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Maternal nutrition, placental growth and fetal programming

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Babies who are small or disproportionate at birth, or who have altered placental growth have increased rates of CHD, hypertension and non-insulin-dependent diabetes in adult life. These associations are thought to reflect fetal 'programming'. Although little is known about the maternal influences which programme the human fetus, initial studies point to the importance of a mother's capacity to satisfy nutrient requirements of her fetus through the placental supply line.

Fetal programming

During prenatal growth and development, periods of rapid cell division occur at different times in the various tissues of the body. During these 'critical periods' the nutrient and hormonal milieu of the conceptus may alter expression of the fetal genome and this may have lifelong consequences. The phenomenon is termed fetal programming (Lucas, 1991). The processes which underlie programmed changes in structure and function include reduction in cell numbers, change in the distribution of cell types and in organ structure, and re-setting of hormonal feedback (McCance & Widdowson, 1974; Widdowson & McCance, 1975).

Experimental studies in animals have documented many examples of fetal programming, including long-term effects of alterations in the mother's diet in pregnancy on postnatal growth, relative organ size and lipid metabolism of the offspring (Barker, 1994). Support for the proposal that programming may lead to the pathological changes that underlie human cardiovascular disease and diabetes in adult life comes from recent animal studies. Lifelong elevation of blood pressure in the offspring has resulted from maternal uterine artery ligation in guinea-pigs (Jansson & Persson, 1990) and from a maternal low-protein diet in rats (Langley & Jackson, 1994). The offspring of rats fed on a diet with a low protein : energy value exhibited a permanently altered balance between hepatic glucose production and utilization; the same diet during postnatal life had no effect on hepatic glucose metabolism (Desai *et al.* 1995). Size at birth appears to be only an indirect proxy for fetal programming, as many influences programme the fetus while exerting only minor effects on its overall growth.

Size at birth and later CHD

The view that adverse influences acting early in an individual's life might exert long-term effects on their health is not new (Rose, 1964; Dubos *et al.* 1966). Recent follow-up studies provide strong evidence of such effects and point to fetal life as a critical period during which they originate.

Studies carried out in Hertfordshire, UK, showed for the first time that CHD is associated with low birth weight (Osmond *et al.* 1993). From 1911 onwards the birth weight of every baby born in the county was recorded. Tracing of 15 726 men and women born during 1911–30 showed that death rates from CHD were twice as high in those who weighed 5·5 pounds (2·5 kg) or less at birth than in those who weighed 9 pounds (4·1 kg) or more (Fig. 1). Another study, of 1586 men born in Sheffield, UK, during 1907–25, showed an increased risk of later CHD in babies who had low growth rates *in utero*, rather than in those who were small because they were born prematurely (Barker *et al.* 1993c). Studies of a large cohort of nurses in USA (Rich-Edwards *et al.* 1995), of men in the Caerphilly Study (Frankel *et al.* 1996), and of men and women in Mysore, India (Stein *et al.* 1996) have confirmed in other populations that small size at birth is an important risk factor for CHD.

Consistent with these findings, babies with retarded fetal growth are at increased risk of developing raised levels of risk factors for cardiovascular disease during adult life.

