
MINIREVIEW

Intrauterine Undernutrition and Programming as a New Risk of Cardiovascular Disease in Later Life

P. SZITÁNYI, J. JANDA, R. POLEDNE¹

First Department of Pediatrics, Second Medical School, Charles University, University Hospital Motol and ¹Institute for Clinical and Experimental Medicine, Center for Experimental Cardiovascular Research, Prague, Czech Republic

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Summary

It is believed that atherogenesis is a multifactorial process, which could already start *in utero*. Development of atherosclerosis progresses over decades and leads to the cardiovascular morbidity and mortality in adulthood. At present, we have no exact explanation for all the risk factors acting in the pathogenesis of atherosclerosis. This review should provide an overview about the possible role of intrauterine undernutrition in the development of risk factors for cardiovascular disease. Intrauterine undernutrition leads to changes in fetal growth and metabolism and programs later development of some of these risk factors. A number of experimental and human studies indicates that hypertension as well as impaired cholesterol and glucose metabolism are affected by intrauterine growth. Intrauterine undernutrition plays an important role and acts synergistically with numerous genetic and environmental factors in the development of atherosclerosis. There is evidence that undernutrition of the fetus has permanent effects on the health status of human individuals.

Key words

Intrauterine undernutrition • Low birth weight • Programming • Atherosclerosis • Risk factors of cardiovascular disease

Introduction

Cardiovascular diseases (CVD), which include coronary heart disease, stroke and peripheral vascular disease, are the main cause of death in developed countries. Current research of atherogenesis has only limited success in explaining the origin of CVD. The question “why one person develops CVD and another does not” is still open. This review should provide an overview of the possible role of intrauterine

undernutrition in the development of risk factors for CVD. Intrauterine undernutrition leads to changes in fetal growth and metabolism. The consequent adaptation to the new conditions results in long-term programming of individual organs.

Programming assumes that the primary cause of risks manifesting themselves in adulthood is intrauterine malnutrition leading to long-term morphological and metabolic defects (Hales 1997, Reynolds and Phillips 1998) (Fig. 1). Affected structure and metabolic function

contribute together with another environmental factors and genetic predisposition to the development of diseases in later life.

Risk factors of atherosclerosis

Atherogenesis is a process affected by a number of endogenous and exogenous factors. The most important risk factors for CVD include: dyslipidemia (quantitative and qualitative changes in the plasma levels of lipids and lipoproteins are the major risk factors for the development of atherosclerosis), hypertension, metabolic syndrome X, positive family history of CVD, male gender and cigarette smoking.

Lipoprotein levels and blood pressure (BP) are influenced by both genetic and environmental factors, the latter including excessive energy intake, high-fat and

high-cholesterol diet, increased proportions of saturated fatty acids, increased sodium intake, low fiber intake and low physical activity. The susceptibility of individuals to these adverse environmental factors is in most cases of a polygenous nature.

In addition to the above listed risk factors related to increased probability of premature atherosclerosis complications, numerous additional factors have been documented. An increased concentration of homocysteine (Stampfer *et al.* 1992), low consumption of fruit and vegetables (Joshipura *et al.* 1999) and an increased concentration of the C-reactive protein (CRP) (Ridker *et al.* 1997) have been proved to contribute significantly to an increased probability of either manifestation of CVD or CVD mortality independently of classical risk factors.

