REVIEW ARTICLE

Markers of Fetal Onset Adult Diseases

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The "fetal origins hypothesis", proposes that non-communicable diseases including coronary heart disease, type 2 diabetes and hypertension originate through the responses of a fetus to undernutrition, that permanently change the structure and function of the body. Associations between low birthweight and disease in later life have been widely studied in Europe and the USA. Studies in southern India have shown that babies who are short and fat tend to become insulin deficient and have high rates of non-insulin dependent diabetes. These findings have important public health implications as it suggests that associations with body size at birth underestimate the contribution of intrauterine development to later disease, and also, that while the primary prevention of coronary heart disease and non-insulin dependent diabetes may ultimately depend on changing the body composition and diets of young women. Therefore, more immediate benefit may come from preventing imbalances between prenatal and postnatal growth among children. The basic premise of the thrifty gene hypothesis is that certain populations may have genes that determine increased fat storage, which in times of famine represent a survival advantage, but in a modern environment result in obesity and type 2 diabetes. The fetal origins theory is of greatest relevance to the developing world and the implications of this work for global health are enormous. To reduce chronic diseases, we need to understand how the human fetus is nourished and how malnutrition changes its physiology and metabolism, so that interventions be implemented to limit the damage. The challenge for the next decade must be to discover the cellular and molecular mechanisms giving rise to these associations. If this aim is accomplished, it might be possible to devise strategies to reduce the impact of these disabling chronic and expensive diseases.

Keywords: *Barker hypothesis, Fetal origins hypothesis, Non-communicable diseases, Thrifty gene hypothesis.*

The core of the theory of fetal origins of disease is that nutritional deprivation of the fetus during critical periods of development forces the baby to resort to adaptive survival strategies, which entail a resetting of the normal course of metabolic, physiological, and anatomical development(1). These adaptations become maladaptive if the organism encounters contrasting nutritional circumstances in later life. It has also become clear that maternal constraint must have a central role in fetal programming. Under such circumstances, maternal uterine constraint becomes a dominant regulator of fetal growth. The proponent of "fetal origins hypothesis" is a British epidemiologist David Barker. The fetal origin, hypothesis was developed by linking records of births in the early 20th century with health in later life from the Hertfordshire records(1-10).

Associations between low birthweight and later disease have been widely replicated in studies in Europe and the USA(11-13). The association between low birth weight and coronary artery disease has been confirmed in studies of men in Sweden(11), Helsinki, Finland, and South Wales(14), and among 80 000 women in the American nurses study(12). The fetal origins theory is of greatest relevance to the developing world, and the implications of this work for global health are enormous(15). Studies in southern India have shown that babies who are short

and fat tend to become insulin deficient and have high rates of non-insulin dependent diabetes(16). These findings were similar to those seen in Pima Indians and also with observations in Sheffield that showed an association between abdominal circumference at birth and death from coronary heart disease(17). Shortness and fatness are thought to be the result of maternal hyperglycaemia, with consequent imbalance in the supply of glucose and other nutrients to the fetus. Studies in Preston showed that babies whose placentas are disproportionately large in relation to their own weight tend to have raised blood pressure (18).

These findings have important public health implications, as it suggests that associations with body size at birth underestimate the contribution of intrauterine development to later disease. While the primary prevention of coronary heart disease and non-insulin dependent diabetes may ultimately depend on changing the body composition and diets of young women, more immediate benefit may come from preventing imbalances between prenatal and postnatal growth among children. Many chronic disorders that manifest later in life may be related to two seemingly opposing factors potentially present early in life; (*i*) poverty (*i.e,* malnourished mothers give birth to malnourished infants with low birth weight [LBW]), and (*ii*) prosperity (exposure of an infant with LBW phenotype to a high caloric diet). These factors contribute to the biological phenomenon of developmental plasticity, or the ability of a genotype to produce multiple forms and behaviors in response to environmental conditioning(19). The Fetal origin hypothesis is summarized in ***Fig.*****1**(19)**.**

Four birth phenotypes associated with later disease have been identified; (*a*) babies who are thin at birth; (*b*) babies who are short at birth; (*c*) babies short and fat at birth, and (*d*) babies born with a large placenta(19). Babies that are thin tend to be insulin

