The maternal intrauterine environment as a generator of children at risk of metabolic syndrome: a review

O ambiente intrauterino como fator de risco para a síndrome metabólica: uma revisão

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Abstract

Nowadays, scientists are paying special attention to the increasing prevalence of obesity and associated co-morbidities, especially metabolic syndrome. This is due to observation of the spread of this syndrome from one generation to another and the growing number of obese pregnant women, which seems to exacerbate this situation. It is not yet well established whether the pathophysiological process underlying metabolic syndrome, namely insulin resistance, is due to changes in the receptor or in the cascade of intracellular processes. This narrative review aims to report on physiological and pathological changes occurring in pregnancy and the presence of Insulin receptor, Insulin Growth Factor-I receptor and the hybrid receptor, focusing on the presence of hyperinsulinemia in the growth and development of fetuses susceptible to metabolic syndrome.

Key words *Obesity, Metabolic syndrome, Insulin, Fetal development*

Resumo

O mundo científico está dando atenção especial ao crescimento da prevalência da obesidade e de suas co-morbidades, de modo particular da síndrome metabólica. Esse fato deve-se à observação da propagação dessa síndrome através de gerações e ao crescimento do número de gestantes obesas que parece agravar esta situação. Ainda não está bem estabelecido se o processo fisiopatológico subjacente à síndrome metabólica, a resistência à insulina, é por alteração no seu receptor ou na cascata de processos intracelulares. Esta revisão visa relacionar as alterações fisiológicas e patológicas da gestação e a presença dos receptores de insulina, Insulin Growth Factor-I e seus híbridos, focando na presença da hiperinsulinemia no crescimento e desenvolvimento do feto, a predisposição à síndrome metabólica.

Palavras-chave *Obesidade, Síndrome metabólica, Insulina, Desenvolvimento fetal*

Introduction

Given the increasing prevalence of obesity and its co-morbidities around the world, this issue has been the subject of much study. The presence of obesity is usually associated with other factors related to metabolic syndrome - characterized by the association between obesity, hypertension, cardiovascular disease, glucose intolerance, type 2 diabetes mellitus and dyslipidemia[1,2] - a major concern being the relation between this syndrome and the increasing prevalence of diabetes and consequent mortality related to cardiovascular disease. Metabolic syndrome or syndrome X is also called insulin resistance syndrome, owing to its pathophysiological basis.

Another reason for attention is the spread of this syndrome across generations. The growing number of obese pregnant women has contributed to this, as both maternal obesity prior to conception and excessive weight gain during pregnancy increase the risk of gestational diabetes mellitus and hypertensive disorders related to pregnancy.[3,4] Pregnancy would appear to be a catalyst of the pathophysiological process of metabolic syndrome, namely insulin resistance, which brings about a change in the receptor and other in a cascade of intracellular processes.[5] During pregnancy, the physiological reduction of insulin response in the tissues stimulates synthesis, thereby resulting in hyperinsulinemia.[5] This condition overloads the already compromised metabolism of obese individuals that makes them prone to such diseases, and changes subsequently occur in order to maintain the equilibrium of the intrauterine environment during gestation.[3,5]

This review aims to examine changes in the insulin receptor, the insulin growth factor-I receptor and its hybrid receptor and the physiological and pathological processes of pregnancy, focusing on the presence of these receptors in the placenta and their importance for growth of the fetus and predisposition to metabolic syndrome.

The hybrids of insulin receptors and IGF-I

In 1989, the hybrid receptors were described. They are composed of one α subunit and one β insulin receptor subunit and one α and one β IGF-I growth-factor receptor.[6] These receptors have subsequently been associated with insulin resistance syndrome,[7] because greater expression of hybrid receptors has been observed in the skeletal muscle[8] and adipose[9] tissues of patients with type 2 diabetes mellitus, in addition to the presence in greater quantities of these receptors in the skeletal muscle of patients with obesity[10] and a higher prevalence of chronic primary hyperinsulinemia.[11] Subsequently, hybrid receptors have been found in the endothelial cells of coronary arteries[12] and vascular smooth muscle cells[13] of healthy individuals. Studies have shown that hybrid receptors may represent the molecular defect of insulin resistance and its location provides the connection between changes in glucose metabolism and cardiovascular diseases associated with metabolic syndrome. The question was whether increased expression of the receptor hybrid is capable of giving rise to insulin resistance.