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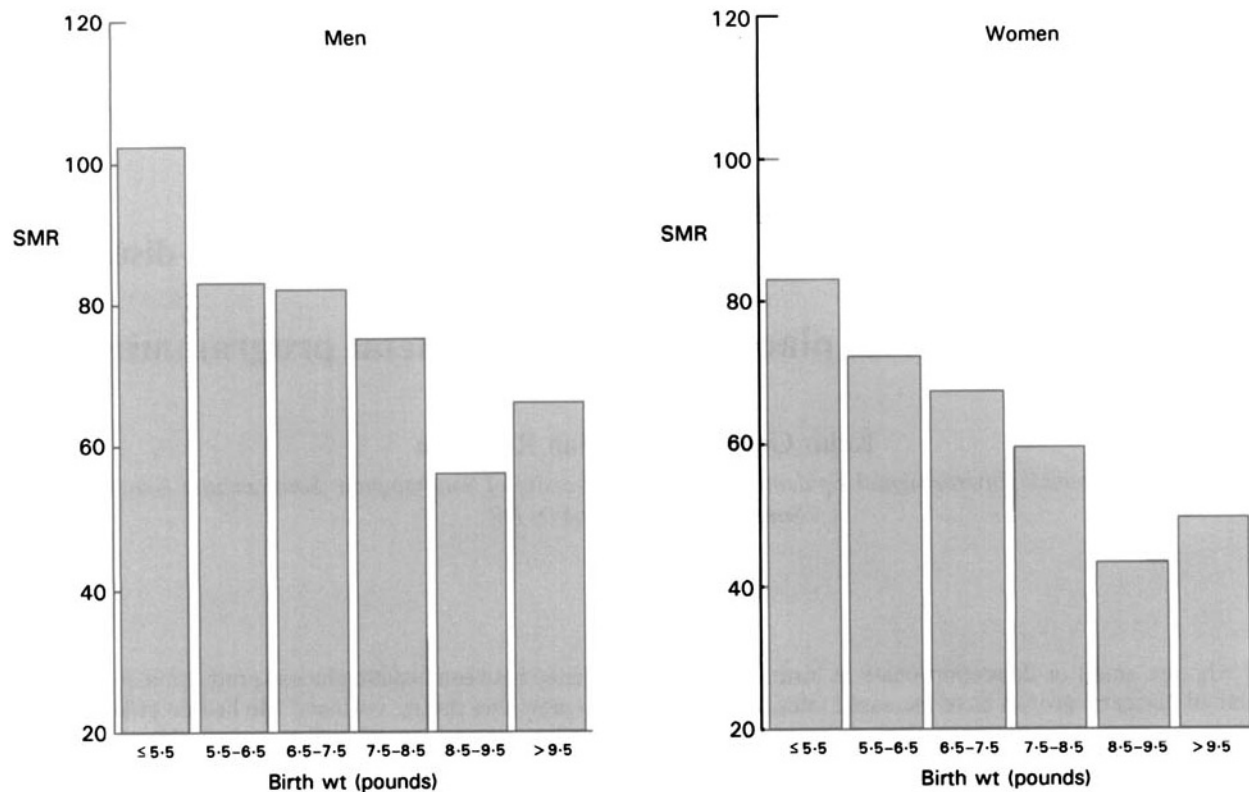
Fig. 1. Death rates (standardized mortality ratios; SMR) from CHD according to birth weight in 10 141 men and 5585 women born in Hertfordshire, UK.

These include increased blood pressure and elevated plasma concentrations of glucose, insulin, fibrinogen and LDL-cholesterol (Barker, 1995). For some risk factors, including impaired glucose tolerance, the effects of poor growth *in utero* are greater in obese subjects; for other factors, including serum LDL-cholesterol concentrations and increased left ventricular thickness, the effects of poor growth *in utero* are independent of adult weight (Barker, 1995). The associations between size at birth and cardiovascular disease and risk factors are independent of the influences of adult social class and smoking, and have been consistently found in different populations. A systematic review of thirty-four studies examining the relationship between birth weight and blood pressure in childhood and adult life found a consistent inverse association apart from in adolescence when the tracking of blood pressure is perturbed by the adolescent growth spurt (Law & Shiell, 1996).

Mechanisms linking fetal programming and adult disease

Progress elucidating the mechanisms linking fetal development with adult disease is, for example, being made in understanding the strong relationship between low birth weight and thinness at birth and impaired glucose tolerance in later adult life (Phillips *et al.* 1994). This association has been confirmed in three studies in the UK (Barker, 1995), three in the USA (McCance *et al.* 1994; Valdez *et al.* 1994; Curhan *et al.* 1996), and one in Sweden (Lithell *et al.* 1996).

Metabolic studies in adults have shown that those who were thin at birth tend to be insulin resistant in adult life

(Barker *et al.* 1993*b*; Phillips *et al.* 1994) and to have other metabolic changes suggestive of a bias towards fuel conservation, including reduced rates of glycolysis in their muscles (Taylor *et al.* 1995). Impaired fetal skeletal muscle development is a feature of thin neonates, and the persistence of adaptations that act to reduce glucose consumption by fetal skeletal muscle may contribute to the metabolic abnormalities seen in adults who were thin at birth.

