TOPIC HIGHLIGHT

Didier Vieau, Professor, *Series Editor*

Consequences of gestational and pregestational diabetes on placental function and birth weight

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Author contributions: Vambergue A and Fajardy I designed and wrote Part I, II, IV, V and part III respectively; all authors approved the final version of the topics (manuscript) to be published.
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Abstract

Maternal diabetes constitutes an unfavorable environment for embryonic and fetoplacental development. Despite current treatments, pregnant women with pregestational diabetes are at increased risk for congenital malformations, materno-fetal complications, placental abnormalities and intrauterine malprogramming. The complications during pregnancy concern the mother (gravidic hypertension and/or preeclampsia, cesarean section) and the fetus (macrosomia or intrauterine growth restriction, shoulder dystocia, hypoglycemia and respiratory distress). The fetoplacental impairment and intrauterine programming of diseases in the offspring's later life induced by gestational diabetes are similar to those induced by type 1 and type 2 diabetes mellitus. Despite the existence of several developmental and morphological differences in the placenta from rodents and women, there are similarities in the alterations induced by maternal diabetes in the placenta from diabetic patients and diabetic experimental models. From both human and rodent diabetic experimental models, it has been suggested that the placenta is a compromised target that largely suffers the impact of maternal diabetes. Depending on the maternal metabolic and proinflammatory derangements, macrosomia is explained by an excessive availability of nutrients and an increase in fetal insulin release, a phenotype related to the programming of glucose intolerance. The degree of fetal damage and placental dysfunction and the availability and utilisation of fetal substrates can lead to the induction of macrosomia or intrauterine growth restriction. In maternal diabetes, both the maternal environment and the genetic background are important in the complex and multifactorial processes that induce damage to the embryo, the placenta, the fetus and the offspring. Nevertheless, further research is needed to better understand the mechanisms that govern the early embryo development, the induction of congenital anomalies and fetal overgrowth in maternal diabetes.

INTRODUCTION

Diabetes in pregnant women is associated with an in-

creased risk of maternal and neonatal morbidity and remains a significant medical challenge.

Diabetes during pregnancy may be divided into clinical diabetes (women with previously diagnosed with type 1 or type 2 diabetes) and gestational diabetes. The American Diabetes Association defines gestational diabetes as "any degree of glucose intolerance with onset or first recognition during pregnancy", but provides diagnostic thresholds for fasting and post-glucose loading values. The International Association of Diabetes in Pregnancy Study Groups recently published a consensus derived from the Hyperglycemia Adverse Pregnancy Outcome study data, suggested that all pregnant women without known diabetes should have a 75 g oral glucose tolerance test at 24-28 wk of gestation[1]. Gestational diabetes would be diagnosed if one or more values met or exceeded the following levels of glucose: fasting 5.1 mmol/L, 1 h post glucose 10.0 mmol/L and 2 h post glucose 8.5 mmol/L.

While diabetes in pregnancy is associated with increased obstetric risk compared with normal pregnancy, the overall contribution of diabetes to most obstetric and neonatal complications on a population basis is low, with the largest impact being on shoulder dystocia. Except malformations, which are likely to have resulted from preconceptional or periconceptional hyperglycemia, improvements in obstetric practice have led to major reductions in adverse outcomes. Prepregnancy care for women with diabetes was introduced a long time ago and is associated with improved pregnancy outcomes. However, overall pregnancy outcomes remain very poor for women with diabetes with only a third receiving prepregnancy care. The importance of other metabolic factors, such as obesity and hypertriglyceridemia, in pregnancy are also now increasingly being recognized.

As well as its effects on perinatal outcomes, the intrauterine environment is a key determinant of child and adult health, particularly of conditions associated with metabolic disturbances[2-4]. Aberrant fetal growth has been linked to the development of metabolic diseases in later life, with many authors describing J or U-shaped curves linking both low and high birth weights with these conditions[5,6].

