Placental pathologic changes in gestational diabetes mellitus

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Abstract

Nowadays, the continuous rise of maternal obesity is followed by increased gestational diabetes mellitus incidence. GDM is associated with adverse fetal and neonatal outcome that often presents with macrosomia, birth trauma, neonatal hypoglycemia, and respiratory distress syndrome. Inclusion of GDM into ‘the great obstetrical syndromes’ emphasizes the role of the placenta in interactions of the maternal and fetal unit.

The placenta acts as a natural selective barrier between maternal and fetal blood circulations. Placenta is sensitive to the hyperglycemic milieu and responses with adaptive changes of the structure and function. Alteration of the placental development and subsequent vascular dysfunction are presented in 6 out of 7 women with all ranges of diabetic severity.

Most placentas from GDM pregnancies present typical histological findings such as villous immaturity, villous fibrinoid necrosis, chorangiosis, and increased angiogenesis. The type of dysfunction depends on how early in pregnancy glycaemia disorders occurred. Generally, if impaired glucose metabolism is diagnosed in the early pregnancy, mainly structural dysfunctions are observed. GDM that is detected in late gestation affects placental function to a greater extent. Moreover many studies suggest that diabetic placental changes are associated with inflammation and oxidative stress that can lead to the chronic fetal hypoxia.

This article aims to review particular changes of the development, anatomy and function of the placenta in the environment of abnormal glucose metabolism which can establish the maternal-placental-fetal interface dysfunction as a potential source of adverse pregnancy outcomes. A detailed sequence of events that leads from hyperglycemia to placental dysfunction and subsequent pregnancy complications may become an important issue for further studies.

Abbreviations:
GDM - gestational diabetes mellitus
VEGF - endothelial growth factor
FGF - fibroblast growth factor
PPAR - peroxisome proliferator-activated receptor-gamma
PLGF - placental growth factor
MAPK - mitogen activated protein kinase
eNOS - nitrogen oxide synthase
EPO - erythropoietin
NRBCs - nucleated red blood cell level
MDA - malodialdehyde
NO - nitrogen oxide
ROS - reactive oxygen species
INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disease defined as progressively impaired glucose intolerance with the onset or first recognition during pregnancy (WHO 2013). The prevalence of GDM varies between populations, ranging from 1.7% to 11.6% (Schnaider et al. 2012). Numerous studies established that GDM is associated with significantly higher risk of short- and long-term maternal and fetal complications. Fetuses with intrauterine exposure to hyperglycemia more often present with macrosomia, birth trauma, neonatal hypoglycemia, and respiratory distress syndrome (Nordin et al. 2006). Adverse long-term outcomes of hyperglycemia are caused by intrauterine fetal programming and consist in a higher prevalence of metabolic-related diseases (Manderson et al. 2002; Dörner et al. 2000). The development of subsequent type 2 diabetes mellitus and cardiovascular diseases are among widely discussed maternal complications (Kwak et al. 2013; Kessous et al. 2013).

The underlying pathophysiology of GDM remains a matter of much debate. Maternal insulin resistance combined with the placental factor, are believed to play an important role. Recent literature reports consider GDM to be a part of the ‘great obstetrical syndromes’, which include pregnancy-related disorders such as preterm labor, preterm premature rupture of membranes, preeclampsia, spontaneous pregnancy loss, stillbirth, and abnormally delayed or accelerated fetal growth (Gabbay-Benziv & Baschat 2014; Bronsen et al. 2011). The concept of the ‘great obstetrical syndromes’ designates the adverse interaction of the maternal-fetal unit as the underlying etiology of pregnancy complications which manifest mainly in the third trimester (Romero 2009). It differs from other theories by pointing to the role of structural and functional changes of the placenta in the development of GDM.

This article aims to review particular changes of the development, anatomy and function of the placenta in the environment of abnormal glucose metabolism which can establish the maternal-placental-fetal interface dysfunction as a potential source of adverse pregnancy outcomes.

IMPAIRED PLACENTAL DEVELOPMENT

The placenta acts as a natural selective barrier between maternal and fetal blood circulations and is capable of controlling nutrient and gas exchange. Moreover, human placenta is responsible for important endocrine function and local maternal immune tolerance. Due to its location, this organ may be exposed to adverse intrauterine conditions and act as a target for maternal and/or fetal metabolic alterations associated with pregnancy pathologies.

