Review article

Fetal growth and developmental programming

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Abstract

The environment in utero and in early neonatal life may induce a permanent response in the fetus and the newborn, leading to enhanced susceptibility to later diseases. This review concentrates on the role and mechanisms of events during the antenatal and immediate postnatal period resulting in later life diseases, concentrating on abnormal growth patterns of the fetus. Fetal overgrowth is related to exposure to a diabetic intra uterine environment, increasing the vulnerability to transgenerational obesity and hence an increased sensitivity to more diabetic mothers. This effect has been supported by animal data. Fetal growth restriction is complex due to malnutrition in utero, catch up growth due to a high caloric intake and low physical activity in later life. Metabolic changes and a transgenerational effect of intra uterine malnutrition has been supported by animal data. In recent years the discovery of alterations of the genome due to different influences during embryonic life, called epigenetics, has led to the phenomenon of fetal programming resulting in changing transgenerational metabolic effects.

Keywords: Developmental programming; diabetes; fetus; obesity.

Introduction

It is known that environmental factors influence health and the development of diseases. Certainly the environment in utero and in early neonatal life may induce a permanent response in the fetus and the newborn, leading to enhanced susceptibility to later diseases. These effects can be transgenerational and are probably due to an epigenetic transmission mediated by the mother [4, 44].

Abnormal environmental factors during pregnancy may lead to increased fetal growth, due to increased transplacental nutrients or may lead to fetal growth restriction, due to decreased transplacental transfer. Both extremes of fetal growth can induce developmental programming through epigenetic adaptations.

The present review will concentrate on the role and mechanisms of events during the antenatal and immediate postnatal period resulting in diseases in later life, concentrating on abnormal growth patterns in the fetus.

Fetal environment and increased fetal growth

Even before the discovery of insulin, Dubreuil and Anderdias [19] described giant islets of Langerhans in the pancreas of a newborn of a diabetic mother. Pedersen proposed that increased transplacental transfer of glucose leads to increased insulin secretion by the fetus, inducing macrosomia [38]. It was confirmed that fetal hyperinsulinism was due to B cell hyperplasia and the hypothesis was put forward that hyperactivity of the fetal B cells might result in reduced secretory capacity in later life. Furthermore, an intact hypothalamic structure was needed to induce B cell hyperplasia, predicting the role of the hypothalamus in perinatal programming [50].

Dörner was among the first to provide evidence that exposure to a diabetic intra-uterine environment increases the risk of developing diabetes in the offspring. Moreover, he showed a transgenerational effect and the importance of good metabolic control in the prevention of long-term consequences [17, 18]. These observations were confirmed by several epidemiologic studies and recently summarized: the excess of maternal transmission of diabetes is consistent with an epigenetic effect of hyperglycemia in pregnancy acting in addition to genetic factors that induce diabetes in next generations. Individuals with genetic susceptibilities may be the most vulnerable to the in utero influences of maternal diabetes [36, 44].

Offspring of diabetic mothers also have an increased risk for obesity related to the degree of fetal hyperinsulinism [48]. Furthermore, impaired glucose tolerance and obesity in adults due to a diabetic intra-uterine environment is independent of the genetic background [10, 11, 39].

Maternal obesity has gained an epidemic proportion in Europe and the developed world [20]. Maternal obesity and increased weight gain during pregnancy are associated with increased birth weight independent of genetic factors. It is also evident that maternal obesity induces higher transplacental transfer of nutrients resulting in fetal hyperinsulinism, increased fetal growth and adiposity [35]. Maternal obesity therefore has a transgenerational effect inducing obesity and diabetes [12].
Animal data

Animal models of diabetes and obesity during pregnancy may unravel the specific effects of an exposure to an abnormal intra-uterine environment independent of inherited traits. In the rat, mild diabetes during pregnancy can be induced with a low dose of streptozotocin, stimulating the insulin producing B cell, hyperinsulinism and increased weight of the fetus. (Over-) Stimulation of the B cells in utero leads to a reduced insulin secretion during later life in conditions of increased demands, such as obesity and pregnancy [1, 16]. In experimental induced gestational diabetes a transgenerational effect was demonstrated [2]. Moreover, normalization of the maternal glycaemia by islet transplantation prevents deleterious effects for the fetus and offspring [3]. It seems clear that (over-) stimulation of the fetal B cell reduces the function of this cell in the offspring [4].