The diabetic intrauterine environment affects the offspring of women with all types of diabetes mellitus (DM). Therefore, type 2 diabetes is very often associated with obesity. It is possible that changes in placental structure and function may exist in obesity independently of diabetes. But, at this time, we do not have sufficient data in the literature to distinguish between what is related to obesity or to diabetes. The offspring of women with diabetes during pregnancy is at higher risk of developing hypertension and other cardiovascular disease. The intrauterine environment represents a vicious cycle with the offspring being at risk of developing gestational diabetes or diabetes at a young age. More recently, it has been evocated that environmental signals can alter the epigenetic state of specific genes and modulate their activity. It is possible that modulation of epigenetic states provides a plausi-

ble mechanism by which maternal diabetes can mediate known long-term effects on risk for type 2 diabetes for the offspring, but we need more information to understand the concept of programming in maternal diabetes.

PLACENTA IN DIABETES

The placenta is located at the interface between the maternal and fetal circulation with fundamental functions for pregnancy. It has been postulated that the diabetic environment may have profound effects on placental development and function. It is very important to be precise that these specific effects will depend on the time period in gestation[7]. Maternal and fetal hyperglycemias are likely to have an impact on the production of various placental proteins. These maternal and fetal hyperglycemiae also affect placental metabolism, growth and development.

Despite the improvement in maternal glycemic control, structural and functional changes of the diabetic placenta at term may occur independently of the type of diabetes. In the case of diabetes, the surface area is particularly increased in the periphery of the villous tree. The diffusion distance between the maternal and fetal systemic circulations is increased due to a thickening of the trophoblastic basement membrane with higher amounts of collagen, predominantly type IV[8].

In type 1 diabetes and in gestational DM (GDM), the villous stroma is slightly edematous with an over-representation of Hofbauer cells which are the placental resident macrophages[9]. The increased number of these cells contributes to a higher release of placental cytokines such as leptin, tumor necrosis factor-α (TNF-α) and interleukins, and subsequently modifies placental metabolic and endocrine functions[10]. Enlargement of the capillary surface area with capillary proliferation and penetration of newly formed vessels has been also described in maternal diabetes[11]. So the result is a hyper-vascularization and an increased surface of exchange that could contribute to oxygen diffusion across the placenta to compensate for the impaired maternal-fetal transfer of diffusion-limited substances.

Placental weight tends to be heavier in diabetes, similar to fetal weight, but the weight gain is more pronounced in the placenta than in the fetus, as is reflected in a higher placental-to-fetal weight ratio than in normal gestation. Placentomegaly is correlated with fetal macrosomia confirming the close correlation of placental weight with that of the offspring[12]. Actually, it is not possible to determine if placental overweight is the cause or the consequence of fetal overweight.

Modification in placental transport
Despite altered expression of placental glucose transporters, an unchanged transplacental glucose transport in GDM has been demonstrated. Taricco *et al*[13] showed that there was an unchanged concentration difference for glucose in umbilical arteries and veins in GDM. The higher flux results from the steeper maternal-to-fetal

concentration gradient as the major reason for increased glucose across the placenta in diabetes.

Amino acid transport may be also altered in diabetes[14]. Changes in placental amino acid transporters are not associated with maternal diabetes, but rather with elevated fetal weight[15]. We do not know if increased nutrient transport will stimulate fetal growth or serve to cover the increased fetal nutrient in case of overgrowth of the fetus.

Modification in materno-placental oxygen supply

The placental structure is altered in pregestational and gestational diabetes. The surface and exchange areas are enlarged as a result of hyperproliferation and hypervascularization. The underlying mechanisms are unclear but we can not exclude the role of the maternal hyperglycemia associated with other maternal factors[16].

