'developmental plasticity'[5]. It has been suggested that fetal programming limits the fetus's developmental plasticity and suppresses its ability to adapt effectively to the changing environment[21].

A more detailed and accurate understanding of the mechanism, by which maternal malnutrition influences fetal intrauterine growth, can be extracted from experimental and animal studies. Such suggested mechanisms include:

1. Simple growth failure: a reduction in size and number of cells in specific tissues, for example, a reduction in pancreatic beta cell mass or in the number of renal nephrons.
2. Alteration in endocrine settings: up-regulation of the hypothalamo–pituitary–adrenal (HPA) 'stress' axis and changed secretion and sensitivity to insulin and IGF-1.
3. Changes in the expression and regulation of DNA.

Intrauterine growth restriction (IUGR) is the end result of many conditions which influence the intrauterine and genetic environment inflicted upon the embryo/fetus. It is beyond the scope of this discussion to encompass the full range of the various maternal manipulations leading to IUGR in the offspring. It is sufficient to state that fetal growth and development depends upon an intricate relationship between maternal supply of nutrients and fetal-placental uptake. Animal models show that fetal growth can be restricted by reducing maternal caloric and protein uptake during pregnancy[22]. This effect has also been demonstrated in humans – mainly in the so called 'Famine studies'[23]. This effect is partly explained by simple deficiency of 'building materials', such as the observed low bone mineral content in children whose mothers suffered from low calcium intake during pregnancy[24], but it is clear that more subtle aspects of this issue await future investigation.

THE ASSOCIATION BETWEEN NUTRITION, MALNUTRITION AND DIABETES

The relationship between IUGR and diabetes or metabolic syndrome is much more complex. Intrauterine exposure to IUGR may be responsible for changes in fat distribution as described in the PMNS[14,15]. Later life obesity is potentiated by alterations in appetite regulation, and by increased adipogenesis. In a similar fashion, hypertension is made more likely by alterations in renal and blood vessel development, while diabetes is associated with alterations in cellular insulin signaling and decreased beta cell function. IUGR is associated with both anatomic changes in the pancreatic islets and with changes in intracellular insulin signaling pathways. The end result of these alterations is a decrease in the individual's capacity to secrete insulin, while at the same time there is an increasing demand for insulin leading to an increased likelihood of frank glucose intolerance[25].

These combined programmatic alterations induce the full metabolic syndrome in the adult. Fetal growth patterns are not the sole contributor to the development of type 2 diabetes. Patterns of childhood weight gain may have a crucial role in the rapidly rising prevalence of type 2 diabetes worldwide. This is owing to what has been referred to as the 'nutritional transition' (increased availability of food, reduced physical activity and increases in obesity). Not surprisingly, urban populations in developed countries, in which nutritional transition is more apparent, manifest the greatest rise in incidence of diabetes[26]. Those who were born small for age and later become overweight are at the highest risk for type 2 diabetes[27–31]. In other words, *adults with impaired glucose tolerance or diabetes tend to be, as a group, overweight. They were not, however, overweight as neonates, rather, they became overweight as a result of an accelerated gain in body mass starting in early childhood. The ability of children to have an accelerated increase in body mass may be a recent phenomenon in developing countries, a consequence of nutritional transition* (Figure 1).

Bhargava *et al.*[26] conducted a longitudinal study of 1400 adults who grew up in Delhi, India, at a time of rapid nutritional transition.

