Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2017, 7, 59-76
http://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Endocrine Disruptors and Fetal Programming

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How to cite this paper: Lucchese, T.A., Grunow, N., Werner, I., de Jesus, A.L. and Arbex, A.K. (2017) Endocrine Disruptors and Fetal Programming. *Open Journal of Endocrine and Metabolic Diseases*, **7**, 59-76.
http://dx.doi.org/10.4236/ojemd.2017.71007

Received: November 21, 2016
Accepted: January 10, 2017
Published: January 13, 2017

Abstract

The concept "fetal programming" shows who still in the intrauterine life, can interfere in factors related to the genesis and development of diseases in childhood, adolescence and adult life. The literature shows that children born to mothers with gestational diabetes mellitus (GDM) are at increased risk for the development of obesity in adulthood, it becomes fundamental to study more about the subject. Obesity is a disease of multifactorial etiology, resulting from complex interactions between genetic and environmental factors. However, the marked increase in its incidence, precocity and severity are not yet fully understood. Several findings suggest that stressor stimuli (e.g. diabetes, nutritional changes) during intrauterine development may promote epigenetic changes, as well as affect mitochondrial metabolism, which may modulate fetal development and predispose to the late development of diseases. Despite the considerable amount of evidence accumulated about intrauterine programming for diseases of adult life, the determinant mechanisms of such programming are not yet clear.

Keywords

Fetal Programming, Obesity, Diabetes Mellitus

1. Introduction

An epidemic of diabetes mellitus (DM) is ongoing. Currently, the world population with DM is estimated to be in the region of 387 million and reaches 471 million in 2035. About 80% of these individuals live in developing countries, where the epidemic is most intense and there is an increasing proportion of people affected in younger age groups, which coexist with the problem that infectious diseases still represent [1].

The number of diabetics is increasing due to population growth and aging,

greater urbanization, the progressive prevalence of obesity and sedentary life, as well as the greater survival of patients with DM. Quantifying the current prevalence of DM and estimating the number of people with DM in the future is important, since it makes it possible to plan and allocate resources in a rational way [1].

The World Health Organization points to obesity with one of the major public health problems in the world. The projection is that by 2025, about 2.4 billion adults will be overweight; and more than 700 million will be obese. The number of overweight and obese children in the world could reach 75 million if nothing is done [2].

The term fetal programming refers to the process by which a stimulus or insult, when occurring in the critical period of development, has permanent effects on the structure and functions of the organism. This is due to the plasticity and sensitivity to changing the environment. This critical period of development, for most human organs and systems, occurs especially in the intrauterine phase. At this stage, the plasticity of the organism requires stable modulation of gene expression [3].

Surprisingly, geographic studies have emerged for the first time that intrauterine events could also be a variable in this paradox. The existence of detailed records of 1366 localities in England and Scotland allowed David Barker to observe a positive association between coronary disease mortality rates in the various regions between 1968 and 1978 and the respective infant mortality rates in those regions about 50 years before [4]. These geographical studies were the origin of the *Barker theory or Theory of fetal origin of adult diseases,* which dates back to 1996, and according to which poor nutrition during pregnancy and early childhood would lead to permanent metabolic and/or structural adaptation that increases the risk of developing coronary heart disease and other associated diseases, such as hypertension, DM and stroke in adulthood—*fetal programming* [5]. This theory is based on the concept of developmental plasticity, that is, the ability of a genotype to originate different morphological or physiological states in response to different exposures during development [6].

The epigenome is re-established at specific developmental ages and is maintained throughout life, becoming a first-line candidate for the basis or origin of fetal programming [7]. The sensitivity of the epigenome to the environment is objectified as an adaptative mechanism by which the developing organism adjusts its metabolic and homeostatic systems to shape itself to the extrauterine environment with which it will contact [8]. The discrepancy between intrauterine and extrauterine environment may predict individual susceptibility to disease development in the future [9].