Li *et al.*[14] have shown that insulin at physiological concentrations does not activate hybrid receptors, although it can do so in large concentrations. Finally, in 2008, a study showed that human microvascular endothelial cells are insulin resistant as a result of the isolation of insulin receptors by hybrids, suggesting that these receptors are involved in the same molecular etiology of insulin resistance, as it has been reported that the affinity of insulin for this receptor is low and does not activate the cascade of intracellular events when insulin is in physiological quantities.[15]

Currently, the liveliest discussion with regard to hybrid receptors addresses the question of whether they precede hyperinsulinemia or are secondary to it. The work of Valensise *et al.*[16] was a milestone in this regard, because it showed that there were more hybrid receptors in the placentas of women with hyperinsulinemia than in those of women with normal levels of insulin. This study thus showed that excess insulin in the mother can induce the emergence of these receptors in the placenta. Another fetal tissue that presents hybrid receptors is the endothelium of the umbilical cord,[17] although it is not known whether there are changes in the quantities of the receptor in children of mothers with hyperinsulinemia.

Interestingly, the metabolic response and cell proliferation and differentiation during embryonic and fetal development depends on the binding of insulin and IGF receptors for insulin and IGF-I. Since there can be no changes in the amounts of these receptors by the expression of hybrid receptors in women with hyperinsulinemia, the whole process may be compromised. This may partly explain the insulin resistance, the restriction of growth and transmission of this trait to offspring.

Nevertheless, additional studies are required to ascertain whether the expression of hybrid receptors is increased in other fetal tissues, as an excess of

these receptors modifies the regulation of the passage of nutrients between mother and fetus and the mechanisms involved in activation and intra-cellular signal transduction in various tissues. This is a promising field of research because it will provide understanding of the molecular processes underlying a clinical disease that is extremely common in contemporary society.

From conception to fetus

Conception is a complex process that involves the mother, the placenta and the fetus itself. We will therefore present an explanation of how some of these factors interact to form an organism capable of survival.

Fetal "Programming"

The ultimate goal of the mother is to produce healthy offspring capable of transmitting their genes to a whole line of descendants. The term "mother system" would include all aspects of the physiology of maternal behavior that contribute to the produc-tion and growth of offspring. Through evolution, the "mother system" would have seized upon mecha-nisms that can lead to greater survival of offspring in both the intra- and the extra-uterine environment, thereby favoring the perpetuation of the species.[18] In adverse conditions, however, all the maternal stress involved in keeping the fetus alive may trigger adjustments to the fetus. In some extra-uterine envi-ronments, these adaptations may lead to a disposi-tion to unfavorable diseases.[2]

Nowadays, two additional hypotheses are accepted to explain these mechanisms. In 1962, Neel[19] proposed the hypothesis of the "thrifty geno-type" to explain the transmission of diabetes mellitus. According to this hypothesis the "thrifty" genes were selected by evolution, when food sources were scarce and there was need for an immediate response to insulin as a way of promoting a rapid increase in fat reserves. Fetal nutrition and growth responses in the prenatal period seem to vary as a result of this genotype.[19] Studies show that the fetal response to prenatal environment has no single outcome, but rather that there are a variety of responses that are potentially modulated by the selected genes.

In 1989, the hypothesis of the "thrifty pheno-type",[2] also called the "hypothesis of fetal origin of adult disease" proposed by Barker and colleagues, based on epidemiological studies that linked low fetal weight, catch-up growth during the first years of life and subsequent development of diabetes and

metabolic syndrome as a result of fetal malnutrition. This hypothesis suggests that fetal growth restriction is an adaptive response to an inadequate supply of nutrients to the fetus resulting in the diversion of these to some organs at the expense of others. An altered availability of nutrients to rapidly growing organs may lead to changes in size, structure and metabolic activity as a whole or in part, and other possible consequences. While these fetal responses help to increase the chances of survival in the intrauterine environment with limited supplies, they also seem to be associated with a long-term cost for the health of the individual. In the intrauterine period, the individual thus "schedules" its metabo-lism to be suitable for the estimated supply of extra-uterine environmental nutrients. If this environment is not restrictive as expected during the intrauterine period, this may facilitate the onset of diseases later in life.

In the postnatal period, catch-up growth occurs in most infants with intrauterine growth restriction as a result of adjustments of metabolic regulation for the provision of energy. There is thus rapid growth and increased weight gain when the body is exposed to an adequate diet or a diet rich in carbohydrates associated with little physical activity. This accelera-tion of the growth rate is particularly likely to occur in the first six months of life, but can be seen up to about two years of age.[20,21]

It has been shown that children born small for gestational age who underwent catch-up growth also had insulin resistance during this period, while those who did not undergo catch-up had normal insulin sensitivity. During the catch-up growth after birth, the accumulation of fat mass is faster than muscle mass. This rapid weight gain predisposes the child to obesity, type 2 diabetes mellitus and cardiovascular diseases.[20-22]

These assumptions can be viewed as comple-mentary because the "thrifty" genes selected during evolution would change the metabolism and growth structures in the fetus, in response to intrauterine environmental stimuli, thereby providing it with protection. The "mother system" can thus serve to regulate the interaction between genes and the envi-ronment.