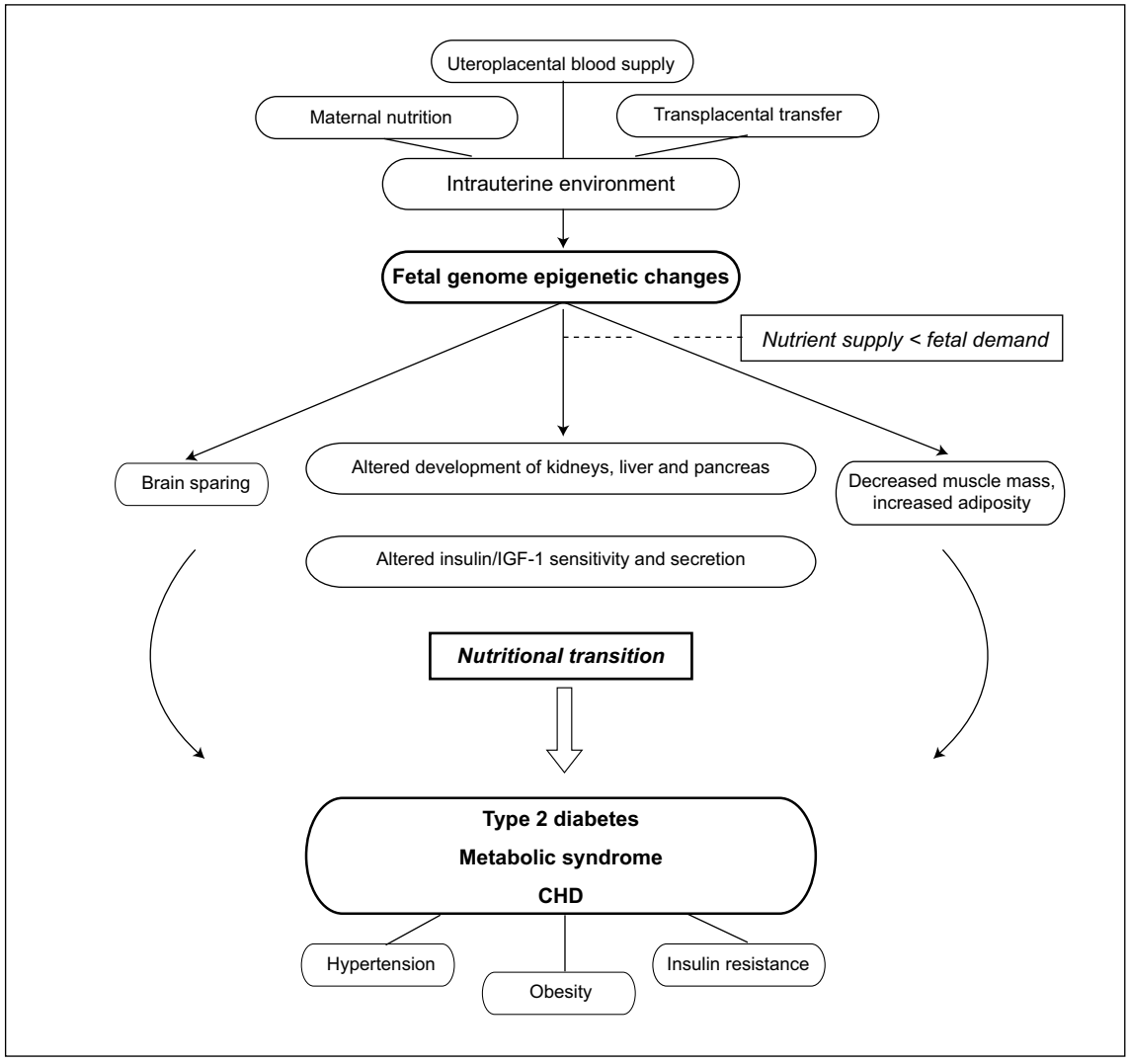

Figure 1 Factors affecting nutritional transition. IGF, insulin-like growth factor; CHD, coronary heart disease

These investigators found that a small size at birth, defined by a low birth weight or ponderal index, was associated with increased plasma glucose and insulin concentrations, and insulin resistance during adulthood.

At the age of 30 years, 15.2% of the study group had impaired glucose tolerance or diabetes, and 4.4% had diabetes. Serial standard glucose tolerance tests showed a sharp deterioration in glucose homeostasis at a relatively young age in adult life[26]. The growth of children in whom impaired glucose tolerance or diabetes later developed was characterized by a low body mass index (BMI) between birth and 2 years of age, a young age at adiposity rebound (as defined by the age after infancy at which the BMI starts to rise), and a sustained accelerated gain in BMI until adulthood.

Childhood obesity was uncommon among 8760 boys and girls who grew up in Helsinki, Finland, during World War II, affecting only 0.4% at the age of 12 years[32]. A total of 290 children in that study developed type 2 diabetes in adult life. They were all small for age at

birth, and all had low weight at 1 year of age. Their mean BMI did not exceed the average for the cohort until the age of 5 years. Thereafter, they had an early adiposity rebound and an accelerated gain in weight and BMI, but not in height. In that study, the prevalence of type 2 diabetes fell progressively from 8.6% in individuals whose adiposity rebound occurred before the age of 5 years to 1.8% in those in whom it occurred after 7 years. Despite these seemingly related findings, it remains unclear which is the most crucial phase during childhood and early adulthood during which excessive weight gain increases most the risk for adult type 2 diabetes.

The increase in prevalence of diabetes is of concern, not only as a healthcare burden on individuals and economies worldwide, but also owing to its effect on the next generations. Multiple studies have helped imprint the concept of hyperglycemia during pregnancy as representing a menacing epidemic in many parts of the world[33]. This spreading ailment carries grave short- and long-term consequences for both mother and child.

Diabetes affects the metabolism of all nutrient components (carbohydrates, fatty acids and proteins), of which glucose is the most prominent. Poor metabolic control may also induce alterations in levels of fatty and amino acids. Glucose and those other metabolites may account for the multitude of pathologies inflicted upon the offspring of a diabetic mother. These pathologic conditions range from congenital malformations and intrauterine fetal death to macrosomia, respiratory distress and hyperbilirubinemia. This creates an altered environment in which the embryo and fetus of the diabetic mother may be exposed to changes in gene expression and increased teratogensis[34,35]. Pederson *et al*.[36,37] and Salvesen *et al*.[38,39] observed the relationship between maternal hyperglycemia, fetal hyperglycemia and hyperinsulinemia. Insulin has an anabolic effect on muscle and adipose tissue linked to fetal macrosomia. On the other hand, long standing diabetes has a detrimental effect on the maternal vascular bed and its uteroplacental blood supply, and thus is linked to IUGR.

Follow-up studies, such as those conducted by Krishnaveni *et al*.[40] and Dabelea *et al*.[41], show that infants of diabetic mothers are at increased risk of obesity and glucose intolerance as early as age 5[40]. *Most importantly, intrauterine exposure to diabetes* per se *conveys a high risk for the development of diabetes and obesity in offspring in excess of the risk attributable to genetic factors alone*[41]. A Danish study[42] also demonstrated high prevalence of type 2 diabetes or pre-diabetes among 597 adults exposed to a hyperglycemic intrauterine environment. More than 20% of offspring born to mothers with diet-treated gestational diabetes mellitus (GDM) and more than 10% of offspring born to mothers with type 1 diabetes had type 2 diabetes or pre-diabetes at the age of 22 years. Compared with offspring from the background population, the adjusted risks of type 2 diabetes/pre-diabetes were increased eight- and fourfold, respectively[42].

These findings are apparently not in agreement with the previously explained theory associating IUGR and later risk for diabetes. They may, however, emphasize two aspects of the same issue, the manner in which intrauterine environmental conditions determine future risks of disease expressed in adult life, which then become the basis of fetal programming.

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