Gestational diabetes is an important health problem considering that abnormalities of glucose metabolism can start in children of 3 years of age and more than 80% of overweight/obese children remain in adult life [10]. Gestational diabetes is thus a good model for studying the mechanisms involved in fetal metabolic programming and also for elucidating new mechanisms that aid in the

diagnosis, treatment, and prevention of its consequences for newborns and future generations. Epigenetics is currently a very promising mechanism of fetal metabolic programming [10].

2. Diabetes and Intrauterine Programming

Diabetes Mellitus is the most prevalent metabolic disorder characterized by hyperglycemia due to pa primary defect in insulin secretion and/or action. Type 1 Diabetes Mellitus (T1DM) is characterized by lack of insulin secretion due to autoimmune destruction of pancreatic beta cells; Conversely, Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and insulin deficiency. The third class is Gestational Diabetes (GDM), where during pregnancy hyperglycemia occurs and improves after childbirth [11] [12]. While T1DM has a very clear origin, T2DM has a multifactorial etiology that was confirmed by numerical studies that revealed the effects of risk factor such as age, sex, ethnicity, sedentary lifestyle, obesity, insulin resistance, diet, socioeconomic profile.

The period from conception to birth is of rapid growth, cell replication and differentiation, and functional maturation of the organ systems. These processes are very sensitive to changes in the intrauterine environment [13]. Epidemiological studies and animals models support the concept that there is a critical period of developmental programming in which exposures to adverse intrauterine environments or neonatal events may make an individual more susceptible to the development of adult illnesses such as obesity and DM [14] [15].

James Neel proposed the "economic genotype" hypothesis to explain the pathophysiological association between adverse events in early life and chronic diseases in adulthood [16]. According to this hypothesis, "economic genes" or "savers" selected by the body at the time of nutritional limitation would increase the ability to store fat. These economic genes would give individuals an advantage in a low-calorie environment, reducing the use of glucose and limiting the body's growth. If individuals with this genotype encountered an environment without food limitation and low energy expenditure in extrauterine life, they would be at increased risk for developing T2DM and metabolic syndrome [17]. Uniquely genetic models, however, fail to explain how the effects of caloric restriction on gestation or early life affect an individual's health, as demonstrated in the Dutch famine cohort, and in various animal models [18].

The presence of maternal diabetes is associated with an incidence of diabetes in offspring that is significantly greater than would be expected only by maternal transmission of genetic traits [19]. The increasing epidemic of T2DM and obesity in developed countries can not only be explained by obesity, sedentary lifestyle and/or genetic factors [20]. Thus, susceptibility to the development of T2DM and metabolic syndrome in a postnatal phase of the individual may be related to previous intrauterine environment [21].

The study of Danna and colleagues has showed evidence that the exposure to obesity in the uterus is associated with T2DM in juvenile independent from diabetes during pregnancy. Intrauterine exposures to diabetes and maternal obesity

are strongly associated with T2DM in young people. In our multi-ethnic population, 47% of T2DM cases in young people can be attributed to the combined effect of these exposures. The data from the study suggest that for the prevention of T2DM a lifelong approach is needed, targeting not only childhood obesity, but also a look at the increase in women with pregnancies complicated by obesity and diabetes [22].

Another study showed that in a relatively lean European population, as in the indigenous Prima population, maternal diabetes mellitus during pregnancy is associated with higher BMI from the adolescence/early adulthood, showing greater intrauterine influence. This, the importance of identifying and adequately treating GDM, not only for immediate perinatal reasons, but also for the health of the child in adult life [10]

The history of T2DM on maternal side of the pregnant woman can be considered as an individual risk factor for intrauterine transmission. Therefore, GDM should be prevented, at least in part. Preventing the fetus from being exposed to an intrauterine diabetic environment [23].

Many risk factors have been studied, however, prenatal exposure to a diabetic intrauterine environment appears to be the major contributory factor to the development of the disease in its future life [15] [22]. The link between the exposure to an adverse intrauterine environment and the development of diseases in adult life has been observed in pregnancy complicated by obesity and DM, however, the molecular mechanisms behind this phenomenon are still not well understood. Thus, exposure to an adverse intrauterine environment, namely an environment characterized by hyperglycemia and hyperinsulinemia, may influence epigenetics and the structural and functional adaptive responses responsible for developmental programming [15]. The increased risk of obesity is related to the degree of fetal hyperinsulinism [24].

