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The role of the placenta in the formation of gestational complications in women with metabolic syndrome

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ABSTRACT

Over the past decade, the prevalence of metabolic syndrome has increased significantly worldwide, and in most countries around the world this non-communicable disease has become a major health threat. Today, the mechanisms of metabolic syndrome influence on the development of various pregnancy complications are actively discussed. Studies of the pathophysiological mechanisms of the relationship between metabolic disorders and placental-associated pregnancy complications deserve special attention. The placenta performs essential functions throughout pregnancy and serves as a site for nutrient exchange and gas exchange between the pregnant woman and the fetus. Metabolic changes in women are closely associated with a number of placentally mediated obstetric complications, including preeclampsia, placental insufficiency, macrosomia, fetal growth restriction and antenatal fetal death. It is believed that it is in the first trimester of pregnancy that trophoblast cells are most sensitive to metabolic changes in homeostasis, which leads to their ischemia, impaired proliferation, invasion and angiogenesis. In pregnancies complicated by metabolic syndrome, the placenta is exposed to inflammation, oxidative stress, dyslipidemia, hyperglycemia, and altered hormone levels. Such metabolic changes can affect the development and function of the placenta, leading to abnormal fetal growth, as well as metabolic and cardiovascular disorders in children in the long term. Despite the wide range of pregnancy complications with metabolic syndrome, the mechanisms of their development have not been sufficiently studied. The purpose of this review was to summarize current knowledge about the pathophysiological mechanisms of the influence of metabolic syndrome on the development and function of the placenta.

Keywords: metabolic syndrome; placenta; gestational diabetes mellitus; obesity; preeclampsia; placental insufficiency; review.

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Роль плаценты в формировании гестационных осложнений у женщин с метаболическим синдромом

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АННОТАЦИЯ

За последнее десятилетие распространённость метаболического синдрома значительно выросла во всём мире, а в большинстве стран мира это неинфекционное заболевание стало основной угрозой для здоровья. На сегодняшний день механизмы влияния метаболического синдрома на развитие различных осложнений беременности активно обсуждаются. Отдельного внимания заслуживают исследования патофизиологических механизмов взаимосвязи метаболических нарушений и плацентарно-ассоциированных осложнений беременности. Плацента выполняет важнейшие функций на протяжении всей беременности и служит местом обмена питательных веществ и газообмена между беременной и плодом. Метаболические изменения в организме женщины тесно связаны с рядом плацентарно-опосредованных акушерских осложнений, включая преэклампсию, плацентарную недостаточность, макросомию, задержку роста плода и антенатальную гибель плода. Считают, что именно в I триместре беременности клетки трофобласта наиболее чувствительны к метаболическим изменениям в гомеостазе, что приводит к их ишемии, нарушению пролиферации, инвазии и ангиогенеза. При беременности, осложнённой метаболическим синдромом, плацента подвергается воздействию воспаления, окислительного стресса, дислипидемии, гипергликемии и изменённого уровня гормонов. Подобные метаболические сдвиги могут повлиять на развитие и функционирование плаценты, привести к аномальному росту плода, а также к метаболическим и сердечно-сосудистым нарушениям у детей в долгосрочной перспективе. Несмотря на обширный спектр осложнений беременности при метаболическом синдроме, механизмы их развития изучены недостаточно. Целью данного обзора стало обобщение современных знаний о патофизиологических механизмах влияния метаболического синдрома на развитие и функцию плаценты.

Ключевые слова: метаболический синдром; плацента; гестационный сахарный диабет; ожирение; преэклампсия; плацентарная недостаточность; обзор.

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BACKGROUND

The placenta connects the blood circulation of the pregnant woman with that of the fetus. Thus, it ensures the transfer of nutrients to the fetus and regulates the exchange of respiratory gases, which promotes the growth and development of the fetus [1, 2]. Under unfavorable conditions, it can adapt to maintain fetus viability, with the greatest emphasis on maintaining the development and functioning of the brain. Thus, it undergoes morphological and functional changes [1].

Metabolic syndrome (MS) is closely associated with numerous obstetric complications, including preeclampsia, placental insufficiency, macrosomia, fetal growth retardation, and antenatal fetal death. Additionally, it is associated with the development of metabolic and cardiovascular disorders in children from the intrauterine period to adulthood [2–5].

In pregnancies complicated by MS, the placenta is exposed to increased inflammation, oxidative stress, dyslipidemia, and altered hormone levels [6, 7]. Such shifts in homeostasis lead to disruption of placental development and function, which is associated with health complications in both the pregnant woman and fetus [8].

In this review, we have summarized the current knowledge regarding the impact of MS on placental development and function and the associated complications during pregnancy, childbirth, and the postpartum period.

