RESIDENT OF THE SECOND STAGE CLINICAL RESIDENCY OF THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY OF

Samarkand State Medical University
Tuychieva Nasiba
Doctor of ultrasound examination of Family Polyclinic No. 3 of the Ishtikhan Healthcare Department:

Vaydullayev Oltinbek
Scientific supervisor: G'oyibov Sanjar Salimovich

Ilm fan taraqqiyotida raqamli iqtisodiyot va zamonaviy ta'limning o'rni hamda rivojlanish omillari

Relevance

Gestational diabetes mellitus (GDM) is a disease characterized by hyperglycemia, first identified during pregnancy, but not meeting the criteria for "manifest" diabetes mellitus (DM) . Hyperglycemia during pregnancy is associated with the development of complications both from the mother's side and from the fetus, the most significant of which are preeclampsia, the birth of a large fetus, birth trauma, neonatal hypoglycemia. In addition, GDM is a risk factor for the development of obesity, type 2 diabetes mellitus (DM2), and cardiovascular diseases in mothers and offspring in the future.
The increasing number of pregnant women with carbohydrate metabolism disorders is associated with a steady increase in the incidence of diabetes and obesity in the general population, which emphasizes the close pathogenetic relationship between these pathologies . The exact prevalence of GDM remains unknown and can vary significantly depending on the diagnostic criteria used for screening. According to various statistical data, the prevalence of GDM worldwide ranges from 4 to 20% and has significant population differences . Differences in epidemiological indicators may be due to the diversity of the population groups studied. Thus, in countries with a low risk of developing GDM in pregnant women, such as Sweden, Australia, and the USA (excluding Native Americans and some other population groups), the prevalence of this pathology is less than 2%, about 9.5%, and 4.8%, respectively. Higher rates are observed in Middle Eastern countries: the United Arab Emirates (20.6%), Qatar (16.3%), Bahrain (13.5%), and Saudi Arabia (12.5%). Some developed countries, such as Canada (17.8%) and France (12.1%), also have higher rates of gestational carbohydrate metabolism disorders [6]. According to Russian authors, the incidence of gestational diabetes in Russia varies widely—from 1% to 14%, averaging approximately 7%—and depends significantly on diagnostic methods .

It is known that during normal pregnancy, many factors contribute to decreased insulin sensitivity, making this period a kind of test for pancreatic β-cells and a "diabetogenic factor" for the body . Changes in carbohydrate metabolism during pregnancy, which, according to some authors, is a "natural stress" for the body, can trigger the development of gestational diabetes mellitus (GDM) in women with an existing predisposition to diabetes . To more fully understand the mechanisms of GDM development, it is first necessary to become familiar with the physiological changes in metabolism, particularly carbohydrate metabolism, during pregnancy.

Physiological Changes in Carbohydrate Metabolism during Pregnancy

During pregnancy, carbohydrate metabolism changes in response to the fetus's increased energy needs, primarily glucose . The main changes can be summarized in two key ways.

Physiological pregnancy is characterized by a state of "accelerated starvation," as the continuous transfer of glucose to the fetus and placenta via the glucose transporters GLUT-1 and GLUT-3 leads to rapid utilization of maternal glucose. During pregnancy, glucose levels fall more rapidly than in non-pregnant women. Glucose crosses the placenta by facilitated diffusion, while the placenta remains impermeable to maternal insulin. Normally, fetal plasma glucose levels are approximately 0.6–1.1 mmol/L lower than maternal levels. By 10–12 weeks of pregnancy, the fetal pancreas begins secreting its own insulin and glucagon, and maternal hyperglycemia stimulates fetal insulin secretion.

From the second trimester onward, the placenta activates steroid hormone synthesis (placental lactogen, estrogens, and progesterone), and cortisol production by the adrenal cortex increases, with a simultaneous change in insulin metabolism and tissue effects. Accelerated insulin breakdown by the kidneys and activation of placental insulinase occur, leading to a state of physiological insulin resistance (IR) with compensatory hyperinsulinemia. This maintains blood glucose levels necessary for the development and functioning of the fetoplacental complex.