However, it may be possible that fetal hyperinsulinism itself may induce malprogramming [41]. Indeed another pathophysiologic mechanism may be related to the hypothalamic control of food intake, body weight and glucose metabolism [40]. The ventromedial hypothalamic nucleus (VMN), the lateral hypothalamic area (LHA) and the arcuate hypothalamic nucleus (ARC) of the medio basal hypothalamus play an important role in this context. Hyperinsulinism in the fetus of pregnant rats with diabetes is associated with increased insulin content in the hypothalamus leading to an impaired organization of the VMN, the antagonistic LHA being unaltered [41]. Hypotrophy and hypoplasia of the VMN may result in a diminished function of the satiety center, together with a relative overactivity of the antagonistic LHA, stimulating appetite and weight gain [43]. Neuropeptides in the ARC play an important role in the regulation of food intake, body weight and metabolism. In particular neuropeptide Y (NPY) is the most potent orexigenic neuropeptide and is regulated via the circulating satiety factors leptin and insulin, both suppressing NPY expression [41]. Perinatal hyperinsulinism induces resistance of the NPYergic system against the regulatory signals leptin and insulin, leading to hyperphagia and overweight in adult offspring [43]. Islet transplantation in induced maternal diabetes prevents the effects in VMN and ARC [23, 28]. Furthermore, malprogramming of the hypothalamic structures is also operational in the diabetic lactating period, suggesting the importance of the milk composition [21, 42].

Recently, several experimental models in rat and mice of diet induced obesity have been reported inducing fetal hyperinsulinism and increased body weight, leading to glucose intolerance, insulin resistance, obesity, hyperphagia and hypertension in the offspring [31, 37, 47]. These effects are transgenerational [31]. It is clear that diet induced obesity during pregnancy in animals show comparable changes in the fetus and the offspring as seen in experimental diabetes. Fetal hyperinsulinism is the result of B cell (over-) stimulation and induces B cell dysfunction in later life. Hyperleptinemia in the early neonatal period induces overweight, hyperphagia, diabetic tendency and cardiovascular problems in later life. Hypothalamic alterations, induced by fetal hyperinsulinism are associated with neonatal leptin resistance with long-term consequences [43]. The important role of induced leptin resistance is confirmed in maternal obesity: young offspring of obese dams are leptin resistant, and remain leptin resistant and hyperphagic when adult [32].

Insulin is also known as a potent mitogenic factor, which is another reason to decrease fetal hyperinsulinism to lower the risk for cancer in later life [52].

Fetal environment and intra-uterine growth restriction human data

The fetus with intra-uterine growth restriction shows a reduced amount of B cells related to low insulin and glucose levels [51]. Studies in England and Wales, demonstrating the association between low birth weight and adult impairment of glucose tolerance, obesity, type 2 diabetes and cardiovascular diseases have led to the Barker hypothesis of fetal origin of adult diseases [5, 6]. Consequent population studies have confirmed the relation between low birth weight and adult diseases [34]. The most vulnerable period in pregnancy is shown in studies of the maternal malnutrition during the Dutch hunger winter in 1944. This malnutrition resulted in a higher incidence of impaired glucose tolerance, type 2 diabetes and cardiovascular risks in the offspring especially when deprivation occurred in the third trimester [45].

The consequences in later life are also determined by caloric intake. A population subjected to poor nutrition in the perinatal period can keep a normal glucose tolerance as long as they remain on a low caloric diet. A change to a higher caloric intake and low physical activity increases the incidence of impaired glucose tolerance and type 2 diabetes increases [4]. In this respect, a high caloric intake in the postnatal period inducing catch up growth will aggravate the consequences in later life [25, 26]. Breastfeeding may prevent accelerated caloric intake in the postnatal period [46].

It is accepted that the underdevelopment of the fetal B cells may lead to reduced B cell function in later life, certainly in periods of increased demands. Leptin may also play an important role. High caloric intake in the newborn after a period of fetal growth restriction may induce a leptin charge. Hyperleptinemia in the early neonatal period induces hyperphagia, overweight, diabetic tendency and cardiovascular problems in later life [43], certainly in situations of previous fetal undernutrition [53].