Maternal glucose crosses the placenta easily and leads to intrauterine hyperglycemia, fetal hyperinsulinemia and possible modification of fetal growth and development [25]. GDM may thus result in both macrosomic offspring and intrauterine growth restriction [13] [24], depending on the degree of hyperglycemia presented [15] [21]. There is growing epidemiological evidence that excesso nutritional intake to the fetus can produce phenotypes similar to those of malnutrition in offspring [8].

3. Impact of Birth Weight on Metabolic and Cardiovascular Risks

Over the last few decades, evidence has emerged showing that size at birth is associated with a high prevalence of metabolic and cardiovascular diseases in adulthood, including hypertension, glucose intolerance, DM, and dyslipidemia. Studies suggest that intrauterine growth retardation and postnatal compensatory growth are involved, to some extent, in the development of obesity and metabolic diseases [26]. Fetal, maternal or environmental factors during pregnancy would affect the development of the fetus, promoting permanent changes in

morphology and physiology, inducing a predisposition to the appearance of pathologies such as metabolic syndrome and cardiovascular diseases [26].

The SGA (Small for Gestational Age) child demonstrates a reorganization of the endocrine system at birth with low insulin concentrations, insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein type 3 (IGFBP-3) in addition to high levels of growth hormone IGFBP-1 and IGFBP-2 [27]. During the first trimester of postnatal life, as nutritional statues improves, insulin and IGF concentrations increase by exposing the fetus to the development of insulin resistance [27]. Na excessive gain of weight and consequent increase of adipose tissue in childhood would increase the risk of developing insulin resistance [28]. In addition, gene and environment interaction has been demonstrated, for example, in Pro12Pro to Pro12Ala peroxisome receptor polymorphism (PPAR), which correlates with birth weight and apparently act as an insulin sensitivity promoting agent and, consequently, protector against DM [29].

Data suggest that exposure to a diabetogenic environment is associated with increased dyslipidemia (increased total LDL), subclinical vascular inflammation and endothelial dysfunction processes in the offspring, all of which are related to the development of cardiovascular diseases in the future [30]. Another fetal implication of exposure to GDM is the development of morphological abnormalities in Langerhans' islets in offspring, demonstrated through its abnormal form, as well as through hyperplasia and hypertrophy of the same [9].

Obesity is a source of complications during pregnancy, such as increased maternal ad fetal mortality, namely increased risk of preeclampsia, need for cesarean delivery, preterm delivery, fetal macrosomia, and fetal mortality [25]. The increase of proinflammatory cytokines, namely IL-1, IL-6 and TNF-α, in obese individuals, has been shown to play a role in the development of cardiovascular diseases [9]. Cytokines promote an insulin resistance environment with high triglyceride content, resulting in increased blood pressure and potentially coronary disease, as well as also increase plaque formation in the development of atherosclerosis and contribute to disease progression [9].

Risk factor such as maternal stress, infections, placental dysfunction, tobacco and alcohol, negatively affect the intrauterine environment and consequently fetal programming. The intrauterine environment during fetal life influences the development of a particular metabolic phenotype in offspring [19] however; the mechanism by which this occurs is not yet fully understood [21].

Cardiovascular diseases were one of the earliest diseases to be recognized as being associated with an adverse intrauterine environment [10]. An increase in the occurrence of hypertension is commonly observed in the severity subject to malnutrition during pregnancy [9]. In general, fetal programming appears to increase susceptibility to the development of cardiovascular disease. Although the exact mechanisms are still unknown, it is becoming increasingly clear that both physiological and genetic mechanisms [9].

The risk of developing chronic diseases after exposure to adverse intrauterine conditions led to the formulation of the hypothesis of fetal metabolic program-

ming (Barker's hypothesis) [22]. These studies correlated the birth weight with the incidence of adult-onset diseases and proposed that the adverse fetal environment with nutritional deficiency followed by high nutritional intake during adulthood could be responsible for the development of chronic diseases in adulthood [30].