In diabetes, it has been shown that the maternal-placental oxygen supply is reduced[17]. In addition to impaired oxygen supply, fetal oxygen demand is increased. This phenomenon could be explained by aerobic metabolism which is stimulated by fetal hyperinsulinemia. The resulting low fetal oxygen levels upregulate the transcription synthesis of proangiogenic factors such as leptin, vascular endothelial growth factor (VEGF) or fibroblast growth factor 2 (FGF2)[18,19]. In excess, these factors promote placental endothelial cell proliferation. In GDM and in type 1 DM (T1DM), alterations in fetal levels of proangiogenic [VEGF, FGF2, leptin, OGF1, insulin-like growth factor (IGF)2, hypoxia] or anti-angiogenic (TNF-α) factors have been reported. Both types of diabetes are characterized by enhanced vascularisation.

The diabetic milieu will have an influence on placental development and function especially during the first trimester. In this period, the placental structures are formed and the placenta is more sensitive to modifications. The hyperglycemia can induce a reduction of trophoblast proliferation which delays placental growth and development, especially in the first gestational weeks[20]. This mechanism could explain the higher incidence of spontaneous abortion, pre-eclampsia and intrauterine growth restriction associated with diabetes, and suggest impaired trophoblast invasion[21].

More recently, it has been shown that placental expression and activity of the matrix metalloproteinases (MMPs) as MMP14 and MMP15 are elevated in diabetes, especially in type 1 diabetes induced by maternal hyperinsulinemia and TNF-α[21]. MMP14 and MMP15 are proteases which are involved in tissue remodeling processes associated with invasion, angiogenesis and proliferation. The active form of placental MMP14 is elevated in diabetes. It is possible that hypoxic situations in the villous placental structure may be implicated as a cause of increased MMP14 activity.

SUITABLE ANIMAL MODELS ARE NEEDED TO STUDY DIABETES DURING PREGNANCY

With regard to diabetes in pregnancy, experimental findings from animal models and particularly rodents were developed with the purpose of enhancing understanding of pathophysiological mechanisms and further finding treatment strategies to maintain the closest to normal metabolic intrauterine milieu, improving perinatal development by preventing fetal growth restriction or macrosomia. Resulting diabetes in various animal species, including sheep, pig and rabbit have been described in many reviews[22-25]. However, the most often used experimental models are rodents (Wistar rat) because of their convenient maintenance, short length of pregnancy and multiparity, thus enabling studies on multiple fetuses and generations. The aim of type 1 and type 2 animal models is to reproduce metabolic maternal and fetal effects similar to pregestational and GDM. But which is the most suitable model? It has been shown that children born from either pre-existing T1DM, type 2 DM (T2DM) and GDM are equally exposed to impaired glucose intolerance[26]. How to reproduce the more accurately metabolic maternal end neonatal effects of diabetes? What is the most efficient tool? The efficiency of an experimental model is based on the observation of a stable hyperglycemia throughout gestation.

We will first distinguish models of inducing maternal diabetes using chemical agents able to damage the maternal β cell with short term consequences in fetuses. Secondly, long term induction of metabolic diseases by nutritional changes occurring before and/or during pregnancy named fetal programming models. We will then expose genetically predetermined diabetes animal models.

Chemical models of diabetes during pregnancy

Chemical methods used to induce damage to the pancreatic β-cells are obtained through the administration of drugs such as streptozotocin (STZ).

STZ: STZ is a potent alkylating agent able to methylate DNA and is often used to induce diabetes in experimental animals due to its toxic effects on pancreatic β-cells[27]. The nitrosurea moiety of STZ is responsible for its cellular toxicity, which is probably mediated through a decrease in nicotinamide (NAD) levels and the production of intracellular free radicals. Beta cells are particularly sensitive to STZ due to their low level of NAD. Many different approaches have been used regarding the mode of injection (intravenous or intraperitoneal), the doses (30 to 50 mg/kg) and the stage (pre gestational and gestational) leading to severe or mild diabetes and subsequent opposite fetal phenotypes (intra-uterine growth restriction or macrosomic[28,29]). In fact, mildly diabetic dams are hyperglycemic (glycemia between 120 and 300 mg/dL), hypoinsulinemic and give birth to macrosomic fetuses. In contrast, severely diabetic mothers are insulin deficient, hyperglycemic with low body weight and give birth to microsomic and malformed fetuses. The mechanisms are a brutal destruction of the mother and fetus's pancreas and intrauterine growth restriction is due to lack of insulin[30]. The altered maternal-fetal metabolic fuel relationship resulting from diabetes in pregnancy modulates fetal growth.