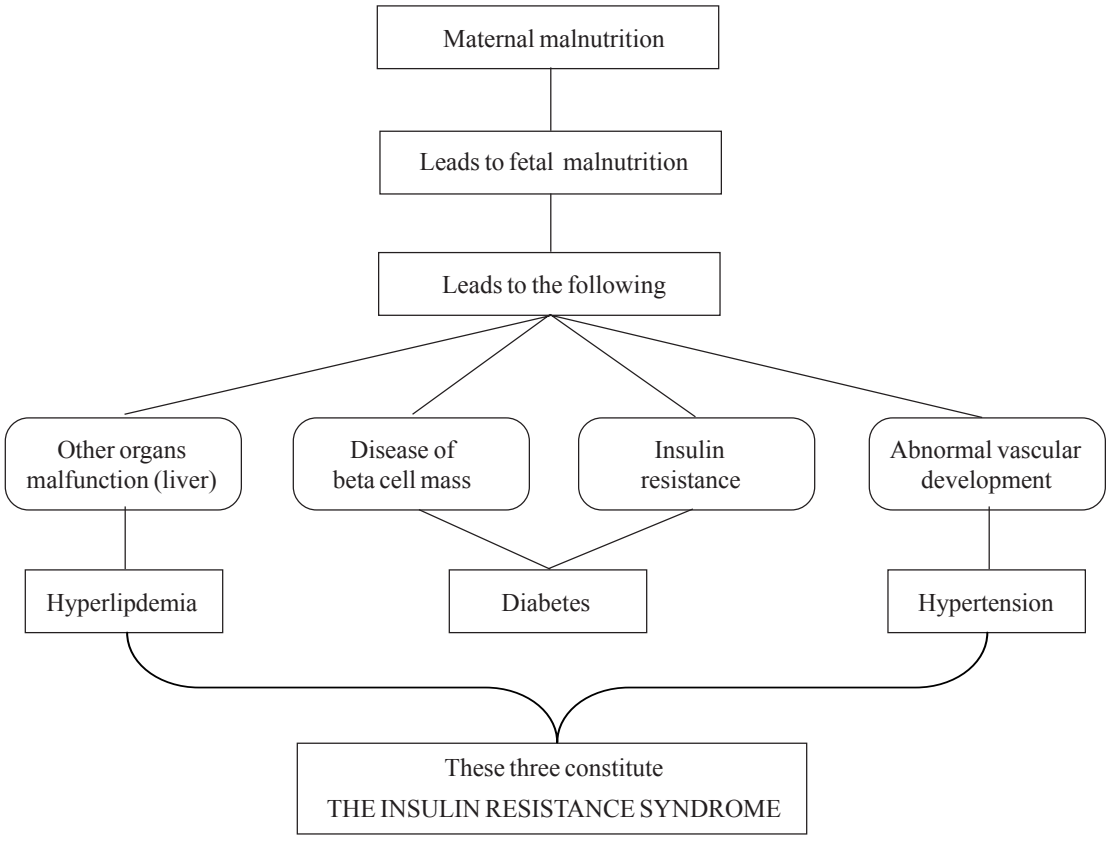

FIG. 1 *Fetal origins hypothesis.*

resistant as children and adults, and are therefore liable to develop the insulin resistance syndrome(20). It could be that the thin baby has adapted to under-nutrition through endocrine and metabolic changes. Babies that are short in relation to their head circumference, and babies that have a reduced abdominal circumference, tend to have persisting abnormalities of liver function, including raised serum LDL cholesterol and plasma fibrinogen concentrations(21,22). Babies that have a small abdominal circumference in relation to their head circumference can result from "brain sparing" circulatory adaptations by which cardiac output is diverted to the brain at the expense of the trunk(23).

THE THRIFTY GENOTYPE AND THE THRIFTY PHENOTYPE

The prospective studies by Yajnik, *et al*.(24) in Pune in India are therefore notable and deserve attention. Caroline Fall from David Barker's Medical Research Council group in Southampton along with Yajnik and his team have used anthropometric measurements of babies to describe their morphology at birth(25). According to Yajnik, maternal uterine constraint becomes a dominant regulator of fetal growth in order to protect the mother from having to deliver an inappropriately large baby. In rural villages mothers average about 44 kg in mid-gestation, with a height of 152 cm and body mass index of 18 kg/m^2(25). This leads to fetal malnutrition, which may be a major component in the susceptibility to coronary heart disease and non-insulin-dependent diabetes.