According to the current diagnostic standards, GDM may be diagnosed at any time in pregnancy if one or more of the following criteria are met: fasting plasma glucose of 5.1-6.9 mmol/l (92-125 mg/dl), 1-hour plasma glucose of >10.0 mmol/l (180 mg/dl), and 2-hour plasma glucose of 8.5-11.0 mmol/l (153-199 mg/dl) following a 75 g oral glucose load (Polish Gynecological Society Standards 2014). The screening model for GDM (between 24-28 gestational weeks) and gradually decreasing insulin sensitivity during pregnancy lead to the diagnosis of diabetes mainly in late gestation. According to Catalano, decreased insulin resistance and the accompanying increase in insulin response may be found already in the first trimester in women who will develop GDM later in pregnancy (Catalano 2014). According to the literature, performing a screening test during the first trimester could detect around 30-40% of all GDM cases before 24-28 gestational weeks (Bartha et al. 2000; Meyer et al. 1996). The question how early in gestation the changes related to hyperglycemia occur in the placenta remains to be elucidated. In general, normal placental development can be profoundly disturbed and followed by structural and functional changes. If diabetes develops early in pregnancy it affects mainly the structure of the placenta, whereas later disturbances in glucose metabolism are more likely to affect its function (Mazdali et al. 2008; Laurini et al. 1987).

In the second half of pregnancy, placental villi undergo extensive angiogenesis and vascularization. In hyperglycemic environment both of them may remain uncompleted. Placental development disorders such as villous immaturity and alteration in villous branching are suggested to be an adaptation to particular intrauterine conditions, mainly related to early onset of diabetes (Taricco et al. 2009; Daskalakis et al. 2008).

PLACENTAL ANATOMY IN DIABETIC PREGNANCY

Macroscopically, a diabetic placenta is enlarged, thick and plethoric and can be described by increased placentalfetal weight ratio (Lao et al. 1997; Taricco et al. 2003). Numerous studies determined that the placenta grows first in a diabetic environment, thus precipitating transport of glucose and other nutrients. This sequence leads to accelerated fetal growth, which is proportional to the degree of hyperglycemia (Gauster et al. 2012).

Various authors suggest that the degree of glucose tolerance induces not only changes in the placentalfetal weight but also its microanatomical morphology. In a study by al-Okail et al. (1994), abundance of varying histologic changes were observed in poorly controlled GDM placentas. The typical changes included villous edema, fibrin deposits in the syncytiotrophoblast, and marked hyperplasia of the cytotrophoblast. Other studies of diabetic placentas revealed alterations such as fibrinoid necrosis and chorangiosis on histologic examination (Mazdali et al. 2008; Taricco et al. 2009; Daskalakis et al. 2008).
In general, a GDM placenta is characterized by a higher number of transversal interconnections between the villous branches. Moreover, higher total length volume and surface areas of villous capillaries are found (Jirkovska et al. 2002)

FUNCTIONAL CHANGES IN A GDM PLACENTA

Angiogenesis is considered to be a crucial process, responsible for the correct function of the placenta. The human placenta is a rich source of angiogenic substances which play an important role in maternal vascular adaptation to pregnancy. The villous vascularization and formation of terminal villi is under constant control of angiogenic factors such as endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF), peroxisome proliferator-activated receptor–gamma (PPAR), and placental growth factor (PIGF) (Reynolds & Redmer 2001; Khalilq et al. 1996). Increased angiogenesis of feto-placental vessels is a typical feature of a placenta exposed to hyperglycemic milieu. Vascular dysfunction may be observed even in cases of well-controlled diabetes mellitus (Leach et al. 2009; Mayhew 2002).

Many studies analyzed potential implications of an imbalance of angiogenic factors in the placental environment which can result in aberrant villous vascularization. In general, VEGF is indicated as the most important factor but a clear correlation between the level of VEGF and impaired vascularization of the placenta involves further investigation. Madazli et al. (2008) examined maternal and cord plasma levels of VEGF and revealed a tendency for lower values in GDM cases and a negative correlation with villous immaturity. On the contrary, Leach et al. (2009), suggest that in case of hyperglycemia, a pseudohypoxic environment with decreased levels of NO is created. These changes lead to an increased production of VEGF and prostaglandin - the leading factors of an inflammatory response.

The GDM placenta is also associated with lower concentrations of adherence and tight junctional proteins. In general, all placental lesions tend to change the permeability of the maternal- fetal barrier. The feto-placental vessels exhibit leakiness to macromolecules larger than albumin as compared to non-diabetic placenta. In a laboratory model, elevated levels of VEGF and increased albumin permeation occurred after a 4h hyperglycemic insult (Leach et al. 2009).

