Maternal nutrition during pregnancy and health of the offspring

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Abstract
The ability of mother to provide nutrients and oxygen for her baby is a critical factor for fetal health and its survival. Failure in supplying the adequate amount of nutrients to meet fetal demand can lead to fetal malnutrition. The fetus responds and adapts to undernutrition but by doing so it permanently alters the structure and function of the body. Maternal overnutrition also has long-lasting and detrimental effects on the health of the offspring. There is growing evidence that maternal nutrition can induce epigenetic modifications of the fetal genome. Only relatively recently has evidence from epidemiological and animal studies emerged suggesting that fetal responses to the intra-uterine environment may underlie the prevalence of many chronic diseases of adulthood including Type 2 (non-insulin-dependent) diabetes. It is now of crucial importance to gain the understanding of the molecular mechanisms underlying the relationship between fetal alterations to the intra-uterine environment and their long-term effects on the health of an individual.

Introduction
Although fetal growth and development are driven by the programme encoded in its genome, the genetic regulation of fetal growth is influenced by the intra-uterine environment in which the fetus grows. One factor that is critical for fetal survival and health is the supply of nutrients and oxygen from the mother. The ability of a mother to provide nutrients for her baby depends on her nutritional status, body size, body composition and metabolism, all of which are being established throughout the mother’s own fetal life, childhood and adolescence. Assuming that adequate nutrition is available, the fetus can reach its growth potential, resulting in the birth of a healthy newborn of appropriate size.

Any abnormality in the intra-uterine environment can be detrimental to fetal growth. Failure to supply the adequate amount of nutrients to meet fetal demand, for example due to maternal malnutrition, inadequate placental function or increased nutritional demand, leads to fetal undernourishment [1,2]. Increased supply of nutrients to the fetus is also detrimental. Fetal overgrowth (macrosomia) can occur due to increased placental transport of glucose and other nutrients from a mother suffering from diabetes [3].

Any stimulus or insult that occurs during the critical period of development may cause a fetal response and adaptation that leads to long-term or permanent changes in the structure or function of the body, a process sometimes referred to as programming [4]. Only relatively recently has evidence from epidemiological and animal studies emerged suggesting that fetal responses to the intra-uterine environment including maternal malnutrition or overnutrition may underlie the prevalence of many chronic diseases, including Type 2 (non-insulin-dependent) diabetes and coronary heart disease [5] (Figure 1).

Fetal response and adaptations to undernutrition
Maternal nutrition may act as a forecast for the fetus of the nutritional environment it will encounter after birth. The fetus responds and adapts to that forecast using a number of strategies in order to maximize its chances of postnatal survival. The immediate response to undernutrition is catabolic consumption of substrates to provide energy [6]. If undernutrition is prolonged, the fetus changes its metabolic rate and alters the production of hormones and the sensitivity of tissues to them. For example, a decrease in maternal food intake leads to fall in the concentrations of fetal insulin, the IGF-1 (insulin-like growth factor-1) and glucose, causing reduced transfer of amino acids and glucose across the placenta, ultimately reducing the rate of fetal growth [7]. Metabolic programming is also thought to occur, for example the fetus prepares to store nutrients as fat in anticipation of poor postnatal nutrition [8]. Cell differentiation is also thought to alter due to a rise in cortisol concentrations [7]. Redistribution of fetal blood flow also occurs to protect key organs, especially the brain, at the expense of other tissues such as muscle, kidneys and the endocrine pancreas [9]. The decreased requirement for substrates and the lowering of metabolic rate lead to slowing of fetal growth and the birth of an infant with lower birth weight, who did not reach its full growth potential.

The thrifty phenotype hypothesis and predictive adaptive response hypothesis
The ‘thrifty phenotype’ hypothesis proposed by Hales and Barker [10] in 1992 aims to provide an explanation for the link between the fetal intra-uterine environment and the susceptibility to chronic diseases in later life [10]. It proposes that if the malnourished fetus is born into an environment of poor postnatal nutrition and remains in such an environment

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throughout childhood and adulthood, the prenatal adaptations are beneficial and the long-term health is unaffected. However, problems occur if a malnourished fetus is born into an environment of adequate or overnutrition. Fetal adaptations permanently alter insulin and glucose metabolism, thus increasing susceptibility to Type 2 diabetes, obesity and the metabolic syndrome in adults. The ‘thrifty phenotype’ hypothesis is widely supported by studies in both human and animal models [11].