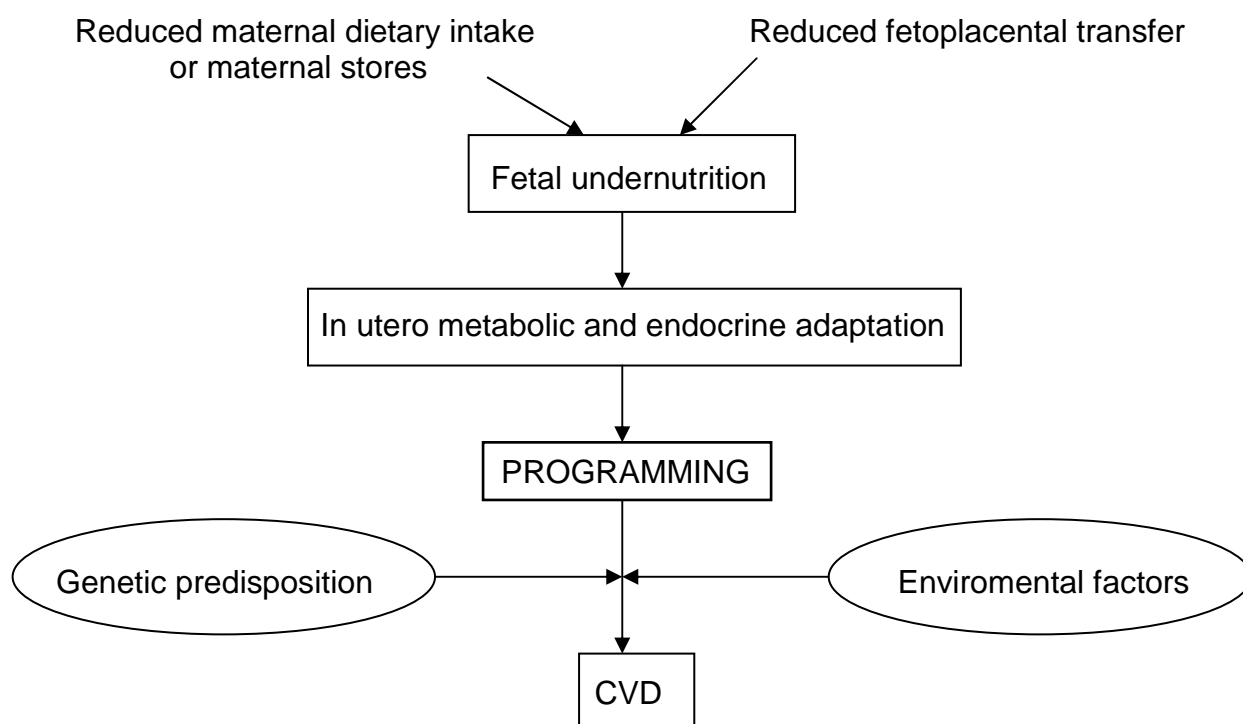


Fig. 1. Mechanism of programming

Pathogenesis of atherosclerosis

Increased intravascular plasma concentration of low-density lipoprotein (LDL) particles carrying cholesterol is a reason for their accelerated transport into the arterial wall. This accelerated transport exceeds the actual needs of cholesterol within the arterial wall to furnish adequate availability of cholesterol for normal smooth muscle cell function. In the subendothelial space of medium and large arteries, LDL particles are trapped

within the extracellular matrix of proteoglycans and collagens and are partly chemically modified (mainly oxidized). If the inflow of LDL cholesterol is adequate (at low intravascular concentrations of LDL similar to other mammalian species and human newborns), almost all LDL particles are utilized as a source of cholesterol for arterial cells. In the excess of LDL particles within the arterial wall, they are cleared from interstitial fluid by monocytes entering the arterial wall by transcellular

transport through endothelial cells. This process of cholesterol homeostasis might be well balanced with the support of high-density lipoprotein (HDL) particles entering the arterial wall with the ability to transport excess cholesterol from smooth muscle cells, monocytes and macrophages back into the intravascular space by a rather complicated process called "reverse cholesterol transport". A small remaining excess of LDL is cleared by monocytes, which leave the arterial wall either back into the lumen or through the vaso-vasorum system. Unfortunately, if both protective processes (fast clearance of LDL by monocytes with their successful removal from the artery and reverse cholesterol transport by HDL) are insufficient to clear abundant LDL in the subendothelial space, the atherogenic process is started (Assmann *et al.* 2002). Accumulation of cholesterol in monocytes is causing them to increase their size and to become transformed into macrophages, residual macrophages and finally into foam cells (beginning of atherogenesis). In addition, oxidized LDL are bound and internalized in monocytes by scavenger receptors (an alternative pathway to regulated LDL receptor) with no feedback regulation of intracellular homeostasis and this process substantially accelerates the transformation of monocytes into macrophages and foam cells.