Mechanisms linking reduced fetal growth and raised adult blood pressure are another area of active research. Initial studies point to the importance of the renin–angiotensin–aldosterone system (Martyn *et al.* 1996*b*), to changes in vascular structure, including loss of elasticity in vessel walls (Martyn *et al.* 1995), and to the effects of glucocorticoid hormones (Edwards *et al.* 1993).

Determinants of fetal growth

The long-term effects raise the important question of the maternal influences that may underlie them and highlight the importance of understanding the principal determinants of fetal growth. Whilst the fetal genome undoubtedly determines growth potential *in utero*, the weight of evidence strongly suggests that the fetal genome plays a subordinate role in determining the growth that is actually achieved (Carr-Hill *et al.* 1987; Snow, 1989). This evidence includes animal cross-breeding experiments (Walton & Hammond, 1938), studies of half siblings related either through the mother or the father (Morton, 1955) and embryo-transfer studies (Brooks *et al.* 1995). For example, in embryo-transfer studies it is the recipient mother rather

than the donor mother that more strongly influences the growth of the fetus (Brooks *et al*. 1995). Thus, it seems that the dominant determinant of fetal growth is the intrauterine environment, in particular the nutrient and O_2 supply to the fetus (Ounsted & Ounsted, 1966).

Before further considering the maternal influences underlying fetal programming two important aspects of development must be borne in mind; these are the setting of fetal demand by its growth trajectory in early pregnancy and the differing effects of fetal undernutrition at specific stages of gestation.

The fetal growth trajectory

Early in development an embryo comprises two groups of cells, the inner cell mass that develops into the fetus and outer cell mass that becomes the placenta. Experiments in animals indicate that the allocation of cells between the two masses is influenced by nutrition and by hormones (Kleeman *et al*. 1994; Walker *et al*. 1996). Alterations in cell allocation change the trajectory of fetal growth, with a fast growth trajectory increasing the fetal demand for nutrients and paradoxically rendering the fetus more vulnerable to a poor nutrient supply in late gestation (Harding *et al*. 1992).

Among ewes, maternal undernutrition in the last trimester has little effect on fetuses on a low growth trajectory. In contrast, those growing more rapidly make a series of adaptations in order to survive, including fetal wasting and placental oxidation of fetal amino acids to maintain lactate output to the fetus (Harding *et al*. 1992). The trajectory of fetal growth is thought to increase with improvements in periconceptual nutrition and is faster in male fetuses (Leese, 1990). The greater vulnerability of such fetuses on a fast trajectory could contribute to the rise in CHD with Westernization and the higher death rates in men.

Effects at different stages of development

The varying critical periods during which organs and systems mature indicate that fetal undernutrition at different developmental stages is likely to have specific short- and long-term effects. Babies that are symmetrically small, short or thin are thought to originate partly through fetal undernutrition at different stages in gestation and follow-up studies suggest they are predisposed to different disorders in adult life (Barker, 1995).

Proportionately small babies are at increased risk of raised adult blood pressure, but do not appear to develop CHD. They may have down-regulated their growth in response to undernutrition early in development, reducing the subsequent demand for nutrients and making the fetus less likely to experience relative undernutrition in late gestation (Barker, 1994). As adults, individuals who were disproportionately short at birth tend to have abnormalities of systems controlled by the liver, including cholesterol metabolism and clotting factor synthesis (Barker *et al*. 1992). *In utero*, they may have invoked the so-called 'brain-sparing' reflex later in gestation, diverting nutrients to spare brain metabolism at the expense of the trunk, limbs and abdominal viscera including the liver (Rudolph, 1984).

Thin babies with a low ponderal index (birth weight/ length^3) at birth are at increased risk of the insulin-resistance syndrome in adult life. Their thinness at birth reflects reduced subcutaneous fat and skeletal muscle in consequence of fetal undernutrition in the weeks before delivery (Barker, 1995).

