Original article

Nutrition and the early origins of adult disease

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There is now overwhelming evidence that much of our predisposition to adult illness is determined by the time of birth. These diseases appear to result from interactions between our genes, our intrauterine environment and our postnatal lifestyle. Those at greatest risk are individuals in communities making a rapid transition from lives of 'thrift' to a lives of 'plenty'. From a global perspective, such origins of diabetes, coronary heart disease and stroke, should render research in these fields as one of the highest priorities in human health care. Prevention will be enhanced by elucidation of the mechanisms by which the fetus is programmed by the mother for the life she expects it to live. At the present time, there is evidence that fetal nutrition and premature exposure to cortisol are effective intrauterine triggers, but a multitude of alternative pathways require investigation. It is also likely that programming extends across generations, and may involve the embryo and perhaps the oocyte. An oocyte that becomes an adult human develops in the uterus of its grandmother, so further research is required to describe the role of environments of grandmothers and mothers in predisposing offspring to health or illness in adult life.

Key words: Cardiovascular disease, diabetes mellitus, fetus, nutrition, pregnancy.

Introduction

Nutrition for the mother and child during pregnancy is a subject of increasing importance for clinicians, public health planners and the general community. Compelling evidence from a range of sources now reveals that the programming of much of our future health begins in the months before birth. A key trigger in this process is the nutritional supply reaching the fetus.

Epidemiological studies

Perhaps the single greatest impetus for the recent increase in awareness of the potential role of maternal health and nutrition in future health of the offspring has been the seminal studies reported by Professor David Barker and colleagues from the UK.[1–4] In an extensive series of studies, these authors addressed the relationships between low birthweight and chronic diseases in adult life.[1–4] What was at first a desire to investigate relationships between poor socioeconomic conditions and the origins of coronary heart disease and diabetes, became an opening for many other exciting new areas of inquiry.

Early work was based on retrospective analyses of birth cohorts from the early 20th century in regional England. These studies demonstrated relationships between low birthweight, body proportions at birth and placental weight, and increased rates of heart disease, hypertension and type II diabetes when the offspring reached adult age. More recent evidence suggests that placental weight is more likely to act as a surrogate for other factors, rather than being a meaningful predictor of adult disease in its own right.[5] Body proportions seem to be of greater importance, with thinness representing preceding intrauterine undernutrition.[6]

Additional insights have since been obtained by study of offspring following the 'Dutch famine'.[7–9] During the final winter of World War II, the civilian population in the urban west of the Netherlands experienced severe nutritional deprivation. Famine in this study was defined as an average daily ration below 1000 calories during any 13-week period of gestation. Individuals who had been exposed to famine mid- or late-gestation had reduced glucose tolerance in adulthood, while those exposed to famine in early gestation had more atherogenic lipid profiles. There was no overall effect of famine on subsequent blood pressure, but blood pressures were associated with the protein/carbohydrate ratio of the average ration during the third trimester of pregnancy. The findings from this study of the Dutch famine suggest the effects of severe nutritional changes during pregnancy are dependent on the stage in gestation when the intervention occurs, and may relate to the balance of macronutrients in addition to total caloric intake.

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Together, the evidence from the epidemiological studies provide strong evidence for a prenatal contribution to the adult condition known as syndrome X consisting of the pentad of hypertension, hyperinsulinism, dyslipidemia, obesity and cardiovascular disease.[10]

The thrifty phenotype hypothesis

The relationship between low birth-weight and diabetes in adult life is clarified by the thrifty phenotype hypothesis.[11] This concept proposes that the fetus is programmed for the metabolic life the mother expects it to live. Programming is a term used to describe the process by which a stimulus or insult during critical periods of growth and development has lasting effects on the structure and function of tissues and body systems.[9] In an environment of poor nutrition, permanent changes are made to the metabolic functions of the fetus to optimize its survival in a postnatal world of thrift. In contrast, if the pregnant woman lives in an environment of plenty, the fetus will be adapted to thrive in a world in which food will be plentiful. Disease results from conflict between the prenatal programming and the postnatal reality. Thus, in what is known as the 'south Asia enigma', the increasing rates of diabetes and heart disease currently seen in middle class populations of India, Pakistan and Bangladesh, are likely the result of prenatal programming for a 'life of thrift', followed after birth by exposure to improved levels of nutrition and inactivity. In contrast, prenatal programming for a life of thrift in sub-Saharan Africa is not followed by high rates of heart disease and diabetes because offspring remain relatively undernourished, living the metabolic life for which they were programmed (Fig. 1).

