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# Pathophysiology of Placenta and Fetus in Diabetes Mellitus

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**ABSTRACT**

Placental transport of substances in conditions of diabetes mellitus The placenta ensures the growth and development of the fetus through the exchange of a wide range of substances with the mother's body. Uteroplacental and fetoplacental blood flow perform an important function for the delivery and removal of metabolic products. The placental barrier is represented by the membrane of the microvilli of the syncytiotrophoblast, which is in direct contact with maternal blood in the interstitial space [1]. This structure of the placenta increases the exchange surface by 7 times.

***KEYWORDS:*** *Approximately 5-10% of the syncytiotrophoblast surface consists of epithelial plates, and 90% is occupied by microvilli*

There are special areas through which various metabolites are transported to the fetus. In the area of these sites, the syncytio-trophoblast is very thin, it lacks cytoplasmic organelles, basal plates of the trophoblast, and the endothelium of fetoplacental vessels is a single complex. This structure makes it possible to reduce the thickness of the diffusion surface between the maternal and fetal blood circulation [1]. Invasion of the cytotrophoblast into the decidual membrane and spiral uterine arteries leads to the remodeling of the latter into vessels of low resistance. Due to the absence of vascular innervation in the fetoplacental complex, their tone depends on the production of local vascular-stimulating signaling molecules (eicosanoids, endothelin-1) and nitric oxide (NO). Any violation of this process leads to a limited inflow of maternal blood into the interstitial space [1]. In mammals, the factor determining intrauterine fetal growth is the trans-placental transport of substances, which is provided by diffusion and numerous systems of various transporters [2]. On the surface of the placenta there are carrier proteins for glucose, lactate, amino acids (AK) and fatty acids (LC). The transfer of these substances depends on the concentration gradient between the blood flow of the mother and fetus. In addition, the placenta is actively involved in the storage and further release of various substances into the fetal plasma. These processes depend on the unique location of carriers on both surfaces of the trophoblast membrane. It was found that the placenta consumes a large amount of nutrients, thereby creating a transplacental concentration gradient for glucose, AK, LC and lipids. These reserves further create a unique metabolic environment in fetal plasma [3]. In mammals, the factor determining intrauterine fetal growth is the trans-placental transport of substances, which is provided by diffusion and numerous systems of various transporters [2]. On the surface of the placenta there are carrier proteins for glucose, lactate, amino acids (AK) and fatty acids (LC). The transfer of these substances depends on the concentration gradient between the blood flow of the mother and fetus. In addition, the placenta is actively involved in the storage and further release of various substances into the fetal plasma. These processes depend on the unique location of carriers on both surfaces of the trophoblast membrane. It was found that the placenta consumes a large amount of nutrients, thereby creating a transplacental concentration gradient for glucose, AK, LC and lipids. These reserves further create a unique metabolic environment in fetal plasma [3]. The transplacental transfer of substances is determined by various parameters, such as the concentration gradient between mother and fetus, blood flow rate, total exchange surface and membrane thickness. The most significant mechanisms determining glucose transfer are the concentration gradient between mother and fetus, as well as the blood flow rate [4]. The increase in the transplacental transport of substances during the entire gestation period is due to the growth of the placenta. The growth of the placenta and its development (size, morphology, number of carriers) are regulated by such embedded genes as the Igf2-H complex [5]. The activity of these genes varies depending on their number. The excessive presence of alleles of the paternal Igf2 gene in comparison with the maternal one leads to an increase in the size of the placenta and fetus. The activity of genes is also subjected to epigenetic programming depending on the influence of the environment on their expression. For example, DNA methylation leads to a restriction of Igf2 activity, which causes a smaller placenta and fetal growth retardation syndrome. The interaction between the placenta and the fetus, in which certain substrates are transported directly to the fetus and then converted into products of both fetal and placental metabolism, also provides a unique environment with specific exchange pathways [6]. Glucose transport. The system of carriers of the GLUT family Nutrition of the fetus almost completely depends on the mother's glucose coming to it through the placenta. Fetus's own glucose production in the early stages of pregnancy is at a minimum level, since his own gluconeogenesis is not yet sufficiently developed. The glucose concentration gradient between mother and fetus is most pronounced in the first trimester of pregnancy. The amount of glucose consumed by the fetus is 38-43 mmol/l, while in a woman its concentration is significantly higher — 100 mmol/l [7]. These values increase in the presence of hyperinsulinism in the fetus due to chronic hyperglycemia in diabetes mellitus (DM) in the mother [8]. It has been established that excessive transplacental glucose transfer is a key factor in fetal development disorders during pregnancy burdened with DM [6]. In most cases, the transplacental transfer of glucose in the direction from the mother to the fetus occurs due to a decrease in the concentration gradient by means of a type 1 carrier protein (GLUT1). Type 8 carrier protein (GLUT8) is also ubiquitously detected in the placenta throughout pregnancy, but its expression is reduced in DM. Accordingly, the role of this transporter in glucose utilization is less significant. In addition, high-affinity GLUT3 and insulin-dependent proteins GLUT4 and GLUT12 were found

