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Metabolism of the mother, placenta and fetus in diabetes

Метаболизам мајке, плаценте и фетуса код дијабетеса

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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 that is them ost significantly pronounced in the third trimester. In pregnancies complicated with pre-gestational or gestational diabetes mellitus these changes are more intensive as they affect fetoplacental unit. In pregnancies complicated with diabetes the increased number of placental macrophages leads to the increased production of different cytokines which include leptin, tumour 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

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 дијабетес 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 утицају који имају хипергликемија мајке и хиперинсулинемија фетуса у дијабетес мелитусу.

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

INTRODUCTION

Physiological pregnancy is associated with numerous physiological changes, among which there are changes in metabolism, in biochemical parameters, immunological and haematological 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 its values are elevated in healthy pregnant women before meals, progressively as the pregnancy progresses. [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 (hPL, 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 oestrogen, progesterone, human placental lactogen [1]. Some other factors, such as cortisol, tumour necrosis factor alpha and interleukins can interfere with the insulin pathway and be associated with insulin resistance during pregnancy [1]. However, these adaptations are exhausted in the pregnancies with diabetes and the insulin resistance in diabetes is associated with the changes in the foetal 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 the 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, as 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 GDM later in pregnancy [5].

Blood glucose and placenta

Changes in the blood glucose levels in the pregnancy with diabetes are associated with the 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 [6]. On the contrary, the basement membrane of the endothelium cells is thinner in pregnancies with diabetes [6].

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, tumour necrosis factor alpha and interleukins [6]. Additionally, the changes in the placental capillary network, such as proliferation of the capillary network are also described [6].

Along with the increase in foetal weight, there is increase in the placental weight in the pregnancies with diabetes and the increase in the placental-to-foetal weight ratio, meaning that the weight increase is more pronounced in the placenta than in foetus [7]. The placental growth can be associated with foetal insulinemia as well, as it was observed among women with diabetes and good glycemic control as well [8, 9].

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 [8-11]. This further leads to foetal hypoxia that stimulates the angiogenesis. Angiogenesis is stimulated by hypoxia through the stimulation of the secretion of factors like FGF-2, VEGF and PLGF [8–11].

The diabetes in pregnancy is well known factor associated with the 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 atherosclerosis 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 [8, 9, 12].

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 the decrease in number of GLUT 1 transporters, which is considered an evolutionary adaptation with aim to protect the foetus from the excessive maternal glucose. The *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 a reduced regulation and control over the expression and activity of glucose transporters (GLUT 1) [13]. These effects seem to be the more permanent and persist despite the strict glycemic regulation after the diagnosis of gestational diabetes has been established [13].

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 foetus 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 [14, 15].

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 foetal circulation and store it in the form of glycogen. Regarding the return flow of glucose from the foetal 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 foetus from glucose overload. This phenomenon is not fully understood, but it may explain why sometimes in circumstances of moderate maternal hyperglycaemia the foetus is of normal weight, while in others the foetus is macrosomic [16, 17].

In pregnancy 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 [18]. 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 [19, 20], the diabetes in pregnancy is still one of the leading causes associated with the late pregnancy loss and stillbirth [21].

CONCLUSION

Placental hormones such as hCG and hPL 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.