In different populations the mix of babies with different phenotypes of fetal growth retardation varies greatly. Data collected in the World Health Organization study of lactational amenorrhoea has, for example, shown that babies born in China tend to be proportionately small, with symmetrical reduction of their skeletal proportions and a high ponderal index, whereas thin babies predominate in India (Barker, 1994). Such patterns could contribute to geographical variations in CHD death rates.

With respect to timing, it is important to appreciate that effects that manifest late in pregnancy may commonly originate much earlier in gestation. Thinness at birth, for example, has been traditionally thought to result from influences operating in the last trimester of pregnancy. This largely has its origins in studies of the Dutch Hunger Winter famine of 1944–5 (Stein *et al*. 1975). Recent studies have suggested, however, that outside the setting of famine, thinness at birth may more commonly result from influences affecting placental development much earlier in gestation (Robinson *et al*. 1994; Godfrey *et al*. 1997).

Maternal influences and fetal programming: maternal nutrition

While a mother's height and cigarette smoking are both strongly related to size at birth they are not related to levels of cardiovascular risk factors in the offspring (Law *et al*. 1991; Whincup *et al*. 1992). In contrast, initial studies suggest that maternal nutrition may have important long-term effects on the offspring (Campbell *et al*. 1996). This may reflect differences in the mechanisms through which height, smoking and nutrition affect fetal development.

Suggestions that normal variations in maternal nutrition may influence the growth of the fetus contrast with the view that fetal development is little affected by changes in maternal nutrition, except in circumstances of famine. This has partly arisen from the relatively disappointing results of human interventional studies of maternal nutrition during pregnancy (Kramer, 1993). Full assessment of the true impact of maternal nutrition, however, may require a more sophisticated view of fetal development and Table 1 lists four issues that need to be addressed.

Cumulative inter-generational effects

Experimental studies in animals have shown that nutrition may have cumulative effects on reproductive performance over several generations. Stewart *et al*. (1975) demonstrated cumulative inter-generational effects on reproductive performance when rats were exposed to a protein-deficient diet over twelve generations; on refeeding with a normal diet, it took three generations to normalize growth and development (Stewart *et al*. 1980).

Strong evidence for major inter-generational effects in human subjects has come from studies showing that a woman's birth-weight influences the weight of her baby

Table 1. Key issues that have yet to be adequately considered in determining the impact of maternal nutrition on human fetal development

Cumulative intergenerational effects
Paradoxical effects on placental growth
Fetal proportions and tissue-specific effects
Effects of dietary balance

(Klebanoff et al. 1989; Emanuel et al. 1992). We recently found (Godfrey et al. 1997) that whereas low-birth-weight mothers tended to have thin babies with a low ponderal index, the father's birth weight was unrelated to the baby's thinness at birth (Fig. 2). This may reflect impaired placentation in mothers who themselves had poor fetal growth, perhaps a result of alterations in uterine vasculature determined during fetal life.

Paradoxical effects on placental growth

The nutrient and hormonal milieu of the fetus is strongly influenced by the placenta. Experiments in sheep have shown that maternal nutrition in early pregnancy can profoundly influence placental growth (Robinson et al. 1994). High nutrient intakes in early pregnancy enhanced placental and, hence, fetal growth in ewes that were poorly nourished around the time of conception; conversely, in ewes well nourished around conception, high intakes in early pregnancy suppressed placental growth, decreasing placental and fetal size (Robinson et al. 1994). Although this suppression appears paradoxical, in sheep farming it is common practice for ewes to be put on rich pasture before mating and then on poor pasture for a period in early pregnancy (Slen, 1969).

In human subjects, we recently demonstrated similar suppressive effects of a high carbohydrate intake in early pregnancy on placental growth, especially if combined with a low dairy-protein intake in late pregnancy (Godfrey et al. 1996c). These changes in placental growth resulted in alterations in the placental weight:birth weight ratio (placental ratio). Such effects may be of long-term importance, since a follow-up study (Martyn et al. 1996a) found a U-shaped relationship between the placental ratio and later CHD (Fig. 3). While babies with a disproportionately small placenta may suffer as a consequence of an impaired placental supply capacity, those with a disproportionately large placenta may experience fetal catabolism and wasting to supply amino acids for placental consumption (Barker et al. 1993a; Robinson et al. 1995). Consequent fetal adaptations may underlie the increased adult CHD death rates in those with both low and high placental ratios.