The corollary of the thrifty phenotype hypothesis is that individuals and communities making the transition from traditional lives of thrift to more sedentary lives of plenty are at high risk of adult disease, principally diabetes and heart disease. The massive number of people in the world today undergoing this transition highlights the importance of unravelling the mechanisms by which this disease predisposition occurs.

Interaction between pre- and postnatal environments

The mechanisms that underpin the thrifty phenotype hypothesis are undoubtedly multifactorial, but current evidence centres on two prenatal triggers. These triggers interact with the individual's genome. The first potential trigger is insufficient fetal nutrition resulting either from maternal undernutrition or disordered placental function. The second potential trigger is the possible role of premature or excessive fetal glucocorticoid exposure. In postnatal life, the predisposition conferred by prenatal programming is then amplified or minimized by environmental influences, such as diet and inactivity. The relationships between these prenatal triggers and postnatal amplifiers are shown in Fig. 2.

Role of maternal nutrition

It has been appreciated for many years that maternal nutrition influences birthweight. If nutrient supply is limited, fetal growth is reduced by a direct lack of nutrients and decreased levels of insulin and insulin-like growth factors (IGF), which function to promote growth and are themselves regulated by nutrient supply.[12–14] As an adaptation to ensure survival, the mother may also constrain the growth of the fetus as a mechanism to protect her ability to deliver the child through her birth canal, but this capacity, at least in humans, is limited.

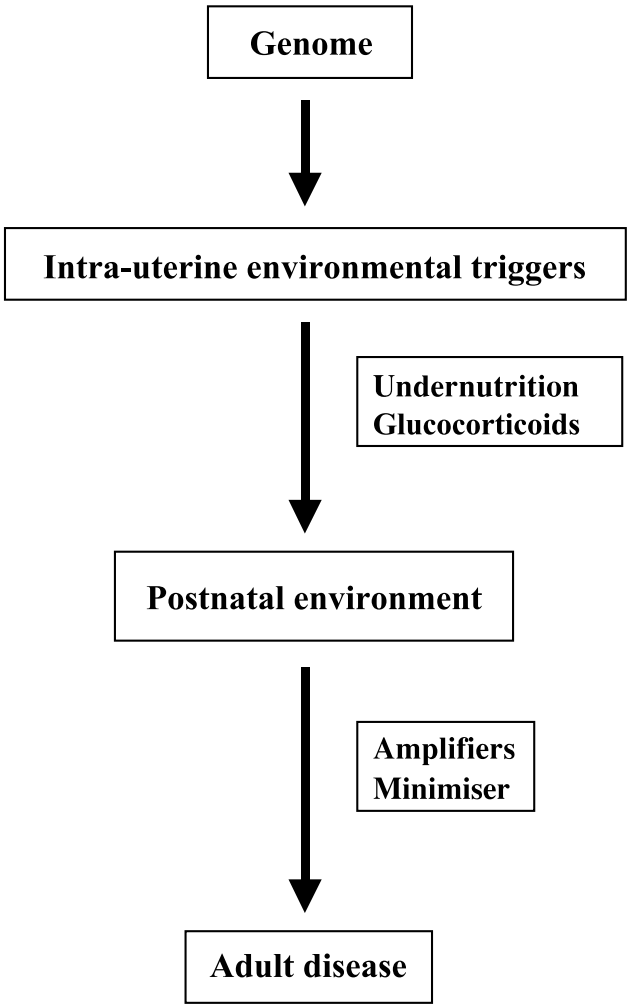

Figure 1. Flow chart demonstrating the interactions between the genome, intrauterine 'triggers' and postnatal 'amplifiers' in the origin of adult disease.

There is a wealth of information in the scientific literature describing the effects of nutrition on pregnancy outcome in animal models. Reducing the nutritional intake of experimental animals during pregnancy reduces birthweight with consequences extending into adulthood. Studies have been performed in a variety of species, including rats,[15–18] guinea pigs,[19] and sheep.[20] Effects on prenatal and postnatal outcomes are influenced by the type, severity and timing of the dietary intervention, but in general these studies show that dietary restriction during pregnancy produces fetal growth restriction, followed in later life by elevated blood pressure, reduced insulin sensitivity and dyslipidemia.