INFLUENCE OF MS ON THE TROPHOBLAST IN EARLY PREGNANCY

In early pregnancy, the trophoblast is most sensitive to metabolic changes. Even small shifts in homeostasis can significantly and negatively impact placental development and pregnancy outcome [8–10]. Metabolic changes in pregnant women are associated with altered levels of growth factors, cytokines, and adhesion molecules [8, 9], indicating the formation of an unfavorable environment for placental development.

DISORDERED TROPHOBLASTIC CELL PROLIFERATION IN MS

Active trophoblast proliferation ensured normal placental formation. *In vitro* studies have demonstrated that hyperglycemia induces cell cycle arrest in the G0 phase in trophoblasts and disrupts phosphatidylinositol phosphate signaling pathways that are involved in cell proliferation [10].

MS can inhibit cell proliferation via epigenetic modifications, which affects the expression of microRNAs[1] (miRs) in the cell [11]. Both hyperglycemia and dyslipidemia enhance miR-137 expression, leading to overexpression of interleukin-6 and inhibition of trophoblast cell proliferation [12]. Furthermore, in MS, the activity of miR-136 increases, which inhibits trophoblast proliferation by suppressing the synthesis of the transcription factor E2F1. Transcription factor E2F1 is an important regulator of the cell cycle that mediates the transition from the presynthetic to synthetic phase [13].

The miR-362-5p regulates the intracellular PI3K/AKT signaling pathway by directly increasing the secretion of glutathione disulfide reductase. In MS, the activity of miR-362-5p decreases, which results in the inhibition of trophoblast cell proliferation [14]. Under conditions of altered homeostasis in MS, the expression of miR-520h increases, which inhibits cell proliferation by reducing the activity of the serine/threonine kinase complex (mTOR) in trophoblastic cells [15].

DISORDERED TROPHOBLAST INVASION

MS causes superficial migration and insufficient invasion of the trophoblast, resulting in the abnormal remodeling of the uterine spiral arteries [16]. In a rat model, insulin resistance resulted in changes in trophoblast invasion, impaired placental blood flow, and increased vascular resistance, which were directly associated with an increase in the incidence of stillbirth and fetal hypotrophy [16].

As the trophoblast invades the decidualized endometrium, the extravillous trophoblast produces enzymes of the fibrinogen activating system, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases, which regulate extracellular matrix remodeling and trophoblast cell invasion [17]. Belkacemi et al. revealed that in MS, trophoblast invasion is reduced by approximately 62%, and the activity of urokinase-type plasminogen, a fibrinogen activation system enzyme, is lowered [18].

An increase in the E-cadherin levels and a decrease in the Twist1 protein and vimentin levels in trophoblast cells due to hyperglycemia and dyslipidemia disrupt the epithelial–mesenchymal transition process. This transition facilitates trophoblast invasion as well as regulates the differentiation of syncytiotrophoblast and cytotrophoblast [19].

Collectively, the aforementioned findings indicate that metabolic disorders in pregnant woman inhibit trophoblast invasion and migration in the first trimester of pregnancy. Furthermore, the aforementioned pathophysiological mechanisms may account for pregnancy complications such as preeclampsia, placental insufficiency, fetal growth retardation, and antenatal fetal death.

TROPHOBLASTIC HYPOXIA IN MS

Several have demonstrated that MS is associated with placental hypoxia [20–22]. In a mouse model, insulin resistance and dyslipidemia were associated with an increase in expression of hypoxia-inducible factor-1α. Furthermore, increased expressions of tumor necrosis factor-α, interleukin-1β, and vascular endothelial growth factor (VEGF) were observed,

[1] RNA — ribonucleic acid.

which resulted in placental hypoxic stress and impaired placental vascular development [20].

Hypoxia-inducible factor-1 regulates the transcription process under hypoxic conditions [22]. Furthermore, ischemia increases the expression of transforming growth factor-β, which inhibits trophoblast cell differentiation [22]. Expression of both hypoxia-inducible factor-1α and transforming growth factor-β decreases as the oxygen concentration increases, which creates an environment for adequate trophoblast differentiation and ensures extensive cytotrophoblast invasion into the spiral arteries [21, 22].

Nteeba et al. demonstrated that under hyperglycemic conditions, the thickness of trophoblast membranes increases significantly due to massive collagen deposition. Such a transformation leads to changes in the oxygen concentration gradient in the placenta, which induces local hypoxia at the placental junction between the pregnant woman and fetus [23]. Moreover, MS can disrupt trophoblast development by reducing the response of stem cells to low oxygen levels [23].