It is possible that an environment with scarce food has selected individuals with a gene expres-sion mechanism that favors greater production of hybrid receptors when exposed to an adverse intrauterine environment. A larger quantity of these receptors would allow adaptation to the intrauterine environment and subsequently make the individual more susceptible to metabolic

syndrome.

Gametogenesis

Environmental effects on the genome are already seen in the early stages of development. During gametogenesis some genes in the egg are subject to the maternal imprinting system. This alters gene expression during development and can result in patterns of non-Mendelian inheritance. The mother can also vary the supply of nutrients and hormones to the gametes, changing the probability of survival of the embryo. These homeostatic processes can occur in many different ways and begin before conception. Ovulation is very sensitive to maternal energy reserves. It limits the beginning of new gestation periods in which nutritional status is more capable of supporting a pregnancy.[23]

The gametes and the preimplantation embryo

The maternal organism tries to optimize production of gametes and survival of the preimplantation embryo by giving them the ability to adapt their metabolic needs, the number of cells and the degree of differentiation prior to implantation *in utero*, thereby resulting in changes while still within the uterine environment.[23,24] Beside the nutritional support provided by the granulosa cells, there is bidirectional communication between the oocyte and granulosa in its normal maturation and development. The IGF-I receptor is present in both granulosa and in human oocytes. Insulin and IGF-I act through this receptor to regulate the expression and translocation of glucose transporters in both the embryo and in oocytes, where glucose uptake has been found to be mediated by such transporters.[24]

The preimplantation embryo uses pyruvate and lactate as its main sources of energy, although it expresses several glucose transporters. The rate of use of pyruvate decreases progressively from the eight-cell stage to the morula, coinciding with increased uptake of glucose into cells. During this period of compaction glycolytic metabolism begins, while the oxidation of lactate and pyruvate continues. Uptake of glucose is present in all stages of development. Before compaction, this is necessary for the development of the fetus, for the prevention of apoptosis and the transcription of some genes. However, it remains essential even after compaction.[24]

In addition to the glucose transporters, the preimplantation embryo expresses insulin and IGF-I receptors at the same time as starting glycolytic metabolism. The IGF-I receptor increases glucose use in response to insulin and IGF-I. Activation of insulin and IGF-I receptors, to allow the entry of glucose, trigger anti-apoptosis signals that are important for normal metabolism of the embryo. High concentrations of insulin or IGF-I lead to a drop in quantities of the IGF-I receptor. This would reduce the uptake of glucose-induced insulin and stimulate apoptosis in the blastocyst and the trophoblast cells.[24]

Fetus

During pregnancy, the "mother system" provides an environment for full fetal development and growth. It is thus possible to observe the physiological changes and pathological conditions that can alter this course.

It is well established that pregnancy is a normal period of physiological resistance to insulin. Throughout pregnancy, there is a progressive increase in resistance to provide an adequate provision of substrates for rapid development and a growth of the fetus. Maternal insulin resistance is important during normal gestation, as it plays an important role in the release of metabolites for fetal growth.[3,5]

Catalano *et al.*[25] showed that there is an increase of 120% in response to the first phase of insulin and 50% in the second phase response in pregnant women between 12 and 14 weeks, showing the early onset of insulin resistance in normal pregnancies. It was also observed that there is a one-third reduction in insulin sensitivity in pregnant women and a three-times higher response to insulin normal pregnant women compared with non-pregnant women. The levels of fasting plasma insulin increase throughout gestation, but these changes do not occur at the same time as reductions in concentrations of glucose.[5] This suggests that concentrations of glucose and insulin are not directly connected unless insulin sensitivity is altered or "glucostatic" pancreatic beta cells altered.