In the words of J V Neel, the initial proponent of the thrifty genotype hypothesis, the thrifty genotype is "rendered detrimental by progress" and leads to high rates of metabolic syndrome and type 2 diabetes(26). This has provided an opportunity to assess the state of the hypothesis and consider its implications for future research and policy(27,28). Along with inadequate fetal nutrient supply, other explanations, including the operation of genetic factors and programming of certain endocrine axes, have also been put forward to explain the origin of these non-communicable diseases and the epidemiological associations(14). In relation to insulin action and diabetes, Hales and Barker have described this phenomenon as the "thrifty phenotype"(29-31). The basic premise of the thrifty gene hypothesis is that certain populations may have genes that determine increased fat storage, which in times of famine represent a survival advantage, but in a modern environment, result in obesity and type-2 diabetes(32,33). Intrauterine growth retardation (IUGR) or clinically abnormal thinness at birth strongly predicts the subsequent occurrence of hypertension, hyperlipidemia, insulin resistance, type 2 diabetes and ischemic heart disease.

The concept of fetal programming during development has been proposed to explain these findings. Fetal undernutrition, during middle gestation in particular, raises the risk of later disease by the programming of blood pressure, cholesterol metabolism, blood coagulation and hormonal settings(1). One third of Indian babies have a low birthweight, on average they weigh around 2.7kg. This makes them highly susceptible to conditions mentioned earlier when they are older. The thinness of Indian babies is due to poor muscle mass and small abdominal viscera and is due to the "thrifty phenotype" of Indian babies, which enhanced survival in subsistence conditions in the past, but becomes detrimental in a modern context of plentiful food and reduced physical activity(34). Yajnik also showed that in the babies of urban mothers in Pune, insulin concentrations in the blood of the cord seem raised compared with British babies and were correlated with subscapular skin-fold thickness(35). Indian babies are much smaller than those in Southampton in all respects except measures of body fat-especially central fat as judged by the subscapular skin-fold thickness. They describe this as the "thin-fat" baby syndrome and believe that it shows that the excess visceral adiposity of most asian adults can be traced back to the neonate(24,36). In a study conducted in Mysore, India, it was found that low birthweight men and women were insulin resistant and that coronary heart disease and its risk factors were linked to features of insulin resistance syndrome(16,37).

The obvious response to the "small baby predicts later disease" paradigm is to propose dietary supplementation of mothers to produce larger babies. We should act to prevent retarded fetal growth in

mothers whose diet is so poor as to limit the baby's expected growth trajectory in relation to its parental and genetic inheritance, and to the maternal uterine environment(38). But it has been seen that low birth weight followed by catch-up growth was an important risk factor for later disease, over and above low birth weight itself(29). Therefore, if we already have short thin-fat mothers producing small thin-fat babies, should we really be feeding them more? This is a tricky question. The answer is probably "no", because this results in augmented fetal growth which will be out of harmony with the baby's inheritance and future growth patterns. The resolution of this conundrum will require focused investment in international studies on the regulation of early human growth and development (38).

INTRAUTERINE PROGRAMING

In conditions of undernutrition, a genotype conferring insulin resistance would be preferentially selected during evolution because this genotype would increase survival among small babies, who would otherwise have a high perinatal mortality. This phenomenon has been referred to as "the surviving small baby hypothesis"(14,17). On the basis of this finding, it has been suggested that this gene, which increased birth weight, might enhance perinatal survival and perhaps paradoxically increase susceptibility to type 2 diabetes(14).

Several genes have already been identified as candidates for the thrifty genotype, including those encoding proteins of the insulin-signaling and leptin pathways, as well as intermediary fat metabolism. Particular interest lies in the peroxisome-proliferator activated receptors. According to Joffe, *et al*.(33), an innovative approach might be to focus on the "mirror image" of the thrifty genotype - congenital lipoatrophic diabetes mellitus, whose molecular defect remains enigmatic. They conclude that the genetic basis of the thrifty genotype probably derives from the multiplicative effects of polymorphisms at several sites, rather than a single regulatory abnormality(33). More recently the molecular biology of this process is emerging as a fascinating conflict between maternal and paternal influences that involves a range of imprinted genes, especially insulin-like growth factor-2 and its receptors(39). The protein '32-33 split pro-insulin' is now identified as a marker of impaired pancreatic beta cell function. This is a biologically inactive precursor of insulin. This is found to be elevated in IUGR and may have a role in future development of type-2 diabetes. It has therefore become apparent that it is the disharmony between fetal growth and later growth rates that seems to be the best predictor of the later pathology(2,40). There is therefore a clear need to study interactions between genes and nutrient supply *in utero*.

