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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Metabolism of the mother, placenta, and fetus in diabetes

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SUMMARY
Metabolic changes occur due to the effects of placental hormones such as human chorionic gonadotropin and human placental lactogen in normal pregnancies. These effects enable the development of insulin resistance among all pregnant women, significantly pronounced in the third trimester. In pregnancies complicated by pre-gestational or gestational diabetes mellitus, these changes are more intensive as they affect the fetoplacental unit. In pregnancies complicated by diabetes the increased number of placental macrophages leads to the increased production of different cytokines which include leptin, tumor necrosis factor alpha, and interleukins. This review addresses placental vascular changes that lead to adverse pregnancy outcomes, along with the effects of the maternal hyperglycemia and fetal hyperinsulinemia.
Keywords: pregnancy; pre-gestational diabetes; gestational diabetes; insulin resistance; placental structural abnormalities

INTRODUCTION

Physiological pregnancy is associated with numerous physiological changes, among which there are changes in metabolism, in biochemical parameters, immunological and hematological systems [1]. Among the metabolic changes, the insulin resistance is pronounced, resulting in changes in the glucose utilization [1]. Insulin secretion increases in healthy pregnant women and, as the pregnancy progresses, its values are gradually elevated before meals [2]. Insulin efficiency decreases by 50–70% in the third trimester, which is evidence of increased insulin resistance in healthy pregnant women. Insulin resistance during pregnancy increases in parallel with the growth of the fetoplacental unit and the level of placental hormones (human placental lactogen, progesterone, cortisol, etc.). This adaptation helps the utilization of carbohydrates by the growing foetus and stimulates the use of fats for energy for the healthy pregnant woman [1].

HORMONES AND INSULIN RESISTANCE AND INSULIN SENSITIVITY

The hormones contributing to the increase in insulin resistance during pregnancy are estrogen, progesterone, human placental lactogen [1]. Some other factors, such as cortisol, tumor necrosis factor alpha (TNF-α), and interleukins can interfere with the insulin pathway and be associated with insulin resistance during pregnancy [1]. However, these adaptations are exhausted in pregnancies with diabetes and insulin resistance in diabetes is associated with the changes in the fetal and placental development.

It is worth noting that certain hormones improve insulin sensitivity, including human chorionic gonadotropin (HCG), produced by the syncytiotrophoblast. Its effects are based on slowing down the enzymatic breakdown of insulin in the placenta or increasing peripheral sensitivity to insulin, both among healthy pregnant women and women with diabetes, so much so that the need for insulin is lowered in the first trimester among women with pregestational diabetes [3, 4]. Higher HCG levels in early pregnancy are associated with lower likelihood for development of gestational diabetes later in pregnancy [3].

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BLOOD GLUCOSE AND PLACENTA

Changes in the blood glucose levels in pregnancy with diabetes are associated with changes in the structure and function of the placenta. These changes include the increase in surface area of the villi, thickening of the trophoblastic basement membrane, and the changes in the collagen structure of the basement membrane, with collagen IV predominance [5]. In contrast, the basement membrane of the endothelium cells is thinner in pregnancies with diabetes [5].

Both metabolic and endocrine functions of the physiological placenta are interrupted in the pregnancy with diabetes as the increased number of placental macrophages leads to the increased production of different cytokines, which include leptin, TNF-α, and interleukins [5]. Additionally, the changes in the placental capillary network, such as proliferation of the capillary network, are also described [5].

Along with the increase in fetal weight, there is an increase in the placental weight in the pregnancies with diabetes and the increase in the placental-to-fetal weight ratio, meaning that the weight increase in more pronounced in the placenta than in fetus [6]. The placental growth can be associated with fetal insulinemia as well, as it was observed among women with diabetes and good glycemic control as well [7, 8].

The thickening of the trophoblast basement membrane seems to have more significant effect on the diffusion of antipyrine and L-glucose compared to the effect of the thinning of the endothelial basement membrane and their diffusion is decreased in pregnancies with diabetes [7–10]. This further leads to fetal hypoxia that stimulates the angiogenesis. Angiogenesis is stimulated by hypoxia through the stimulation of the secretion of factors like fibroblast growth factor type 2, vascular endothelial growth factor, and placenta growth factor [7–10].

The diabetes in pregnancy is a well known factor associated with a decreases in placental blood flow, including both uteroplacental and cord blood flow. Different mechanisms have been described to cause these changes; however, most described are changes in secretion of thromboxane and prostacyclin, and the increase in their vasoconstrictor activity. Acute atherosis of uteroplacental blood vessels can lead to obstruction and thus to impaired blood flow through the intervillous space, mainly due to the increase in the parenchymal tissue of the villi and a reduction in the volume of the intervillous space. Some other factors can also contribute, such as the changes in the production of nitric oxide [7, 8, 11].