In human clinical trials, the effects of altering maternal nutrition have been less dramatic than in animal studies,

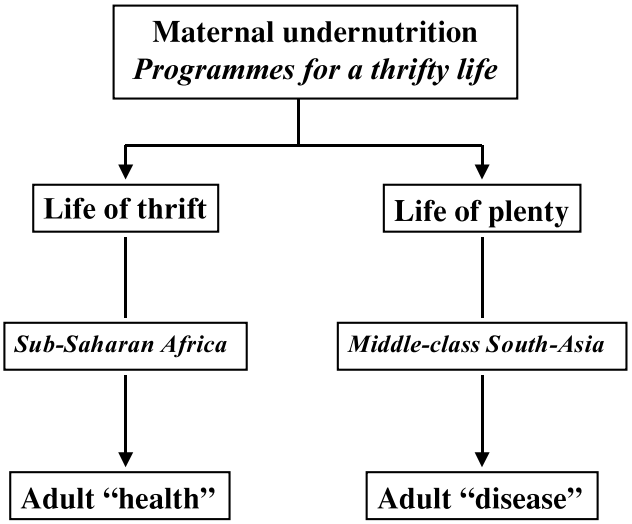

Figure 2. The 'thrifty phenotype' hypothesis and the south Asia enigma. Maternal undernutrition programmes the offspring for a life of thrift, and adult disease results from lifestyles in conflict with prenatal programming.

probably because the interventions have not been as substantial. Randomized trials have been reviewed and the results published in the Cochrane Database of Systematic Reviews. Supplementation of maternal diet with balanced energy and protein was associated with modest increases in maternal weight gain and a small increase in birthweight, amounting to a mean increase of 25 g.[21] The reduction in the incidence of low birthweight babies was more impressive, with an odds ratio of 0.64 (confidence interval 0.53–0.78). There was a suggestion from three of the trials of a reduction in stillbirth and neonatal deaths, but there was no other evidence of improved outcome for mother or child. In trials in which the intervention consisted of advice to improve diet, rather than formal supplementation, alterations in pregnancy outcomes were minor and inconsistent.[22] None of these trials were designed to investigate the role of nutrition in programming the fetus for adult disease, and none has the power to investigate this question.

Obesity

The major challenge in this field of research is the quest to uncover the mechanisms by which the individual is programmed for these disturbances. One of the most exciting areas of investigation in recent years has centred on the key role of obesity. Obesity is a cardinal feature of syndrome X and is linked to insulin resistance. The origin of excess adipose tissue involves far more than just overeating and inactivity, and there is now important evidence of underlying abnormalities in the regulation of appetite and metabolism. Vickers *et al*.[23] and Breier *et al*.[24] developed a rodent model of obesity and hyperphagia by applying undernutrition throughout gestation, which resulted in reductions in fetal and placental growth of approximately 25%. In adult life, these rats display hyperphagism, obesity, hypertension and hyperinsulinism, and these features are amplified by the administration of a hypercaloric diet.[23] The development of this animal model has contributed to the current uncertainty regarding the relative benefits and potential harm of promoting 'catch-up growth' in children who are growth-restricted at birth. These children are known to be at risk of obesity[25] and heart disease[26] in later life, and the role that accelerated weight gain after birth plays in amplifying the risk of adult disease is of concern.

The mechanism underpinning obesity and hyperphagia appears to centre on the interplay between insulin and leptin.[24] Leptin is produced in the periphery and inhibits appetite centrally. Insulin promotes the production of both adipose tissue and leptin secretion, while leptin inhibits the production of insulin from the β-cells of the pancreas. This adipo–insular axis links the peripheral tissues, brain and pancreas, and provides the feedback loops by which accumulating fat stores increase leptin levels and inhibit further insulin release, while decreasing fat stores are associated with lower leptin levels and stimulated insulin release. The rodent model of prenatal undernutrition and postnatal hyperphagia, obesity and hypertension, is associated with hyperleptinism, and levels of this hormone are further amplified by hypercaloric nutrition.[23] Concomitant increases in insulin and leptin levels are suggestive of underlying leptin resistance, as such increases promote a cascade of increasing appetite, adipose deposition and eventual diabetes. It has been speculated that leptin resistance may be a key mechanism by which the fetus is programmed for a future 'life of thrift'.[24] In the presence of intrauterine undernutrition, leptin resistance promotes insulin release and hence the deposition of fat stores to optimize survival when nutrients are available, in preparation for times when food is in short supply.