The expression of maternal genes may alter the fetal environment, but the maternal intrauterine environment might, influence and modify fetal genetic expression and influence birth weight [13]. Many studies have shown that intrauterine growth restriction (IUGR) is associated with increased oxidative stress in human fetuses, because the limited availability of nutrients results in a change in redox status in susceptible fetal tissues leading to oxidative stress [13]. In the IUGR, low levels of oxygen are observed, showing a decrease in the activity of complexes of the electron transport chain, which will increase the levels of reactive oxygen species (ROS), which in turn initiate several oxidative reactions that will cause lesions, not only in the mitochondria but also in the cellular proteins, lipids and nucleic acids [13]. Nevertheless, it is important to mention that it will be a conceptual mistake to affirm that low birth weight alone can cause disease at a later stage in the life of the subject [10]. The restructuring of body tissues in the early life of the individual, the reprogramming of the endocrine and metabolic axes, i.e. fetal programming, will be the true responsible for the long-term consequences on the subject's life, since this programming can occur in the absence of changes in the weight of the newborn [8]. These associations with birth weight actually occur because the insults that program the function often also reduce birth weight and growth [8].

No association between low birth weight and hypertension in adulthood has already been demonstrated in numerous clinical and experimental studies. The mechanisms and pathophysiological that mediate this phenomenon, although still little understood, are probably multiple and complex. Most of the investigation of the intratuterine origins of arterial hypertension today has been directed to the kidneys, the neuroendocrine system and the vascular tree [30].

The major renal mechanisms involved in intrauterine programming of arterial hypertension are reduction in the number of nephrons and changes in the renin-angiotensin-aldosterone system [31]. Nephrogenesis is a complex process that requires structural reforming. In it, apoptosis participate fundamentally [32]. Adults with essential hypertension have a reduced number of nephrons [33]. Based on these observations and the fact that arterial hypertension is more prevalent in communities with lower socioeconomic status, Brenner *et al.* proposed that low birth weight would be associated with a congenital deficit in the number of nephrons, which would lead to less renal excretion of sodium, which would consequently increase the susceptibility to essential hypertension, especially in the presence of an excess of this ion [34]. Mechanisms associating an adverse intrauterine environment with a reduction in the number of nephrons have not yet been fully elucidated. In addition to protein restriction, environmental factors that interfere with nephrogenesis include vitamin A deficiency, zinc and

iron, hyperuricemia, ingestion of alcohol and certain drugs such as antibiotics and aminoglycosides [35].

No association between programming of hypertension and excessive exposure to glucocorticoids in fetal life has been documented [36]. In sheep, a brief fetal exposure to high levels of dexamethasone produced normal weight animals, but hypertensive animals at 3 - 4 months of life [37]. In humans, elevated levels of cortisol have been documented in association with restricted intrauterine growth [38]. In adult plasma, cortisol levels are inversely proportional to birth weight which may directly contribute to arterial hypertension [39].

4. Hormones Involved in Intrauterine Programming

Several hormones known to regulate fetal growth and development play a central role in intrauterine programming. This includes anabolic hormones such as insulin, insulin-like growth factors (IGF-1, IGF-2), prolactin and thyroid hormones, as well as catabolic hormones such as glucocorticoids [7]. All these hormones act in nutritional and maintenance signaling. They adapt the fetal development to the intrauterine conditions of the moment, thus maximizing the possibilities of survival in utero and after birth [7]. These mechanisms of endocrine adaptation may have benefited in the short term for the well-being of the endocrine system that predisposes to physiological functions and, ultimately, disease.
Insulin is an important growth hormone in the uterus. Its deficiency causes retardation in growth. The fetal growth reduction is uniform. The weight gain in response to fetal hyperinsulinemia is greater in the human species, due to having a high body fat content at birth [40]. Like insulin, IGFs stimulate growth in the uterus. One study showed that deletion of the IGF-1 or IGF-2 gene in mice reduces fetal full term body weight and leads to developmental abnormalities in various fetal tissues. Deletion of the IGF-1 receptor causes a greater degree of growth retardation [40]. IGFs act at various stages of the cell cycle and affect cell proliferation, differentiation, maintenance, regeneration, and apoptosis. Both IGF-1 and IGF-2 are mitogenic and act on various mesenchymal cells. They also stimulate cell differentiation in the fetal muscle, bone, bran and adrenal cells, particularly at the end of gestation. Therefore, IGFs have specific developmental effects on individual tissues, as well as stimulate uterine growth [40].