GLUT 1 and GLUT 3 glucose transporters mediate the glucose transport through the placenta, and they are in the syncytiotrophoblast and endothelium. Among women with diabetes, studies have found a decrease in the number of GLUT 1 transporters, which is considered an evolutionary adaptation with the aim of protecting the fetus from the excessive maternal glucose. *In vitro* studies have shown the reduction of the level of GLUT 1 ribonucleic acid in placenta due to hyperglycemia, which could indicate that in pregnant women with diabetes there is reduced regulation and control over the expression and activity of glucose transporters (GLUT 1) [12]. These effects seem to be the more permanent and persist despite the strict glycemic regulation after the diagnosis of gestational diabetes has been established [12].

This is why it is very important that in the modern approach to monitoring pregnancy with diabetes, the mother's glycemia is regulated as accurately as possible and control of the development of the fetus is established early and continuously. Glycosylated hemoglobin values need to be normalized before conception, as once the arrangement and the quantity of glucose transporters is created, no clinical monitoring or intervention methods available can change it [13, 14].

Additionally, placenta in women with diabetes has the increased glycogen levels, which is not associated with either glucose nor insulin in the trophoblast, which indicates that the synthesis of glycogen is being conducted in cells other than trophoblast. The histochemical analyses showed that glycogen is located predominantly around the fetoplacental blood vessels, especially in type 1 diabetes. Since the endothelium is rich in glucose transporters, primarily the high-affinity glucose transporter GLUT3, endothelial cells have a molecular mechanism by which they withdraw glucose from the fetal circulation and store it in the form of glycogen. Regarding the return flow of glucose from the fetal circulation to the placenta, it can be assumed that the placenta could have a buffer function for excess glucose, and thus the ability to protect the fetus from glucose overload. This phenomenon is not fully understood, but it may explain why sometimes in circumstances of moderate maternal hyperglycemia the fetus is of normal weight, while in others the fetus is macrosomic [15, 16].

In pregnancies with diabetes, the third-trimester fetal hyperinsulinemia is common even among the eutrophic fetuses, as it was shown that there is a significantly higher difference in the blood glucose concentration between the umbilical vein and umbilical artery, suggesting the significant glucose utilization by the fetus [17]. Importantly, fetal hyperinsulinemia is associated with the higher likelihood for the intrauterine fetal death, due to impaired metabolism and hypoxia and consequential hyperplasia of the beta cells in the fetal pancreas. The beta cells hyperplasia is associated with the well-described neonatal complication among infants of diabetic mothers – hypoglycemia. However, it can also be associated with the metabolic acidosis in the full-term neonates, and the risks of prolongation of pregnancy after the 38th week of gestation. Although some authors suggest individual approach to each patient with diabetes in pregnancy in terms of planning and timing of delivery, based on individual maternal and fetal data [18, 19], the diabetes in pregnancy is still one of the leading causes associated with the late pregnancy loss and stillbirth [20].

CONCLUSION

Placental hormones such as HCG and human placental lactogen cause complex changes in the metabolism of carbohydrates during normal pregnancies. Fetoplacental unit is mostly affected by those changes in diabetic pregnancies. The mechanism behind them lays in placental vascular modifications directed by different cytokines such as TNF-α and leptin, as well as up- and down-regulation of various GLUT transporters. Maternal hyperglycemia and fetal hyperinsulinemia lead to adverse pregnancy outcomes.

Conflict of interest: None declared.

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Метаболизам мајке, плаценте и фетуса код дијабетеса

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САЖЕТАК

Метаболичке промене настају услед деловања плацентних хормона као што су хумани хорионски гонадотропин и хумани плацентни лактоген у физиолошким трудноћама. Дејство ових хормона омогућава развој инсулинске резистенције код свих трудница, која је најизраженија током трећег триместра трудноће. У трудноћама компликованим прегестацијским или гестацијским дијабетесом мелитусом ове промене су интензивније и утичу на фетоплацентарну јединицу. Повећан број макрофага у плаценти доводи до повећане продукције цитокина који укључују лептин, фактор некрозе тумора алфа и интерлеукини. Овај прегледни рад се бави васкуларним променама плаценте које доводе до неповољних исхода трудноће, као и утицајем који имају хипергликемија мајке и хиперинсулинемија фетуса у дијабетесу мелитусу.

Кључне речи: трудноћа; прегестацијски дијабетес мелитус; гестацијски дијабетес мелитус; инсулинска резистенција; структурне абнормалности плаценте