The increase in fetal glucose and insulin availability with maternal diabetes is strongly associated with the development of fetal macrosomia but severe DM or diabetes of long duration restricts fetal growth. Rat fetal body weight correlates positively with maternal glucose in diabetic rats with a glucose level less than 220 mg/dL but it correlates negatively in rats with a level above 220 mg/dL. Merzouk and Soulimane-Mokhtari[31] verified that mildly hyperglycemic dams have fetuses that are large for gestational age, classified as macrosomic, but this data has been hardly reproduced in other studies[32]. In 2010, other authors observed an increase of placental weight in their mildly diabetic rats showing a compensatory mechanism to assure the maternal fetal exchanges contribution to fetal development[33]. The degree of fetal damage and placental dysfunction and the availability and utilization of fetal substrates can lead to the induction of macrosomia or microsomia. We observed a U-shaped relationship between offspring weight and metabolic changes, like in clinical studies.

STZ + NAD chemical model: NAD is an anti oxidant molecule that protects the β cell destruction induced by STZ. In 1998, Masiello and co-workers developed NAD-STZ diabetes model induced by STZ and partially protected with a suitable dose of NAD[34]. In this NAD-STZ model, the diabetic syndrome shares a number of features with human T2DM such as a stable moderate hyperglycemia, glucose intolerance, an altered insulin secretion and a reduction in pancreatic β cell mass. So a mild diabetic model might be induced by STZ under NAD protection.

Using STZ in experimental models: Chemical models are characterized by a toxic action against β cells leading to a destruction of producing insulin cell without insulin resistance. These models mimic a type 1 diabetic state, despite the lack of immunological and genetic disorders. Thus, we obtain a type 1 maternal diabetes quite different from gestational diabetes which is characterized by a lack of adaptation of β cells to metabolic changes occurring during pregnancy and by an enhanced resistance to insulin.

Nevertheless, some authors have tried to mimic gestational diabetes by varying the doses and the window of injection of STZ (in the neonatal period[35,36], before mating[37] or during pregnancy[38]).

Drawbacks of chemical models: The efficiency of a model is based on the observation of a stable hyperglycemia throughout gestation and depends on multiple parameters such as the dose and mode of injection (venous or peritoneal route)[38]. Moreover, the efficiency varies according to the sex, with a lower metabolic sensibility in females[39]. The authors reported a sexual dimorphism in insulin sensibility with females being less sensitive to insulin than males, leading to a higher susceptibility to the rapid development of a more severe form of diabetes.

Females have more islets compared to males: higher insulin rates and lower glucose rates and rat male pancreatic β cells are protected by testosterone against STZ induced apoptosis[40]. In light of these data, it is clear that we have to take into account these variations in experimental model settings.

Dietary interventions

Exposure to an adverse environment *in utero* programs the physiology and metabolism of the offspring permanently with long term consequences for health[41]. This is the basis of the thrifty phenotype hypothesis driven from epidemiological studies showing a strong statistical link between birth weight, further metabolic syndrome and maternal nutrition in a context of type 2 diabetes[42]. Nutrition is a key environmental factor and it has been shown that inappropriate nutrition *in utero* has consequences into adulthood[43]. We speak about nutritional programming as the effect that occurred long after the stressor has been removed. Beta cell development is irreversibly damaged by inadequate nutrition during critical periods of fetal development[44]. This is a fetus organogenesis adaptation to the fetal-placenta unit environment.

Others studies suggest that the post natal period, when catch up growth occurs, may be more important than the *in utero* period[45]. The two arguments are now taken into account to suggest that a combination of intrauterine deprivation followed by accelerated post natal growth induce the highest risk of further metabolic disease. In other words, increased risk of disease arises if there is an imbalance between pre natal and post natal nutritional uptake. This is the basis of two steps nutritional models.