ANGIOGENESIS IN THE PLACENTA IN MS

Angiogenesis in the placenta continues throughout pregnancy, which allows for adequate fetomaternal blood flow [24–28]. Trophoblast cells secrete angiogenic factors during remodeling of the uterine spiral arteries. VEGF destroys vascular smooth muscle and endothelial cells. Placental growth factor, which is expressed in trophoblast villi, promotes angiogenesis under hypoxic conditions [24].

Angiopoietins (types 1 and 2) and their receptor Tie-2 are important in the destruction of blood vessels [25]. Fibroblast growth factor and platelet-derived growth factor are involved in vasculogenesis and angiogenesis [26]. Fms-like tyrosine kinase-1 is a soluble form of VEGFR-1 with high affinity for VEGF, but without a signal transduction function [27]. Soluble endoglin inhibits transforming growth factor-β and blocks the activation of endothelial nitric oxide synthase, thereby disrupting angiogenesis [28]. Several studies have demonstrated a decrease in the secretion of VEGF, placental growth factor, and urokinase-type plasminogen and a simultaneous increase in the concentration of antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 and soluble endoglin in trophoblast cells in MS [18, 29, 30].

In the placenta of patients with MS, increased levels of VEGF, angiopoietins, endoglin and endothelin can lead to an imbalance between angiogenic and antiangiogenic factors [31]. Furthermore, Tirpe et al. demonstrated that mild glycemia in women with gestational diabetes mellitus and lipidemia in obese patients did not change VEGF expression by themselves, which contrasts with the findings in MS [32]. Alqudah et al. demonstrated that the level of FK506-binding protein, which acts as an antiangiogenic protein and inflammatory regulator, decreased in the placenta of mice with obesity and long-term hyperglycemia [33]. However, there are controversial data demonstrating that hyperglycemia and obesity promote angiogenesis via phosphatidylinositol-3-kinase (PI3K) signaling in the placenta [34, 35]. Membrane-type MMP-1 (MT1-MMP) reportedly plays a key role in angiogenesis and vasodilation [34, 35].

Hiden et al. demonstrated that in fetoplacental endothelial cells in women with hyperglycemia and a body mass index > 24.9 kg/m^2, the expression of total and active MT1-MMP increases by 54% relative to women with normoglycemia and a body mass index < 24.9 kg/m^2 [35]. Furthermore, antibodies blocking MT1-MMP reduce angiogenesis *in vitro* by 29%, and high levels of insulin and insulin-like growth factor-2 stimulate MT1-MMP expression by transmitting PI3K signals via insulin receptors [34].

Despite the controversial information regarding angiogenesis in the placenta in patients with MS and the factors that determine it, the balance between angiogenic and antiangiogenic factors is disturbed. This may account for the pathogenesis of preeclampsia, fetal growth restriction, and placental insufficiency.

IMMUNE RESPONSE IN THE PLACENTA IN MS

During pregnancy, the uterus is colonized by numerous immune cells, the most common of which are decidual natural killers (dNK) and macrophages [34–36].

The peak concentration of dNK coincides with the onset of spiral artery remodeling. As pregnancy progresses, the dNK concentration gradually decreases [36, 37]. Because dNKs produce tumor necrosis factor-α, placental growth factor, VEGF, and MMPs, the main biological function of dNK is associated with spiral artery remodeling [38]. In a mouse model with MS, dNK deficiency resulted in decreased vessel density and impaired spiral artery remodeling [39].

In MS, the placenta is infiltrated by peripheral blood NK cells [40]. McElwain et al. and Monaco-Brown et al. demonstrated that the number of cytotoxic CD16$^+$ and CD56$^-$ NK cells increases both in the maternal blood and placental extravilli in patients with MS [41, 42]. Furthermore, the CD16$^+$ and CD56$^-$ levels were directly proportional to the duration of MS [41, 42].

Macrophages secrete interleukin-33, granulocyte colony-stimulating factor, chemokine CXCL1, transforming growth factor-β, and tumor necrosis factor-α, which are involved in the regulation of invasion and migration of trophoblast cells [40]. Leptinemia and hyperglycemia stimulate the *in vitro* release of interleukin-8, interferon-γ, tumor necrosis factor-β, chemokine CXCL1, and granulocyte colony-stimulating factor in concentrations higher than that observed in normal pregnancy. These create a proinflammatory environment at the placental junction between the pregnant woman and fetus [34, 36, 37].

Cytokines secreted by macrophages into the villous stroma do not enter the systemic circulation and accumulate in the placenta [39, 40]. This may contribute to the initiation of an intraplacental inflammatory cascade with the accumulation of

multiple proinflammatory mediators, which can cause chronic villitis [39, 40].