Animal data

Several animal models mainly in the rat have studied the impact of reduced fetal nutrition on long-term consequences. Global food restriction by semi starvation or by unilateral uterine artery ligation during pregnancy results in underdevelopment of the fetal B cells, low insulin levels and intra-uterine growth restriction [15, 24]. In adult rats, insulin resistance and subtle changes in vascular function are found [29, 30]. However, hypertension did not seem to be a consequence [30, 49].
An isocaloric, but low protein diet has been frequently used for the induction of intra-uterine growth restriction. A reduced B cell mass and reduced insulin secretion in the fetus was correlated with the occurrence of gestational diabetes in the offspring [13, 14]. Offspring from pregnancies with low protein diet do seem to have an increased blood pressure [33]. Here, also the deficiency in the total islet mass and specifically in the B cell mass during fetal life, results in a reduced adaptation in adult life leading to gestational diabetes with macroscopic fetuses, indicating a transgenerational effect [7, 8].

Intra-uterine growth restriction, as such, does not program the hypothalamus towards increased appetite and obesity. However, high caloric intake and increased leptin concentration in the neonatal period may induce hyperphagia and obesity in later life [43].

**Epigenetic adaptations**

Exposure to environmental changes *in utero* has been investigated as epigenetic events resulting in transgenerational effects, such as macrosomia, obesity and diabetes. The alterations on the genome, without changes of the DNA are characterized as epigenetics. This is a slow process of changing methyl groups on cytosine bases in DNA by methyltransferases. Modifications are identified as de-methylation, histone deacetylation and increased histone acetylation, independent from replication [22]. Therefore, DNA methylation appears to occur before cellular differentiation, as no *de novo* methyltransferases are present after cellular differentiation. This suggest a role for environmental influence, such as excessive nutrition, nutritional restriction or low folic acid and vitamin B12 levels, on DNA methylation in early life development [27, 36].

Especially during periconception and embryonic life the rate of DNA synthesis is high and therefore susceptible for alterations in DNA methylation, leading to metabolic imprinting for leptine, SOC3 and glucose transporter mechanisms for energy homeostasis [12]. Whether these changes are irreversible is not yet clear, although animal studies on developmental programming indicate that an obese phenotype is not transmitted to their offspring by mating, but merely by uterine environmental influence. This stresses the importance of embryonic environment on epigenetic imprinting for metabolic mechanisms on the future generations [9, 12, 54].

**Conclusions**

It seems clear that events *in utero* induces a response in the fetus and newborn, leading to enhanced susceptibility for later diseases. In maternal diabetes and in maternal obesity increased transplacental nutrient supply to the fetus induces B cell hyperactivity, hyperinsulinism and increased fetal growth. Fetal hyperinsulinism is responsible for changes in the hypothalamus resulting in malprogramming of food intake, body weight and glucose metabolism. Insulin is also known as a potent mitogenic factor. From the clinical point of view it is therefore evident that in maternal diabetes and in maternal obesity, fetal hyperinsulinism should be avoided. Early detection of gestational diabetes and strict metabolic control are essential. Obesity needs to be prevented preferably at adolescence and certainly before pregnancy.

Intra-uterine growth restriction is associated with a reduced B cell mass and low insulin secretion, the underdeveloped fetal B cell is responsible for a reduced B cell activity in later life. Neuroendocrine mechanisms, such as leptin charge, are involved through malprogramming leading to excessive catch up growth, therefore efforts should be made to prevent intra-uterine growth restriction by early detection and management of hypertensive disorders in pregnancy and by optimal nutrition of the pregnant women.

Not every overweight newborn and not every newborn with intra-uterine growth restriction will develop problems in later life. It depends on bad or good adaptation and to the plasticity of its adaptation later on [25]. This is called epigenetics, which means that by different environmental influences, alterations are made during early intra-uterine life on gene expressions, leading to aberrant metabolic phenotypes, like obesity. More profound understanding of the effect of fetal programming and the transference to future generations will be possible with further studies exploring epigenetic mechanisms. [54].

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