Fetal proportions and tissue-specific effects

McCance & Widdowson (1974) demonstrated the principle that dietary manipulations during early development could have tissue-specific effects, resulting in alterations in an animal's proportions. Thus, compared with those fed on an energy-deficient diet, pigs fed on a protein-deficient diet in the first year of life had a disproportionately large head, ears and genitalia.
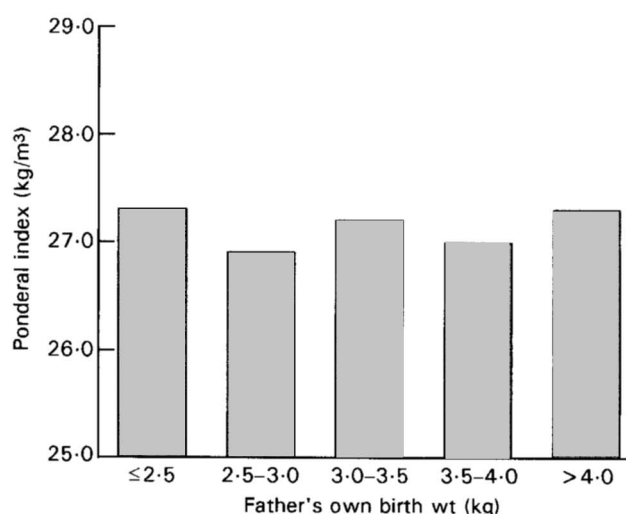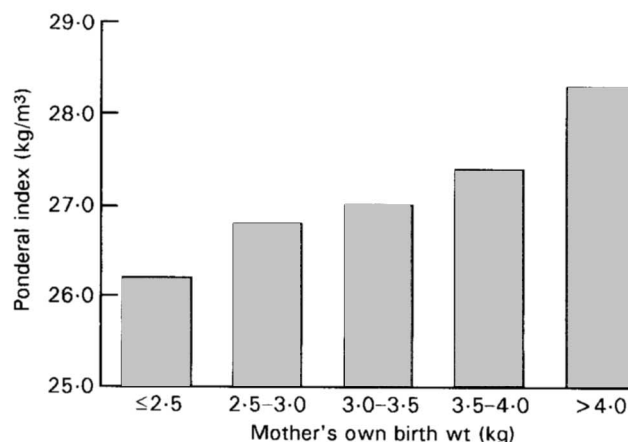

Fig. 2. Ponderal index (birth weight/length^3) at birth according to the mother's and father's own birth weights in 492 term babies. The relationship between mother's own birth weight and ponderal index was significant (linear regression; $P < 0.0001$), while that for father's own birth weight and ponderal index was not significant (linear regression; $P = 0.9$).
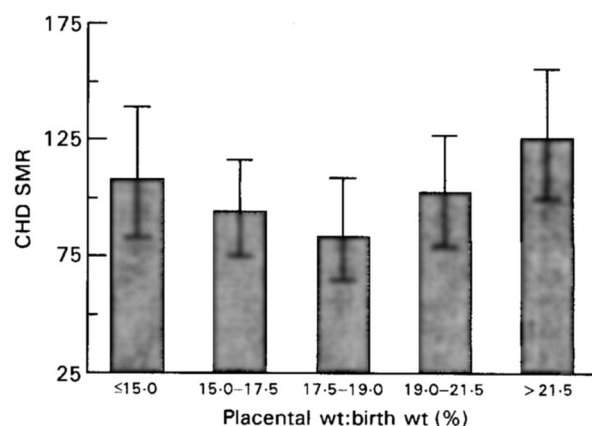

Fig. 3. Death rates (standardized mortality ratios; SMR) from CHD according to placental weight:birth weight ratio in 2571 men born in Sheffield, UK between 1907 and 1930. Error bars represent 95% CI. P (quadratic trend) $= 0.03$.