We will consider four main nutritional models: high fat, low protein, high carbohydrate and two steps nutritional programming model.

High fat diet model: In humans, consuming a high fat diet model (HFD) causes an increase in body fat deposition and a decrease in insulin sensibility which leads to insulinoresistance and T2DM.

HFD diet is more representative of the eating habits of the current society in both the developing and westernized world. Diets rich in saturated fats before and during pregnancy may result in pathological manifestations in rodents similar to the human condition of GDM.

Ozaki *et al*[46] have shown that a diet that includes 20% fat during pregnancy changes blood pressure in the offspring. This is explained by alterations in the fatty acid profiles of the membrane of the aorta. Fatty acid oxidation inhibits both glucose oxidation and its ability to enter cells. HFD increases insulin resistance in rats by secretion of cytokines and TNF in several tissues[47].

Rats fed with HFD develop obesity, hyperinsulinemia and insulin resistance but not frank hyperglycemia and diabetes. HFD impairs the glucose signaling system of the β cell and the capacity of insulin secretion and leads to a reduction of β cell mass and an increased apoptosis[48].

Otherwise, by increasing the fat component in the diet, the levels of the other macronutrients would be also affected, leading to nutrient deficiencies.

Low protein model: Low protein diet exposure during the first 3 or 6 wk of life in rats have consequences on growth and insulin secretory response[49]. During pregnancy, these animals are unable to match or adapt to insulin request and become glucose intolerant. Authors concluded that temporary protein energy malnutrition in young rats reduces the ability to increase insulin production to meet the needs of pregnancy.

Glucose regulation is perturbed and glucose and other nutrients are transferred to fetuses in increased amounts. This stimulates pancreatic β cell growth and insulin secretion and thus the occurrence of macrosomia in the offspring. The length of diet exposure has an impact on fetus development and physiology. A diet restricted to the first week of gestation leads to hypoglycemic and low weight fetuses with a high risk of further T2DM[50]. Diet during complete gestation leads to hyperglycemic fetuses and permanent β cell alterations such as reducing β cell volume and content and consequently the capacity of insulin secretion[51].

Carbohydrate model: Infusions of glucose during pregnancy in rats lead to a transient hyperglycemia[52]. However, significant effects on fetuses need repeated injections of glucose and the window of injection is important with a positive effect restricted to early pregnancy. This finding matches clinical observations of macrosomia despite a good glycemic control in second trimester. This suggests that metabolic control in early pregnancy is an important determinant for fetal-placental growth throughout gestation.

Two steps programming nutritional models: We consider a first step of restrictive diet (food restriction, FR30) occurring at the first generation during the 1st period of life and gestation, and a second step of high caloric diet submitted to the offspring after birth and weaning. Fetuses of this second generation will develop a metabolic syndrome[53].

Pregnant genetically determined diabetes
Pregnant animals with genetically determined type 1 diabetes: The Non Obese Diabetic (NOD) mice and Bio Breeding (BB) rats develop spontaneous pre-gestational diabetes and thus represent good candidates for type 1 maternal diabetes models. In common with human diabetes, β cells are submitted to an immune attack and animals have to be treated with insulin during gestation. Stopping insulin treatment induces a loss of maternal weight, ketosis, high rate of fetus resorption, lower fetal weight and higher placental weight[54]. Therefore, BB rats are a good model for the study of perinatal morbidity, microsomia and malformations. NOD mice develop a mild form of diabetes with macrosomic fetuses and adiposity. It has been shown that maternal hyperglycemia is not the only causative factor of macrosomia, partially explained by a dysregulation of placental glucose transporters and hexokinase protein production unable to protect the fetus from hyperglycemia and hyperinsulinemia[55].

