Fetal Intrauterine Life — A Window to Adult Disease?

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It has long been recognized that events in the early life of animals may have a profound influence on their adult physiology. There is growing evidence that the uterine environment programs the metabolic abnormalities that lead to cardiovascular disease in adult life. Studies in humans have shown that the rate of coronary heart disease and related disorders such as strokes, diabetes and hypertension is increased in men and women who were small at birth in relation to their placentas, thin at birth, or despite average birth weight were short in relation to head size and had a lower than average infant weight gain. In fact, early epidemiological studies that supported the notion of programmed adult disease were based on the simple strategy of examining middle-aged and elderly men and women whose body measurements were recorded at birth.

This review will discuss the link between the failure to realize growth potential *in utero* and adult cardiovascular disease. If the fetal origin hypothesis of adult cardiovascular disease is correct, preventive medicine *in utero* and more specific advice for pregnant women must await further studies.

The concept of early nutrition being an important contributor to adult disease, as reflected in anthropometric variables measured at birth and during infancy, has received substantial attention in the medical literature, particularly from a group of UK investigators headed by Professor David Barker [1,2]. Barker and colleagues, working in Southampton, proposed the hypothesis that "a baby's nourishment before birth and during infancy, as manifest in patterns of fetal growth, 'programmes' the development of risk factors such as elevated blood pressure, fibrinogen concentration, hyperlipidemia and glucose intolerance, and hence these are key determinants of coronary heart disease" [2]. The group has elaborated upon this hypothesis in at least 40 studies and two books [3] since 1987.

Numerous animal experiments have shown that poor nutrition and other growth-impairing influences during critical periods of early life may permanently affect (program) the structure and physiology of a range of organs and tissues, including the endocrine pancreas, liver, and blood vessels [4]. In his book published in 1994, Barker [5] refined his ideas to suggest that fetal undernutrition operating in different phases of fetal intrauterine life will have different effects on birth weight and subsequent disease patterns.

During the earliest stages of pregnancy (embryonic life) — the first 8 weeks after conception — the nutrient requirements are quantitatively insignificant, though all essential nutrients must be present and in equilibrium due to the delicate processes of differentiation and organization [5]. At this stage, nutrient deficiencies, such as a zinc or folate deficit, may result in malformation of the developing embryo [6]. Both hyper- and hypoglycemia in early embryogenesis may be associated with low birth weight.

The fetal period, month 3 to month 6, is characterized by some cell multiplication, but predominantly by an increase in the size of existing cells. Different tissues of the body grow during periods of rapid cell division [7]. The timing of these so-called critical periods varies for each tissue. Nutrient deficiencies during the fetal stage generally impede growth or induce subtle changes in function. The main adaptation of the fetus to undernutrition is to slow its rate of all cell division, especially in those tissues that are in critical periods at the time. Brief periods of undernutrition may permanently reduce the number of cells in particular organs. Chronic vascular insufficiency caused by maternal malnutrition causes fetal growth retardation, in which the fetus has about 80–90% of the number of cells it should have in all its organs [6]. This is one of the mechanisms whereby undernutrition may permanently change or program the body [7]. Some of the memories of the body at early undernutrition are translated into pathology during adult life.

Blood pressure in adult life and its relation to growth

It has been suggested that elevated blood pressure is linked with an unfavorable intrauterine environment and a long-term risk of cardiovascular disease [8]. Birth weight as a measure of intrauterine influence has accordingly been found to be inversely associated with blood pressure in childhood [8,9] as well as in adulthood [8,10,11]. Altogether, 21 studies have shown an association between low birth weight and elevated blood pressure in childhood and adult life. Lau et al. [12] proposed that adult hypertension develops as a result of a process initiated during intrauterine life and is amplified as years advance.