in the placenta [9]. Their contribution to the transport of glucose from mother to fetus is insignificant. These mediators play an important role in the reverse transport of glucose from the fetus to the placenta and when capturing it into the surrounding cells. Basically, glucose transport from the mother to the fetus occurs through GLUT1. GLUT1 is located both on the basement membrane of both surfaces of the syncytiotrophoblast and on endotheliocytes and amnion cells, which makes it possible to regulate bilateral glucose transfer from mother to fetus. The transport system has a high saturation capacity at a glucose level of more than 20 mmol/l. This system is designed for the rapid transport of glucose from the maternal to the fetal bloodstream. The activity of GLUT1 located on the trophoblast depends on the glucose level: it increases with hypoglycemia and decreases with hyperglycemia. The decrease in GLUT1 functionality on the trophoblast surface is explained by a decrease in GLUT1 transcription and an increase in its translation [11]. Studies have shown that a decrease in the content of GLUT1 on the surface of these cells changes glucose uptake only at its concentration of about 15 mmol/L [12]. In addition to glucose, ketone bodies and insulin also have no less effect on the activity of GLUT1. The glucose transporter GLUT3 is located in the vessels of the fetoplacental complex. In an experimental study on sheep, it was shown that glucose uptake by the GLUT3 transporter is 40% of the total uptake by the end of pregnancy [13]. GLUT3 has a greater affinity for glucose than GLUT1. Localized on the membrane and surface of the syncytiotrophoblast, this messenger actively regulates glucose transport from mother to fetus and reverses. Other glucose carriers of the GLUT2 and GLUT4 families are mainly localized in the placental stroma. It has been shown that the above-mentioned transporters are able to capture glucose from the fetal bloodstream into endothelial cells, where it is subsequently stored as glycogen [11]. Thus, excess glycogen deposits expressed in the placenta in maternal DM may be the result of increased glucose uptake from the fetoplacental bloodstream [14] Fetal insulin, influencing GLUT4 and GLUT2, also stimulates glucose uptake by endothelial cells. The amount of accumulated placental and fetal glycogen may decrease when there is an urgent need for its use by the fetus (with prolonged labor, hypoxia). In this case, lactate acts as a reserve metabolic product in the fetus [15]. In vitro studies have shown that changes in the concentration of glucose transporters correlate with their throughput [16]. In type 1 diabetes, there is an increased expression of GLUT1 on the basement membrane compared to the surface of syncytiotrophoblast microvilli [3]. No such features were noted in gestational diabetes mellitus (GSD) [17]. There were no distinctive features of expression in the placenta of other glucose transporters (GLUT3, GLUT4) in maternal diabetes [18]. As for the activity of these messengers, with type 1 diabetes, GLUT1 activity decreases, but GLUT3 activity increases [13]. This helps to maintain normal fetal homeostasis in adverse conditions. In the presence of GSD, the expression of glucose transporters differs depending on the degree of compensation of carbohydrate metabolism. In women who received diet therapy, the content of transporters in the placenta does not change, whereas when using insulin therapy, it increases [19]. It has been experimentally established that the borderline value of the glycemic level, which determines violations of GLUT1 expression, is 8 mmol/L. These changes are based not only on the level of glycemia, but also ultrastructural changes in the placenta: enlarged syncytiotrophoblast surface and thickening of the basement membrane [19]. Despite a large number of studies, there is still insufficient data on the regulation of placental glucose transporters in different types of diabetes mellitus [20]. Amino acid transport Among maternal plasma proteins, only IgG and albumin are able to overcome the transplacental barrier in an unchanged amount. Maternal amino acids serve as the main source of nitrogen for fetoplacental tissues. The content of most amino acids in the placenta exceeds their concentrations in the maternal and fetal bloodstream, since it synthesizes AK itself. This explains the increased content of amino acids in syncytiotrophoblast [20]. High levels of AK are usually associated with protein synthesis and are characteristic of fast-growing tissues. The