FEATURES OF GLUCOSE METABOLISM IN THE FETUS WITH DIABETES MELLITUS

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Abstract. *The main nutrients for the fetus are glucose and amino acids. Glucose, including the product of its metabolism lactate is the main energy substrate for the fetus, involved in maintaining basal metabolism, storing energy reserves necessary for protein synthesis and growth.*

Keywords: *glycemia, hypoinsulinemia.*

Amino acids provide both a structural basis for protein synthesis and an oxidizing substrate in energy production with a lack of glucose. Fatty acids are used by the fetus as structural components of membranes, as well as for the growth of adipose tissue. In humans, the oxidation of LC begins immediately after birth. This process occurs primarily in the fetus, in contrast to the oxidation of glucose. Hormonal regulation of metabolic substrates utilization and the effect of insulin and insulin-like dew factors (IGF) on the fetus are of secondary importance in providing nutritive substrates. With a decrease in the level of glycemia in the fetus, glucose consumption decreases directly proportionally [37]. In conditions of a short period of time, the oxygen consumption of the fetus remains at a level close to normal, which is ensured by the active reciprocal oxidation of other substrates, such as glycogen, lactate, amino acids, fatty acids and ketone bodies. With a longer period of lack of sufficient glucose intake (> 2 weeks), the consumption of oxygen by the fetus decreases by 25-30%. A decrease in the degree of oxygenation of fetuses with a prolonged nutrient deficiency reflects the dependence of a reduced level of protein synthesis and metabolites necessary for fetal growth. On the other hand, excessive delivery of nutrients to the fetus with DM in the mother leads to a decrease in the oxidation of amino acids. The level of glucose transport to the fetus, as well as the amount of its capture by the fetus, directly depends on the mother's glycemia [38]. The growth rate , glycogen deposition, and fat formation also depend on the amount of glucose received by the fetus and the degree of its capture. It is not surprising that the fetus from a mother suffering from diabetes has more liver, muscle glycogen and fat than from mothers with normal levels of glycemia. The processes of glucose accumulation in the uterus and fetus are directly regulated by the level of glycemia in the fetus [39]. A relatively high concentration of fetal glucose reduces the degree of its transplacental transfer in favor of its consumption by the placenta. At the same time, a relative decrease in the concentration of glucose in the fetus will limit the consumption of glucose by the fetus and increase the transport of glucose to the fetus. The glucose content in the fetal plasma is slightly reduced compared to the indicators of the mother. This increases the concentration gradient , providing a steady flow of glucose for the growing fetus. The maintenance of adequate transplacental transfer of glucose to the fetus is based on several physiological mechanisms. Firstly, enhanced cellular metabolism and growth of brain tissues that require an adequate level of glycemia. Secondly, an increase in the secretion of fetal insulin due to an increase in the number of pancreatic islets and beta cells of the pancreas.