Intrauterine undernutrition

A newly discovered potential cause of the development of some of these risk factors, and a new line of research into cardiovascular diseases seems to be the hypothesis put forth by Barker and coworkers proposing that CVD is significantly determined already *in utero* (Barker 1996, 1998). This hypothesis assumes that fetal malnutrition during gestation results in a disproportional growth of the fetus and programs the later development of the risk for CVD in adulthood (Barker 1995, Godfrey and Barker 2000).

During intrauterine life, the organism passes through so-called critical periods of rapid tissue growth with increased cell division. The affection of the organism in these critical periods leads to permanent changes in individual organs. One of the possible influences (besides hypoxemia, infection, etc.) is insufficient nutrition, which can negatively program the development of tissues and organs. Programming, according to Lucas (1991), is said to occur "when an early stimulus or insult, operating at a critical or sensitive period, results in a permanent or long-term changes in the structure or function of the organism".

Experimental studies

Up till now, most studies concerning humans have been epidemiological, but there is a number of experimental studies supporting the hypothesis of fetal determination of adult diseases (Lucas 1998, Hoet and Hanson 1999). The concept of nutritional programming is not new. Widdowson (1971) demonstrated in pigs that undernutrition at different periods of gestation resulted in altered and/or disproportionate growth and led to selective organ damage. The field of developmental physiology has a long tradition in Czech science. Early nutritional manipulation has been considered as an important factor for later development of the organism. Research of prematurely weaned animals led to a new term "late effects of early adaptations" (for review see Křeček and Koldovský 1995). A group of Czech investigators has shown that plasma cholesterol levels in adult animals depend on their early nutritional history. Levels were lowest in normally weaned rats and highest in prematurely weaned rats (Hahn and Koldovský 1976). The exposure of pregnant rats to a high fat diet also led to an augmented hypercholesterolemic response in adulthood (Coates *et al.* 1983).

To clarify the mechanism of influence exerted by intrauterine undernutrition, numerous models were used. In some of them an isocaloric low-protein diet has been used, other studies have investigated varying degrees of global undernutrition in pregnancy. Another approach was the ligation of the uterine artery during pregnancy (Persson and Jansson 1992).

As far as hypertension is concerned, studies in rats have shown that low-protein diet during pregnancy reduces fetal-placental weight ratio and elevates arterial blood pressure (BP) in the offspring (Langley and Jackson 1994). BP homeostasis is affected by many factors so that it is difficult to explain hypertension by a single simplified model. The development of hypertension depends on the interaction of different regulatory systems. In fact, the expression of genetic information is modified by numerous environmental factors acting in specific ontogenetic periods. Several critical periods (developmental windows), in which particular stimuli affect the further development of the cardiovascular phenotype, were identified in the rat. The hypertensive processes triggered at such critical periods are of eminent importance (Zicha and Kuneš 1999).

Besides the cardiovascular system, the development of other tissues may be affected by nutritional restrictions in pregnancy. The decreased number of pancreatic beta-cells and decreased number of

renal glomeruli have been correlated with low birth weight. Protein-calorie malnutrition in early life persistently impairs the insulin secretion and may predispose for diabetes (Swenne *et al.* 1987).

To evaluate the effect of intrauterine undernutrition on cholesterol metabolism, experimental model with reduced food intake in pregnant rats has been used. A significantly higher cholesterolemia was reported in rats undernourished in their intrauterine life compared with animals without food restriction in pregnancy (Sztányi *et al.* 2000). There is no doubt that extrapolation of any experimental model to the human being is difficult, but experimental data confirms programming and experimental models enable to study the mechanisms involved.

Human epidemiological studies

The concept of an intrauterine effect on later organ functions in humans is based on the extensive body of data emerging from epidemiological studies.

