

Fetal nutrition and adult disease¹⁻³

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ABSTRACT Recent research suggests that several of the major diseases of later life, including coronary heart disease, hypertension, and type 2 diabetes, originate in impaired intrauterine growth and development. These diseases may be consequences of “programming,” whereby a stimulus or insult at a critical, sensitive period of early life has permanent effects on structure, physiology, and metabolism. Evidence that coronary heart disease, hypertension, and diabetes are programmed came from longitudinal studies of 25 000 UK men and women in which size at birth was related to the occurrence of the disease in middle age. People who were small or disproportionate (thin or short) at birth had high rates of coronary heart disease, high blood pressure, high cholesterol concentrations, and abnormal glucose-insulin metabolism. These relations were independent of the length of gestation, suggesting that cardiovascular disease is linked to fetal growth restriction rather than to premature birth. Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with cardiovascular disease in later life. Impaired growth and development in utero seem to be widespread in the population, affecting many babies whose birth weights are within the normal range. Although the influences that impair fetal development and program adult cardiovascular disease remain to be defined, there are strong pointers to the importance of the fetal adaptations invoked when the maternoplacental nutrient supply fails to match the fetal nutrient demand. *Am J Clin Nutr* 2000;71(suppl):1344S–52S.

KEY WORDS Maternal nutrition, fetal growth retardation, coronary heart disease, hypertension, type 2 diabetes, polycystic ovary syndrome, maternal body composition, programming

PROGRAMMING AND THE “FETAL ORIGINS” HYPOTHESIS

The “fetal origins” hypothesis proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic, and endocrine disease in adult life (1). The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed *programming* (2). In evolutionary terms, the phenomenon is likely to reflect the benefits of plasticity during early development. Consistent with this, it is thought that coronary heart disease may be a consequence of fetal adaptations to undernutrition that are beneficial for short-term survival, even though they are detrimental to health in postreproductive life (3).

Experimental studies in animals have documented many examples of fetal programming, with recent studies showing that alterations in maternal nutrition can have long-term effects on the offspring that are relevant to human cardiovascular disease. For example, feeding pregnant rats a low-protein diet results in lifelong elevation of blood pressure in the offspring (4). Rats whose mothers had been fed a diet with a low ratio of protein to energy during pregnancy showed a permanently altered balance between hepatic glucose production and utilization; control rats fed the same diet during postnatal life had no alterations in hepatic glucose metabolism (5). Other notable long-term effects of alterations in maternal nutrition include changes in cholesterol metabolism, insulin secretion, and renal development (3).

Although some effects of nutrition may be direct consequences of alterations in substrate availability, several are thought to be mediated by hormonal effects. These may alter the development of specific fetal tissues during sensitive periods of development (6, 7), or may lead to long-lasting changes in hormone secretion or tissue hormone sensitivity (8). Experiments in animals have implicated the fetal hypothalamus as a key site that can be programmed by transient changes in prenatal endocrine status (3).

FETAL GROWTH AND CORONARY HEART DISEASE

At the start of the twentieth century, the incidence of coronary heart disease rose steeply in Western countries to become the most common cause of death. In many of these countries, the steep rise was followed by a fall over recent decades that cannot be accounted for by changes in adult lifestyle. The incidence of coronary heart disease is now rising in other parts of the world to which Western influences are extending, including China, India, and Eastern Europe.

Although the steep rise in coronary heart disease in Britain and other Western countries was associated with rising prosperity, geographic studies have shown that rates are now twice as high in the poorer areas of the country and in lower-income groups (3). Combined with the limited ability of adult lifestyle risk factors to predict coronary heart disease, this paradox led to the hypothesis