Obese women have a reduced tolerance to carbohydrates, which is aggravated by pregnancy. In obese women, therefore, fasting and post-prandial plasma insulin concentrations are higher than in non-obese women. In obese women, the excess insulin resistance induced by pregnancy or excess weight associated with an insufficient amount of insulin can result in the development of gestational diabetes.[3,5]

Insulin resistance is present in normal pregnancy and obesity is also involved in the pathogenesis of various complications of pregnancy such as gestational diabetes and hypertension.[5] As mentioned above, obese women have a higher concentration of insulin and lower insulin sensitivity when compared

to non-obese women. Despite these changes in insulin, there are cases where blood glucose levels rise. However, there are studies showing that women with a pre-conception body mass index greater than 30 kg/m2 have 3.6 times greater risk of developing gestational diabetes than those with normal weight. Women with gestational diabetes have a high prevalence of hypertension (35-40%) compared to normoinsulinemic patients (5-10%).[3]

Obesity in pregnancy appears to be a risk factor for hypertension even in the absence of diabetes.[5] Pregnant women with hyperinsulinemia present systolic and diastolic blood pressure greater than those with normal levels of insulin, even when they cannot be classified as hypertensive women.[26] A positive association has been demonstrated between hyperinsulinemic women in the second quarter and the development of hypertension and pre-eclampsia.[27] Martinez *et al.*[28] showed an insulin concentration four times higher in women with pre-eclampsia in the oral glucose tolerance test when compared to the control group. The prevalence of pregnancy-induced hypertension in obese women is double that among those of normal weight, with an increased incidence of 4.8% in non-obese women compared to 10.2% in those who are obese.

It can thus be seen that obesity, diabetes and hypertension during pregnancy are interconnected and also that there is a fine line between the insulin resistance of normal pregnancy and high-risk pregnancies complicated by these diseases.

These changes during pregnancy have been implicated in the spread of the phenotype of insulin resistance across generations. Obesity is more common in the children of obese mothers, especially if the latter had gestational diabetes or if the children were macrosomic Obese mothers thus contribute to the geometric growth of the pandemic of obesity and its comorbidities.[5,26,29]

As mentioned above, the children of mothers with pregnancy problems such as obesity, diabetes and hypertension are more likely to develop insulin resistance. Wang *et al.*[30] have shown that this is seen very early in the postnatal period. It is not known, however, whether the early parameters of metabolic syndrome depend on individual genetic predisposition and/or exposure to environmental factors during life.

Subjection of the fetus to a favorable intrauterine environment triggers predictive adaptation to the extra-uterine environment, and failure to predict this correctly may lead the emergence of diseases. This phenomenon is called "fetal programming".[2]

The follow sections outline the more interesting aspects of the insulin receptor and IGF-I located in the placenta that may be involved in this "programming".

The placenta as a sensor of nutritional ecology

Nutrients and other factors establish the local nutritional ecology of the intrauterine fetus. The sensitivity of fetal growth to received nutrition means that the nutrients released by the placenta stimulate the production of fetal insulin and IGFs, which are essential for maintaining the fetal growth rate.[31] A sophisticated repertory of maternal metabolic responses helps maintain a stable intrauterine nutritional environment. During pregnancy, the woman should have the ability to maintain fetal nutrition even when intake is compromised. It is notable that maternal nutrition plays a role in both ways: meeting the energy demands of the mother and having a positive effect on the growth and weight of the fetus.[23]

The placenta supplies the fetus with nutrients and oxygen. The functional capacity of the placenta to meet this demand is controlled by maternal and fetal signals. Fetal-placental signaling regulates the demand for nutrients by the fetus. The nutrients transferred by the placenta are used for energy production and growth. Fetal demand is the main determining factor in the supply of nutrients through the placenta and is adjusted according to the needs of fetal irrespective of the size of the placenta. The placenta seems to be able to change its structure and number of carriers in response to the demand for nutrients for growth of the fetus. Placental efficiency and growth are part of a closely controlled dynamic system that is able to respond to changes in the intrauterine environment.[32,33]

The insulin – IGF axis

The placenta expresses large quantities of insulin receptors compared to other body tissues. The location of these receptors changes with development. At the beginning of pregnancy, they are located in the microvilli of the syncytiotrophoblast, while, at the end, they are found predominantly in the endothelium. This finding strongly suggests a change in control of insulin-dependent processes from the mother in early pregnancy to the fetus towards the end. Insulin stimulates mitogenesis by acting on the trophoblast and the metabolic process when it stimulates the endothelium. This explains the biphasic growth of the placenta and fetus.[34]

The location of the IGF-I receptors in the placenta differs from the location of insulin receptors. In early gestation, the IGF-I receptors are in

the cytotrophoblast, which is consistent with its proliferative effect. At term gestation, the IGF-I receptors are in the syncytiotrophoblast and villous cytotrophoblast, which can bind to the IGF-I and IGF-II in the fetus' circulatory system.[34,35]