Another factor which may influence placental functional disorders is increased level of insulin. Hyperinsulinemia is the response of fetal pancreas to the increased transplacental flux of glucose from the maternal circulation. In case of poor diabetes control, fetal hyperglycemia occurs and results in pancreatic B cells hypertrophy to meet the demand for increased insulin secretion. In the second and third trimester, insulin receptor expression is switched to the luminal surface of fetal capillaries, which suggests insulin as a regulator factor of angiogenesis and vascular permeability (Hiden et al. 2009; Desoye et al. 1994). Constantly higher circulating level of insulin has direct access to maternal as well as fetal endothelium. The important role of insulin in angiogenesis has been shown by many studies. There is evidence demonstrating that by stimulating several pathways such as eNOS, mitogen activated protein kinase (MAPK), small GTPase Rac1 and expression of the matrix metalloproteinases, hyperinsulinemia is able to influence the angiogenesis. High insulin level correlates with increased endothelial VEGF and junctional disruption and increased vascular leaks (Lucas et al. 2008; Nelson et al. 2009; Jahan et al. 2011).

FETAL CONSEQUENCES OF PLACENTAL ALTERATION

Alteration of the placental development and subsequent vascular dysfunction are presented in 6 out of 7 women with all ranges of diabetic severity (Jones & Fox 1976). The pivotal question is how placental lesions such as villous fibrinoid necrosis, villous immaturity and chorangiosis may affect fetal development. Maternal hyperglycemia directly stimulates metabolic and hormonal changes in the fetus. Increased level of insulin accelerates fetal metabolism and subsequently enhances fetal oxygen demands. Both, placental abnormalities and increased oxygen consumption often lead to chronic fetal hypoxia (Hytinatti et al. 2000; Taricco et al. 2009). In the vast majority of cases, oxygen saturation in the umbilical vein is significantly decreased as compared to non-diabetic pregnancies. Fetal hypoxia tends to increase erythropoiesis by induction of erythropoietin (EPO) secretion. Significantly elevated level of EPO in cord blood is correlated with enhanced nucleated red blood cell level (NRBCs) (Madazli et al. 2008; Daskalakis et al. 2008). Both of them are suggested as markers of chronic intrauterine fetal hypoxia (Ferber et al. 2005). Hypoxia is one of the basic triggers for increased angiogenesis.

Another factor that can affect the physiology of placental vasculature is oxidative stress. This assumption can be confirmed by widely presented oxidative stress markers such as 8-isoprostane, increased activity of superoxide dismutase and glutation peroxidase, or elevated levels of malodialdehyde (MDA) in diabetic placentas (Madazli et al. 2008; Coughlan et al. 2004). The transient dysregulation of NO and reactive oxygen species (ROS) synthesis may induce vasoconstriction of the placental vessels and activate synthesis of pro-inflammatory cytokines. An increased expression of antioxidant gene may be explained as an adaptation to altered oxidative stress status.

Elevated total placental weight, low-grade inflammation, and altered vascular permeability are followed by increased materno-fetal nutrient transfer. Diabetic milieu leads to upregulation of genes involved in lipid pathways. Transport of triglyceride and cholesterol is
significantly enhanced in GDM placentas (Radaelli et al. 2009). Placental amino acid exchange is also altered in GDM. Interestingly, even in cases of well-controlled glycemia, the concentration of amino acids increases in umbilical venous and arterial plasma as compared to maternal circulation (Cetin et al. 2005). Generally, enhanced nutrient transport and anabolic metabolism induced by hyperinsulinemia contribute to an increased fetal fat accumulation and, subsequently, accelerated intrauterine fetal growth.

CONCLUSIONS
Gestational diabetes mellitus is associated with adverse fetal and neonatal outcomes. Despite efforts to explain the pathophysiology of GDM, effective screening and prevention remain to be established. Nowadays, inclusion of GDM into ‘the great obstetrical syndromes’ emphasises the role of the placenta in maternal-fetal interaction. Particular location between the maternal and fetal bloodstream makes the placenta a mediator in the maternal-fetal ‘dialogue’. On the one hand, the placenta plays an important endocrine function and on the other hand, it remains sensitive to adverse intrauterine environment and presents anatomical and functional adaptive changes. In pregnancies complicated by gestational diabetes mellitus, particular conditions of hyperglycaemia and hyperinsulinemia are created. Adverse metabolic milieu initiates a chain of events that, due to placental dysfunction, may lead to increased neonatal morbidity and mortality.