Table 1. Death rates from CVD according to birth weight (n=15726, modified from Barker 1996)

Birth weight (kg)	Standardized mortality ratio	Number of deaths
≤ 2.5	100	57
2.95	81	137
3.41	80	298
3.86	74	289
4.31	55	103
>4.31	65	57
Total	74	941

Analysis of the mortality rate has shown that among 15726 men and women (born during 1911-1930), the death rate from CVD fell progressively with increasing birth weight (Table 1). These findings suggest that anthropometric parameters at birth (birth weight, length, circumference of the head, abdomen and chest, ponderal index) may be related to the future health status of an individual. Intrauterine growth retardation, assessed using the above anthropometric data, is also a major predictor of so-called syndrome X (hypertension, type-2 diabetes, hyperlipidemia) and the rate of death from

cardiovascular disease in adulthood (Barker *et al.* 1993c, Fall *et al.* 1995, Phillips 1998).

Disproportional birth dimensions were also related to the insulin resistance syndrome and reduced glucose tolerance. The authors noted that a low ponderal index (birth weight/birth length³), low birth weight and a shorter head circumference were present in patients of either sex with syndrome X (Barker *et al.* 1993a). These patients showed an increased current body mass index (BMI) in adulthood. The prevalence of syndrome X was not related to cigarette smoking, alcohol consumption or the social class at the time of birth. Insulin resistance was the highest in patients who were lean (a low ponderal index) at birth and obese in adulthood (Phillips *et al.* 1994). During fetal life, insulin and insulin-like growth factor play a key role in stimulating cell division (Gluckman and Harding 1997). Khan and Cooper (1994) confirmed a direct association between a low birth weight, reduced number of pancreatic beta-cells and earlier development of insulin-dependent diabetes mellitus.

Further study indicated that neonates with a small abdominal circumference and a short body (related to head circumference) have disorders in cholesterol metabolism (increased total cholesterol, LDL-C, apoB) and disorders in coagulation parameters (fibrinogen, factor VIII) (Barker *et al.* 1992). The levels of total cholesterol, LDL-C and apoB showed an upward tendency in individuals with a low birth weight, but only the trend in apoB was statistically significant (Barker *et al.* 1993b).

It can be summarized that systolic BP rises with age and its inverse correlation with birth weight is evident from the first months of life up to the age of 71 years (Law 1995). This correlation becomes increasingly significant with age. It has been found that systolic BP decreased by 4 mm Hg with each kg of birth weight and rose by 1 mm Hg for every unit increase in BMI at age 64 years (Law *et al.* 1993). The highest systolic BP was found in patients with a low birth weight and the highest current body weight (Martyn *et al.* 1995). Unlike the yet unknown mechanism of the action on cholesterol metabolism, a possible explanation is available for hypertension (Mackenzie and Brenner 1995). Their theory for the development of hypertension in later life in relation to a low birth weight is based upon a reduced total number of nephrons. In ontogenesis, the system involving a reduced number of nephrons, which have long been "overloaded", manifests itself by sodium retention and arterial hypertension. Programmed

deficiency in the number of nephrons could represent the renal factor of hypertension.

Genetic predisposition

Barker's group originally claimed that all CVD risk factors for the development of premature atherosclerosis are produced by environmental influences acting either temporarily (recent diet, physical activity, sodium intake, etc.) or through intrauterine nutrition. This

means that no genetic determination would be involved. The individual effect of "so-called genetic determinant" would only be the consequence of early programming altered by intrauterine undernutrition. It is more than probable that the effect of different candidate genes for hyperlipoproteinemia, hypertension and insulin resistance is independent, but it might work in concert with prenatal effects.

Table 2. Mean birth weight and apoE4 genotype frequencies (number of apoE4/number of probands) in tertiles of low cholesterol group (LCG), high cholesterol group (HCG) and in whole groups.

