Low birth weight and early life origins of adult disease: insulin resistance and type 2 diabetes

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The hypothesis that some adult diseases can originate during prenatal life arises from a series of epidemiological researches. An association between low birth weight and modified glucose metabolism has been reported in interesting studies from Europe, the United States and Australia; they have revealed narrow relations between various indexes of poor fetal growth and susceptibility to developing glucose intolerance and insulin resistance in adulthood [1].

More detailed studies using resonance magnetic spectroscopy with P31 have found that adults that had low birth weight have a reduced velocity of glycolysis and production of ATP, as well as a low concentration of lipids in the muscular tissue [8]. Measuring energy metabolism by means of indirect calorimetry or carbohydrates marked with C13 showed that low birth weight is accompanied by a reduced postprandial oxidation of glucose [1].

To explain the hypothesis that some adult diseases can initially originate during prenatal life, Hales and Barker proposed the hypothesis of the "thrifty phenotype", founded on the fact that poor fetal or neonatal nutrition imposes mechanisms of nutritional saving that involve damage to the endocrine pancreas and great susceptibility to developing diabetes type 2 [2], as happens in the adult as a reaction to poor nutrition [3]. The fundamental characteristics of this hypothesis are that poor fetal growth has a nutritional basis and the consequent altered intrauterine environment irreversibly damages the development of metabolic functions of the organs.

Maternal nutrition can affect fetal growth both directly, through the availability of nutrients to transfer to the fetus (growth and vascularity of the placenta), and indirectly, exposing the fetus to a distorted maternal metabolic condition. These metabolic alterations are advantageous for the survival of the nutritionally deficient fetus through two mechanisms: selective variations of velocity of growth of specific organs and adaptations of fetal metabolism.

Diseases as diabetes type 2 arise if there is a conflict between the nutritional conditions to which the fetus has been programmed, and those faced in postnatal life.

However is the fetus born "thrifty" or does it become so?

Indeed the premise is that 62% of the weight at birth depends on the uterine environment, 20% of the maternal genes and 18% of the fetal genes [4].

According to an alternative hypothesis, the "thrifty genotype", fetal growth is restrained by factors of fetal genome as in environmental factors such as maternal nutrition. This hypothesis is derived from the high incidence in the Western world of diabetogenic genes, which are advantageous for survival under conditions of subsistence, but are harmful for survival under conditions of hyper nutrition [5]. A "thrifty genotype" (maternal and/or fetal) could be the cause of poor fetal growth, eventually worsened by malnutrition of maternal origin.

The fetus would be forced to adapt its glucose metabolism toward a condition of insulin resistance and this would represent an advantage for survival under conditions of precarious subsistence. The mechanism connecting poor fetal growth to insulin resistance could be explained by a gene or genes expressed as insulin resistant both in the fetus and the adult.

Insulin has a central role in fetal growth, assuring a velocity of growth commensurate with nutrition. Insofar, insulin resistance jeopardizes fetal growth. After birth, the passage from malnutrition to an abundant nutrition easily involves the onset of obesity and insulin resistance in adult life, as the ability to produce insulin is reduced. An amplification of this idea has brought about the proposal of the "surviving small baby hypothesis", according to which the predisposing genes to insulin resistance and the diabetes in adult life can be important for the survival of the fetus exposed to malnutrition in utero [6].

A "thrifty genotype" includes an insulin gene associated with LGA fetuses and to diabetes type 2 in the adult; these effects can be connected with the genotypes inherited from the father. In contrast, the mechanisms that restrict fetal growth and protect maternal survival can be inherited from mitochondrial DNA or genes expressed by the mother as IGF2R [7].

The manipulation of maternal nutrition can alter the expression of genes through variations in the methylation of DNA. Methylation of DNA is the base of genomic imprinting. Generally, methylated genes are repressed and those hypomethylated are induced [8]. Methylation of DNA silences the expression of genes and is governed by the methio-

Revised manuscript accepted for publication February 6, 2006

nine homocysteine pathway, and is sensitive to nutritional factors as the availability of amino acids, folic acid, vitamin B12 and vitamin B6 [9].

The hypothesis of "fetal insulin" is based on the possibility that there is a gene responsible for both low birth weight and diabetes type 2: insulin resistance, genetically determined, would be the cause of both the fetal growth defect and the susceptibility to diabetes type 2 during adulthood life [10, 11]. Mutations have been identified in the gene that codify glucokinase and cause low birth weight and maturity onset diabetes of the young (MODY). Nevertheless, these mutations are rare and scanning of the genome have not identified a common susceptible gene to diabetes.

