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Fetal malnutrition and long-term outcomes

Caroline HD Fall

MRC Lifecourse Epidemiology Unit, University of Southampton, UK

Abstract

Epidemiological studies have shown that lower birthweight is associated with a wide range of adverse outcomes in later life, including poorer 'human capital' (shorter stature, lower cognitive performance); increased risk factors for later disease, (higher blood pressure and reduced glucose tolerance, and lung, kidney and immune function); clinical disease (diabetes, coronary heart disease, chronic lung and kidney disease); and increased all-cause and cardiovascular mortality. Higher birthweight is associated with an increased risk of cancer, and (if caused by gestational diabetes) obesity and diabetes. The "developmental origins of health and disease" (DOHaD) hypothesis proposes that fetal nutrition has permanent effects on growth, structure and metabolism ('programming'). This is supported by studies in animals showing that maternal under- and over-nutrition during pregnancy can produce similar abnormalities in the adult offspring. Common chronic diseases could potentially be prevented by achieving optimal fetal nutrition, and this could have additional benefits for survival and human capital. Recent follow-up of children born after randomised nutritional interventions in pregnancy provides weak evidence of beneficial effects on growth, vascular function, lipid concentrations, glucose tolerance and insulin resistance. Animal studies indicate that epigenetic phenomena may be an important mechanism underlying programming, and that nutritional interventions may need to start pre-conceptionally.

Fetal undernutrition and long-term outcomes

The first convincing evidence that fetal undernutrition could have a long-term influence on human health came from the follow-up of adults who were *in utero* during the Dutch Famine ('Hunger Winter') of 1944-45. Young men whose mothers lived in famine-affected areas of the Netherlands during early pregnancy had an increased risk of obesity compared to men whose mothers lived in non-famine areas (2.7% versus 1.5%) [1]. Men whose mothers were exposed to famine in late pregnancy or early post-natal life had lower rates of obesity. The authors speculated that these findings reflected permanent effects of nutritional deprivation on fetal hypothalamic centres, causing lifelong changes in food intake and growth.

The science of 'developmental origins of health and disease' (DOHaD) started to attract intense interest some 20 years later, when Barker and Osmond linked birthweight (collected by health visitors in the UK from 1911-1930) with death certificate data and discovered that men and women who had a lower birthweight were at increased risk of death from cardiovascular and chronic lung disease [2]. Following on from this, a large number of birth

cohort studies have now linked lower birthweight to other adverse outcomes in later life. These include reduced 'human capital' (shorter stature, lower lean body mass, and poorer cognition, educational achievement, work capacity, income and reproductive performance) [3]; increased risk factors for later disease, (higher blood pressure [3], central adiposity [4], insulin resistance [3] and stress responses [5], and reduced glucose tolerance [6], lung function [7], glomerular filtration rate [8] and immune function [9]); increased clinical disease (type 2 diabetes, coronary heart disease, chronic renal disease and chronic lung disease) [3,6,7]; and increased all-cause and cardiovascular mortality [10]. The associations with risk factors for disease have been shown in children as well as adults. The associations extend across the range of birth weight, and are not limited to low birthweight (<2500 g), although in some studies an upturn in risk is observed at high birthweights for some outcomes (see below, fetal 'over-nutrition'). Most studies have been carried out in predominantly full-term births, suggesting that the phenomenon is linked to low birthweight for gestational age (interpreted as an indicator of fetal nutrition) rather than low birthweight due to pre-term birth. However, there is some evidence that pre-term birth is also a risk factor for cardio-metabolic outcomes like hypertension, insulin resistance and the metabolic syndrome [11].

Research in animals had already shown that transient environmental conditions, including nutrition, in early life could permanently alter or "programme" the body's structure and function [12]. Subsequent work in animal models has shown that fetal under-nutrition, achieved either by under-nourishing the mother during pregnancy, or by impairing the fetal supply line (uterine artery ligation, placental reduction or gene knock-out models that impair placental growth), produces permanent effects on a wide range of tissues and systems [13–15]. For example, there are several maternal under-nutrition models in animals that produce obesity, insulin resistance and diabetes in the offspring, who show changes at whole animal level (eg. sedentary behaviour), tissue level (eg. altered arrangement of cell types in hepatic lobules, reduced cell numbers and vascularisation of pancreatic islets), and molecular level (eg. altered expression of genes in the insulin signalling pathway). This evidence from animal studies suggests that the associations between birthweight and later health in humans are likely to reflect the programming of a variety of tissues by intra-uterine nutrition (Figure 1). The associations with birthweight occur because the same factors that perturb/programme metabolic function can also reduce fetal growth; animal studies have shown that programming can occur in the absence of reductions in birth size [13–15].