The major growth-inhibiting hormones appear to be glucocorticoids. These hormones act as signs of nutritional insufficiency and increase in the presence of hypoxia and fetal hypoglycemia (5-endo). Administration of glucocorticoids to the mother or fetus during late pregnancy leads to a delay in fetal growth in several species, including humans [40]. The degree of fetal growth retardation depends on the dose and the glucocorticoid used, frequency, route of administration, sex and gestational age [41]. At the cellular level the glucocorticoids alter receptors, enzymes, ion channels and transporters. They may also change the expression of growth factors, cytoskeletal proteins, myelination, binding proteins, coagulation factors and intracellular signaling pathways involved in growth, such as the mTOR pathway [40]. Glucocorticoids affect the expression

of primary glucose transporters, GLUT1 and GLUT3 in rat and human placentas, and long-term exposure is associated with intrauterine growth restriction [41]. Glucocorticoids increase proteolysis rather than reduce protein synthesis. These changes are accompanied by changes in amino acid metabolism and the relative contribution of different amino acid to the oxidative metabolism of the fetus. These catabolic actions restrict the formation of tissues in the fetus.

Human beings have a growth hormone (GH) and placental lactogen (PL) located on the long arm of chromosome 17 (q22-24). This group contains five related genes: GH-H encodes pituitary growth hormone, GH-V encodes placental growth hormone and hPL-A, hPL-B and hPL-L encode placental lactogen. The major placental lactogens derive from the hPL-A and hPL-B genes; the function of hPL-L is not yet clear [42]. GH-N is produced by the pituitary somatotrophs, while the GH-V and the three human placental lactogen (hPL) genes are expressed in the placental syncytiotrophoblast [42]. GH-N concentrations decrease progressively in early pregnancy and are not detected in the maternal circulation after 24 weeks of gestation. However, GH-V rises sharply after mid-gestation to a peak of 20 - 40 ng/ml. After one hour of delivery, it disappears from the maternal circulation, with the return of GH-N secretion. In summary, the placenta replaces the pituitary gland in the mother during pregnancy [43]. GH-V secretion is regulated in part by the size of the placenta and maternal glycemia, it functions as an antagonist given insulin and impairs the use of maternal glucose. hPL is structurally similar to GH, but functionally closer to prolactin (PRL) [42]. The concentrations of hPL and PRL increase progressively during gestation. Secreted by the maternal pituitary, PRL peaks at 150 - 180 ng/ml. Secreted directly into the fetal and maternal circulation. hPL is detected at the maternal blood test after 6 weeks of gestation. Their concentrations increase linearly and reach peak levels of 5000 - 7000 ng/ml. Early studies suggest that maternal hPL levels may increase in fasting, as lactogens may serve an adaptive role in nutrient homeostasis. Lactogenic hormones can lead to the development of fatty tissue and resistance to leptin [44].

The metabolic homeostasis of the hand and fetal growth depends on the precise control of storage and mobilization of maternal nutrients, placental growth and nutrient transport. The somatogenic and lactogenic hormones of the placenta and pituitary gland act together to interact the metabolic response to pregnancy with demands for fetal and neonatal development. Deregulation of GH-V and hPL production during gestation may reflect placental dysfunction. Levels of these hormones have important consequences for fetal growth and long-term metabolic function [42].

Maternal insulin does not cross the placental structures and Beta cells produced by the Langherhans are not developed until 12 weeks of gestation, so the production of insulin is not performed until this time. Early hyperglycemia can lead to congenital malformations and miscarriages, which is about 2 to 3 times more likely in patients with type 1 and 2 diabetes mellitus than in healthy pregnant women [23].