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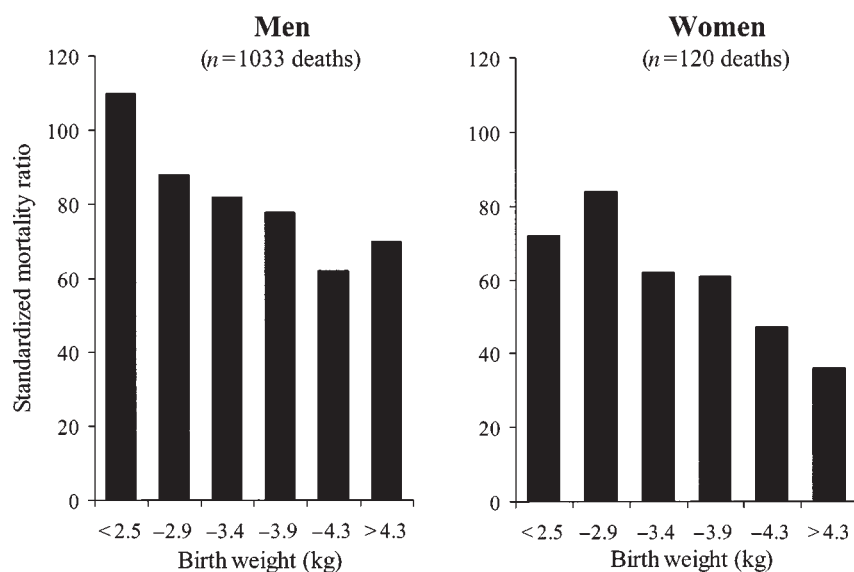


FIGURE 1. Coronary heart disease death rates, expressed as standardized mortality ratios, in 10 141 men and 5585 women born in Hertfordshire, United Kingdom, from 1911 to 1930, according to birth weight. Derived from Osmond et al (12).

that adverse influences in early life might play an important role. Support for this hypothesis came from the observation by Rose (9) that siblings of patients with coronary heart disease had still-birth and infant mortality rates that were twice as high as those of control subjects. This led him to conclude that “ischaemic heart disease tends to occur in individuals who come from a constitutionally weaker stock” (9). Further support subsequently came from geographic studies reported by Forsdahl (10), showing that past infant mortality correlated with later arteriosclerotic heart disease in the 20 counties of Norway. Although these studies suggested that a poor standard of living in childhood and adolescence was a risk factor for heart disease, geographic comparisons in England and Wales pointed more strongly to the importance of an adverse environment in intrauterine life and early infancy (11). Areas with high neonatal and postneonatal mortality earlier this century were found to have markedly elevated coronary heart disease death rates (11). Because low birth weight is strongly associated with elevated neonatal and postneonatal mortality, these observations led to the hypothesis that low-birth-weight babies who survived infancy and childhood might be at increased risk of coronary heart disease as adults.

The early epidemiologic studies that pointed to long-term effects of an adverse intrauterine environment were based on the strategy of following up men and women in middle and late life whose body measurements at birth had been recorded. A follow-up study of men and women born in Hertfordshire, United Kingdom, showed for the first time that those who had had low birth weights had relatively high death rates from coronary heart disease in adult life (12). Thus, among 15 726 men and women born during 1911–1930, death rates from coronary heart disease fell progressively with increasing birth weight in both men and women (Figure 1) (3). A small rise in death rates from coronary heart disease at the highest birth weights in men could relate to the macrosomic infants of women with gestational diabetes. Another study, of 1586 men born in Sheffield during 1907–1925, showed that it was particularly people who were small at birth as a result of growth retardation, rather than those born prematurely, who were at increased risk of the disease (13).

Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with coronary heart disease in later life. For example, confirmation of a link between low birth weight and adult coronary heart disease has come from studies of 70 297 nurses in the United States (14); of 1200 men in Caerphilly, South Wales (15); and of 517 men and women in Mysore, South India (16). In the latter study, for example, the prevalence of coronary heart disease in men and women aged ≥ 45 y ranged from 15% in those who weighed ≤ 2.5 kg at birth to 4% in those who weighed ≥ 3.2 kg (16).

Studies examining the mechanisms underlying these associations have shown that the trends in coronary heart disease with birth weight are paralleled by similar trends between restricted early growth and traditional cardiovascular disease risk factors (3). Subsequent studies have found that a wide range of organs and systems may be programmed by the intrauterine environment. These findings are in keeping with the results of experimental studies in animals and suggest that programming reflects a general principle of developmental biology. Listed in Table 1 are several key tissues and systems for which evidence exists in humans pointing to programming by the nutrient and hormonal milieu of the fetus. Observations linking the intrauterine environment with later hypertension, diabetes, elevated blood cholesterol and fibrinogen concentrations, and polycystic ovary syndrome serve to illustrate some of the principles that underlie fetal programming and are described in more detail below.