A consistent feature of the human studies is that the highest risk of cardio-metabolic disease and its risk factors is in children or adults who had a low birthweight but became relatively heavy (Figure 2). This 'small becoming big' pattern is also seen in animal models, in which post-natal high-energy or high-fat feeding amplifies the adverse cardio-metabolic effects of pre-natal under-nutrition [13–15]. It fits with the concept that the fetus programmed by under-nutrition develops metabolic traits (higher blood pressure, insulin resistance, central adiposity) that make them vulnerable to disease when exposed to additional stressors in later life such as inadequate exercise, excess energy intake and obesity. It could also explain the recent rise in cardio-metabolic disease in low-income countries undergoing rapid economic transition. This has raised the question of whether paediatricians should try and limit post-natal weight-gain in lower birthweight infants. Even

if this were possible, there is no evidence to support such a strategy in infancy; current evidence from low and middle-income countries suggests that greater infant weight gain is associated with benefits for survival and human capital, and is neutral in terms of later cardio-metabolic risk [3].

Nutritional interventions in under-nourished pregnant women

The DOHaD concept has stimulated enormous scientific interest, but has had little impact on how the 'common women' thinks about nutrition in pregnancy, or on national policies on maternal nutrition. Human evidence for fetal programming is still largely based on observational data and on birth measurements, which are only crude indicators of fetal nutrition. However, the DOHaD hypothesis is beginning to be tested by studying children of undernourished women who took part in nutrition supplementation trials in pregnancy (**Table 1**). If maternal under-nutrition is an important cause of fetal under-nutrition, better outcomes would be expected in children whose mothers were supplemented. The published trials include a variety of interventions and ages at follow-up, but fall into three groups (mainly protein-energy supplementation [16–18], multiple micronutrient supplementation [19–21]), or both [22]). All started in pregnancy, usually in the second or third trimester, and the offspring outcomes most frequently studied were growth and cardio-metabolic risk factors.

In the INCAP trial in Guatemala, villages were randomised to receive either a protein-energy drink (Atole) or a low-energy drink (Fresco) which were supplied daily to pregnant women and children <7 years of age [16]. There was no significant difference between Atole and Fresco villages in birthweight. This is the oldest trial and the only one with adult follow-up data. It showed lower triglyceride and higher HDL cholesterol concentrations in men and women who received Atole before the age of 24 months (either given to the mother in pregnancy or to the children themselves post-natally). There were no significant effects on adult blood pressure or fasting glucose. In the Gambian trial, women received a daily high energy biscuit, from 20 weeks of pregnancy (intervention group) or during lactation only (controls). The intervention certainly influenced fetal nutrition, increasing birthweight by a mean 136 g and halving perinatal mortality. In the adolescent offspring (11–17 years), there was a small reduction in fasting plasma glucose concentrations (mean -0.05 mmol/l) but no differences in adiposity, blood pressure, insulin concentrations or serum lipids [17]. In India, pregnant mothers and children under 6 years of age in intervention villages received food-based energy and protein supplements. At 16 years, the children had lower insulin resistance and arterial stiffness compared to children born in control villages [18]. There were no differences in their blood pressure or lipid concentrations. In both the Guatemala and Indian trial, offspring of intervention mothers were taller, and in Guatemala an increase in height was also observed in the next generation.

Two of the multiple micronutrient (MMN) trials (both in Nepal) showed a small increase in birth weight in the MMN groups [19,20]. Two-year old children whose mothers received multiple micronutrient supplements during pregnancy were heavier and had larger head, chest and mid-arm circumferences and larger skinfold thickness, but lower systolic blood pressure, than children of control women, who received only iron and folic acid [19]. In the

other trial, 7-year old children whose mothers received vitamin A, iron, folic acid and zinc were taller and less adipose than children of control mothers (vitamin A alone) and had lower triglyceride concentrations, while children whose mothers received folic acid had a lower prevalence of metabolic syndrome than controls [20]. There were no effects on blood pressure, other lipids, glucose or insulin. In a trial in Peru, infants of mothers who were supplemented with iron, folic acid and zinc were heavier and had larger chest circumference and calf muscle area than those of women who received iron and folic acid without zinc [21].