The genes of leptin and adiponectin are known as some of the possible culprits for obesity and type 2 diabetes mellitus since they are secreted by adipose tissue and are involved in energy metabolism and regulation of insulin sensitivity, the genes of these well known adipokines being candidates for causing metabolic disorders [45]. They were studied in the sense of perceiving the impact of gestational diabetes on the epigenetic profile of the newborn. The role of adiponectin in fetal programming is somewhat less clear than the role of leptin [22]. Leptin affects the pathophysiology of gestational diabetes mellitus and has been reported to play an important role in fetal obesity programming [45].

The leptin, a product of the obesity gene primarily synthesized by adipose tissue and placenta, acts as a satiety factor, decreasing appetite. However, in the fetus and newborn, it promotes the development of satiety pathways [7]. Low-birth-weight fetuses and newborns have significantly lower plasma leptin concentrations because of decreased adipose tissue [7]. The increase in leptin levels in the maternal circulation in early pregnancy is a predictive factor of gestational diabetes mellitus, regardless of adiposity before pregnancy [22].

Adiponectin is produced exclusively, and abundantly, by adipose tissue and has insulin sensitizing, anti-inflammatory and anti-atherosclerotic properties [22]. Unlike leptin, adiponectin levels are low in patients with both obesity and type 2 diabetes mellitus. In a normal pregnancy, circulating adiponectin levels increase in the first half of pregnancy and decrease proportionally to weight gain and resistance Induces pregnancy. In a pregnancy complicated by gestational diabetes mellitus adiponectin levels are considerably lower than normal [45].

5. The Obesity Phenotype

The fetus is largely dependent on the placenta for the functioning of lipids, being the mechanism that regulates the fatty acid, its transport and metabolism partially understood. The placentas of obese mothers accumulate lipids, so it is hypothesized that esterification of fatty acids is higher and their oxidation is lower compared to lean women. According to a study developed by Navarro *et al*., Through the analysis of placenta gene components of 500 healthy women with normal glucose tolerance, recruited at the time of scheduled end-stage cesarean section, placental lipid metabolism markers were investigated in newborns of obese mothers (BMI 39 ± 1.1 kg/m^2 and Gestational Age 38.7 ± 0.1 weeks) and lean (BMI 21.9 ± 0.4 kg/m^2 and Gestational Age 38.8 ± 0.5 weeks). It was concluded that maternal obesity can significantly affect placental lipid metabolism by modulating the expression of transporters and decreasing the expression of genes involved in the oxidation of fatty acids, in addition to increasing their esterification. Such changes maintained in the postnatal period may predispose to obesity and metabolic disease of the baby [46].

Interventions on gestational weight gain are limited by poor understanding of metabolic changes in this gestational period. The changes in maternal energy expenditure were studied by Berggren *et al*., according to the study, it was concluded that in normal weight patients, the basal metabolic rate in gestation is

inversely associated with gestational weight gain, variations in "free mass of Fat" has a significant impact on total energy expenditure. The linear association provides that for a woman with a normal BMI with basal metabolic rate of 33.5 kcal/kg has a total energy expenditure for the "fat-free mass" between the 25th and 75th percentiles, ranging from 1642 to 1916 Kcal/day. The data suggest a relationship between energy expenditure and body composition, these factors being essential to optimize weight gain during pregnancy [47].

The analysis of large epidemiological databases have suggested that babies and children showing accelerated growth "catch-up" and adiposity in childhood, are predisposed to the development of obesity, type 2 diabetes and cardiovascular disease in adulthood. Childhood adiposity is responsible for hyperinsulinemia and for a disproportionately higher rate of body fat recovery than lean tissue, which is called "catch-up fat" by Dulloo authors. This preferential fat gain phenotype is ubiquitous throughout the life cycle as a risk factor for obesity and insulin-related complications, not only in infants, but in fetal or neonatal fetal growth, or preterm infants. It has also been observed in adult patients with weight recovery after substantial weight loss due to hunger, disease, cachexia, restrictive diet [48].