Hormones have also been implicated to regulate fetal growth and development of individual fetal tissues, and they have a central role in intrauterine programming. Nutritional challenges that reduce fetal nutrient availability lower anabolic hormones [*e.g.* insulin, insulin-like growth factor (IGF)-I, thyroxine (T_4)] and increase catabolic hormone concentrations [*e.g.* cortisol, catecholamines, growth hormone (GH)]. Challenges that increase the fetal nutrient supply raise anabolic and reduce catabolic hormone levels in the fetal circulation. Certain patterns of intrauterine growth, particularly growth retardation, can be related to specific postnatal outcomes. Hormones have a central role in intrauterine programming, and insulin, insulin-like growth factors, thyroxine and the glucocorticoids act as nutritional and maturational signals and adapt fetal development to prevailing intrauterine conditions, thereby maximizing the chances of survival both in utero and at birth. However, these adaptations may have long-term sequelae(41).Of the hormones known to control fetal development, it is the glucocorticoids that are most likely to cause tissue programming in utero. They are growth inhibitory and affect the development of all the tissues and organ systems most at risk of postnatal pathophysiology when fetal growth is impaired. Their concentrations in utero are also elevated by all the nutritional and other challenges known to have programming effects. Glucocorticoids act at cellular and molecular levels to alter cell function by changing the expression of receptors, enzymes, ion channels and transporters. They also alter various growth factors, cytoarchitectural proteins, binding proteins and components of the intracellular signaling pathways. Glucocorticoids

act directly on genes and indirectly through changes in the bio-availability of other hormones. These glucocorticoid-induced endocrine changes may be transient or persist into postnatal life with consequences for tissue growth and development both before and after birth. In the long term, prenatal glucocorticoid exposure can permanently reset endocrine systems, such as the somatotrophic and hypothalamic–pituitary–adrenal axes, which, in turn, may contribute to the pathogenesis of adult disease. Endocrine changes may, therefore, be both the cause and the consequence of intrauterine programing(41). Glucocorticoids act at cellular and molecular levels to alter cell function by changing the expression of receptors, enzymes, ion channels and transporters. They also alter various growth factors, cytoarchitectural proteins, binding proteins and components of the intracellular signaling pathways(41).

INFLUENCES THAT ACT IN POSTNATAL LIFE

Influences that act in postnatal life add to the effects of low birth weight. The highest prevalence of non-insulin dependent diabetes is found in people who had low birth weight but were obese as adults. The highest death rates from coronary heart disease occurred in men who were thin at birth but had accelerated weight gain in childhood. We do not yet know whether this association is because of the pathological effects of a high fat mass persisting into adult life, deleterious effects of catch up growth, or the intrauterine resetting of endocrine axes that control growth(10). It is not known why catch-up growth is detrimental, but one speculation is that fetal growth restriction leads to reduced cell numbers, and subsequent catch-up growth is achieved by overgrowth of a limited cell mass. A possible link between catch-up growth and coronary heart disease is that it reflects persisting changes in secretion of hormones, including insulin, insulin-like growth factor 1, and growth hormone, which are established *in utero* in response to undernutrition and influence both childhood growth and coronary heart disease. It is also possible that if they develop a high body mass in childhood they have a disproportionately high fat mass(42).

Babies born in countries undergoing rapid transition would face malnutrition in their intrauterine life and a state of relative over nutrition in later life, which provides oppurtunities for 'catch up'. Babies which catch–up in body weight, fat and height are more insulin resistant as children(43). It is always better to take steps to prevent low birth weight babies being born rather than giving post natal nutritional supplementation because it is more rewarding to avoid obesity in those who were small at birth(44). An understanding of the mechanisms regulating fetal development is important and an improved understanding of these mechanisms will emphasize new approaches to prevent diseases such as atherosclerotic vascular disease and type 2 diabetes(14). If fetal development can be better optimized, there is definitely the potential to reduce the escalating impact of type 2 diabetes and atherosclerotic vascular disease.

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