High blood pressure and hypertension

A systematic review of 34 studies examining the relation between birth weight and blood pressure in different populations around the world found strong support for an association between low birth weight and high blood pressure in prepubertal children and adults (34). The relation was found less consistently in adolescents, perhaps because the tracking of blood pressure is perturbed by the adolescent growth spurt (34). Similarly to coronary heart disease, high blood pressure is found in people who were small for gestational age rather than those born prematurely (3).

TABLE 1Tissues and systems for which there is evidence of programming in humans¹

Tissue or system	Examples of programming	Reference
Cardiovascular system	Vascular compliance	17
	Endothelial function	18
Respiratory system	Lung volume	19
Endocrine system	Hypothalamic-pituitary-adrenal axis	20
	Glucose-insulin metabolism	21, 22
	Growth hormone-IGF-I axis	23
Reproductive system	Age at menarche	24
	Polycystic ovary syndrome	25
Central nervous system	Schizophrenia	26
Skeletal muscle	Insulin resistance	8
	Glycolysis during exercise	27
Bone	Bone mineral content	28
Kidney	Renin-angiotensin system	29
Liver	Cholesterol metabolism	30
	Fibrinogen and factor VII synthesis	31
Immune system	Thyroid autoantibodies	32
	IgE concentrations	33

¹IGF-I, insulin-like growth factor I; Ig, immunoglobulin.

Follow-up studies of men and women who had detailed neonatal anthropometric measurements have shown that those who were disproportionate (thin or short) at birth also tended to have high blood pressure and a greater risk of hypertension in adult life (3).

It has been argued that people who were exposed to an adverse environment in utero and failed to grow well continue to be exposed to adverse influences in childhood and adult life, and it is these later influences that produce the effects attributed to programming in utero. There is, however, little evidence to support this argument. Rather, associations between birth weight and adult blood pressure, for example, are found in each social group and are independent of influences such as smoking, alcohol intake, and obesity in adult life (1, 3).

Type 2 diabetes and insulin resistance

An association between low birth weight and altered glucose metabolism was reported in 9 studies of men and women in Europe, the United States, and Australia (3, 8, 21, 22, 35–38). In most populations, the prevalence of type 2 diabetes and impaired glucose tolerance was found to fall progressively between those who were small and those who were large at birth. The trends are strong, as illustrated by a study of 370 men aged 65 y born in Hertfordshire, shown in **Table 2**. The prevalence of type 2 diabetes and impaired glucose tolerance fell from 40% among those who weighed ≤ 5.5 lb (2.54 kg) at birth, to 14% among those who weighed >9.5 lb (4.31 kg) (21). In populations with a high prevalence of diabetes in pregnancy, such as the North American Pima Indians, a U-shaped relation has been found, with high rates of diabetes also occurring in those who weighed ≥ 4.5 kg at birth (36).

As for high blood pressure, the associations between birth weight and later glucose tolerance are independent of adult lifestyle influences (1). Adult obesity does, however, add to the intrauterine effects, such that the highest prevalence of type 2 diabetes and impaired glucose tolerance is seen in people who were small at birth but obese as adults (21, 38). There is some evidence that poor fetal growth led to a reduced number of pancreatic β cells and a diminished capacity to make insulin, making them

less able to withstand the stress of becoming obese as adults (39). There is stronger evidence that people who were thin at birth tend to be insulin resistant in adulthood and to have metabolic changes suggestive of a bias toward fuel conservation (8). Thus, insulin-tolerance tests in a group of 103 men and women aged 50 y born in Preston, United Kingdom, showed that those who had a low ponderal index and were thin at birth had a slower fall in blood glucose after an insulin challenge (40). More detailed studies using ³¹P magnetic resonance spectroscopy found that adults who were thin at birth had reduced rates of glycolysis and glycolytic ATP production (27) and that the lipid content of tissues such as muscle was low in these subjects (41). Measurements of metabolic fuel utilization with indirect calorimetry or ¹³C-labeled carbohydrate suggest that low birth weight is associated with reduced postprandial glucose oxidation (42).