Barker et al. [13] measured the blood pressures of 449 men and women born in a hospital in Preston during the years 1935–43 and still living in Lancashire, and studied their obstetric records. Barker's group shows that in both sexes, systolic and diastolic pressures were strongly related to placental weight and birth weight. Mean systolic pressures rose by 15 mmHg as placental weight increased from 450 g to >675 g, and dropped by 11 mmHg as birth weight increased from 2,475 g to >3,375 g. These relations were independent so that the highest blood pressures occurred in people born as small babies with large placentas. Martyn et al. [14] examined adult systolic and diastolic blood pressure and arterial compliance, as measured by pulse wave velocity in two arterial segments, in 337 men and women born in Jessop Hospital, Sheffield, between the years 1939 and 1940. Both systolic and diastolic blood pressures were higher in people whose birth weight was low, who were short or who had small abdominal or head circumference at birth. Arterial compliance was lower in those who had been small at birth.

Possible mechanisms linking retarded fetal growth and elevated blood pressure are at present a matter for speculation. Maternal undernutrition leads to fetal undernutrition, leading to adaptive changes in the concentration of fetal and placental hormones and in the sensitivity of different tissues to them [15]. One possibility is that these changes may contribute to elevated blood pressure by altering levels of growth factors trophic for key constituents of blood vessel walls, and by loss of elasticity in vessel walls [16]. Intrauterine growth retardation is associated with altered Doppler flow velocity waveforms in several vascular beds, including the descending aorta and cerebral vasculature. Decreased blood flow in the descending aorta and the arteries of the lower limb in fetuses with growth retardation may initiate changes in the arterial structure, contributing in the long term to the maintenance of elevated blood pressure and the pathogenesis of cardiac hypertrophy [14]. An alternative etiology — increased fetal exposure to maternal glucocorticoids — is supported by findings in rats; namely, that decreased activity of the enzyme that acts as a placental barrier to maternal glucocorticoids (11–hydroxysteroid dehydrogenase) is associated with low birth weight [17,18]. It is possible that increased exposure of the fetus to exogenous glucocorticoids contributes to low birth weight and subsequent hypertension in adulthood.

Robinson et al. [19] proposed an alternative etiology that links fetal anthropometry measurements and high adult blood pressure. They suggested that one such process could be the intrauterine "setting" of heart rate, since pulse rate is known to relate positively to blood pressure both in children and in adults. These researchers showed that higher fetal rate at 19 weeks of pregnancy was associated with lower ponderal index, a smaller head circumference and smaller mid-arm circumference at birth. Alternatively, a rapid heart rate could be an early adaptive response to adverse influences that later cause growth failure. In their study, term babies with low ponderal index, small heads, thin arms and less subcutaneous fat already differed from other babies in early gestation. The intrauterine "setting" of heart rate may be one mechanism linking impaired fetal growth with later blood pressure.

Coronary heart disease, serum cholesterol, blood clotting factors, glucose tolerance in adulthood and growth *in utero*

Barker and colleagues [20] traced a group of men born in a maternity hospital in Sheffield before 1925, and related their size at birth to their subsequent death rates due to cardiovascular disease. Standardized mortality ratios for cardiovascular disease dropped from 119 in men who weighed 2,495 g or less at birth to 74 in men who weighed more than 3,856 g at birth. Standardized mortality ratios also fell with increasing head circumference and increasing ponderal index. A follow-up of 468 men born in the years 1920–30 showed that fasting plasma concentrations of glucose, insulin and 32–33 split pro-insulin were inversely proportional to birth weight [21]. Glucose and insulin concentrations at 30 and 120 minutes after an oral glucose load showed similar trends. A study of the Sheffield records [21] showed that men and women who had a small abdominal circumference at birth had elevated serum concentrations of total and low density lipoprotein, cholesterol and apolipoprotein B as adults. This relationship was independent of the duration of gestation.

Serum concentrations of total cholesterol fell by 0.25 mmol/L with each 2.54 cm increase in abdominal circumference. Reduction of serum cholesterol concentration from 6.5 to 6 mmol/L has been shown to reduce the risk of coronary heart disease by 30–31% [20]. The association between abdominal circumference at birth and LDL-C concentration was independent of social class, current body weight, cigarette smoking and alcohol consumption [21].