Maternal hypercholesterolemia

There is increasing evidence that maternal hypercholesterolemia promotes atherosclerosis in offspring. Napoli *et al*. studied aortas from aborted fetuses and preterm newborns who had died soon after birth, and related the findings to maternal cholesterol levels.[27] Sixty-three per cent of fetuses from normocholesterolemic mothers showed signs of fatty streak formation in the aorta and the lesions were larger and more frequent in those whose mothers were hypercholesterolemic. A study of their composition suggested that intimal low-density lipoprotein (LDL) accumulation and oxidation were responsible for the lesions. The mechanism appears to be non-genetic because diet-induced hypercholesterolemia in rabbits produces similar lesions in the fetus and atherosclerosis can be inhibited by lipid-lowering and antioxidant interventions.[28] Further, the fetal lesions induced by maternal hypercholesterolemia have been shown to progress in childhood.[29] This increase in fatty-streak formation in children of mothers with hypercholesterolemia could result from one of several possible mechanisms, but there is recent evidence that the intrauterine environment can cause persistent changes in arterial gene expression. In a study of genetically uniform mice, Napoli *et al*. demonstrated, using DNA microarray analysis, that 139 of the 11 000 murine

genes in offspring were significantly regulated by maternal hypercholesterolemia and that the changes persisted.[30] Together, these recent studies provide compelling evidence that maternal diet and cholesterol levels predispose offspring to atherosclerotic disease by altering gene expression in the vascular wall. Prevention of cardiovascular disease clearly needs to begin at this early time in life.

Elastin in vascular walls

There is far more involved in predisposition to cardiovascular disease than disorders of lipid metabolism. Another important element amenable to programming before birth is the amount and proportion of elastin in the vascular walls. Elastin is a high molecular weight, insoluble protein polymer, which, in the aorta, provides most of the elastic properties enabling the vessel wall to contract and expand.[31] Cross-linked elastin has a very slow turnover with a half-life of approximately 40 years, is largely laid down in fetal life, and has very little new production in adulthood. With advancing age, the amount of elastin in the vessel wall decreases rendering the vessel wall much stiffer because of the higher proportion of collagen. Martyn *et al*.[32] have shown that 50-year-old men and women with decreased aortic elasticity, as shown by measurement of pulse-wave velocity, tended to have been of lower birthweight, and the association was independent of current blood pressure. The effects of growth restriction induced by fetal undernutrition are at present unknown, but elastin deposition is known to be regulated by IGF 1 and glucocorticoids,[33] raising the possibility that vascular compliance throughout life may be altered by the hormonal milieu of the intrauterine environment.

Role of glucocorticoids

There is evidence that some aspects of programming may be mediated by premature or excessive exposure of the fetus to glucocorticoids. During most of fetal life, the fetal hypothalamic–pituitary–adrenal (HPA) axis produces very little cortisol,[34] and cortisol from the mother is inactivated by 11 β-hydroxysteroid dehydrogenase type 2 as it crosses the placenta. Towards term, the fetus produces increasing amounts of cortisol for the purpose of enhancing maturation of the lungs and other organs, redirecting energy from growth towards maturation, and promoting the sequence of events resulting in labour. In rats, inhibiting the function of 11 β-hydroxysteroid dehydrogenase, and thus increasing fetal exposure to maternal endogenous glucocorticoids, reduces birthweight and causes hypertension and glucose intolerance in adulthood.[35,36] The activity of 11 β-hydroxysteroid dehydrogenase in rats has been shown to be regulated by maternal nutrition, suggesting a possible mechanism by which undernutrition may programme the fetus by permitting excessive exposure to maternal cortisol.[37]

In clinical practice, pharmacological doses of 'cortisol' are administered to pregnant women at risk of early preterm birth to enhance fetal maturation.[38] The drug employed is either betamethasone or dexamethasone, used because neither are inactivated by placental enzymes. This treatment has been shown conclusively to reduce the rate of respiratory distress syndrome and death in the newborn period, but the lifelong consequences of repeated doses are unknown. Using a sheep model, we have shown that repeated intramuscular injections of betamethasone to the pregnant ewe, in doses that effectively mature the fetal lungs,[39] produce growth restriction,[39] and delayed myelination in the central nervous system,[40] followed in postnatal life by altered responses of insulin and the HPA axis to challenges.[41] If repeated injections are given intramuscularly to the fetus under ultrasound guidance, there are similar effects on lung maturation,[42] minimal effects on growth,[43] inconsistent effects on brain development,[44] and postnatal alterations in insulin and HPA responses.[41,45] These differential outcomes that depend on the route of glucocorticoid administration provide an opportunity to dissect out the lifelong consequences of prenatal glucocorticoid exposure from those of fetal growth restriction.[45] The evidence to date suggests that prenatal exposure to glucocorticoids alters subsequent insulin responses, regardless of the route of exposure, and that fetal growth disturbance is not a mandatory component of the programming sequence. Further research in this field will clarify the role played by glucocorticoid exposure in the process by which undernutrition programmes the fetus for postnatal life.

