Neuroendocrinology Letters Volume 36 No. 2 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Placental pathologic changes in gestational diabetes mellitus

Patrycja Jarmuzek, Mirosław Wielgos, Dorota A. Bomba-Opon

1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

Correspondence to: Assoc. Prof. Dorota A. Bomba-Opon, MD, Ph.D
1st Department of Obstetrics and Gynecology,
Medical University of Warsaw
Plac Starynkiewicza 1/3, 02-015 Warsaw, Poland.
tel: + 48225830301; fax: +48225830302; e-mail: dorota.bomba-opon@wum.edu.pl

Submitted: 2015-03-06 Accepted: 2015-03-12 Published online: 2015-05-18

Key words: **great obstetrical syndromes; gestational diabetes mellitus; placenta; hypoxia; oxidative stress; VEGF**

Neuroendocrinol Lett 2015; **36**(2):101–105 **PMID:** 26071574 NEL360215R01

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

REVIEW ARTICLE

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 (Madazli *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 placental to fetal 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 placental 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 reveled alterations such as fibrinoid necrosis and chorangiosis on histologic examination (Madazli *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 brunches. 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 (PlGF) (Reynolds& Redmer 2001; Khaliq *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 Racl 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 (Hytinantti *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 glycaemia, 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' emphasizes the role of the placenta in materno-fetal interaction. Particular location between the maternal and fetal bloodstream makes the placenta a mediator in the materno-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 hyperglycemia 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, 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. 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

1 Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R (2000). Gestational diabetes mellitus diagnosed during early pregnancy. Am J Obstet Gynecol. **182**: 346–50.
2 Brosens I, Pijnenborg R, Vercruysse L, Romero R (2011). The "great obstetrical syndromes" are associated with disorders of deep placentation. Am J Obstet Gyneacol . **204**:193-201
3 Catalano PM (2014). Trying to understand gestational diabetes. Diabet Med. **31**:273-81
4 Cetin I, de Santis MS, Taricco E, Radaelli T, Teng C, Ronzoni S, et al: (2005). Maternal and fetal amino acids concentrations in normal pregnancies and in pregnancies with gestational diabetes mellitus. Am J Obstet Gynecol. **192**: 610-7.
5 Coughlan MT, Vervaart PP, Permezel M, Georgiou HM, Rice GE (2004). Altered placental oxidative stress status in gestational diabetes mellitus. Placenta. **25:** 78-94.
6 Daskalakis G, Marinopoulos S, Krielesi V, Papapanagiotou A, Papantoniou N, Mesogitis S, *et al.* (2008). Placental pathology in women with gestational diabetes. Acta Obstet Gynecol Scand. **87**:403–7.
7 Desoye G, Hartman M, Blaschitz A, Dohr G, Hahn T, Kohnen G et. Al (1994). Insulin receptors in syncytiotrophoblast and fetal endothelium of human placenta. Immunohistochemical evidence for development changes in distribution pattern. Histochemistry. **101**: 277-285.
8 Dörner G, Plagemann A, Neu A, Rosenbauer J (2000). Gestational diabetes as possible risk factor for Type I childhood-onset diabetes in the offspring. Neuro Endocrinol Lett. **21**:355-359.
9 Ferber A, Minior VK, Bornstein E, Divon MY (2005). Fetal 'nonreassuring status' is associated with elevation of nucleated red blood cell counts and interleukin- 6. Am J Obstet Gynecol. **192**: 1427-1429.
10 Gabbay-Benziv R, Baschat AA (2014). Gestational diabetes as one of the "great obstetrical syndromes" - the maternal, placental, and fetal dialog. Best Pract Res Clin Obstet Gynaecol. S1521-6934
11 Gauster M, Desoye G, Totsch M, Hiden U (2012). The placenta and gestational diabetes mellitus. Curr Diab Rep. **12**:16-23.
12 Hiden U, Glitzner E, Hartman M, Desoye G (2009). Insuline and the IGF system in the human placenta of normal and diabetic pregnancies. J Anat.**215**:60-8
13 Hytinantti TK, Koistinen HA, Teramo K, S, Karonen S-L, Koivisto VA, and Andersson S (2000). Increased fetal leptin in type I diabetes mellitus pregnancies complicated by chronic hypoxia. Diabetologia. **43**: 709–713
14 Jahan S, Ahmed CM, Zinnat R, Hasan Z, Habib SH, Saha S *et al.* (2011). Influence of maternal diabetes on serum leptinemic and insulinemic status of the offspring: a case study of selected patients in a tertiary care hospital in Bangladesh. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, vol. 5, no. 1, pp. 33–37.
15 Jirkovska M, Kubinova L, Janacek J, Moravcová M, Krejcí V, Karen P (2002). Topological properties and spatial organization of villous capillaries in normal and diabetic placentas. J Vasc Res. **39**:268–78.
16 Jones CJ, Fox H (1976). Placental changes in gestational diabetes. An ultrasound study. Obstet Gynecol. **48**: 274-80.
17 Kessous R, Shoham- Vardi I, Pariente G, Sherf M, Sheiner E (2013). An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity. Heart. **99**: 1118-1121.