These data have led to the hypothesis that adult insulin resistance could indicate persistence of a fetal glucose-conserving adaptation (8). In fetal life, the glucose-insulin-like growth factor I axis has a key role in stimulating cell division (43); insulin resistance in specific tissues, including skeletal muscle, might conserve glucose by reducing growth and result in diminished muscle mass and thinness at birth. In adult life, persistence of insulin resistance in skeletal muscle would, however, result in a range of metabolic abnormalities and could underlie the strong association between low birth weight and thinness at birth and the insulin resistance syndrome in adult life.

Cholesterol metabolism and blood coagulation

Studies of several groups of adult men and women in the United Kingdom showed that those whose fetal growth was restricted tended to have high serum concentrations of total cholesterol, LDL cholesterol, apolipoprotein B, fibrinogen, and factor VII (3, 30, 31). These abnormalities were found particularly in those who had had abnormal body proportions at birth and a short body in relation to their head size. The birth records of people studied in Sheffield, United Kingdom, included their abdominal circumference at birth; in particular, a low value for this birth measurement predicted high serum LDL-cholesterol and plasma fibrinogen concentrations in adult life (30). The differences in cholesterol concentrations across the range of abdominal

TABLE 2Prevalence of type 2 diabetes (2-h glucose ≥ 11.1 mmol/L) and impaired glucose tolerance (2-h glucose 7.8–11.0 mmol/L) in 370 men aged 59–70 y¹

Birth weight in lbs (kg)	Percentage with type 2 diabetes	Percentage with impaired glucose tolerance	Odds ratio
			(95% CI) of type 2 diabetes or impaired glucose tolerance ²
	%	%	
<5.5 (2.54) ($n = 20$)	10	40	6.6 (1.5–28)
-6.5 (2.95) ($n = 47$)	13	34	4.8 (1.3–17)
-7.5 (3.41) ($n = 104$)	6	31	4.6 (1.4–16)
-8.5 (3.86) ($n = 117$)	7	22	2.6 (0.8–8.9)
-9.5 (4.31) ($n = 54$)	9	13	1.4 (0.3–5.6)
>9.5 (4.31) ($n = 28$)	0	14	1.0
All ($n = 370$)	7	25	

¹Derived from Hales et al (21).²Adjusted for current BMI.

circumferences were large, statistically equivalent to a 30% difference in mortality from coronary heart disease.

Disproportion in body length relative to head size is thought to result from cranial redistribution of oxygenated blood away from the trunk to sustain brain metabolism—an adaptive response present in mammals (44). This impairs the growth of the liver and may underlie permanent abnormalities in the regulation of cholesterol and clotting factors.

Polycystic ovary syndrome

The clinical presentations and endocrinology of women with the polycystic ovary syndrome are heterogeneous but include women with normal body weight and high serum luteinizing hormone (LH) concentrations as well as overweight women with androgenization and high plasma concentrations of LH and testosterone (45). Experimental studies in rats have shown that the pattern of gonadotropin release by the hypothalamus can be programmed by the concentration of androgens during early development (46). Female rats exposed to high androgen concentrations have persisting changes in reproductive physiology, including anovulatory sterility and polycystic ovaries (47, 48).

A study of 235 women aged 40–42 y born in Sheffield, United Kingdom, suggested that the 2 common forms of polycystic ovary syndrome may have different origins in intrauterine life (25). Women with polycystic ovaries who were of average or below average body weight were more likely to have been born post-term; this could have resulted in permanent alterations in the hypothalamic control of LH release. Obese, hirsute women with polycystic ovaries and high ovarian secretion of androgens were found to be of higher birth weight and tended to have mothers with a high body mass index in pregnancy (25). These observations suggest that patterns of hormone release and tissue sensitivity established in utero could influence the development of disease in later adult life.

FETAL NUTRITION

The finding that normal variations in fetal size at birth have implications for health throughout life has prompted a reevaluation of the regulation of fetal growth and development. Although the fetal genome determines growth potential in utero, the weight of evidence suggests that it plays a subordinate role in determining the growth that is actually achieved (49, 50). Rather, it seems that the dominant determinant of fetal growth is the nutritional and hormonal milieu in which the fetus develops, and in particular, the nutrient and oxygen supply (51, 52).