Reduced abdominal circumference at birth reflects impaired liver growth and consequent reprogramming of liver metabolism. Impaired growth of the liver in late gestation leads to permanent changes in LDL-C metabolism [22]. Circulating fibrinogen and factor VII concentrations are largely regulated by the liver. Martyn's study of 202 men and women shows that the plasma concentrations of fibrinogen and factor VII dropped by 0.12 g/L for each pound increase in birth weight and by 0.10 g/L for each inch increase in abdominal circumference [23]. The high adult concentrations of fibrinogen and factor VII associated with reduced infant growth may be a persistent response to impaired liver development during a critical early phase [23].

Since both cholesterol and fibrinogen metabolism are regulated by the liver, one interpretation of these findings is that reduced abdominal circumference at birth reflects impaired liver growth and consequent reprogramming of

LDL-C = low density lipoprotein cholesterol

liver metabolism. Experiments on rats have shown that undernutrition *in utero* can permanently alter the balance of two liver enzymes, phosphoenolpyruvate carboxykinase and glucokinase, which respectively synthesize and break down glucose [24]. A low protein diet during gestation permanently changes the balance of enzyme activity in the offspring in favor of synthesis [24]. The fourfold increase in the ratio of phosphoenolpyruvate carboxykinase to glucokinase, observed in the low protein group, was still evident in the 11-month-old rats that had been exposed to a low protein diet during early life [24].

The working hypothesis of the Barker group is that maternal undernutrition leading to fetal undernutrition is associated with changes in the concentration of fetal and placental hormones [1]. Insulin and the insulin-like growth factors, hormones thought to have a central role in the regulation of fetal growth, rapidly respond to changes in fetal nutrition. The link between lower birth weights and high rates of death from cardiovascular disease in men and women may reflect persisting changes in the secretion of insulin or the sensitivity of tissues to it [1]. This link is associated with changes in certain tissues, including blood vessels and the endocrine pancreas. These changes program blood pressure, glucose and insulin metabolism, and cardiovascular disease in adult life. The nature of the changes, which could include modification of gene expression, permanent reduction in cell numbers or modification of organ structures, is unknown [20]. Research in animals has shown that restriction of growth during critical periods of early life may permanently affect organ size and function [20].

Controversy over Barker's hypothesis

It is not surprising that a complex series of hypotheses such as these was the subject of considerable criticism. In their editorial [3], Paneth and Susser stated that fetal origin hypotheses rest only on the "very general" proposition that fetal undernutrition causes coronary heart disease; they felt that extrapolations were being made from very small cohorts and selection bias might be operating. They suggested that fetal and infant anthropometry did not bear a simple relation to maternal and infant nutrition but is multifactorial.

The fetal origin hypothesis suggests that growth retardation *in utero* and during infancy increases the risk for several diseases and for early death. Twins experience retardation in intrauterine growth, but Christensen et al. [25] reported that the mortality among surviving twins differs little from that of the general population. Following 8,495 twin individuals born during the years 1870–1900, they found similar mortality patterns among twins and the general population. The fetal origin theory suggests that the ratio of placental to fetal weight has an important role in the prediction of coronary heart disease in adult life, and that maternal undernutrition is associated with this relationship. In contrast, Perry et al. [26] found no relation between maternal hemoglobin concentration in early pregnancy and fetal/placental ratio at delivery, but confirmed the positive association between the ratio and maternal body mass index [26]. Maternal diabetes and maternal smoking may also influence the relation of birth weight to placental weight [3].