Pregnant animals with genetically determined type 2-like diabetes: There are models of obesity and diabetes affecting a common pathway, a defect in the leptin receptor (*db*) and a defect in the leptin gene (*ob*). The deficiency of leptin has consequences in multiple areas of metabolism, ingestive behavior and reproduction (insulin resistance, hyperphagia and infertility). Most of these experimental models at the homozygous state are infertile. Therefore, mating heterozygotes animals is necessary to inbreeding. Three main models exist: C57 BIKS Lepr $^{db\,+}$ and C57Bl/6j mice and Goto-Kakizaki rats. Heterozygous Lepr $^{db+}$ mice are normoglycemic before pregnancy and present significant glucose intolerance restricted to the gestation period and associated with fetal macrosomia[56]. After delivery, glycemia reverts to a normal state, making Lepr db mice a good model for GDM investigation. C57BL/6j mice develop diabetes only after a high-fat and sucrose-rich diet. This model induced diabetes and obesity with hyperinsulinemia and hyperlipidemia, and females return to normal weight and glucose tolerance after gestation[57]. *Goto Kakizaki (GK)* is a rodent model of non obese type 2 diabetes that was produced by selective breeding of individuals with mild glucose intolerance from a non diabetic Wistar rat colony. A stable and heritable DM is obtained by selection of a diabetic line isolated by repeated breeding of normal animals[58]. These rats are not obese and not hyperinsulinemic. Offspring of GK females is exposed *in utero* to mild diabetes throughout gestation. Fetuses present a reduced β-cell mass associated with a lack of pancreatic reactivity to glucose. Thus, maternal mild hyperglycemia might contribute to endocrine pancreas defects in the first offspring generation.

ROLE OF THE INSULIN/INSULIN-LIKE GROWTH FACTORS SYSTEM

The insulin/IGF system is implicated in the regulation of fetal and placental growth and development. The feto-placental expression of insulin, IGF1, IGF2 and their receptors is regulated in a tissue-specific manner and can be affected by nutritional and endocrine conditions[59]. Hiden *et al*[60] have demonstrated that there is a spatio-temporal change in placental insulin receptor (IR) expression, suggesting a shift in the regulation of placental insulin effects from mother to fetus. In the first trimester, IR is predominantly expressed on the syncytiotrophoblast facing the maternal circulation, whereas at term, the placental endothelial cells facing the fetal circulation are the main expression site. The placental IGF1 receptor (IGF1R) is mainly expressed on the basal membrane of the syncytiotrophoblast. Hence, it is predominantly accessible for fetal IGF1 and IGF2[61]. *IGF2* overexpression

enhanced fetal growth, whereas targeted disruption of the fetal *IGF1*, *IGF2* or *IGF1R* genes in mice resulted in retardation of fetal growth.

The IGF-binding proteins (IGFBPs) are important players in the IGF system. They are key modulators of the ligand-receptor interaction. In humans, the most prevalent IGFBPs in fetal plasma and tissue are the IGFBPs 1-4. The serum of pregnant women contains the placenta-derived IGFBP3 protease. It cleaves IGFBP3 into smaller fragments with lower affinities for IGFs. Decidual cells of the basal plate region express mRNA of all six IGFBPs in the second and third trimester, with IGFBP1 being the most abundant. In the placenta, IGFBP3 is expressed in the extravillous cytiotrophoblasts. Fetal cord blood data suggest that these binding proteins may be dysregulated by diabetes during pregnancy[62]. *IGFBP3* mRNA is increased in maternal T1DM[63]. In the cord blood, increased IGFBP3 levels correlate with IGF1 levels and the incidence of macrosomia. This is consistent with the observation that IGF1 and IGFBP3 levels directly correlate with birth weight in diseased states[64].

The endocrine interaction between mother, fetus and placenta is exemplified by the effect of maternal and fetal insulin on the placenta. Maternal insulin affects placental development *via* receptors expressed on the microvillous membrane of the syncytiotrophoblast[21]. Fetal insulin affects gene expression in endothelial cells from placental arteries and veins, which will affect placental development. The spatio-temporal change of IR expression in the placenta allows a shift in the control of insulin regulation from the mother to the fetus. In the first trimester, maternal insulin influences the placenta by interaction with trophoblast IRs. This may in turn affect the mother by secretion of other factors as cytokines and hormones. Later, the fetus takes over control of insulin-dependent placental processes by fetal insulin interacting with placental endothelial cells.