The Bangladesh 'Minimat' trial combined protein-energy and MMN interventions; women were randomised to receive food supplements 'early' (~9 weeks gestation) or at the usual time (~14 weeks), with (in a factorial design) either additional MMN or iron+folic acid. This is the only trial that attempted to correct both macronutrient and micronutrient deficiencies in the mother, and started in the first trimester of pregnancy, but it is so far published only in abstract form [22]. Early food supplements were associated with less stunting and lower LDL-cholesterol concentrations in the children. Multiple micronutrient supplementation was associated with lower insulin concentrations, and, interestingly, more stunting.

These studies provide some evidence that improving the nutrient intake of under-nourished human mothers in pregnancy has benefits for growth and cardio-metabolic risk in the children, but it cannot be called strong evidence. All took place in low-income populations, where levels of cardio-metabolic risk factors are still relatively low and where the opportunity for 'becoming big' post-natally is low compared with high-income settings. This would tend to reduce any differences between children from intervention and control groups. If early pregnancy is a critical time for nutritional programming of adiposity, as suggested by animal studies [23] and the Dutch Famine studies [24], effects of supplements started later in pregnancy may be limited. The only study with adult follow-up (Guatemala) had a very small sample size, and the age at follow-up in the other trials (either in young children or adolescents) was not ideal for examining programming effects. Longer follow-up of these trials is needed, and data are required from studies in other populations and of other interventions, including pre-conceptional trials, before conclusions can be reached.

Fetal 'over-nutrition' and long-term outcomes

Maternal diabetes during pregnancy exposes the fetus to an excess of nutrients. Diabetic mothers are not only hyperglycaemic, but also have elevated circulating lipids and amino acids. The fetal pancreas and liver are stimulated to secrete increased insulin and insulin-like growth factors, resulting in the macrosomic infant of the diabetic mother. Freinkel suggested 30 years ago that this could cause obesity and diabetes in later life ("fuel mediated teratogenesis") [25] and it is now established that gestational diabetes is a risk factor for later diabetes in the offspring [4]. There are therefore problems at both extremes of birthweight. In most populations, the predominant association of birthweight with later diabetes risk is linear and inverse, except in very large studies such as the US Nurses' Study, in which gestational diabetes produces a small upturn in risk at high birthweights [6]. In populations with a very high prevalence of gestational diabetes, such as the Pima Indians, the curve becomes U-shaped [6].

Lesser degrees of maternal glucose intolerance may also be associated with increased adiposity in the children. In a US study of 9439 women routinely screened for gestational diabetes, there was a positive association, even in the non-diabetic group, between maternal glucose concentrations and overweight in the children [26]. Maternal insulin resistance and glycaemia form part of the normal process of fetal nutrition, and we do not yet know the optimal levels of glucose and other fuels and nutrients in the mother. There is also increasing interest in whether maternal obesity, in the absence of diabetes, causes fuel-mediated teratogenesis and programmes cardio-metabolic risk in the children. In animal models, maternal obesity, or high-fat feeding during pregnancy, cause obesity, insulin resistance and diabetes in the offspring [15]. Like the diabetic mother, an obese mother has increased circulating glucose, insulin, lipids and pro-inflammatory factors. Maternal obesity is associated with an increased risk of obesity and metabolic syndrome in the children [27], and children born to obese mothers before they underwent biliopancreatic bypass surgery have a lower risk of obesity than siblings born before surgery [28], but better evidence of a causal *intra-uterine* effect is awaited.

Another important disease to mention in relation to higher birthweight (and thus possibly to a fetal 'over-nutrition' effect) is cancer. There is consistent evidence that breast cancer and leukaemia are more common among people of higher birthweight, and cancer mortality is higher in men of higher birth weight [10].

As mothers become heavier in almost all populations, the incidence of diabetes in pregnancy is increasing, and this is likely to make an increasing contribution to the burden of obesity and diabetes in future generations. This may be a particularly important phenomenon in transitioning populations, in which mothers who themselves had a low birthweight are at increased risk of developing gestational diabetes and thus exposing their offspring to fuel-mediated teratogenesis (Figure 3). Improved management of diabetes in pregnancy reduces fetal macrosomia but it is not yet known whether this prevents later effects in the children.

Mechanisms linking fetal nutrition to long-term outcomes

Possible mechanisms for the long-term programming of health and disease by fetal nutrition have been extensively reviewed [15,29,30]. The simplest mechanism is inadequate growth and/or re-modelling of tissues, due to inadequate substrates at critical periods of development. Fetal tissues develop during specific times and in a specific order, and inadequate nutrients at these times could lead to permanently reduced cell numbers, and/or altered structure due to selection of more 'robust' alternative cell types. There is good evidence for this in the kidney; protein deprivation in pregnant animals during fetal nephrogenesis results in smaller offspring nephron number, and later hypertension [30]. There is also evidence from animal studies of tissue re-modelling in the pancreas, liver and hypothalamus in response to fetal under-nutrition.