Insulin and the IGFs do not cross the placenta. The main function of insulin is to regulate metabolic processes, including the placenta. In the trophoblast, insulin stimulates vasculogenesis and near the end of gestation, the deposition of lipids. In the endothelium, it stimulates the synthesis of glycogen. The fetal insulin hypothesis suggests that fetal insulin regulates fetal IGF-I production. This could explain the effect of insulin on fetal growth.[35]

IGF-I and IGF-II are important growth factors synthesized by the placenta and the fetus. IGF-I is present in the syncytiotrophoblast and in the cytotrophoblast throughout gestation. The IGF-II is only expressed in villous and extravillous cytotrophoblast during early gestation. It is no longer detected when pregnancy reaches term. In the early stages of pregnancy, IGF-II is a major modulator of embryonic growth and placental development, stimulating angio- and vasculogenesis.[34]

During the first half of pregnancy, the maternal IGF-I alters the division of nutrients between mother and fetus and enables adaptation to pregnancy. It increases the uptake of substrate and suppresses fetal catabolism, thereby contributing to the success of pregnancy.[31] In the placenta, it induces the uptake of glucose and aminoacids.[33] Coincidentally IGF-I receptors are present in the same membranes as the amino acid carriers.[33,34] Both IGFs stimulate the passage of placental aminoacids.[31] In humans, fetal IGF-I decreases when malnutrition or hypoxia is present in the mothers.[36,37]

The transport of glucose

Insulin indirectly controls the entry of glucose through the exposure of glucose transporters in the plasma membrane that act by way of facilitated diffusion. The passage of glucose from the placenta to the fetus is regulated by glucose transporters and by changes in acute and chronic concentrations of glucose.[32]

Glucose is the main energy substrate for the placenta and fetus and is essential for normal metabolism and growth of the fetus. During pregnancy, maintenance of the concentration of maternal glucose is the result of increased maternal glucose production and the development of maternal glucose intolerance associated with a physiological insulin resistance. Any glucose that goes to the fetus comes from the mother. The glucose that reaches the fetus is directly related to the concentration of maternal glucose. The passage of maternal glucose is regulated by the concentration of fetal glucose. If this concentration is low, the fetus provides a steeper concentration gradient of maternal-fetal glucose and there subsequently increased transfer of glucose to the fetus. The consumption of glucose by the placenta is directly related to the concentration of glucose in the fetal blood.[32,36,38]

During the second half of pregnancy the fetus grows sevenfold. The passage of glucose through the placenta also increases to meet the requirements of fetal metabolism. The increased capacity to transport glucose stems from the greater number of glucose transporters in the membranes caused by stimulation of uterine IGF-I. The energy needs of the trophoblast then increase considerably to maintain the amino acid transport system and cluster ions, which are active and thus only serve to expend energy.[32,38]

Hypoglycemia is the hallmark of pregnancies in which intrauterine growth is restricted. This phenomenon produces a steeper maternal-fetal glucose concentration gradient which helps to offset the reduced capacity of placental glucose transport and flow of glucose from mother to fetal circulation occurs because of the small size of the placenta. The rate of fetal glucose metabolism depends directly on the simultaneous interaction of plasma glucose concentrations and fetus insulin.[32,34,36,37]

The fetal insulin hypothesis proposes that the insulin secreted by the fetal pancreas in response to the maternal glucose concentration is the key to fetal growth.[39] Fetal insulin secretion is one of the determinants of fetal growth, mainly in the latter stages of gestation when the weight of the fetus increases greatly. Pederson[39] has proposed that fetal macrosomia is not the result of increased direct passage of nutrients, but is mediated indirectly by increased secretion of insulin by the fetus in response to maternal hyperglycemia. Insulin-related fetal growth thus reflects not only the fetal blood, but also genetic factors of the fetus that regulate insulin secretion by the fetal pancreas and the sensitivity of fetal tissue to the effects of insulin.