Evidence supporting the importance of the intrauterine environment comes from animal cross-breeding experiments (53), from studies of half-siblings related through either the mother or the father (54), and from embryo transfer studies (55). For example, among half-siblings, those with the same mother have similar birth weights, the correlation coefficient being 0.58; the birth weights of half-siblings with the same father are, however, dissimilar, the correlation coefficient being only 0.1 (54). In embryo transfer studies, it is the recipient mother rather than the donor mother that more strongly influences the growth of the fetus; a fetus transferred to a larger uterus will achieve a larger birth size (55). Although maternal cigarette smoking is known to restrict fetal growth, follow-up studies have found that it is not related to the development of cardiovascular risk factors in the offspring in childhood (56, 57).

Animal experiments have suggested that fetal undernutrition in early gestation produces small but normally proportioned offspring, whereas undernutrition in late gestation may have profound effects on body proportions but little effect on birth weight (3). The varying critical periods during which organs and systems mature indicate that an adverse intrauterine environment at different developmental stages is likely to have specific short- and long-term effects. A critical period for gonadal development exists, for example, very early in gestation (58), as compared with a critical period for renal development later in gestation, between 26 and 34 wk of pregnancy (59). Consistent with these differing critical periods, follow-up studies of babies that were symmetrically small, short, or thin at birth showed that these infants are predisposed to different disorders in adult life (1).

Proportionately small babies are at increased risk of high adult blood pressure but do not appear to develop coronary heart disease (3). By down-regulating growth in response to undernutrition early in development, the fetus may reduce its demand for nutrients, tending to protect itself from relative undernutrition in late gestation (3). As adults, individuals who were disproportionately short at birth tend to have abnormalities of systems controlled by the liver, and have increased rates of coronary heart disease (60). These may reflect adverse effects on liver development associated with cranial redistribution of blood flow later in gestation (43). Thin babies with a low ponderal index (birth weight/length³) at birth are thought to be at increased risk of the insulin resistance syndrome and coronary heart disease as a result of fetal undernutrition in the weeks leading up to delivery (3). Consistent with this, a recent follow-up study of men and women whose mothers were exposed to famine in pregnancy showed that third-trimester famine exposure resulted in impaired glucose tolerance in the offspring in later adult life (61). As might be expected, the predominant phenotype of fetal growth retardation and the mix of babies with different types vary greatly in different populations (3). These variations may contribute to geographic differences in the prevalence of coronary heart disease.

With respect to timing, it is important to appreciate that effects that are manifest late in pregnancy may commonly originate much earlier in gestation. For example, studies of the famine of 1944–1945 in the Netherlands (62) led to the dogma that thinness at birth results from influences operating in the last trimester of pregnancy. Outside the setting of famine, both animal and human studies indicate that fetal undernutrition late in pregnancy is, however, more commonly a consequence of an inadequate maternoplacental supply capacity set up earlier in gestation (63, 64). Thus, although the short- and long-term effects of an acute, severe famine are of great scientific importance, we must be aware that these effects could result in erroneous conclusions about timing in nonfamine situations.

Maternal influences on fetal nutrition

Size at birth reflects the product of the fetus's trajectory of growth, set at an early stage in development, and the maternoplacental capacity to supply sufficient nutrients to maintain that trajectory. In Western communities, it has been thought that regulatory mechanisms in the maternal and placental systems act to ensure that human fetal growth and development is little influenced by normal variations in maternal nutrient intake and that there is a simple relation between a woman's body composition and the growth of her fetus. Recent experimental studies in animals and our own observations in humans challenge these

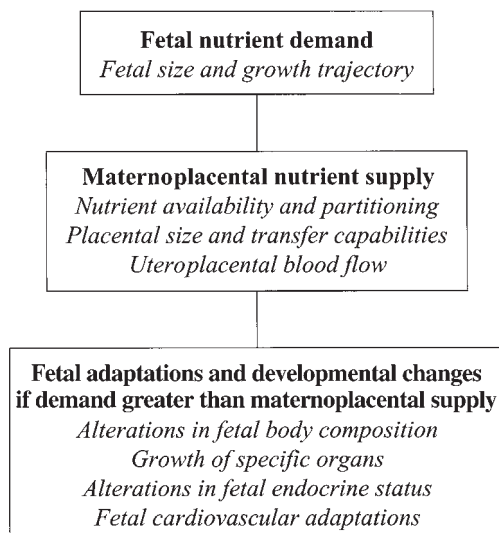


FIGURE 2. Framework for understanding the maternal regulation of fetal development and programming.

concepts (3). These studies suggest that a mother's own fetal growth and her dietary intakes and body composition can exert major effects on the balance between the fetal demand for nutrients and the maternoplacental capacity to meet that demand. Failure of the maternoplacental supply line to satisfy fetal nutrient requirements results in a range of fetal adaptations and developmental changes; although these adaptations may be beneficial for short-term survival, they may lead to permanent alterations in the body's structure and metabolism and thereby to cardiovascular and metabolic disease in adult life (3). A conceptual framework illustrating this hypothesis is shown in **Figure 2**.