18 Khaliq A, Li XF, Shams M, Sisi P, Acevedo CA, Whittle MJ *et al.* (1996). Localization of placenta growth factor (PIGF) in human term placenta. Growth Factors. **13**:243–50.
19 Kwak SH, Choi SH, Jung HS, Cho YM, Lim S, Cho NH (2013). Clinical and genetic risk factors for type 2 diabetes at early or late post-partum after gestational diabetes mellitus. J Clin Endocrinol Metab. **98**: E744-E752.
20 Lao TT, Lee CP, Wong WM (1997). Placental weight to birthweight ratio is increased in mild gestational glucose intolerance. Placenta. **18**:227e30.
21 Laurini RN, Visser GHA, van Ballegooie E, Schoots CJ (1987). Morphological findings in placentas of insulin-dependent diabetic patients treated with continuous subcutaneous insulin infusion (CSII). Placenta. **8**:153e65
22 Leach L, Taylor A, Sciota F (2009). Vascular dysfunction in the diabetic placenta: causes and consequences. J Anat. **215**:69-76
23 Lucas J, Thomas R, Ikram A, Leach L (2008). The effect of fetal hyperinsulinemia of human placental vascular function: Perfusion of fetal microvascular bed results in increased vascular leakage and loss of junction B caterin. Microcirculation. **15**: 672- 673.
24 Manderson JG, Mullan B, Patterson CC, Hadden DR, Traub AI, McCance DR (2002). Cardiovascular and metabolic abnormalities in the offspring of diabetic pregnancy. Diabetologia. **45**: 991-6.
25 Madazli R, Tuten A, Calay Z, Uzun H, Uludag S, Ocak V (2008). The incidence of placental abnormalities, maternal and cord plasma malondialdehyde and vascular endothelial growth factor levels in women with gestational diabetes mellitus and nondiabetic controls. Gynecol Obstet Invest. **65**:227e32.
26 Mayhew, TM (2002). Enhanced fetoplacental angiogenesis in pre-gestational diabetes mellitus: the extra growth is exclusively longitudinal and not accompanied by microvascular remodeling. Diabetologia. **45**:1434–1439.
27 Meyer WJ, Carbone J, Gauthier DW (1996). Early gestational glucose screening and gestational diabetes. J Reprod Med. **41**:675–9.
28 Nelson SM, Coan PM, Burton GJ, Lindsay RS (2009). Placental structure in type 1 diabetes: relation to fetal insulin, leptin, and IGF-I1. Diabetes **58**: 2634-2641.
29 Nordin NM, Wei JWH, Naing NN, Symonds EM (2006). Comparison of maternal- fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. J Obstet Gynaecol Res. **32**: 107-114.
30 al-Okail MS, al-Attas OS (1994). Histological changes in placental syncytiotrophoblasts of poorly controlled gestational diabetic patients. Endocr J. **41**:355–60.
31 Radaelli T, Lepercq J, Varastehpour A, Basu S, Catalano PM, Hauguel-De Mouzon S (2009). Differential regulation of genes for fetoplacental lipid pathways in pregnancy with gestational and type 1 diabetes mellitus. Am J Obstet Gynecol. **201**: 209 e201-209 e210.
32 Reynolds LP, Redmer DA (2001). Angiogenesis in the placenta. Biol Reprod. **64**:1033–40.
33 Romero R (2009). Prenatal medicine: the child is the father of the man. 1996. J Maternal Fetal Neonatal Med. **22**: 639-9.
34 Schneider S, Block C, Wetzel M, Maul H, Loerbroks A (2012). The prevalence of gestational diabetes in advanced economies. J Perinat Med. **40**: 511-20.
35 Taricco E, Radaelli T, Nobile de Santis MS, Cetin I (2003). Foetal and placental weights in relation to maternal characteristics in gestational diabetes. Placenta. **24** :343e7.
36 Taricco E, Radaelli T, Rossi G, Nobile de Santis MS, Bulfamante GP, Avagliano L *et al.* (2009). Effects of gestational diabetes on fetal oxygen and glucose levels in vivo. Bjog. **116**:1729–35.
37 Wender-Ozegowska E, Bomba-Opoń D, Brazert J, Celewicz Z, Czajkowski K, Karowicz-Bilińska A (2014). Actualisation of Polish Gyneacological Society standards of medical care in management of women with diabetes. Ginekol Pol. **85**:476-8.
38 Word Health Organization (2013). Diagnostic Criteria and Classification hyperglycemia first detected in pregnancy. Geneva