Most placentas from GDM pregnancies present typical histological findings such as villous immaturity, villous fibrinoid necrosis, chorangiis, and increased angiogenesis. The type of dysfunction depends on how early in pregnancy glycemia disorders occurred. Generally, if impaired glucose metabolism is diagnosed in the early pregnancy, mainly structural dysfunctions are observed. GDM that is detected in late gestation affects placental function to a greater extent. Interestingly, histologic changes are present in both, well and poorly controlled GDM.

Many studies suggest that diabetic placental changes are associated with inflammation and oxidative stress. The role of this intrauterine environment in fetal development remains unclear and further investigation is needed. Despite normal umbilical artery flow presented in most cases of GDM pregnancies, increased levels of erythropoietin and nucleated red blood cells in cord blood are very common. Elevated markers of chronic fetal hypoxia may explain adverse neonatal outcome in GDM pregnancies.

The continuous rise in the rate of maternal obesity is followed by increased GDM incidence. A detailed sequence of events that leads from altered glucose metabolism to placental dysfunction and subsequent pregnancy complications may become an important issue for further studies. The concept of the ‘great obstetrical syndromes’ points to the underlying etiology of adverse interactions between the materno-placental and fetal unit. Ways to modify or even prevent this sequence of changes remains a challenge for future research.

Conflict of interest statement: The authors declare that there are no conflicts of interest.

REFERENCES
Introduction

Gestational diabetes mellitus (GDM), a common pregnancy disorder, increases the risk of fetal overgrowth and later metabolic morbidity in the offspring. The placenta likely mediates these sequelae, but the exact mechanisms remain elusive. The observed changes in placental mitochondrial dynamics in GDM likely reflect deranged placental metabolism, with plausible implications for the short-term and long-term health of the offspring. Variations in placental mitochondrial metabolic flexibility may contribute to the heterogeneity and unpredictability of adverse pregnancy outcomes in diabetes. Pub Med / Medline: Neuro Endocrinol Lett. Placental pathologic changes. in gestational diabetes mellitus. Patrycja Jędrzejczak, Mirosław Winiarski, Dorota A. Bień, Mirosław Wisniewski. 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland. Gestational diabetes mellitus incidence. GDM is associated with adverse fetal and neonatal outcome that often presents with macrosomia, birth trauma, neonatal. Gestational diabetes mellitus (GDM) is a condition in which a hormone made by the placenta prevents the body from using insulin effectively. Glucose builds up in the blood instead of being absorbed by the cells. Unlike type 1 diabetes, gestational diabetes is not caused by a lack of insulin, but by other hormones produced during pregnancy that can make insulin less effective, a condition referred to as insulin resistance. The placenta supplies a growing fetus with nutrients and water, and also produces a variety of hormones to maintain the pregnancy. Some of these hormones (estrogen, cortisol, and human placental lactogen) can have a blocking effect on insulin. This is called contra-insulin effect, which usually begins about 20 to 24 weeks into the pregnancy. Gestational diabetes mellitus (GDM) and preeclampsia (PE) are both characterized by endothelial dysfunction and GDM women have higher incidence of PE. The placenta plays a key role in PE pathogenesis but its contribution to PE during GDM remains unclear. Relative expression and fold change were calculated according to Livak and Schmittgen. sFlt1 and PlGF enzyme-linked immunosorbent assay (ELISA). Total proteins were isolated from placental biopsies using 1X Radio Immuno-precipitation Assay (RIPA) buffer supplemented with Protease Inhibitors. Increased placental mitochondrial fusion in gestational diabetes mellitus: An adaptive mechanism to optimize feto-placental metabolic homeostasis? BMJ Open Diabetes Res. Care. This could be number of placenta with placental dysmaturity in each due to the fact that obesity is a risk factor for gestational group. diabetes (White’s group A) and that most patients in Another common finding in the diabetic placenta is White’s group B have type II diabetes mellitus (non-in- fetal artery thrombosis the cause of which remains un- sulin. Singer DB (1984) The placenta in pregnancies complicated by diabetes mellitus. Med Clin North Am 49:1053-1060 diabetes mellitus. Perspect Pediatr Pathol 8:199-212. 6. Fox H (1969) Pathology of the placenta in maternal diabetes 19. Cellular Changes in the Placenta in Pregnancies Complicated with Diabetes Cambios Celulares en la Placenta en Embarazos Complicados con Diabetes. By Adrian Martinez.