Extending the thrifty phenotype, Gluckman and Hanson [12] proposed the ‘predictive adaptive response’ hypothesis. It postulates that the developing fetus assesses the plane of nutrition it receives in utero, predicts the postnatal nutritional plane (low or high) that it will encounter and adapts to the predicted environment in a way that would give it the best chance of survival. If the diet in adulthood diverges from the predicted plane, disease manifests itself.

**Fetal malnutrition and its effect on the long-term health of the individual**

In humans, it is not always possible to establish whether fetal malnutrition results from maternal malnutrition or other factors such as maternal, placental and/or fetal pathology. There are no clinical measures routinely available to determine the optimal fetal growth potential, so birth weight is often used in epidemiological studies as a proxy indicator of disturbed fetal growth and development.

The association of low birth weight with development of disease in adulthood was first observed in relation to cardiovascular disease when it became apparent that there was a relationship between year of birth and year of death [13]. It was suggested that the early life environment, particularly maternal influence, might be underlying this association.

Subsequently, it was shown that there is a strong and inverse relationship between birth weight and blood pressure, which is a major cardiovascular risk factor [14]. To date, the origins of many diseases of adulthood are thought to lie in fetal life (Table 1).

The first study linking low birth weight with glucose intolerance and Type 2 diabetes was carried out on 64-year-old Hertfordshire men in the early 1990s [15]. The proportion of men with poor glucose tolerance (impaired glucose tolerance or frank diabetes) gradually increased as birth weight decreased. The relative risk was continuous across birth weight categories, with low birth weight individuals being seven times more likely to currently have poor glucose tolerance in comparison with men from the highest birth weight group. The worst glucose tolerance was observed in low birth weight men who became obese. The molecular mechanisms underlying the relationship between low birth weight and increased risk of developing Type 2 diabetes mellitus in adulthood are not known. However, it has been shown recently that low birth weight men have reduced muscle expression of protein kinase Cζ, GLUT4 and phosphoinositide 3-kinase p85α and p110β subunits [16]. These changes precede the onset of impaired glucose tolerance.

The evidence that fetal undernutrition has varying effects on the long-term health of an individual depending on its timing in pregnancy came from the study of individuals in utero during the Dutch Winter Famine, which lasted for 27 weeks during the winter of 1944–1945 [17]. The birth weight of newborns fell with the onset of famine and progressively decreased till it reached the lowest after 18 weeks. Individuals exposed to famine in the last trimester of pregnancy had lower birth weight and body length than those who were exposed

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**Table 1 | Metabolic disorders and diseases of adulthood that have been associated with nutritional imbalances during fetal life**

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<td>Psychiatric disorders</td>
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<td>Schizophrenia</td>
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in early gestation [17]. Individuals who were exposed to famine in early gestation had increased rates of obesity at 19 years of age, while those exposed in late gestation showed reduced rates of obesity at that age [18]. At 50 years of age, a greater risk of developing coronary heart disease was associated with exposure to famine in early gestation. Adults exposed to famine in mid to late gestation had poor glucose tolerance and increased concentrations of proinsulin and insulin, and additionally, individuals who had low birth weight and became obese in adulthood presented with the highest 2h glucose concentrations [17]. Thus there appears to be different critical time windows for different organ systems.

Maternal nutrition as early as at the time of conception plays an important role for the physiology of the fetus as it can influence cell number and differentiation in the blastocyst (pre-implantational embryo that consists of two cell types: the inner cell mass that will become the fetus and outer cell mass that will form the placenta). Maternal nutritional restriction can lead to fewer cells in the inner cell mass, which in turn is associated with lower birth weight, restricted postnatal growth, altered organ/body weight ratios and development of hypertension [19].