Role of the placenta

The fetus derives its nutrition from the placenta. In most pregnancies, the placenta remains competent in terms of respiratory and nutrient support until term, when intrauterine development is complete and labour ensues. However, in some cases, the functioning of the placenta becomes insufficient, resulting in inadequate fetal nutrition. If this condition is severe enough, respiratory insufficiency and death may result.[46] Placental failure rarely results from maternal undernutrition and in contemporary society most often is of unknown cause, sharing common pathways with many cases of pre-eclampsia. After many decades of focused research, we remain unable to improve placental function and our understanding of the mechanisms by which the functioning of this organ becomes insufficient is incomplete.

Modern obstetric management centres on the detection of fetal growth disorders and the monitoring of fetal welfare to ensure that it remains safe for the child to remain undelivered. This approach is largely successful in preventing hypoxia and death, but the lifelong consequences of placentally induced fetal undernutrition are uncertain. If the lessons from animal laboratories equate to the human disease of placental insufficiency, and there is little reason to expect they would not, then insulin resistance and cardiovascular disease are likely consequences. The retrospective cohorts linking birth and adult outcomes studied so far are of limited use because the birth data are from eras when accurate gestational-age dating was not possible, and the relative contributions of prematurity and growth restriction to low birth-weight infants were unknown.

The relationships between maternal nutrition and placental function are also uncertain. However, it can be said with

confidence that in general perinatal practice, clinically evident fetal growth restriction is more frequently the result of placental disease than of maternal undernutrition. This observation complicates research investigating the role of maternal nutrition in perinatal outcomes, and is inadequately addressed as a confounding variable in most studies in this field.

Multigenerational effects

The increased propensity to disease described in the thrifty phenotype hypothesis encompasses the continuation of disease tendencies in subsequent generations.[11] The possibility that future generations can be programmed by environmental influences on the mother is attracting increasing interest and the mechanisms require elucidation. It has been known for many years that experimentally induced glucose intolerance in rats is passed from mother to offspring, and the abnormality can persist through several generations.[47] Evidence from a study of a rat colony maintained on marginal protein deprivation through 12 generations suggests a predisposition to adult disease can persist for three generations.[48] In this nutritional environment, re-feeding during pregnancy caused offspring to be prone to obesity during adulthood and the return of the colony to normal characteristics required three generations of appropriate dietary supply. The mechanism of this heritability must involve altered gene expression and may occur during very early stages in development. Indeed, altering the environmental milieu of the embryo can have profound effects on lifelong health and body size through programming. In sheep, *in vitro* embryo culture procedures can produce a condition of excessive growth of the fetus and lamb known as 'large offspring syndrome' (LOS).[49] One process by which LOS occurs has been shown to centre on reduced methylation of fetal DNA, and expression of the ovine IGF2R gene suggesting epigenetic alterations in imprinted genes.[50] The effects of nutritional influences and environmental chemicals on development of the oocyte and embryo warrant detailed investigation. Nevertheless, the evidence available at this time suggests that fetal programming can persist for several generations.

Conclusions

This manuscript has outlined some of the evidence that human predisposition to adult disease is programmed before birth. The process appears to involve one or more intrauterine triggers interacting with the genome, and the risk is then amplified or minimized by postnatal lifestyle. Fetal nutrition and cortisol are capable of acting as intrauterine triggers, but it is likely that there are many other possible pathways. The multigenerational aspects of the process also make it likely that programming extends to earlier times in life than the fetus, including the embryo and perhaps the oocyte. The origins at early times in life and the interactions between the genome, intrauterine and postnatal environments, suggest that this emerging field would be better described as the 'early origins of adult disease', rather than its previous label of the 'fetal origins of adult disease'.

Acknowledgements. The present work was supported by grants from the National Health and Medical Research Council of Australia (980578 and 110301), the Women and Infants Research Foundation of Western Australia and the Institute of Human Development, Child and Youth Health, Canada.

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