Collectively, the aforementioned findings indicate that prepregnancy chronic inflammation in female patients triggers a cascade of events that create an inflammatory environment in the uterus. The inflammatory environment during fetal development may negatively impact the health of the offspring in the long-term, including the risk of development of neuropsychiatric disorders (e.g., autism and attention deficit hyperactivity disorder) and metabolic diseases (e.g., obesity and type 2 diabetes mellitus) [43].

IMPACT OF MS ON THE PLACENTA IN LATE PREGNANCY

Maternal MS leads to an increase in the mass and transport surface of the placenta, which can contribute to fetal macrosomia [44, 45]. In a meta-analysis, Kubler et al. identified a linear correlation between the placental volume in the first trimester of pregnancy and the body weight of the newborn [44]. However, there is also a controversial opinion that the placental mass is inversely proportional to its effectiveness due to changes in the vascular network structure [46].

Sureshchandra et al. and Daskalakis et al. demonstrated a delay in the maturation of the villous chorion in the placenta of women with obesity, which manifested as a reduction in the number of villi [47, 48]. Furthermore, the villi were immature, which resulted in a significant decrease in the effectiveness of the placenta [48]. Such changes can lead to fetal growth retardation and the birth of children who are small for gestational age.

ENDOCRINE FUNCTION OF THE PLACENTA

The placenta performs several endocrine functions throughout pregnancy, including the synthesis of hormones in the syncytiotrophoblast cell layer such as human chorionic gonadotropin, placental lactogen (PL), and placental growth hormone [49]. Maternal MS reportedly leads to a decrease in the levels of PL RNA and placental growth hormone [50, 51]. This disruption in the regulation of PL synthesis can affect the fetus' metabolic status in adulthood [51].

To study the complications caused by PL deficiency, Fleenor et al. created a mouse model that lacked PL receptors. The parameters of the mouse model were compared with those of healthy mice. They determined that the offspring of PL receptor-lacking mice exhibited a lower body weight and higher blood glucose concentration than healthy mice on the seventh day of life. During the first weeks of life, the receptor-lacking mice also experienced growth retardation and developed hypoglycemia. Over the next months of follow-up, the receptor-lacking mice developed obesity, hyperleptinemia, fasting hyperglycemia, and insulin resistance [52]. These results indicate that PL may be involved in the regulation of fetal growth and development of its metabolic status.

NUTRIENT TRANSPORT IN THE PLACENTA

Placental transport proteins localized in the syncytiotrophoblast are responsible for the selective transport of fatty acids, glucose, oxygen, amino acids, and vitamins [53, 54]. MS is associated with a decrease in expression of transport proteins, which may affect nutrient supply to the fetus.

The placenta regulates the delivery of fatty acids to the developing fetus via lipid transportation and metabolism [54, 55]. The maternal surface of the syncytiotrophoblast contains endothelial lipase, which hydrolyzes triglycerides to release fatty acids [54–56]. Maternal dyslipidemia and hyperglycemia contribute to decreased fatty acid oxidation in the placental mitochondria [56–58]. Furthermore, both obesity and gestational diabetes mellitus are independently associated with a decrease in the expression of endothelial lipase messenger RNA and its membrane transport proteins FATP1 and FATP4 [59].

The human placenta comprises three isoforms of the glucose transporter, namely GLUT1, GLUT3, and GLUT4 [58, 59]. GLUT1 expression in the basement membrane increases in obese women who give birth to macrosomic infants, and it positively correlates with the birth weight of the infants [57–59]. Similar results have been observed in female patients with gestational diabetes mellitus, in whom GLUT1 expression in the placental basement membrane increases by approximately two times the expression level in normoglycemic women [60].

Controversially, Nogues et al. demonstrated that the RNA expression of GLUT1 messenger significantly reduces only on the embryonic side of the placenta in women with MS. Furthermore, they proposed that the placenta can adapt the expression of its carrier genes to balance the excess nutrient need of the fetus [61].

CONCLUSION

MS affects the formation and functioning of the placenta at the molecular, genetic, and cellular levels. It disrupts the intracellular processes in the trophoblast, its invasion, and the oxygen–transport function of the placenta. These changes are associated with complications such as placental insufficiency, preeclampsia, fetal growth retardation, macrosomia, antenatal fetal death, and development of metabolic disorders in children in the long-term.

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ADDITIONAL INFORMATION

Authors' contribution. A.Ak.O. — conceptualization, supervision, project administration; E.V.M. — formal analysis, writing — original draft; I.V.B. — methodology, writing – review & editing; A.Ag.O. — investigation, visualization; Zh.Zh.S. — writing — original draft, visualization.

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