Quite apart from any long-term effects on health in adult life, specific issues that have not been adequately addressed in previous studies of maternal nutrition include 1) effects on the trajectory of fetal growth, 2) intergenerational effects, 3) paradoxical effects on placental growth, 4) effects on fetal proportions and specific tissues, and 5) the importance of the balance of macronutrients in the mother's diet and of her body composition.

The fetal growth trajectory

A rapid trajectory of growth increases the fetus's demand for nutrients. This reflects effects both on maintenance requirements, greater in fetuses that have achieved a larger size as a result of a faster growth trajectory, and on requirements for future growth. In absolute terms, the fetal demand for nutrients is small until late in pregnancy. Experimental studies of pregnant ewes showed that, although a fast growth trajectory is generally associated with larger fetal size and improved neonatal survival, it does render the fetus more vulnerable to a reduced maternoplacental supply of nutrients in late gestation. Thus, maternal undernutrition during the last trimester adversely affected the development of rapidly growing fetuses with high requirements while having little effect on those growing more slowly (65). Rapidly growing fetuses were found to make a series of adaptations to survive, including wasting of fetal lean mass to provide amino acids for oxidation in the placenta to maintain lactate output to the fetus (65).

The trajectory of fetal growth is thought to be set at an early stage in development. Experiments in animals have shown that

periconceptual alterations in maternal diet and plasma progesterone concentrations can alter gene expression in the preimplantation embryo to change the fetal growth trajectory (66, 67). Environmental effects have been shown on both embryonic growth rates and on cell allocation in the preimplantation embryo. Maternal progesterone treatment can, for example, permanently alter the trajectory of fetal growth by changing the allocation of cells between the inner cell mass that develops into the fetus and the outer trophoblast that becomes the placenta (66, 67). The trajectory of fetal growth is thought to increase with improvements in periconceptual nutrition, and is faster in male fetuses (68). One possibility is that the greater vulnerability of such fetuses on a fast growth trajectory could contribute to the rise in coronary heart disease with Westernization and the higher death rates in men.

Intergenerational effects

Experimental studies in animals have shown that undernutrition over many generations can have cumulative effects on reproductive performance over several generations. Thus, feeding rats a protein-deficient diet over 12 generations resulted in progressively greater fetal growth retardation over the generations; when the rats were refeed with a normal diet, it then took 3 generations to normalize growth and development (69).

Strong evidence of major intergenerational effects in humans has come from studies showing that a woman's birth weight influences the birth weight of her offspring (70, 71). We found, moreover, that whereas low-birth-weight mothers tend to have thin infants with a low ponderal index, the father's birth weight is unrelated to ponderal index at birth (**Figure 3**); crown-heel length at birth is, however, more strongly related to the father's birth weight than to the mother's (64). The effect of maternal birth weight on thinness at birth is consistent with the hypothesis that the maternoplacental supply line may be unable to satisfy fetal nutrient demand in low-birth-weight mothers. Potential mechanisms underlying this effect include alterations in the uterine or systemic vasculature, programmed changes in maternal metabolic status, and impaired placentation. The strong effect of paternal birth weight on crown-heel length may reflect paternal imprinting of genes important for skeletal growth, such as those regulating the concentrations of insulin-like growth factors (72).

Placental size and transfer capabilities

Although the size of the placenta gives only an indirect measure of its capacity to transfer nutrients to the fetus, it is nonetheless strongly associated with fetal size at birth. Experiments in sheep showed that maternal nutrition in early pregnancy can exert major effects on the growth of the placenta and thereby alter fetal development (63, 73). The effects produced depended on the nutritional status of the ewe in the periconceptual period. In ewes poorly nourished around the time of conception, high nutrient intakes in early pregnancy increased the size of the placenta. Conversely, in ewes well nourished around the time of conception, high intakes in early pregnancy resulted in smaller placental size (63). 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 (74).