Thus, pregnancy represents a physiological "stress test," and maintaining normal glucose tolerance is possible with a sufficient supply of maternal β-cells.

Characteristics of Lipid Metabolism in GDM

During pregnancy, in addition to changes in carbohydrate metabolism, changes in lipid metabolism are observed. Thus, lipolysis, which is enhanced by steroid hormones during pregnancy, leads to an increase in the concentration of free fatty acids (FFA) in the plasma, which results in the activation of ketogenesis

with the risk of developing hyperketonemia . Ketone bodies freely cross the placenta and are used by the fetus as an energy source. With insufficient glucose intake from the mother's body, especially during early toxicosis, acetone may appear in the urine even in a healthy woman. It has been established that, as a result of increased lipolysis, the level of FFA increases, which contributes to the development and subsequent aggravation of hepatic IR. At the same time, the level of serum cholesterol and triglycerides (TG) initially tends to decrease in the early stages of pregnancy, and then progressively increases until delivery. After delivery, the level of serum TG decreases, but remains more pronounced in lactating women compared to those who have stopped breastfeeding. Probably, the mechanism of the increase in FFA levels in the late stages of gestation is associated with a decrease in insulin sensitivity in pregnant women. It was also noted that high levels of FFA in women influenced the formation of excess fetal weight, especially the accumulation of adipose tissue.
Pathophysiology of GDM

In some pregnant women, insulin resistance, accompanied by increased insulin demand, exceeds the functional reserve of pancreatic β-cells. This leads to the identification of hidden defects in the insulin system, which ultimately manifests as GDM. This suggests that decreased insulin secretion plays a leading role in its development. Possible causes of pancreatic β-cell dysfunction and, consequently, the development of carbohydrate metabolism disorders include defects in the insulin system, disturbances in the incretin axis, genetic factors leading to altered insulin sensitivity in insulin-dependent tissues, and molecular defects in the proteins that transmit insulin signals. The result of insulin resistance and insufficient insulin secretion to overcome it is an increase in plasma glucose, free fatty acids, certain amino acids, and ketones. Between meals, insulin resistance is accompanied by excessive glucose synthesis by the liver, which is the main cause of fasting hyperglycemia in pregnant women. After a meal, insulin resistance (IR) contributes to a decrease in insulin-mediated glucose utilization by tissues, leading to an excessive increase in postprandial glycemia. Decreased tissue sensitivity to insulin is exacerbated by increased maternal caloric intake, decreased physical activity, and gestational weight gain.

The Role of Obesity in the Development of GDM

One of the most significant and widespread risk factors for the development of GDM is obesity, which is accompanied by a decrease in the number of insulin receptors on the cell surface, leading to a reduction in its effects. According to various estimates, the prevalence of obesity among pregnant women ranges from 18.5 to 38.3% . In overweight patients, the action of placental hormones can lead

to an increase in existing IR, resulting in a 2.0-6.5-fold increase in the risk of developing carbohydrate metabolism disorders. In obese patients, these figures are even higher—approximately 17%. Furthermore, pregestational obesity is an established modifiable risk factor for adverse perinatal outcomes: neural tube defects , abnormal fetal growth , preeclampsia and thromboembolic complications , stillbirth , increased incidence of labor induction , fetal shoulder dystocia and Erb's palsy [19]. There are reports indicating a positive correlation between neonatal weight and maternal TG and FFA concentrations during pregnancy. Children of obese mothers with elevated TG and FFA levels not only had increased body weight and skinfold thickness but also elevated serum FFA levels compared to children born to women with a low body mass index (BMI) .