Seidman et al. [27] analyzed weight, height and blood pressure in 32,580 Israeli 17 year olds according to their birth weight, and concluded that birth weight has little effect on blood pressure. But, they claimed, factors that lead to excess weight during adolescence may have a major role in preventing hypertension in adults. Ben-Shlomo and Smith [28] suggested that postnatal environmental factors might be responsible for more of the differences in adult disease mortality and morbidity than Barker had suggested. Similarly, Paneth et al. [29] suggested that the "early life experience hypothesis" (in contrast to the "early nutrition hypothesis") is likely to be true, and stressed the importance of cardiovascular prevention and the need to improve the social and economic circumstances of mothers and children. Another team, Kramer and Joseph, in their commentary in *The Lancet* [30], define problems with the fetal/infant origins hypothesis, as follows:

a) The hypothesis does not explain temporal and international trends in coronary heart diseases.
b) The results of Barker et al. sometimes vary from one study to another.
c) Other studies have yielded negative or opposite results.
d) Some potential confounders are not measured.
e) Some long-term studies are based on a small fraction of the original cohort.

Discussion

Genetic factors, intrauterine infections, limited substrate availability from low maternal substrate concentration, or reduced permeability, are disparate factors that could restrict fetal growth [31]. Epidemiological studies have indicated that low growth rates *in utero* and during infancy are associated with high death rates from cardiovascular disease and are associated with increased prevalence of known risk factors for cardiovascular disease, including blood pressure, high plasma concentrations of glucose, factor VII, fibrinogen, LDL-C and apolipoprotein B. They are found not only among babies with intrauterine growth restriction, defined by birth weight at the lowest centiles, but also among babies of average or even above average weight at birth. Some of the subjects were small at birth in relation to the size of their placentas [12], others were thin at birth [32] and yet others, despite average birth weight were short in relation to head size and had a lower than average infant weight gain [2].

These observations are extremely important. If the developing fetus is directly influenced by the nutritional status of the mother, both prior to conception and during pregnancy [6], maternal undernutrition is a risk factor for coronary heart disease and diabetes in the infant and should

therefore be avoided. Fetal growth is thus a complex, multifactorial phenomenon, influenced predominantly by the mother and the uterine environment [6]. In the earliest stages of pregnancy, embryonic and trophoblast growth are influenced by the concentration of nutrients. Hyperglycemia in the mother delays embryonic growth and is implicated in the development of malformation. Thus, both hyperglycemia and hypoglycemia in early embryogenesis may be associated with low birth weight [15]. The amino acids arginine and lysine seem to be especially important for the growth of the blastocyst, and reduced metabolic growth occurs when the mother consumes a low protein diet [6]. Malformation of the developing embryo results if there are nutrient deficiencies (zinc and folate) during the third through eighth postovulatory weeks. Nutrient deficiencies during late pregnancy generally impede growth or induce subtle changes in function.

Another aspect of the diet of the mother and newborn infant is the importance of essential fatty acid availability for subsequent neurological and intellectual development of the child [33]. It is generally believed that inappropriate lifestyles and genetic factors can explain many of the diseases that characterize our civilization. Now comes a new paradigm: the precursors of coronary heart disease and other adult chronic disease, and hence also the potential for their prevention, are determined *in utero*.

The human organism is a complex machine, it is a living system that exchanges matter and energy from the moment of conception, grows, and changes its structure. It is a cell-organizing system and, according to Barker, disease may be the result of a disorder of the process of self-organization early in life, caused by maternal malnutrition or placental exchange defects [7]. Is this indeed true? The Barker hypothesis has come under heavy criticism, based on several major problems of the published evidence [30], and neither perinatal nor cardiovascular epidemiologists have universally embraced the fetal/infant origins hypothesis. Clearly, more extensive epidemiological and obstetric research is required to resolve some of the crucial questions pertaining to intrauterine life. What exactly is poor nutrition or undernutrition? What are the effects of various nutrients on human embryogenesis and fetal growth? How do other determinants of fetal growth interact with these influences? How does the fetus adapt to limited nutrients and oxygen, and how does this adaptation program the physiology, metabolism and structure of organs? These and other questions will be of interest to obstetricians. If Barker's thesis is correct, preventive medicine *in utero*, dietary recommendations and more specific advice for pregnant women must await further studies.