As part of a study designed to evaluate whether the normal variations in maternal diet found in Western communities could influence fetal growth and development, we have found evidence of a similar suppressive effect of high dietary intakes in early pregnancy on placental growth (75). Thus, among 538



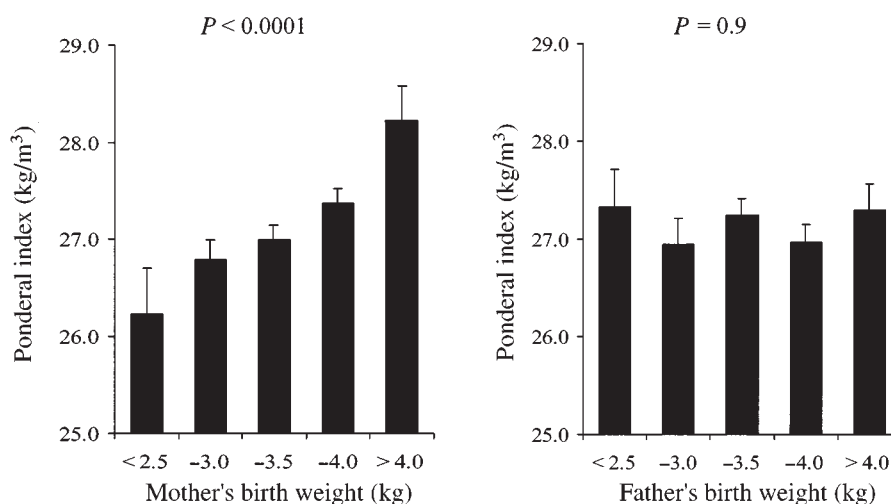


FIGURE 3. Ponderal index at birth in 492 term Southampton pregnancies according to the mother's and father's birth weights. Values are means (\pm SEs) adjusted for sex and gestation. Derived from Godfrey et al (64).

women who delivered at term, those with high dietary intakes in early pregnancy, especially of carbohydrate, had smaller placentas, particularly if combined with low intakes of dairy protein in late pregnancy (Table 3) (75). These effects were independent of the mother's body size, social class, and smoking status, and resulted in alterations in the ratio of placental weight to birth weight (placental ratio). Confirmation that maternal diet can alter placental growth has come from analyses of the Dutch famine of 1944–1945, in which famine exposure in early pregnancy increased placental weight (76).

Effects on placental growth may be of long-term importance. A follow-up study of men born earlier this century in Sheffield found a U-shaped relation between the placental ratio and later coronary heart disease (77). Whereas 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 (52, 78). Consequent fetal adaptations may underlie the increased death rates of adult coronary heart disease in those with both low and high placental ratios.

Effects on specific fetal tissues

Experimental studies in animals have shown that dietary manipulations during early development can have tissue-specific effects, resulting in alterations in an animal's proportions. For example, in pigs fed differing diets in the first year of life, those

fed a protein-deficient diet had a disproportionately large head, ears, and genitalia compared with those fed an energy-deficient diet (6). Recent experiments in guinea pigs showed that maternal undernutrition in pregnancy resulted in offspring that not only had altered body proportions at birth, but also showed profound elevations of serum cholesterol concentrations when fed a high-cholesterol diet in the postweaning period (79).

In humans, 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. Any such effects may be important because adult coronary heart disease and type 2 diabetes are more strongly associated with altered birth proportions than with birth weight (38, 80). We found that women with low dairy protein intakes in late pregnancy tended to have babies that were thinner at birth (64); maternal dairy protein intakes were not, however, related to birth weight (75). Furthermore, a recent follow-up study of children whose mothers took part in a randomized, controlled trial of calcium supplementation in pregnancy found that although maternal supplementation was associated with a lowering of the offspring's blood pressure in childhood, this effect was not associated with any change in birth weight (81).