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REFERENCES

1. Hernandez TL, Friedman JE, Barbour LA. Insulin Resistance in Pregnancy: Implications for Mother and Offspring BT - Insulin Resistance: Childhood Precursors of Adult Disease. In: Zeitler PS, Nadeau KJ, editors. Cham: Springer International Publishing; 2020. p. 67–94. Available from: https://doi.org/10.1007/978-3-030-25057-7_5
2. Papachatzopoulou E, Chatzakis C, Lambrinouadaki I, Panoulis K, Dinas K, Vlahos N, Sotiriadis A, Eleftheriades M. Abnormal fasting, post-load or combined glucose values on oral glucose tolerance test and pregnancy outcomes in women with gestational diabetes mellitus. *Diabetes Res Clin Pract.* 2020 Mar; 161:108048. doi: 10.1016/j.diabres.2020.108048. Epub 2020 Feb 3. PMID: 32027925
3. Liu Y, Guo F, Maraka S, Zhang Y, Zhang C, Korevaar TIM, Fan J. Associations between Human Chorionic Gonadotropin, Maternal Free Thyroxine, and Gestational Diabetes Mellitus. *Thyroid.* 2021 Aug;31(8):1282-1288. doi: 10.1089/thy.2020.0920. Epub 2021 Mar 22. PMID: 33619987.
4. Yanachkova VE, Staynova R, Bochev I, Kamenov Z. Potential role of biochemical placentation markers - pregnancy associated plasma protein-A and human chorionic gonadotropin for early gestational diabetes screening - a pilot study. *Ginek Pol.* 2021 Sep 20. doi: 10.5603/GP.a2021.0129. Epub ahead of print. PMID: 34541644.
5. Liu, Y.; Guo, F.; Maraka, S.; Zhang, Y.; Zhang, C.; Korevaar, T.I.M.; Fan, J. Associations between Human Chorionic Gonadotropin, Maternal Free Thyroxine, and Gestational Diabetes Mellitus. *Thyroid* 2021, 31, 1282–1288, doi:10.1089/thy.2020.0920. PMID: 33619987
6. Vambergue, A.; Fajardy, I. Consequences of Gestational and Pregestational Diabetes on Placental Function and Birth Weight. *World J. Diabetes* 2011, 2, 196, doi:10.4239/wjd.v2.i11.196 PMID: 22087356
7. Ehlers E, Talton OO, Schust DJ, Schulz LC. Placental structural abnormalities in gestational diabetes and when they develop: A scoping review. *Placenta* [Internet]. 2021;116:58–66. Available from: <https://doi.org/10.1016/j.placenta.2021.04.005> PMID: 33958235 PMCID: PMC9295324 DOI: 10.1016/j.placenta.2021.04.005
8. Hiden U, Lang I, Ghaffari-Tabrizi N, Gauster M, Lang U, Desoye G. Insulin action on the human placental endothelium in normal and diabetic pregnancy. *Curr Vasc Pharmacol.* 2009 Oct;7(4):460-6. doi: 10.2174/157016109789043973. PMID: 19485889.
9. Atallah R, Gindlhuber J, Platzer W, Bärnthaler T, Tatzl E, Toller W, et al. *Sucnr1* is expressed in human placenta and mediates angiogenesis: Significance in gestational diabetes. *Int J Mol Sci.* 2021;22(21):1–19. PMID: 34769478 PMCID: PMC8585094 DOI: 10.3390/ijms222112048
10. Knöfler M, Haider S, Saleh L, Pollheimer J, Gamage TKJB, James J. Human placenta and trophoblast development: key molecular mechanisms and model systems. *Cell Mol Life Sci.* 2019 Sep;76(18):3479-3496. doi: 10.1007/s00018-019-03104-6. Epub 2019 May 3. PMID: 31049600; PMCID: PMC6697717.
11. Villota SD, Toledo-Rodriguez M, Leach L. Compromised barrier integrity of human feto-placental vessels from gestational diabetic pregnancies is related to downregulation of occludin expression. *Diabetologia.* 2021;64(1):195-210. doi: 10.1007/s00125-020-05290-6. Epub 2020 Oct 1. PMID: 33001231; PMCID: PMC7716932.
12. Dorenkamp M, Müller JP, Shanmuganathan KS, Schulten H, Müller N, Löffler I, Müller UA, Wolf G, Böhmer FD, Godfrey R, Waltenberger J. Hyperglycaemia-induced methylglyoxal accumulation potentiates VEGF resistance of diabetic monocytes through the aberrant activation of tyrosine phosphatase SHP-2/SRC kinase signalling axis. *Sci Rep.* 2018 Oct 2;8(1):14684. doi: 10.1038/s41598-018-33014-9. PMID: 30279491; PMCID: PMC6168515..
13. Borges MH, Pullockaran J, Catalano PM, Baumann MU, Zamudio S, Illsley NP. Human placental GLUT1 glucose transporter expression and the fetal insulin-like growth factor axis in pregnancies complicated by diabetes. *Biochim Biophys Acta Mol Basis Dis.* 2019 Sep 1;1865(9):2411-2419. doi: 10.1016/j.bbadis.2019.06.002. Epub 2019 Jun 5. PMID: 31175930; PMCID: PMC7122587
14. Poo ZX, Wright A, Ruochen D, Singh R. Optimal first trimester HbA1c threshold to identify Singaporean women at risk of gestational diabetes mellitus and adverse pregnancy outcomes: A pilot study. *Obstet Med.* 2019 Jun;12(2):79-84. doi: 10.1177/1753495X18795984. Epub 2018 Nov 15. PMID: 31217812; PMCID: PMC6560840.
15. Bernea E, Uyy E, Mihai D-A, Ceausu I, Ionescu tirgoviste C, Suica V-I, et al. New born macrosomia in gestational diabetes mellitus. *Exp Ther Med.* 2022;24(6):1–12. PMID: 36382102 PMCID: PMC9634345 DOI: 10.3892/etm.2022.11646
16. Sibiak R, Ozegowska K, Wender-Ozegowska E, Gutaj P, Mozdziak P, Kempisty B. Fetomaternal Expression of Glucose Transporters (GLUTs)-Biochemical, Cellular and Clinical Aspects. *Nutrients.* 2022 May 12;14(10):2025. doi: 10.3390/nu14102025. PMID: 35631166; PMCID: PMC9146575
17. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental growth and metabolism. *Biochim Biophys Acta - Mol Basis Dis.* 2020;1866(2):165359. Available from: <https://doi.org/10.1016/j.bbadis.2018.12.010>. doi: 10.1016/j.bbadis.2018.12.010.. PMID: 30593896; PMCID: PMC6594918.

18. Sharma AK, Singh S, Singh H, Mahajan D, Kolli P, Mandadapu G, Kumar B, Kumar D, Kumar S, Jena MK. Deep Insight of the Pathophysiology of Gestational Diabetes Mellitus. *Cells*. 2022 Aug 28;11(17):2672. doi: 10.3390/cells11172672. PMID: 36078079; PMCID: PMC9455072.
19. Metcalfe A, Hutcheon JA, Sabr Y, Lyons J, Burrows J, Donovan LE, Joseph KS. Timing of delivery in women with diabetes: A population-based study. *Acta Obstet Gynecol Scand*. 2020 Mar;99(3):341-349. doi: 10.1111/aogs.13761. Epub 2019 Dec 8. PMID: 31654401; PMCID: PMC7065101.
20. Maso G, Piccoli M, Parolin S, Restaino S, Alberico S. Diabetes in pregnancy: timing and mode of delivery. *Curr Diab Rep*. 2014 Jul;14(7):506. doi: 10.1007/s11892-014-0506-0. PMID: 24811363.
21. Management of Stillbirth: Obstetric Care Consensus No. 10. *Obstet Gynecol*. 2020 Mar;135(3):e110-e132. doi: 10.1097/AOG.0000000000003719. PMID: 32080052.

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