In humans, fetal insulin secretion is altered by changes in glucose concentration, depending on the pattern, magnitude and duration. In fetuses subjected to sustained chronic hyperglycemia, there is a decrease in glucose tolerance, in basal and glucose-induced insulin secretion. However, when hyperglycemia is intermittent, there is increased secretion of insulin.[32,38]

Interestingly, human fetuses submitted to chronic hypoglycemia also have reduced secretion of basal

and insulin-induced glucose, which are consistent with the findings of a reduction in development of the pancreas and its ability to secrete insulin in fetuses with intrauterine growth restriction.[30,32,36,37]

In sheep submitted to restricted intrauterine conditions it has been shown that there is a reduction in concentrations of insulin and IGF-I abnormalities, similar to those that occur in humans, an increase in the number of insulin receptors and a suppression of glycogen synthase kinase-3-β. Low levels of this enzyme favor the activity of glycogen synthase and hence increase the formation of glycogen.[32] With the increase in numbers of insulin receptors, there is also further stimulation of proximal signaling. This is not effective, however, because there is a decrease in the proteins that regulate protein synthesis, which are part of the cascade of intracellular events. In cases of intrauterine growth restriction, there is, therefore, a tendency to increase the energy producing substrates such as glucose, and decrease the ability of protein synthesis for growth. The glucose that reaches the fetus is then divided into a store of fat and glycogen and oxidation (energy production).[37] The behavior of insulin receptors in sheep with intrauterine growth restriction is similar to that of the hybrid receptors.

Transport of amino acids

The transport of amino acids by the placenta is essential for fetal growth, because his absence is associated with a deficiency of this transport. After going through the microvilli and basal membranes of the trophoblast, amino acids, such as glucose, can spread freely in the fetal connective tissue and cross the endothelium reaching the circulation of the fetus. Amino acids are important both for protein synthesis and as an energy source for some metabolic processes, such as the synthesis of nucleotides.[33] The transport of amino acids is a complex process because it involves multiple systems of active transport. In the placenta of human fetuses with growth restriction there is a decrease in the activity of system A transport of amino acids in the membrane of the microvilli.[36,37]

The study of women with pregnancies complicated by fetal growth restriction receiving supplementation of amino acids by direct infusion of amino acids in the maternal circulation showed increased concentrations of some amino acids in the umbilical vein.[40]

In pregnant women with controlled gestational diabetes mellitus, it was also observed that there was a higher concentration of amino acids in umbilical blood than in normal pregnant women. This finding

is the opposite of that found for pregnancies with fetal growth restriction.[38]

Amino acids, like glucose, also stimulate the secretion of insulin from the pancreas of the fetus. Fetal growth is thus stimulated by insulin by a direct association between plasma concentrations of nutrients and growth.[34,37-39]

Final considerations

The condition of insulin resistance thus progresses throughout pregnancy, and may be exacerbated by the presence of hybrid receptors in the placenta of women with hyperinsulinemia. The change in the placental response to the action of the maternal hyperinsulinaemia could represent a stimulus to the fetus that results in higher levels of expression of hybrid receptors in the fetus. This change would cause an intrauterine predisposition to disease in adulthood. This is a complex process that is still not fully understood.

Unanswered questions include: whether the endothelial cells from the umbilical cord of babies born to obese women with hyperinsulinemia have a higher expression of hybrid receptors, whether this is related to the birth weight of newborns, whether the expression of hybrid receptors is increased in other fetal tissues, whether obese women with gestational diabetes and/or hypertensive pregnancy disorders have a different number of hybrid receptors expressed, whether there are changes in the transport of the nutrients and oxygen of these placentas, nutritional changes that lead to a predisposition to metabolic syndrome, and which factors in life outside of the womb trigger disease in adults.

In view of the foregoing, it can be concluded that maternal hyperinsulinemia is involved in fetal growth that is more or less in accordance with its nutritional status, as well as the supply of nutrients to the fetus during pregnancy.

Pregnant women with normal levels of insulin, proper weight and a healthy and adequate diet for normal development of the conceptus have newborns with appropriate weight for gestational age. If these same women had a higher insulin levels than expected for this gestation the fetus would probably have grown more and gained more weight. This increase in maternal insulin impacts the insulin resistance of maternal tissues that results in maternal hyperglycemia passing more glucose to the fetus. Fetal hyperglycemia, when intermittent, stimulates insulin production by the fetal pancreas, resulting in fetal hyperinsulinemia. This condition is associated with nutrients appropriate to the need for increased

secretion of IGF-I to stimulate fetal growth.

Women with adequate weight prior to conception but with inadequate nutrient intake during pregnancy or underweight before pregnancy will not have adequate passage of glucose through the placenta, even though it has hyperinsulinemia, because the small amount of maternal glucose must be shared between the woman and the fetus. Moreover, there is a deficiency of active transport of amino acids stemming from decreased availability and glucose being used as an energy source for this type of transport. In this case, there is no fetal hyperinsulinemia or increased IGF-I and, consequently, fetal growth will suffer.