Mitochondria have their DNA (mtDNA) and a system of independent replication. The mtDNA is inherited only by the mother and mutations sequentially accumulate through maternal descent. It is hypothesized that the characteristic anomaly of diabetes type 2 would reside in a mitochondrial dysfunction [12]. On the other hand, poor fetal nutrition would lead to mitochondrial modifications that contribute to developing insulin resistance and diabetes type 2. The beta cells containing pancreatic anomalous mitochondria have a limited secretive response of insulin to glucose stimuli. A polymorphism in the varying region of the mtDNA is associated with insulin resistance. About 0.5-1.5% of diabetics show some defects in mtDNA such as duplications, puntiform mutations, and deletions. The majority of the known mutations of mtDNA cause diabetes thus affecting insulin secretion. There are also quantitative modifications of mtDNA: the number of copies is lower in the muscles of diabetics. Moreover, in the peripheral blood a decreased density of mtDNA precedes the appearance of diabetes type 2, indicating that mitochondrial anomalies could be the cause of diabetes type 2.

Anomalies of mitochondrial DNA decrease mitochondrial oxidative phosphorylation and increase intracellular lipids, disturbing the insulin signal and increasing insulin resistance.

The maternal concentration of mtDNA in the peripheral blood is correlated with birth weight and with the concentration of mtDNA in the umbilical cord blood.

The following hypotheses could explain the mechanism through which malnutrition in the initial phases of life causes a reduction in mtDNA, which persists up to adult age without improvement, despite the recovery of nutrition: impaired stability of the tRNA of mtDNA caused by reduced availability of taurine, exhaustion of the pool of nucleotides caused from decreased availability, imprinting of the genome, and oxidative stress.

Protein malnutrition is associated with reduced protection by the antioxidant system and with increased oxidative stress [13]. In contrast, the hypothesis of the "thrifty phenotype" has also been confirmed by studies on monozygotic twins with different birth weights; the smallest twin has a great probability of being afflicted with diabetes in adult age [14, 15].

These observations suggest that the relation between poor fetal growth and the following diseases does not depend on major genetic influences, but on a fetal programming. Nutritionally associated low birth weight is more important than low birth weight due to genetic origin, and predicts insulin-resistance and NIDDM in adult age. To explain this phenomenon the idea of programming or physiological imprinting during the first phases of the life has been advanced [4]. This programming has been documented in a variety of systems and consists of a nech during a sensitive period or window of development that manages effects on the organization, persistent during the life.

Programming factors can include growth factors, hormones and nutrients. They cause adaptations which permanently modify metabolism during adult life and responses that optimize survival in conditions of malnutrition, stress or other deficiencies.

In humans, the famine in Holland, from October 1944 to April 1945, confirmed that maternal malnutrition is a factor of fetal programming; particularly protein deficiency with excessive carbohydrates is related to many diseases [16].

The hypothesis of the "thrifty phenotype" has brought about interesting developments in the concept of "fetal programming" [2]. The term "programming" is defined as a "process whereby a stimulus or insult, at a critically sensitive period of development, has lasting or lifelong significance" [17]. There are four essential principles that form the basis of the concept of programming:

– In the early phases of the life, nutritional manipulation causes different effects at different times;
– The rapidly growing fetus and newborn are more vulnerable to these manipulations;
– Manipulations in the early phases of life have permanent effects;
– The permanent effects include a reduced number of cells, an altered structure of the organs, and a new regulation of the hormonal axes.

The principles of programming have recently been revised and completed using animal models [18].

1) During development, there are critical periods of vulnerability to suboptimal conditions. Vulnerable periods occur at different times for different tissues. Cells dividing rapidly are at greater risk. Factors that increase risk include:

– Too much of a normal chemical (e.g. hormone, critical nutrient or vitamin);
– Deficiency of a normal chemical (e.g. hormone, critical nutrient or vitamin);
– Abnormal chemicals (e.g. alcohol or nicotine); and,
– Abnormal physical forces (e.g. high blood pressure).

2) Programming has permanent effects that alter responses in later life and can modify susceptibility to disease.