Progressive fat gain is mainly driven by energy conservation mechanisms with suppressed thermogenesis (mainly the primary use of glucose, saving oxidation in skeletal muscle, directing metabolism to lipogenesis and new storage in white adipose tissue). It is related to the early development of insulin and resistance to leptin, genetic constitution of the individual, highly energetic eating habits and sedentary lifestyle [48].

Studies have suggested that people who had low birth weight or whose growth declined in childhood but who subsequently exhibited a "catch-up" growth are more susceptible to the development of obesity, type 2 diabetes and cardiovascular disease later in life [49]. Studies from South Africa, Brazil, Russia, China and India suggest that children with short stature have 2 - 8 times greater risk of overweight and/or increased risks for cardiovascular and metabolic disorders [50] [51]. Risk factors for cardiovascular disease in children include birth size, nutritional pattern, and level of physical activity [49].

6. Influence of Perinatal Environmental Factors and Diseases in the Future: Small and Large for Gestational Age

Recent studies suggest that fetal growth and postnatal growth are associated with the development of diseases in adult life. According to results of the study by Gomes, L. Paulo, the hypothesis that size at birth is a risk factor for metabolic and cardiovascular diseases, especially for males. Physical activity, especially aerobic activity, can reduce these risks [52].

During the last decades, evidence has emerged showing that size at birth is associated with a high prevalence of metabolic and cardiovascular diseases in adulthood, including hypertension, glucose intolerance, diabetes mellitus, and

dyslipidemia [53] [54]. Studies suggest that intrauterine growth retardation and postnatal compensatory growth are to some extent associated with the development of obesity and metabolic diseases [55].

The link between child size at birth and disease in adulthood suggests that these diseases may originate even during fetal development. Fetal, maternal or environmental factors during pregnancy would affect the development of the fetus by promoting permanent changes in morphology and physiology, inducing a predisposition to the appearance of pathologies such as the metabolic syndrome and cardiovascular diseases [55] [56].

Researches in this area have intensified after the publications made by the group of David Barker two decades ago, giving rise to the concept that a fetal programming can be the origin of pathologies in the adult life. Some studies have reinforced the relationship between size at birth and diseases in childhood, adolescence and adulthood, as well as an association with the increase and distribution of adipose tissue and reduction in lean mass and with increased blood lipids [56]. However, no support was found in other studies [55] [57].

Feeding can influence growth and development even in the intrauterine phase. A study performed with pregnant women showed an inverse correlation between maternal fat intake and fetal birth weight, suggesting that excessive fat consumption, especially *trans* fats, during pregnancy, would affect fetal growth by inhibiting the biosynthesis of the arachidonic and docohexaenoic polyunsaturated fatty acids [58]. In childhood, the small birth for gestational age associated with excess weight gain would be associated with an increase in blood pressure [59] [60].

The size that a child presents at birth represents their development and growth during gestation. Several factors can influence intrauterine growth, including genetic, environmental, hormonal factors, placental development, maternal well-being and nutrient supply [61].

The adaptations undergone by the fetus as a result of intrauterine malnutrition may temporarily benefit survival but result in health impairment in adulthood [56] [62]. This hypothesis is currently known as "fetal programming" [55]. Mechanisms leading to this association between size at birth and diseases in adulthood have not been fully clarified. The decrease in the number of nephrons in the kidneys with consequent glomerular hyperfiltration and hypertension [63] [64], changes in microarchitecture and liver function [63], structural changes in blood vessels [65] and pancreatic changes are among the suggested mechanisms [66].

In the context of the association between birth weight and diseases in adult life, another environmental factor that would apparently influence the risk of diabetes and cardiovascular disease would be the intensity of postnatal growth and the intensity of weight gain [29] [67] [68]. According to Gluckman *et al*., intrauterine nutritional deprivation would not only lead to relevant adaptive responses to fetal survival but would also influence nutritional demand in adult life [68].