Women who were obese prior to conception or who became obese during pregnancy pass more glucose to the fetus, and transfer more amino acids, as this is dependent on glucose. These fetuses grow more if maternal hyperinsulinemia is present during pregnancy, because this stimulates secretion of IGF-I by insulin and both are stimulated by the large quantity of available nutrients.

Whereas the presence of hybrid receptors brings a peripheral insulin resistance which could be beneficial, when there is an intrauterine environment with a shortage of or excess glucose, helping to maintain a glucose level suitable for the survival of the fetus during this period of life and a greater quantity of these receptors may be deleterious for the individual during extra-uterine life when he or she comes into contact with environmental factors that overwhelm the body metabolically. It can be argued that the greater quantity of these receptors, the types of tissues affected and the intensity of exposure to external environmental factors make possible the emergence of a broad spectrum of clinical manifestations of metabolic syndrome.

Referências

1. Kashyap SR, Defronzo RA. The insulin resistance syndrome: physiological considerations. Diab Vasc Dis Res. 2007; 4: 13-9.

2. Hales CN, Barker DJP. The thrifty phenotype hypothesis. Br Med Bull. 2001; 60: 5-20.

3. Galtier F, Raingeard I, Renard E, Boulot P, Bringer J. Optimizing the outcome of pregnancy in obese women from pregestational to long-term management. Diabetes Metab. 2008; 34: 19-25.

4. Barker DJP. Obesity and early life. Obes Rev. 2007; 8 (suppl 1): 45-9.

5. Ciampelli M, Lanzone A, Caruso A. Insulin in obstetrics: a main parameter in the management of pregnancy. Hum Reprod Update. 1998; 4: 904-14.

6. Moxham CP, Duronio V, Jacobs S. Insulin-like growth factor I receptor beta-subunit heterogeneity. Evidence for hybrid tetramers composed of insulin-like growth factor I and insulin receptor heterodimers. J Biol Chem. 1989; 264: 13238-44.

7. Fratalli AL, Treadway JL, Pessin JE. Insulin/IGF-I hybrid receptors: implications for the dominant-negative phenotype in syndromes of insulin resistance. J Cell Biochem. 1992; 48: 43-50.

8. Frederici M, Zucaro L, Porzio O, Massoud R, Borboni P, Lauro D, Sesti G. Increased expression of insulin/IGF-I hybrid receptors in skeletal muscle of noninsulin-dependent diabetes mellitus subjects. J Clin Invest. 1996; 98: 2887-93.

9. Frederici M, Porzio O, Zucaro L, Giovannone B, Borboni P,Marini MA, Lauro D, Sesti G. Increased abundance of insulin/IGF-I hybrid receptors in adipose tissue from NIDDM patients. Mol Cell Endocrinol. 1997; 135: 41-7.

10. Federici M, Porzio O, Lauro D, Borboni P, Giovannone B, Zucaro L, Hribal ML, Sesti G. Increased abundance of Insulin/Insulin-like growth factor-I hybrid receptors in skeletal muscle of obese subjects is correlated with In vivo sensitivity. J Clin Endocrinol Metab. 1998; 83: 2911-5.

11. Federici M, Lauro D, D'Adamo M, Giovannone B, Porzio O, Mellozzi M, Tamburrano G, Sbraccia P, Sesti G. Expression of insulin/IGF-I hybrid receptors is increased in skeletal muscle of patients with chronic primary hyperinsulinemia. Diabetes. 1998; 47: 87-92.

12. Chisalita SI, Nitert MD, Arqvist HJ. Characterisation of receptors for IGF-I and Insulin: evidence for hybrid insulin/IGF-I receptor in human coronary artery endothelial cells. Growth Horm IGF Res. 2006; 16: 258-66.

13. Johansson GS, Arnqvist HJ. Insulin and IGF-I action on insulin receptors, IGF-I receptors, and hybrid insulin/IGF-I receptors in vascular smooth muscle cells. Am J Physiol Endocrinol Metab. 2006; 291: E1124-10.

14. Li G, Barret EJ, Wang H, Chai W, Liu Z. Insulin at physiological concentrations selectively activates insulin but not insulin-like growth factor I (IGF-I) or insulin/IGF-I hybrid receptors in endothelial cells. Endocrinology. 2005; 146: 4690-6.

15. Johansson GS, Chisalita SI, Arqvist HJ. Human microvascular endothelial cells are sensitive to IGF-I but resistant to insulin at the receptor level. Mol Cell Endocrinol. 2008; 296: 58-63.

16. Valensin H, Liu YY, Federici M, Lauro D, Dell'anna D, Romanini C, Sesti G. Increased expression of low-affinity insulin receptor isoform and insulin/insulin-like growth factor-I hybrid receptors in term placental from insulin-resistant women with gestational hypertension. Diabetologia. 1996; 39: 952-60.