penetration of AK into the cell occurs due to conveyor systems. For neutral, positively and negatively charged AK, there are their own classes of these systems [21]. Maternal and fetal plasma membranes include general and special amino acid transport systems. Currently, there is no clear information about the spatial location of AK carriers on the microvilli and the basement membrane of the syncytiotrophoblast. In addition, transport and transport systems on cells and outside the trophoblast have not yet been studied. It is known that the endothelium provides transport of AK not only from the mother to the fetus, but also in the opposite direction [22]. As the gestation period increases, the fetus' need for protein synthesis increases. An adequate nitrogen balance in fetuses is maintained by increasing the transplacental transfer of AK. This enhanced transport is facilitated by an increase in placental perfusion, the metabolic surface of the trophoblast membranes, the concentration of transporters on the trophoblast and the potential difference of its membranes [21]. Due to the dominant effect of active AK transport, small differences in the degree of uterine and umbilical cord blood flow do not affect the capture and transport of AK through the placenta in any way. Some AK transport systems increase their activity with increasing gestation period [23]. Changes in the concentration of AK vectors and their transport capacity are regulated at the local level. For example, the activity of placental transporters and the associated transfer of AK are reduced in pregnant rats that are on a low-protein diet. This helps to reduce the growth rate of the fetus. Similar data were obtained in an experiment on sheep, in which exposure to adverse factors disrupted the system of AK carriers and the content of the latter in the fetal blood [24]. The shift of the amino acid transport vector from the mother to the fetus is facilitated by an increase in the trans-port activity of both the basement membrane and the microvilli membrane. Amino acids are concentrated in the intracellular matrix of the trophoblast by Na/K+-adenosine triphosphatase and H+-dependent transporter proteins on the maternal surface of microvilli membranes, and then transferred to the fetal plasma. The plasma content of these substances ranges from 1.0 to 5.0 mmol/l. The activity of this transport process decreases under conditions of hypoxia and hypoglycemia. Protein molecules the size of albumin or gamma globulin pass through the placental barrier by pinocytosis, the activity of which increases with increasing gestational age. As an experimental study has shown, the intake of these proteins does not provide much energy value for the fetus [14]. The total total absorption of amino acids in the fetus can be up to 30-40% of the carbon requirement and 100% to provide nitrogen [26]. There are several papers that report that the ability to maintain normal levels of certain amino acids in fetal plasma is impaired during pregnancy complicated by

diabetes [6]. However, there is no clear data on the features of the plasma content of amino acids in various types of DM. In pregnant rodents that are experimental models of type 1 diabetes mellitus with varying degrees of severity (against the background of streptozotocin administration), the content of most AK in the fetus is reduced [27]. This also applies to non-protein amino acids, such as taurine and gamma-aminobituric acid, which regulates the synthesis of fetal insulin [28]. Interestingly, the alanine transporter system is reduced in pregnant women with DM who have fetal macrosomia [29]. During pregnancy against the background of GSD, the content of some amino acids (methionine, iso-leucine, leucine, phenylalanine, alanine, proline) is increased in the fetal, but not changed in the maternal bloodstream [20]. It was found that the expression of AK and their carriers is well visualized on the plasma membrane of syncytiotrophoblast vessels. On the other hand, there are data confirming the low level of some amino acids in the fetal plasma during GSD on insulin therapy [30]. Interestingly, even short periods of metabolic disorders at an early stage of pregnancy with this type of diabetes can affect the growth of the placenta and its transport function throughout the rest of pregnancy [31].

Thus, various experimental models often contradict each other and there is no consensus on the effect of DM on placental carriers of AK and their content in fetal blood.

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