The small child for gestational age demonstrates a reorganization of the endocrine system at birth, with low concentrations of insulin, IGF-1 and IGF-1 binding protein type 3 (IGFBP-3), as well as elevated levels of growth hormone and IGFBP-1 and IGFBP-2 [69]. During the first trimester of postnatal life, as nutritional status improves, insulin and IGFB concentrations increase by exposing the fetus to the development of insulin resistance [70]. An excessive gain of weight and consequent increase of adipose tissue in childhood would increase the risk of developing insulin resistance [63] [71]. In addition, gene and environment interaction has been demonstrated, for example, in Pro12Pro to Pro12Ala peroxisome receptor polymorphism (PPAR), which correlate with birth weight and apparently act as an insulin sensitivity promoting agent and therefore protective against diabetes [72].

With regard to the development of lean mass and fat mass, a child born small for gestational age could have greater ease of forming adipose tissue, since the crucial period of muscle growth occurs around 30 weeks of intrauterine life and probably few muscle cells they replicate after birth [73].

The distribution of body fat seems to be another factor related to size at birth. Children and adolescents born small for gestational age present a more central distribution of body fat, with a higher proportion of fat in the trunk region than in the limbs [74] [75] [76], a distribution associated with a higher occurrence of metabolic syndrome.

7. Placenta Associated with Diabetes Mellitus

During fetal growth, the placenta fulfills several functions, being the intermediate between fetus and mother. Because of its position, it is exposed to the regulation of hormones, cytokines, growth factors and substrates present in both the mother and fetus, and are always propitious to be affected by changes in any of these [65]. In turn, this organ produces molecules that can affect both, and any disturbance can contribute to complications. With obesity becoming increasingly common, cases of GDM have grown in parallel. The placenta, acting as a selective barrier during gestation, has a great influence on the regulation of insulin because it contains, practically, all known cytokines [65].

In the cases of GDM, the placentas, considerably larger, have a very characteristic and visible morphology, such as villous immaturity, fibrinous necrosis of the villi, chorangiosis and increased angiogenesis, being these observable from the beginning of pregnancy due to the analysis of the metabolism related to glucose [77]. Hyperglycemia, which results from defects in insulin secretion or its inadequate action due to the intense flow of glucose, characterizes diabetes mellitus, promoting damage to different organs. Under GDM conditions, glucose intolerance occurs only during pregnancy, resolving after delivery. Still, there is the possibility that this intolerance persists after childbirth. Maternal hyperglycemia influences the fetus stimulating its metabolism and hormonal changes due to the higher concentration of insulin, which consequently increases the fetal oxygen demand, leading to hypoxia, being one of the factors that increase angi-

ogenesis [78].

As regulators of gene expression [79], microRNAs are also produced in the placentas. The different microRNAs expressions during pregnancy suggest that they have specific functions at each stage [79]. One of the roles of microRNAs in the placenta is to regulate the growth of the placenta by the growth of trophoblast cells and their apoptosis which is directly linked to the development of the fetus. Hypoxia is linked to the microRNA-210, whose concentration increases when there are low levels of oxygen, being a hypoxia sensor. There is great evidence of the role of microRNAs in placental vascularization, since Dicer is commonly found in perivascular stroma villi, indicating its role in artery remodeling. The elimination of Dicer impairs the formation of blood vessels, strengthening the role of microRNAs in angiogenesis [80].

During GDM levels of miR-132, -29a and -222 microRNAs decreased significantly at similar weeks during gestation. With this in mind, it is possible to use microRNA expression to diagnose not only diabetes mellitus, such as other diseases, to monitor fetal growth [79].

8. Conclusions

Faced with the growth of diabetes, the distribution of information about its consequences is very important. Not only during pregnancy, monitoring of fetal growth becomes essential, but also throughout adult life, in order to avoid an epidemic.

The relationship between the onset of this metabolic disease with endocrine disruptors during pregnancy in its incidence is strengthened since it is possible to program fetal metabolism in some ways. The conditions in which the fetus is found during the gestational period actually exert influence on its health in adult life. Thus, it becomes feasible to prevent several diseases, such as diabetes, by hormonal analysis of the fetus, thus suppressing the occurrence of these in the population.

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