Thirdly, increased growth of insulin-sensitive tissues (skeletal muscles, cardiac and adipose tissue). The dependence of the transplacental transport of glucose and its consumption by the uterine tissue and placenta were shown in studies on pregnant sheep who were injected into a state of chronic hypoglycemia. In this experiment, fetal gluconeogenesis increased, which maintained glucose consumption at the required level [40]. Thus, the production of glucose by the fetus can compensate for its lack in hypoglycemia of the mother. There are a number of factors that can affect the transplacental transport of glucose: placental surface area, insufficiency of the barrier between maternal and fetal blood flow, changes in the rate of uterine and fetal blood flow, imbalance of glucose consumption by the placenta. What role the thickness of the placenta plays in glucose transport has not yet been fully studied, but a direct correlation has been found between the gradient of glucose concentration in the arterial blood of the mother and fetus and the thickening of the fetoplacental membrane [39]. The rate of glucose uptake by fetal organs depends on the level of glycemia. It is still unknown to what extent the basal concentration of insulin affects the absorption of glucose by individual tissues and organs in the fetus. Fetal hyperglycemia stimulates increased insulin production by the fetus. In contrast to a sharp increase in the concentration of fetal insulin, which contributes to an increase in the rate of glucose utilization and a decrease in its concentration in plasma, a sudden decrease in the content of this hormone (with somatostatin infusion) does not affect the concentration of fetal glucose or the rate of its use in any way [41]. It is possible that a decrease in the concentration of insulin contributes to the gluconeogenesis of the fetus, which limits the transfer of glucose to the fetus from the placenta, thereby preventing an increase in the concentration of glucose in the fetal plasma. Nevertheless, in the experiment, chronic hypoinsulinemia in fetuses (with pancreatectomy or streptozotocin injections) leads to an increase in the level of glycemia in the fetus [42]. With hypoglycemia, as a result of a compensatory increase in fetal gluconeogenesis and a relative increase in glucose concentration , the degree of glucose transfer through the placenta and the synthesis of fetal insulin decreases. This confirms the somatotropic effect of insulin. GLUT1, being the main glucose transporter from plasma, is expressed in all fetal tissues. GLUT4 is found in the heart, adipose tissue and skeletal muscles. In the experiment on pregnant sheep, the concentration of GLUT1 increases under conditions of hypoglycemia and hypoinsulinemia in skeletal muscles and fat tissue, while remaining unchanged in nervous tissue. On the contrary, hyperglycemia causes a decrease in the concentration of GLUT1 in most tissues. GLUT4 activity is regulated by the level of glycemia in skeletal, muscular and adipose tissues of the fetus. In response to hyperglycemia, its concentration initially increases, and then decreases to a normal level [43]. A sharp increase in the insulin content leads to an increase in glucose consumption by the fetal skeletal and cardiac muscle tissue, while its plasma content decreases. Also, hyperinsulinemia in fetuses affects an increase in the concentration of both GLUT1 and GLUT4 [42]. Various studies of tissues, gestational age, levels of glycemia and insulinemia show a significant variability in the concentrations of glucose transporters during pregnancy [44]. Intrauterine secretion of insulin and insulin-like growth factors (IGF1s) In sheep fetuses, glucose- stimulated insulin secretion increases more than five -fold in the second half of pregnancy [45]. It is assumed that the same thing occurs in human fetuses. Such results were obtained during in vitro studies of pancreatic islets of human embryos and premature newborns [46]. Fetal insulin secretion can be characterized by the duration and structure of changes in glucose concentration in fetal plasma. Experiments on sheep fetuses have shown that persistent hyperglycemia actually reduces basal and glucose-

stimulated insulin secretion [47]. In addition , sensitivity to amino acids (arginine) decreases. Similar results were found in sheep embryos that received a course of bolus glucose administration [48]. Thus, the main reason for increased fetal insulin secretion is a change in the amount of glucose concentration in conditions of wave-like hyperglycemia. Fatty acids also stimulate insulin secretion in the fetus. Their concentration increases in pregnant women suffering from diabetes and in fetuses at a late gestation period [49]. Acute, chronic hypoglycemia, as well as a decrease in the concentration of amino acids in blood plasma, cause a decrease in insulin secretion by the fetus [40]. The mechanisms of this effect are unknown, but it is believed that glucose directly affects the insulin gene. Interestingly, hypoglycemia induced by insulin infusion in sheep fetuses at a late stage of pregnancy leads to an increase in the insulin content in fetal blood, but reduces the glucose-stimulated insulin secretion [49]. Abrupt changes in the concentration of IGF-1 in fetal plasma have practically no effect on glucose metabolism [47]. However, the effect of glucose is realized at the level of gene transcription by regulating the production of IGF-1 and IGF-2 [50]. Insulin also independently contributes to the synthesis of IGF-1. These data show that the transport of glucose into the cell and its concentration affect the production IGF-1 in the fetus. In turn, an increase in the concentration of IGF-1 and insulin in plasma can inhibit protein dissimilation. Thus, insulin and IGF-I indirectly increase the ability of glucose to stimulate AK synthesis and fetal growth. In sheep fetuses, a sharp increase in insulin concentration triggers an intracellular cascade of mitogen-dependent proteins, which can have a direct effect on protein synthesis, cell growth and division. A sudden increase in the concentration of insulin in sheep fetuses enhances the utilization of AK. These effects are short-lived, since the constant intake of insulin into the fetal plasma slightly increases tissue growth. However, the effect of glucose is realized at the level of gene transcription by regulating the production of IGF-1 and IGF-2 [50]. Insulin also independently contributes to the synthesis of IGF-1. These data show that the transport of glucose into the cell and its concentration affect the production IGF-1 in the fetus. In turn, an increase in the concentration of IGF-1 and insulin in plasma can inhibit protein dissimilation. Thus, insulin and IGF-I indirectly increase the ability of glucose to stimulate AK synthesis and fetal growth. In sheep fetuses, a sharp increase in insulin concentration triggers an intracellular cascade of mitogen-dependent proteins, which can have a direct effect on protein synthesis, cell growth and division. A sudden increase in the concentration of insulin in sheep fetuses enhances the utilization of AK. These effects are short-lived, since the constant intake of insulin into the fetal plasma slightly increases tissue growth. In addition, insulin has a positive effect on the production and storage of lipids in adipose tissue. Metabolism of amino acids in the fetus In the fetus, the rate of oxidation of AK occurs at a high level. This is confirmed by the following observations: amino acids are absorbed by the fetus in excess, there is a high degree of urea production in the fetus, the absorption of carbon-labeled amino acids stimulates the production and release of labeled carbon dioxide [29]. The amount of urea formed in sheep fruits depends by 25% on the absorbed nitrogen from amino acids. This value can also be up to 2% of the total carbon capture by the fruit and 6% of the amino acid content. The level of urea growth in the fetus exceeds neonatal and adult indicators, which indicates a relatively rapid exchange and oxidation of proteins [51]. The rate of receipt of several irreplaceable AK from the umbilical cord blood is much less than the rate of their use, which underscores the need for increased AK production in the fetus. The rate of protein synthesis also quite high. In an experimental study, the intensity of fractional protein synthesis and fractional growth in sheep fetuses were compared using two indicators of 14C-leucine and 14C-lysine at