Animal studies have provided further evidence and understanding of the association between maternal malnutrition during pregnancy and the long-term health of the offspring. For this reason, various animal nutritional models have been developed including maternal calorie restriction, maternal protein restriction and maternal anaemia [20,21]. The most extensively studied model characterized by early growth restriction is the maternal low-protein rat model, which shows a striking number of parallels to individuals with Type 2 diabetes and/or metabolic syndrome. This model involves feeding pregnant dams a low (5–8%)-protein diet in comparison with a control (20%) diet. The low protein offspring had reduced birth weight (15%) [22]. If the maternal protein restriction is continued during lactation, the offspring is permanently growth-restricted. These low protein offspring have better glucose tolerance than controls in young adult life [23] but their glucose control deteriorates with age and is significantly worse by 15 months [24]. This is associated with insulin resistance. Maternal protein-restricted offspring has also been shown to have increased blood pressure [25]. Hypertension might be related to changes in kidney structure and the activity of the renin–angiotensin system. Additionally, if maternal protein restriction is accompanied by obesity, an independent and additive effect is observed on blood pressure [26]. Maternal nutrition can also influence longevity. The low protein offspring has reduced lifespan when overnutrition is encountered during the suckling period [27].

Maternal overnutrition

As the prevalence of obesity is reaching epidemic proportions, understanding the effect of maternal overnutrition on the growth and development of the baby and its long-term consequences for long-term health are of particular importance. In the U.S.A., 18–38% of pregnant women are obese [28]. These women usually continue to overeat throughout gestation, gaining more weight during the first pregnancy and reaching higher body weight with each subsequent pregnancy [29]. There is growing evidence that maternal overnutrition not only contributes to the development of gestational diabetes and pre-eclampsia [30], but also has long-lasting consequences for the health of the infant independently of whether exposure to overnutrition is or is not a feature of postnatal life.

The excess consumption of dietary fat is a feature of diets in many societies. Studies in Pima Indian populations have shown that fetal overnutrition increases susceptibility to Type 2 diabetes in adulthood [31]. It has been shown recently that a relationship exists between maternal glycaemia during pregnancy and increased birth weight and risk of diabetes in Pima Indian offspring, even among mothers who are normally glucose-tolerant during pregnancy [32]. High level of maternal dietary fat intake during pregnancy increases the incidence of cardiovascular risk factors in children [33].

Pregnant rats fed lard-enriched but normal carbohydrate diet reduced their daily food intake so that their daily caloric intake was similar to that of the controls but their fat intake was increased by 4-fold [34]. The phenotype of the offspring therefore may not be determined by the increased maternal energy intake as such but by increased exposure to dietary fat. These offspring were hyperglycaemic and hyperinsulinaemic [35]. The insulin–secretory capacity of pancreatic β-cells was also reduced at 6 months of age and was accompanied by whole body insulin resistance [36]. Insulin secretion in response to an oral glucose load had been shown to be increased in the offspring of dams fed lard-rich diet during pregnancy but not in the offspring of dams fed fat derived from polyunsaturated fat-rich fish oil [37], suggesting that the intake of saturated fatty acid component of the lard-rich diet may be the programming stimulus. Additionally, it has been shown that 6-month-old offspring of fat-fed dams have reduced mitochondrial copy number in the kidney, which may contribute to the development of metabolic syndrome [36]. A maternal high-fat diet during pregnancy not only alters glucose homoeostasis in the offspring but also leads to development of other features that resemble human metabolic syndrome including hypertension, abnormal serum lipid profiles, endothelial dysfunction, increased adiposity and hyperleptinaemia [38]. Limiting the high-fat feeding regimen to either pregnancy or lactation still resulted in increased adiposity, hypertension and hyperinsulinaemia in the offspring [39].

Maternal nutrition and epigenomics

There is growing evidence that maternal nutrition during pregnancy and maternal metabolic status can programme adult disease susceptibility by altering the epigenetic state of the fetal genome [40]. All biological methylation reactions are dependant on dietary methyl donors such as methionine and choline, and on cofactors, which include folate acid, vitamin B12 and pyridoxal phosphate. The methyl donors and cofactors are not only required for the re-establishment of the
patterns of cytosine methylation after implantation but also for the maintenance of these patterns during many cycles of cellular proliferation during fetal and early postnatal life. Thus DNA methylation and histone modifications may be affected by an inadequate supply of amino acids and micro-nutrients. It has been reported that the supplementation of maternal diet with methyl donors and cofactors increases methylation at the Avy locus of agouti mice [41]. The allelic methylation and expression of imprinted genes have also been shown to be altered by nutrition, when various culture media were used in in vitro studies of mouse embryos [42,43].

Conclusions
It is clear that maternal nutrition during pregnancy can exert long-lasting effects on the health of the offspring. In light of the current epidemic of Type 2 diabetes and obesity, it is vital that the importance of diet during pregnancy is widely known and that the mechanisms by which it influences the long-term health of the offspring are understood.

References

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