3) Fetal development is activity dependent. Normal development is dependent on continuing normal activity. Each phase of development provides the required conditions for subsequent development.

4) Programming involves several different structural changes in important organs:

– The absolute number of cells in the organ may increase or decrease;

– The relative proportions and distribution of different types of cells within the organ may be unbalanced;

– The normal blood supply to the organ may not form; and

– Too many or too few hormone receptors may form with a resulting resetting of feedback and other control mechanisms.

5) The placenta plays a key role in programming.

6) Fetal compensation carries a price. In an unfavorable environment, the developing baby makes attempts to compensate for deficiencies. Following compensation, birth weight may be normal or slightly decreased. However, the compensatory effort carries a price.

7) Attempts made after birth to reverse the consequences of programming may have their own unwanted consequences. When postnatal conditions prove to be different from those for which the fetus is prepared problems may arise.

8) Fetal cellular mechanisms often differ from adult processes. Fetuses react differently to suboptimal conditions than do newborn babies or adults.

9) The effects of programming may pass across generations by a mechanism that does not necessarily involve changes in the genes.

10) Programming often has different effects in males and females.

Indeed, prenatal malnutrition damages the pancreas. In the prenatal pancreas, the mass of endocrine tissue depends on three processes: neogenesis of endocrine cells from the epithelium of the pancreatic ducts, proliferation of the cells that are destined to endocrine differentiation, and apoptosis of these endocrine cells in the pancreatic islets during development [7].

Prenatal malnutrition reduces the number of pancreatic beta cells, the pancreatic islets are small and slightly vascularized; the result is an insufficient production of insulin and inadequate secretive response to glucose and amino acids, i.e., glucose intolerance [19].

The insulin content of the fetal pancreas is inversely proportional to the fetal levels of corticosterone. Maternal malnutrition causes a stress that increases the levels of corticosterone in the mother and fetus [19].

Maternal stress and prenatal exposure to glucocorticoids programs specific effects in the fetus on the hypothalamic-pituitary-adrenal (HPA) axis, and also on the dopaminergic and immunitary systems.

Fetoplacental 11β-hydroxysteroid dehydrogenase type 2 catalyzes the rapid inactivation of cortisol and corticosterone to inactive 11-ketoderivates. This enzyme in the placenta and in some fetal tissues protects the fetus from excessive maternal glucocorticoids.

Maternal deficiency of proteins during pregnancy produces hypertension in the fetus and selectively attenuates fetoplacental 11β-hydroxysteroid dehydrogenase type 2. These data point out that this enzyme, regulating fetal exposure to the glucocorticoids, influences fetal growth and the programming of diseases. The lack of this barrier toward the maternal glucocorticoids represents a pathway through which the maternal environment influences the programming fetus for diseases.

In the fetus, glucocorticoids modify the velocity of maturation and differentiation of the lung, liver, heart, kidney, muscle, fat, and bowel; they act on the liver enzymes that manage glucose and lipid metabolism; they regulate the disposition and function of adipocytes; they attenuate sensitivity to insulin [16]. This morphological and functional stimulus activates a lot of biochemical modifications that are not needed during intrauterine life, but are essential for postnatal survival.

Glucocorticoids signal adverse intrauterine conditions and adapt fetal development for the purpose of assuring the best possibilities of survival both in utero and at birth [20].

Prenatal glucocorticoid exposure delays fetal growth. Cortisol is augmented in the small-for-gestational-age fetus, increases the blood pressure in the fetus, and reduces the placental mass [21].

The negative effects of the fetal programming are emphasized in the newborn. A reduced availability of nutrients during fetal life irreversibly modifies adipoinsular feedback causing compensatory hyperinsulinemia and hyperleptinemia from the pancreatic delta cells after birth. The "programmed" newborns manifest hyperphagia, hyperleptinemia, hyperinsulinism and obesity during adult life [22].

Generally, a nutritional challenge that reduces the availability of nutrients lowers the concentrations of anabolic hormones (insulin, IGF-1, thyroxin) and increases some catabolic hormones (cortisol, catecholamine, growth hormone). The concentration of fetal insulin is positively correlated with fetal glucose and birth weight. Lack of fetal insulin causes asymmetrical intrauterine growth retardation (IUGR), without anomalies in the tissues. The insulin has negligible effects on the differentiation and maturation of fetal tissues, but increases the growth of the tissues through its anabolic effect on fetal metabolism and through the stimulation of the production of IGF-1.