Metabolic and Inflammatory Markers in GDM

As noted, obesity and metabolic syndrome during pregnancy are significant risk factors for the development of GDM and its subsequent transformation into type 2 diabetes. Adipokines produced by adipose tissue likely contribute to the mechanisms of gestational carbohydrate metabolism disorders. Leptin and adiponectin have been shown to play a significant role in the pathogenesis of pregnancy-associated IR by influencing insulin secretion and insulin receptor signaling . Adiponectin is an adipose tissue hormone that has anti-inflammatory properties, improves tissue sensitivity to insulin, and promotes decreased glucose synthesis by the liver. Decreased adiponectin levels are accompanied by decreased tissue sensitivity to insulin and, therefore, are a factor that aggravates IR. Several studies have found evidence that low maternal adiponectin levels are associated with an increased risk of developing GDM .

According to available data, leptin, another of the most studied adipokines, is significantly elevated in women with GDM compared to women without impaired carbohydrate metabolism . Elevated leptin levels in early pregnancy, regardless of the woman's obesity status, are considered a prognostic marker for GDM in late pregnancy. A study by C. Qiu et al. found that every 10 ng/ml increase in leptin levels was associated with a 20% increased risk of developing GDM .

At the same time, the systemic inflammatory response, caused by the overexpression of proinflammatory cytokines (C-reactive protein, interleukin-6, TNF-α, and leptin), contributes to the development of pathological IR in obesity. Excess adipocytes in obesity produce large quantities of these cytokines, which have a damaging effect on insulin receptors. Thus, the results of some studies indicate the possibility of using interleukin-6 as a marker for predicting the development of GDM regardless of the presence of obesity . There are also studies that have confirmed that women suffering from gestational carbohydrate

metabolism disorder have significantly higher levels of tumor necrosis factor α (TNF-α) compared to control groups . These inflammatory markers influence changes in post-receptor insulin signaling, increasing insulin resistance . Moreover, pregnancy, during which physiological changes in the immune system are aimed at preventing rejection of the developing fetus, is itself a pro-inflammatory factor with activation of the humoral immune system. Thus, a state of systemic chronic inflammation with excessive cytokine production is associated with an increase in IR and contributes to the development of GDM . Given the above data, it can be concluded that, to assess the prognosis of the development and course of GDM, it is potentially appropriate to use not only the concentrations of leptin and adiponectin, but also proinflammatory proteins, whose changes are closely linked to the level of adipose tissue hormone production.

Conclusion

All of the above undeniably demonstrates that the pathogenesis of GDM is diverse and complex. Research into the molecular genetic and epigenetic mechanisms of carbohydrate metabolism disorders during pregnancy will enable more effective identification of women at high risk of developing GDM and the most optimal measures for its active prevention, as well as the development of pathogenetically based treatments.

References:

1. Алгоритмы специализированной медицинской помощи больным сахарным диабетом. Под ред. И.И Дедова, М.В. Шестаковой, А.Ю. Майорова (9-й выпуск). Сахарный диабет. 2019;22:135. DOI: 10.14341/DM221S1. [Algorithms for specialized medical care for patients with diabetes. Eds. I.I. Dedova., M.V. Shestakova, A.Yu. Mayorova (9th edition). Diabetes. 2019;22:135. DOI: 10.14341 / DM221S1 (in Russ.)].
2. Albrecht S.S., Kuklina E.V., Bansil P. et al. Diabetes trends among delivery hospitalizations in the U.S., 1994–2004. Diabetes Care 2010;33:768–773. PMID: 20067968. DOI: 10.2337/dc09-1801.
3. DeSisto C.L., Kim S.Y., Sharma A.J. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. Prev Chronic Dis 2014;11:E104. PMID: 24945238. DOI: 10.5888/ pcd11.130415.
4. Kharroubi A.T., Darwish H.M. Diabetes mellitus: The epidemic of the century. World J Diabet. 2015;6(6):850–867. DOI: 10.4239/wjd.v6.i6.850.
5. Setji T.L., Brown A.J., Feinglos M.N. Gestational Diabetes Mellitus. Clinical Diabetes. 2005;23(1):17–24. DOI./10.2337/diaclin.23.1.17.
6. Bener A., Saleh N.M., Al-Hamaq A. Prevalence of gestational diabetes and