Maternal dietary balance and body composition

Indications that the balance of macronutrients in the mother's diet can have important short- and long-term effects on the offspring

TABLE 3

Mean placental weight in 538 women who delivered at term in Southampton, United Kingdom¹

Dairy protein intake in late pregnancy (g/d)	Carbohydrate intake in early pregnancy (g/d)			All
	≤ 265	340	> 340	
≤ 18.5	539	507	494	516
26.5	556	546	509	540
> 26.5	582	533	536	544
All	554	531	517	534 ²

¹ Values are adjusted for sex and the duration of gestation at delivery. Significant association with placental weight for carbohydrate, $P = 0.002$ and dairy protein, $P = 0.005$. Derived from Godfrey et al (75).

² Overall SD = 121 g.

came from a series of experimental studies in pregnant rats. These studies found that maternal diets with a low ratio of protein to carbohydrate and fat alter fetal and placental growth and result in life-long elevations of blood pressure in the offspring (4). A follow-up study of 40-y-old men and women in Aberdeen, United Kingdom, suggested that alterations in the maternal macronutrient balance during pregnancy could have similar adverse effects on the offspring (82); the relations with maternal diet were, however, complex, and studies to replicate them are in progress. Among women who reported animal protein intakes <50 g/d, a high maternal carbohydrate intake was associated with higher adult blood pressure in the offspring; among those who reported animal protein intakes >50 g/d, a low maternal carbohydrate intake was associated with higher blood pressure. These increases in blood pressure were associated with reduced placental size (82).

Support for the thesis that alterations in fetal and placental development may result from a low ratio of animal protein to carbohydrate came from observational studies of maternal nutrition in pregnancy (75). Support for adverse effects of a high ratio of animal protein to carbohydrate came from a review of 16 trials of protein supplementation showing that supplements with a high protein density were consistently associated with lower birth weights (83).

Evidence that maternal body composition has important effects on the offspring came from studies showing that extremes of maternal body composition in pregnancy are associated with adverse long-term outcomes in the offspring. Follow-up of a group of Jamaican children showed that those whose mothers had thin skinfold thicknesses in pregnancy and a low pregnancy weight gain had relatively higher blood pressure at the age of 11 y (84). A subsequent study of 11-y-old children in Birmingham, United Kingdom, found similar associations (85). Studies in India found that a low maternal weight in pregnancy is associated with an increased risk of coronary heart disease in the offspring in adult life (16).


At the other extreme of maternal body fatness, evidence of long-term effects of maternal obesity came from follow-up of a group of men in Finland born earlier this century (80). Markedly raised coronary heart disease death rates were found in men whose mothers had a high body mass index in pregnancy. This effect was independent of an association between thinness at birth and increased rates of adult coronary heart disease. Modeling the data to derive contour lines of similar coronary heart disease death rates indicated that increasing maternal body mass index had little effect on the offspring's death rates in tall women, but strong effects in short women (3, 80). One interpretation of these findings is that greater maternal body fatness may increase fetal growth and hence the fetal demand for nutrients; short women may not be able to meet this increased demand as a result of a constrained nutrient supply capacity determined during their own intrauterine development (80).

IMPLICATIONS AND FUTURE WORK

The finding that normal variations in fetal size and thinness at birth have implications for health throughout life has prompted a reevaluation of the regulation of fetal development. Impetus has been added to this reevaluation by recent findings showing that a woman's diet and body composition in pregnancy are related to cardiovascular disease risk factors and the prevalence of coronary heart disease in her offspring in adult life. These observa-

tions challenge the view that the fetus is little affected by changes in maternal nutrition except in circumstances of famine.

If, as we believe, a woman's own fetal growth and diet and body composition before and during pregnancy play a major role in programming the future health of her children, mothers will want to know what they can do to optimize the intrauterine environment they provide for their babies. The complexities of fetal growth and development are, however, such that currently available data form no basis for changing dietary recommendations for pregnant women. The long time-scale over which the effects of an adverse intrauterine environment act dictate that we now need to progress beyond epidemiologic associations to greater understanding of the cellular and molecular processes that underlie them.

Future work will need to identify the factors that set the trajectory of fetal growth and the influences that limit the maternoplacental delivery of nutrients and oxygen to the fetus. We also need to define how the fetus adapts to a limited nutrient supply, how these adaptations program the structure and physiology of the body, and by what molecular mechanisms nutrients and hormones alter gene expression. Further research requires a strategy of interdependent clinical, animal, and epidemiologic investigations. Such an approach may allow us to use the information outlined here to reduce the prevalence of major diseases. 

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