Concentrations of thyroid hormones are reduced during the hypoxia associated with IUGR. Fetal hypothyroidism causes asymmetrical IUGR, with reduction of the muscular mass. The thyroid hormones influence the growth and differentiation of the tissues; they stimulate these processes through modulation of the production of IGF and the metabolic effects that increase the consumption of oxygen. Thyroid hormones promote fetal development and act as signals of the availability of energy.

IGF-I and IGF-II in fetal plasma derive from a variety of fetoplacental tissues. The plasma concentration and tissue expression of the IGFs are also regulated by other key hormones that regulate fetal growth. IGFs act as factors of progression in the cellular cycle, they prevent apoptosis and increase the synthesis of DNA and proteins in fetal tissues.

IGFs also have an anabolic action similar to insulin on the fetus. IGF-I is more sensitive than IGF-II to the nutritional condition, therefore it signals a nutritional sufficiency that regulates the growth of tissues. IGF-II provides a more general stimulus on cellular growth and regulates the specific variations of every tissue in cellular differentiation in the advanced phases of pregnancy and reacts to adverse intrauterine conditions [20].

The fetal tissues accustomed to insulin and IGF-1 deficiency and exposed after birth to an increase of these hormones, oppose them by developing insulin-resistance as a metabolic defence against hypoglycemia. This hypothesis, called "catch-up growth", has been proposed to explain the association between the fast neonatal growth of preterm neonates and the increase in indicators of the metabolic syndrome in adult age [23]. Such hypothesis is based on the argument that these newborns often have lower levels of insulin, IGF-1, IGFBP-3, but higher levels of growth hormone (GH) and IGFPB-2 in comparison to normal newborns. The normalization of insulin and IGF occurs during the first three months of life which coincides with a rapid resumption of growth [24].

It is therefore credible that tissues chronically depleted of insulin and IGF-1 during fetal life and suddenly exposed to high concentrations of the two hormones can counterbalance developing insulin resistance as a metabolic defence of survival against hypoglycemia, which could be the basis of the association between catch-up growth and elevated risk of insulin resistance.

One of the mechanisms of the thrifty phenotype hypothesis is that of oxidative stress. The reactive oxygen species (ROS) inevitably originate as by-products in the transport of electrons in the mitochondrial respiratory chain and in a lot of cellular and extra cellular ox-red reactions.

An excess of ROS causes oxidation of proteins, lipids and DNA, in other words "oxidative stress". The reactive forms of oxygen regulate enzymes and expression of the genes sensitive to oxide-reductions. These trials are balanced by scavengers (vitamin C) and by detoxifying enzymes (superoxide dismutase, glutathione reductase).

Oxidative stress can act directly, modulating the expression of genes, or indirectly, through the negative effects of oxidized lipids or other molecules during the critical window of development. Consequently a new regulation/programming of susceptibility to the metabolic syndrome is produced. Oxidative stress is transferable from the mother to the fetus and, acts directly by modulating expression of the genes or indirectly through the effects on oxidyzed molecules.

Nutritional deficiency can jeopardize antioxidant competence because proteins provide the necessary amino acids for the synthesis of antioxidants as glutathione and albumin (scavengers of ROS) and many micronutrients that are in the same antioxidants [25].

Oxidative stress is also present in the SGA newborns of undernourished mothers, as well as in preterm newborns. Malnutrition causes deficiency of proteins or micronutrients implicated in the synthesis of antioxidant enzymes, or they are themselves antioxidants [26-28].

Metabolic activity of placental mitochondria also produces oxidative stress in normal pregnancy, but is exacerbated in case of IUGR, diabetes and preeclampsia. This metabolic activity can also provoke nitrative stress (formation of peroxynitrite) which causes covalent modification of the proteins that alter its activity.

Hypoxia, oxidative and nitrative stress alters the development of the placenta and this mechanism binds the altered placental function to fetal programming [29].

To answer the initial question are we born "thrifty" or do we become so, there are a variety of hypotheses today that confirm the relationships among poor fetal growth, insulin resistance and diabetes type 2 in adult age, on a genetic or epigenetic basis.

The imbalance between fetal energy requirements and maternal supply constrain the fetus to suffer stress, and thus to program its glucose and hormonal metabolism to increase the possibilities of survival. The complexity of such adaptative modifications is still the object of study.

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