different gestation periods [52]. A higher rate of protein synthesis was observed in the middle of pregnancy, which corresponds to a higher rate of glucose metabolism and utilization at this stage of gestation. Thus, protein synthesis relative to the amount of oxygen consumed is fairly constant from the middle of pregnancy to the moment of delivery. A decrease in the rate of protein synthesis during pregnancy is also associated with a change in body weight. For example, the mass of skeletal muscles grows faster than the mass of other organs in late pregnancy. The content of many anabolic and endocrine-paracrine factors, such as insulin, pituitary and placental growth hormone, placental lactogen, IGF, increases in late pregnancy. In parallel, the active synthesis of proteins takes place and the density of their receptors changes, which interact and regulate the action of various growth factors. These processes modulate their direct effects on cell division and growth. Skeletal muscles of sheep fruits absorb interchangeable and essential amino acids from the blood circulation, which reflects the relatively high rate of protein synthesis. In conditions of hyperinsulinemia, the consumption of most AK increases due to an increase in muscle musculature, which is manifested in a decrease in the rate of proteolysis compared to the rate of protein synthesis Protein synthesis depends more on the content of AK in the plasma than on the content of insulin. Glucose utilization also increases the protein balance in the fetus. At the same time, insulin and IGF-1 can effectively stimulate nitrogen growth during pregnancy [53]. Lipid metabolism in the fetus The transfer of lipids depends on the transport capacity of the placenta. The highest degree of transplacental transport is observed in the human hemochorial placenta [54]. Brown fat is the same for all mammalian species. It is necessary for postnatal thermogenesis. Many lipids in the fetus are qualitatively different from those found in the uterus and placenta. This implies an active placental metabolism of separate lipid substances. More complex metabolic pathways are lipoprotein dissociation caused by the activity of placental lipoprotein lipase, the absorption of triglycerides and their metabolism (including metabolic oxidation pathways, chain elongation, synthesis and interrelationships) and release in fetal plasma in the form of free fatty acids (FFA) or lipoproteins. The degree of absorption of free LC by the placenta and their transfer into the fetal bloodstream increases during pregnancy in response to increased activity of placental lipoprotein lipase, which, in turn, is stimulated by glucose and insulin. In addition, during pregnancy burdened with diabetes, the expression of the placental fatty acid transporter protein L–FAB increases [32]. All these changes contribute to a more intensive transfer of lipids through the placenta and as a result lead to fetal macrosomy in GSD. The scheme of absorption of lipids by the placenta, their metabolism, transport and metabolic interaction with the fetus. The amount of free fatty acids and the concentration of lipids in maternal plasma affect the development of fetal adipose tissue. A "larger" fetus develops in pregnant women who have an increased plasma content of LC and other lipids. This is especially true for women with GSD. In humans, the arteriovenous difference in the concentrations of LC in the umbilical cord blood means that the flow of non-esterified LC into the fetal bloodstream fills the need for the fetus in late pregnancy. Other studies show that up to 50% of fetal needs in LC are met by transplacental transfer. Apparently, there is a direct relationship between the permeability of the placenta to lipids, especially LC, and fetal obesity [54]. aAn increase in the concentration of insulin in the plasma promotes the activation of the transplacental transport of LC and lipids by increasing the utilization of LC in the fetus. An increase in the use of LC by fetal tissues reduces their concentration in plasma compared to that in the maternal bloodstream, thereby increasing the concentration gradient. Concentration The LC of the mother's venous blood is directly related to the concentrations of free fatty acids in the artery

and vein of the umbilical cord. In the placenta of guinea pigs in vitro, a decrease in the concentration of LC on the fetal side compared with the maternal side indirectly contributes to an increase in the transfer of LC through the placenta [35].

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