Re-modelling of tissues that regulate endocrine and metabolic pathways could have wide-ranging effects. For example, the hypothalamus is the main brain centre regulating appetite and feeding behaviour, and monitors and responds to signals about nutritional state (the presence of food in the gut, circulating fuels, stored fat and glycogen). Different populations

of hypothalamic cells stimulate or suppress food intake via projections to other brain areas, for example altering feeding behaviour. Animal research shows that the cell proliferation, migration, differentiation, growth and apoptosis required to make these projections can be altered by the nutritional environment during fetal development [31]. Leptin and insulin, which are important fetal growth hormones and respond to fetal nutrition, are thought to regulate this hypothalamic development.

The above mechanisms would have to involve changes in gene expression, and there is great interest currently in effects of fetal nutrition on epigenetic phenomena, such as DNA methylation, that have a role in switching genes on and off. Patterns of DNA methylation are substantially established during embryogenesis and fetal development, and are sensitive to the nutritional environment. For example, maternal protein restriction during pregnancy, which causes hypertension and increased adiposity in rat offspring, appears to act, at least partially, through altered methylation and expression of specific genes involved in energy and lipid metabolism [32]. Both the altered methylation and the later abnormalities are prevented by supplementing the maternal diet with folic acid. Human data is limited, but epigenetic changes have been shown in newborns whose mothers took part in a randomised controlled trial of pre-conceptional multiple micronutrient supplements; in Gambian children conceived in the 'hungry' versus the 'harvest' season; and in adult offspring of women exposed to the Dutch famine [33]. Epigenetic variation in umbilical cord tissue has also been related to later outcomes such as childhood adiposity [34].

Epigenetic patterns can be inherited, which could explain how transient alterations in fetal nutrition can alter body composition and metabolic parameters across more than one generation [29]. Epigenetic perturbations in a limited number of key metabolic genes could also explain the striking phenomenon in animal models whereby widely differing nutritional interventions in the mother (from global nutrient restriction to high-fat feeding) apparently result in the same 'metabolic syndrome' phenotype in the offspring [30]. Nutritional effects on epigenetic characteristics could produce the 'plasticity' of phenotype in early life that is inherent to the concept of fetal programming. Furthermore, this type of plasticity means that the programming of long-term outcomes may not require major nutritional deficits during organogenesis and differentiation, but could result from short-lived and subtle changes in the nutritional environment at stages of development when nutrient demands for growth are still quite small, such as during the peri-conceptional period and early embryogenesis [23]. A further intriguing aspect of epigenetic programming is that it could act through paternal as well as maternal nutrition. Offspring of male mice fed a low-protein diet from weaning until sexual maturity had increased hepatic expression of genes involved in lipid and cholesterol biosynthesis [35]. In future we may need to consider the nutrition of fathers, as much as that of mothers, among the inter-generational determinants of health and disease.

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Figure 1. The fetal programming hypothesis; adult chronic disease resulting from the effects of fetal under-nutrition on the development of different tissues

Fetal under-nutrition can occur because of an inadequate maternal diet, inability of the mother to mobilise and transport sufficient nutrients, or an impaired vascular and placental supply line to the fetus. It can also occur if there is high fetal demand, for example because of faster growth. Changes in fetal structure and physiology could occur because of a simple lack of the nutrients or building blocks required to construct high-quality organs and tissues, or because of adaptations to reduce nutrient demand eg by slowing fetal growth or prioritising essential organs. Endocrine systems (especially for hormones that regulate fetal growth and maturation) are re-set, and tissues are supported or sacrificed differentially. It is hypothesised that the resulting metabolic changes persist and increase the risk of developing diabetes and cardiovascular disease, especially if additional stressors are acquired in later life (such as obesity and physical inactivity).

Figure 2. Lower birthweight followed by the development of above average weight or BMI in childhood or adulthood is associated with increased insulin resistance and impaired glucose tolerance (data from 3 Indian birth cohorts)

Figure 3. Inter-generational effects of fetal nutrition on diabetes risk.

Intergenerational under-nutrition results in low birthweight, and a number of adverse later outcomes, including impaired human capital (left-hand circle). Rapid childhood or adult weight gain on a background of low birthweight is associated with an increased risk of cardio-metabolic disease (left to right arrow), and (in women) with gestational diabetes, which exposes her fetus to excess fuel mediated teratogenesis, another route to increased diabetes risk (right-hand circle).