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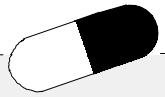
Capsule



Vitamin E, fish oil and ischemic heart disease

For diverse reasons, there has been interest in capturing the genie of the Mediterranean diet in a capsule. The motivations have ranged from a purely scientific aspiration to gain new insights into atherogenesis, through provision of a rationale for encouraging wider adoption of the diet, to commercial interest in sales of vitamins and other health products. The GISSI-Prevenzione (GISSI-P) trial reported in *The Lancet* is a laudable and ambitious attempt to answer questions about whether ischemic heart disease can be influenced by supplements of two specific dietary constituents — the n-3 polyunsaturated component of fish oil (n-3 PUFA) and vitamin E. For both of these dietary components, there is a wealth of circumstantial evidence for benefit, including an inverse relation between risk of death from myocardial infarction and estimated intake of n-3 PUFA or vitamin E. Some of the evidence has come from studies with a single population, and others from comparisons, for different countries, of median levels of intake with published mortality data. For each dietary component, there has also been one positive prospective trial. However, the evidence has been conflicting, and adverse effects have been found.

What has GISSI-P shown? The researchers conclude that among Mediterraneans who have had a myocardial infarction, n-3 PUFA supplements, but not a moderate dose of synthetic vitamin E, reduce long-term complications of myocardial infarction to a clinically important extent. What precisely is the benefit, and what are the true clinical or scientific implications? Other large studies of antioxidant vitamins for the prevention of ischemic heart disease are underway, so at this stage it is perhaps best just to consider what questions could be addressed by GISSI-P.

GISSI-P dispensed, it seems, with two of the most expensive provisions of trials leading to registration of a drug or new indication — namely, masked treatment, and independent monitors at each center. Whether the results of such trials are positive is assessed according to the hypothesis that the trial is designed to test which is especially important when several questions are being addressed. In GISSI-P, the hypothesis was a 20% benefit, presumably at a 1% level of significance; but in the primary, intention-to-treat comparison of patients who received n-3 PUVA against those who did not, treatment reduced the composite endpoint of death and non-fatal myocardial infarction and stroke by only 10%. In the comparison of each supplement against no treatment, n-3 PUFA and vitamin E reduced risk by 15% and 11%, respectively, but only the former was statistically significant. So the trial provides support for only some of the non-regulatory interests in dietary supplements discussed above.

The GISSI investigators have been doing trials in patients with myocardial infarction and have used such patients for GISSI-P. However, a trial carried out among patients who have had a myocardial infarction, especially Mediterranean patients, may provide an underestimate of the benefits of Mediterranean-diet supplements in the prevention of atherosclerosis. The lipid-oxidation hypothesis proposed by Steinberg and Mitchinson suggests that high concentrations of LDL are not atherogenic unless their oxidation (or other modification) leads to macrophage uptake and activation. Steinberg predicted that antioxidants might be effective only over many years and for primary prevention. Whether patients who had a myocardial infarction despite a lifetime of Mediterranean diet, and are subsequently treated with a statin (about 50% in GISSI-P), would be expected to benefit from vitamin E is not clear, especially since many of the complications of myocardial infarction depend more on the state of the myocardium than of the coronary arteries. The only study to show that vitamin E had an effect was done on patients with angiographic atherosclerosis recruited from the low risk, non-Mediterranean enclave of East Anglia. The investigators of that study have subsequently reported that those patients had a 3-5-fold increased frequency for a polymorphism in the gene for endothelial nitric oxide synthase, which is associated with reduced endothelial function, and they speculated that vitamin E in such a population may confer benefit independently of effects on LDL by protecting nitric oxide from rapid destruction. So another reason for the negative finding on vitamin E in GISSI-P might be not just that Italian patients are nutritionally less deprived than the English but also that they might differ in the prevalence of the eNOS polymorphism.

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