In human subjects, few studies have examined the possibility of maternal nutrition during pregnancy having tissue-specific effects on the fetus, leading to greater alterations in neonatal proportions than in birth weight. We have found that women with low dairy-protein intakes in late pregnancy tended to have babies that were thinner at birth; however, maternal dairy-protein intakes were not related to birth weight (Godfrey *et al*. 1996c, 1997). Initial follow-up studies have shown that while indices of maternal nutrition in pregnancy are related to the off-spring's subsequent blood pressure, these effects are not mediated through alterations in birth weight (Godfrey *et al*. 1994).

Effects of dietary balance

Experimental studies in pregnant rats have shown that feeding the mother on a diet with a low protein : carbohydrate and fat value alters fetal and placental growth and results in lifelong elevation of blood pressure in the offspring (Langley & Jackson, 1994). Follow-up of 40-year-old men and women whose mothers had taken part in a study of nutrition in pregnancy found that at either extreme of the balance of maternal animal-protein : carbohydrate intakes the offspring had both alterations in placental weight at birth and raised blood pressure in adult life (Campbell *et al*. 1996).

Support for the thesis that adverse effects on fetal and placental development may result from a low animal-protein : carbohydrate value comes from a study of 538 term deliveries in Southampton, UK (Godfrey *et al*. 1996c). Support for the thesis that a high animal-protein : carbohydrate value may also have adverse effects comes from a re-analysis of human studies providing dietary supplements to pregnant women (Rush, 1989). This review of sixteen trials of protein supplementation showed that supplements with a high percentage of energy derived from protein were consistently associated with lower birth weight.

The future

As yet, we do not know the true impact of maternal nutrition on fetal development. Recent observations challenge the view that fetal development is little affected by changes in maternal nutrition, except in circumstances of famine. Birth weight is an inadequate summary measure of fetal growth, and we need to adopt a far more sophisticated view of maternal nutrition and fetal development. This needs to not only take account of periconceptual effects on later fetal demand and early pregnancy effects on the materno–placental supply capacity, but also of the inter-generational and long-term sequelae of fetal adaptations to undernutrition (Fig. 4).

It could be argued that little progress has been made since Edward Mellanby (1933) observed: 'It is certain that the significance of correct nutrition in child-bearing does not begin in pregnancy itself or even in the adult female before pregnancy. It looms large as soon as a female child is born and indeed in its intrauterine life.'. Improvements in dietary recommendations to pregnant women require a strategy that includes progression beyond epidemiological
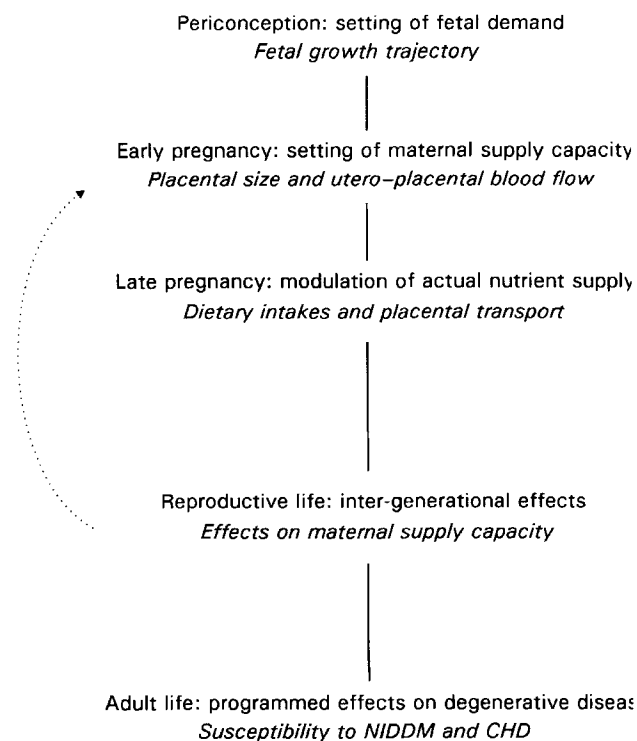

Periconception: setting of fetal demand
Fetal growth trajectory

Early pregnancy: setting of maternal supply capacity
Placental size and utero–placental blood flow

Late pregnancy: modulation of actual nutrient supply
Dietary intakes and placental transport

Reproductive life: inter-generational effects
Effects on maternal supply capacity