In addition, in the first trimester, IGF1 and IGF2 produced by trophoblasts stimulate various processes that are involved in trophoblast invasion into the maternal uterus such as invasiveness, migration, MMP2 production, proliferation and MT1-MMP expression. Lower maternal IGF1 levels in T1DM may thus contribute to impaired trophoblast invasion. Hence, in GDM, transplacental amino acid transport and fetal growth may be promoted by the diabetes-associated increase in maternal concentrations of growth factors. TNF-α inhibits trophoblast invasion, whereas VEGF, leptin, insulin, IGF1 and IGF2 promote trophoblastic invasion. Changes can also be seen in the fetal circulation. However, the consequences of these changes for the fetus remain unclear.

ROLE OF LEPTIN

Maternal and fetal hyperleptinemia are well-established in diabetes and obesity. The extensive cross-talk between insulin and leptin signaling cascades may represent a major factor to the diabetes-induced placental changes.

In humans, leptin levels correlate with adiposity. This hormone has different functions such as stimulation of angiogenesis, regulation of hematopoiesis and inflammatory response[65]. During gestation, maternal leptin concentration rises by 30% and the placenta becomes the primary leptin source. The leptin receptor is expressed in the syncytiotrophoblast. Hauguel-de Mouzon *et al*[65] have shown that leptin induces hCG production, enhances mitogenesis, stimulates amino acid uptake and increases the synthesis of extracellular matrix proteins and metalloproteinases. So leptin plays a role in the regulation of placental growth. However, hyperleptinemia contributes to other placental modifications in the case of diabetes as basement membrane thickening owing to its ability to alter collagen synthesis[66].

Hiden *et al*[67] have proposed a hypothetical model for diabetes-induced alterations in human placenta. Elevated maternal TNF-α and reduced IGF1 levels in T1DM may inhibit placental invasion, paralleling a higher incidence of early pregnancy loss in diabetes. Maternal hyperglycemia induces thickening of the placental basement membrane, hence reducing oxygen transport. Increased levels of placental leptin may even further contribute to the excessive extracellular matrix synthesis. Different factors elevated in the placenta (IGF2, leptin), maternal (insulin, VEGF) or fetal (insulin, IGF1, IGF2, leptin) circulations in diabetes promote proliferation and placental growth. Placental hypervascularization may be supported by elevated levels of placental IGF2 and leptin, increased fetal IGF1, IGF2, leptin, FGF2, and reduced TNF-α, as well as fetal hypoxia. These modifications in the feto-placental compartment are characteristic of GDM, overt diabetes or both[67].

CONCLUSION

Placental structure and function can be changed as a result of maternal diabetes. The nature and extent of these changes depend on the type of diabetes and on the gestational period. For a complex disease syndrome, no animal model can be expected to serve all needs of research. Although each animal model has limitations and strengths, used together in a complementary fashion, they are essential for research on the metabolic syndrome and for rapid progress in understanding the etiology and pathogenesis towards a cure. Animal models have shown convincingly that diabetes may be transmitted by intrauterine exposure to maternal hyperglycemia. Intrauterine exposure to mild hyperglycemia is associated with normal weight or macrosomic newborns and IGT at adult age, related to a deficient insulin secretion. In contrast, a newborn offspring of severely hyperglycemic mothers is microsomic and displays, at adult age, a decreased insulin action. In addition, long-term and persistent effects of gestational diabetes on glucose homeostasis in the offspring may be transmitted through generations. These data support the concept of programming of physiological metabolism in offspring by manipulating maternal nutrition. It is known

that hyperglycemia is not the only causal factor. Maternal and fetal concentrations of several growth factors, hormones and cytokines are altered in diabetes and may affect the placenta and the fetal development. It is thus necessary to identify the specific biological effects and the mechanisms underlying them.

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