Parameter	Group	1st tertile	2nd tertile	3rd tertile	Whole group
Birth weight	LCG	3.00±0.23	3.52±0.14	3.94±0.21	3.48±0.43*
	HCG	2.67±0.40	3.20±0.13	3.78±0.26	3.21±0.54*
ApoE4+	LCG	3/24 [#]	2/24 [#]	2/24 [#]	7/72 [#]
	HCG	9/23 [#]	7/22 [#]	5/22 [#]	21/67 [#]

Data are means ± S.D., *[#] significantly different ($p < 0.01$) from LCG group.

Essentially, the theory of the fetal origin of the disease, which does not manifest itself until adulthood, is an early defect in programming of the development of structure and function of individual organs and leads to the development of CVD several decades after the original insult. The situation is no doubt aggravated by genetic factors and by the impact of later diet and environmental factors (Lucas 1991, Godfrey and Barker 2000). The "fetal origin" theory highlights the importance and sensitivity of the organism in the early stages of its development (Goldberg and Prentice 1994). It should be noted that this theory is based on retrospective data not taking into account the long-term effect of the environment, diet and lifestyle. A genetically determined increased susceptibility to these effects in the tested population has likewise not been analyzed.

Our main approach to this topic was to analyze the significance of birth weight in a genetically defined population. In a retrospective study we have shown a synergic effect of intrauterine growth retardation and apoprotein E polymorphism on the development of hypercholesterolemia. Probands with genetically enhanced sensitivity to hypercholesterolemia had significantly lower birth weight compared to the controls (Table 2). According to the cholesterol levels, intrauterine

undernutrition seems to be more influential in predisposed children (Szitányi *et al.* 1998).

Conclusions

The development of atherosclerosis progresses in the course of decades and is already believed to start in childhood. The process of atherogenesis is multifactorial and at present we do not have an exact explanation for the action of all risk factors. There is synergic action of numerous genetic and environmental factors. Some effects of the main risk factors of CVD might be explained through the molecular biology concept of atherogenesis. Hyperlipoproteinemia accelerates cholesterol inflow into the arterial wall, which is further augmented by high blood pressure. Smoking has been proved to decrease the protective endothelial cell barrier of the artery (as well as high blood pressure) and to increase LDL oxidation by an accelerated free radical production. Insulin resistance and diabetes accelerate the synthesis of very low-density lipoprotein in the liver and thus increase LDL production – predominantly LDL particles of small diameter, which are more susceptible to oxidation processes. Low consumption of fruit and vegetable decreases the availability of antioxidant vitamins transported within LDL particles and thus increases the probability of LDL oxidation (an effect of

flavonoids, other antioxidants in vegetables and fruit-like, must also be considered). Decreased physical activity stimulates free fatty acid release from the adipose tissue and their inflow into the liver, increasing synthesis of very low-density lipoproteins on the one side and decreasing their clearance by muscle lipoprotein lipase on the other. Infection and immune reactions also play a role in cardiovascular mortality. They increase adhesion of monocytes to the vascular wall and alter their behavior within the arterial wall (Hubáček *et al.* 1999).

Intrauterine undernutrition may represent another environmental factor, which affects the process of atherogenesis. There is evidence that undernutrition of the human fetus has permanent effects on its health status later in life. The theory of intrauterine programming of risk factors for CVD has shifted the interest in research of atherogenesis into much earlier periods of human development. A full understanding of the mechanism of their action could be beneficial for the prevention of atherosclerosis. Further research projects are urgently

needed for obtaining epidemiological facts and to get an insight into the pathophysiological processes involved. We need to progress beyond epidemiological relations to a better understanding of the underlying cellular and molecular processes. Such an approach should enable to use the obtained information in order to reduce the prevalence of major diseases. The information available indicates a great potential for ameliorating long-term health status by improved intrauterine development. From the practical point of view, it seems that individuals with the history of “intrauterine undernutrition” (mostly expressed as low birth weight or pre-term delivery) are at risk for the development of CVD. This fact should lead to a preventative approach in these individuals.

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Reprint requests

P. Szitányi, First Department of Pediatrics, Second Medical School, Charles University, University Hospital Motol, V úvalu 84, 150 06 Prague 5, Czech Republic. E-mail: szitanyi@yahoo.com