Adult life: programmed effects on degenerative disease
Susceptibility to NIDDM and CHD

Fig. 4. The effects of maternal nutrition acting at different stages from conception. NIDDM, non-insulin-dependent diabetes mellitus.

associations to greater understanding of the metabolic and molecular processes that underlie them. Animal studies indicate that if fetal demand exceeds the materno–placental supply capacity, cardiovascular, metabolic and endocrine adaptations are brought into play (Fig. 5). While we are only in the earliest stages of understanding the mechanisms that might mediate the effects of maternal nutrition on human fetal development, initial studies point to the importance of the glucose–insulin–insulin-like growth factor-1 axis (Godfrey *et al*. 1996a,b). Further research will require interdependent clinical, animal and epidemiological investigations.

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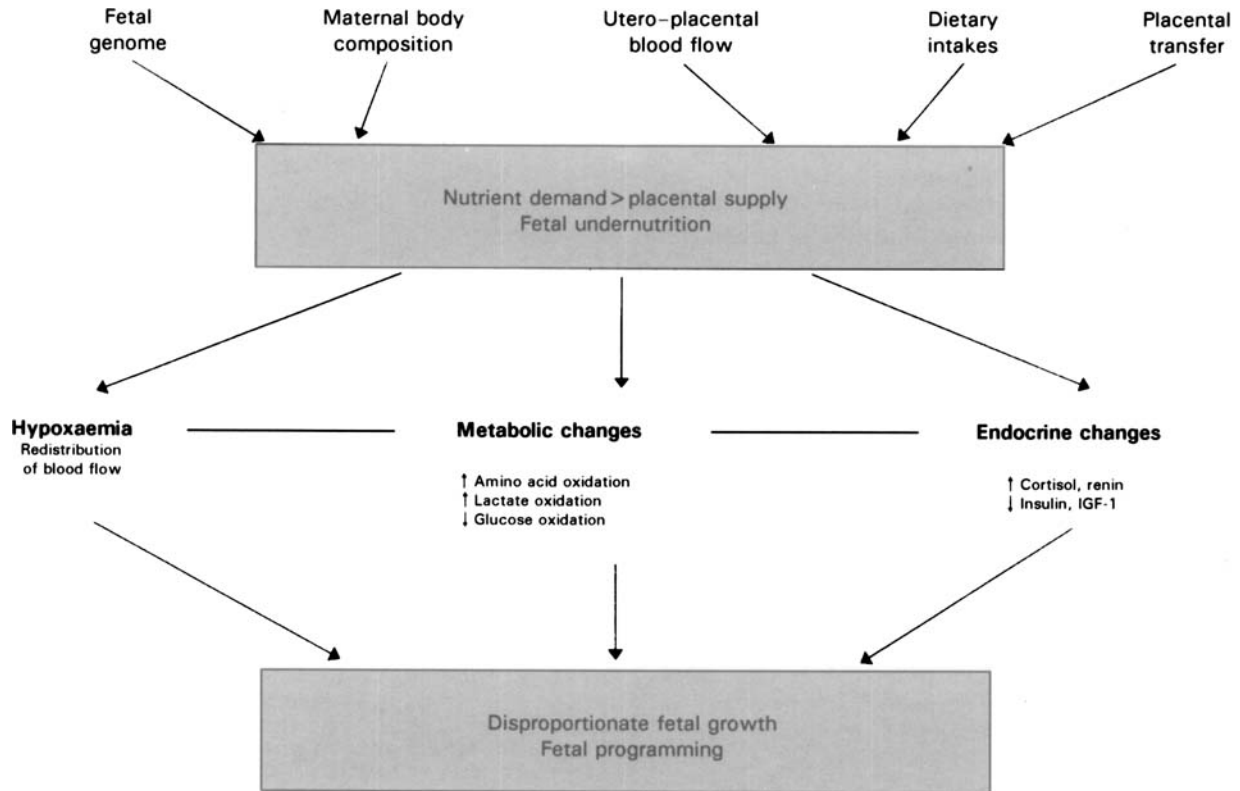
Fig. 5. A working framework for studying the influences underlying fetal undernutrition and the resultant adaptations. IGF-1, insulin-like growth factor-1.

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