17. Nitert MD, Chisalita SI, Olsson K, Bornfeldt KE, Arqvist HJ. IGF-I/insulin hybrid receptors in human endothelial cells. Mol Cell Endocrinol. 2005; 229: 31-7.

18. Horton TH. Fetal origins of developmental plasticity: animal models of induced life history variation. Am J Hum Biol. 2005; 17: 34-43.

19. Neel JV. Diabetes Mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Gent. 1962; 14: 353-62.

20. McMillen C, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity and programming. Physiol Rev. 2005; 85: 571-633.

21. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocrine Rev. 2007; 28: 219-51.

22. Dulloo AG. Regulation of fat storage via suppressed thermogenesis: a thrifty phenotype that predisposes individuals with catch-up growth to insulin resistance and obesity. Horm Res. 2006; 65 (suppl 3): 90-7.

23. Kusawa CW. Fetal origins of developmental plasticity: are fetal cues reliable predictors of the future nutrition environments? Am J Hum Biol. 2005; 17: 5-21.

24. Purcell SH, Moley KH. Glucose transporters in gametes and preimplantation embryos. Trends Endocrinol Metab. 2009; 20: 483-9.

25. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in non obese pregnant women. Am J Obstet Gynecol 1991; 165: 1667-72.

26. Kumar SMJM, King A, Shin AC, Sirivelu MP, Kumar PSM, Fink GD. Developmental programming of cardiovascular disorders: Focus on hypertension. Rev Endocr Metab Disord. 2007; 8: 115-25.

27. Hamasaki T, Yasuhi I, Hirai M et al. Hyperinsulinemia increases the risk of gestational hypertension. Int J Obstet Gynecol. 1996; 55: 141-5.

28. Martinez Abundis E, Gonzalez Ortiz M, Quinones Galvan A, Ferrannini E. Hyperinsulinemia in glucose-tolerant women with preeclampsia: a controlled study. Am J Hypertension 1996; 9: 610-4.

29. Satpathy HK, Fleming A, Frey D, Barsoom M, Satpathy C, Fossen K. Maternal obesity and pregnancy. Postgrad Med. 2008; 120: E01-9.

30. Wang X, Cui Y, Tong X, Ye H, Li S. Glucose and lipid metabolism in small-for-gestational-age infants at 72 hours of age. J Clin Endocrinol Metab. 2007; 92: 681-4.

31. Roberts CT, Owens JA, Sferruzzi-Perri AN. Distinct actions of insulin-like growth factors (IGFs) on placental development and fetal growth: lessons from mice and guinea pigs. Placenta. 2008; 29 (Suppl A): S42-7.

32. Hay WW Jr. Placental-fetal glucose exchange and fetal glucose metabolism. Trans Am Clin Climatol Assoc. 2006; 117: 321-40.

33. Cleal JK, Lewis RM. The mechanisms and regulation of placental amino acid transport to the human foetus. J Neuroendocrinol. 2008; 20: 419-26.

34. Hiden U, Glitzner E, Hartmann M, Desoye G. Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. J Anat. 2009; 215: 60-8.

35. Desoye G, Hauguel-de Mouzon S. The human placenta in gestational diabetes mellitus – The insulin and cytokine network. Diabetes Care. 2007; 30 (suppl 2): S120-6.

36. Cetin I, Alvino G. Intrauterine growth restriction: implications for placental metabolism and transport. A review. Placenta. 2009; 30 (suppl A): S77-82.

37. Regnault TRH, Friedman JE, Wilkening RB, Anthony RV, Hay WW Jr. Fetoplacental transport and utilization of amino acids in IUGR – A review. Placenta. 2005; 26 (suppl A): S52-62.

38. Jansson T, Cetin I, Powell TL, Desoye G, Radaelli T, Ericsson A, Sibley CP. Placental transport and metabolism in fetal overgrowth - A Workshop report. Placenta. 2006; 27 (suppl A): S109-13.

39. Pederson J. Hyperglycaemia-hyperinsulism theory and birthweight. In: The pregnant diabetic and her new born: problems and management. Baltimore: Williams & Wilkins; 1977. p 211-20.

40. Ronzoni S, Marconi AM, Paolini CL, Teng C, Pardi G, Battaglia FC. The effect of a maternal infusion of amino acids on umbilical uptake in pregnancies complicated by intrauterine growth restriction. Am J Obstet Gynecol. 2002; 187: 741-6.