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KEY RISK FACTORS AND DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES

Khakberdiyeva Vazira Jamshid qizi
Student of the Faculty of General Medicine

Makhmudova Aziza Nugmanovna
Scientific Supervisor, Samarkand State Medical University
Samarkand, Uzbekistan

Abstract
This article presents the risk factors for the development of gestational diabetes mellitus and the problems of diagnosing this disease. The risk factors for well-known problems of our time are considered: obesity, hypertension and insulin-dependent diabetes. Attention is drawn to an increase in the frequency of rarer causes: iatrogenic gestational diabetes mellitus caused by the use of counterinsular glucocorticosteroids, diabetes after in vitro fertilization (IVF). The controversial issues of the diagnosis of gestational diabetes mellitus are highlighted, the results of the study "Hyperglycemia and adverse pregnancy outcomes" (NARO), which caused the revision of diagnostic criteria for gestational diabetes mellitus, are discussed, and the effectiveness of existing Russian recommendations is analyzed.

Keywords: Gestational diabetes mellitus, pregnancy, risk factors, diagnosis, venous plasma glucose, oral glucose tolerance test

Introduction

The first mention of hyperglycemia that occurred during pregnancy dates back to 1824 and belongs to the German scientist H.G. Bennewitz [1], who identified this condition as one of the symptoms of pregnancy. A prospective study of carbohydrate metabolism during pregnancy was first conducted in 1954 in Boston. For this, a screening test with 50 g of glucose and the determination of glycemia after 1 hour was applied. This test was later widely adapted in the world. In 1961, J.B. O'Sullivan first used the term "gestational diabetes". The first criteria for the diagnosis of gestational diabetes mellitus (GSD) were developed in 1964 by J.B. O'Sallivan and C.M. Mahan [2]. However, it should be noted that the term GSD was not widely used among the medical community until 1980, when a fundamental article by Freinkel (1980) was published. In his work, he not only provided new data on the pathophysiology of glucose metabolism, but also assessed the consequences of the erroneous use of

insulin [3]. In 1980 For the first time, the World Health Organization (WHO) pays close attention to GSD and introduces the concept of "diabetes of a pregnant woman". GSD should be understood as an increase in the level of glycemia, first detected during pregnancy. After childbirth, reclassification is necessary. It was in 1980 that it was recommended to apply the same criteria for the diagnosis of GSD as for other groups of people. In 1994. WHO introduces a new term "gestational disorders of glucose tolerance", and in 1999 revised its classification of diabetes mellitus (DM) and, following the American Diabetes Association (AAD), delimits GSD from DM in a pregnant woman. In order to reconcile the two opposing positions, the AAD is also considering the possibility of conducting a 75-gram test, but the diagnostic indicators remain unchanged. In 1999 The Japanese Diabetes Association has also adopted the GSD classification and diagnostic tactics recommended by the AAD, but it continues to use the 75-gram two-hour test. It should be noted that the Japanese population is characterized by a high prevalence of GSD. This is due to the fact that type 2 diabetes prevails among diabetics in Japan at an early age in 95% of cases, which is often first detected in women during pregnancy, with its greatest detectability occurring in the first trimester [4]. For many years, gestational diabetes mellitus has been understood as the presence of glucose tolerance disorders that developed during pregnancy or were first diagnosed during pregnancy. Despite the fact that in most cases this condition resolves after childbirth, it is necessary to understand whether it will persist after pregnancy. It is also impossible to exclude the possibility that newly diagnosed disorders could develop in parallel with pregnancy. This concept made it possible to develop a unified strategy for the diagnosis of GSD. After discussing this issue in 2008 - 2009. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) and an international group that includes representatives of various organizations on obstetrics and diabetes, including AAD, recommended that if diabetes is detected in pregnant women at high risk in early pregnancy and standard diagnostic methods are used, a diagnosis should be made manifest DM, not gestational [5]. In a large international epidemiological study "Hyperglycemia and Adverse Pregnancy Outcomes" (Hyperglycemia and Adverse Pregnancy Outcomes Study (NARO) [6] with a total cohort of 25,000 patients, it was found that the risk of developing adverse outcomes in both pregnant women and fetuses, as well as after the birth of a child in the neonatal period, continuously increases depending on from the level of glycemia at 24-28 weeks (even if the value obtained is within the normal range). For most complications, there is no threshold value for risk stratification. The results obtained led to a revision of the diagnostic criteria of GSD. Two strategies have been proposed for GSD screening: (1) one–stage strategy – oral glucose tolerance test

(PGTT) with 75 g of fasting glucose and (2) multi-stage strategy - stage 1: glucose level test with a load (50 g of fasting glucose), if the obtained glucose value is greater than or equal to 10 mg/dl, then stage 2 is performed, including PGTT with 100 g of glucose on an empty stomach. Due to the use of different diagnostic criteria for the diagnosis of GSD, there are different thresholds for glucose levels and, accordingly, different risk groups for both pregnant and fetal [5]. When considering risk factors, it should be noted that there are common factors for the development of both GSD and DM. These include: burdened heredity for diabetes mellitus, previous GSD in previous pregnancies, a history of fetal birth with a body weight over 4000 g, disorders of carbohydrate metabolism, a history of glucosuria, obesity and overweight [7], hypertension, hyperlipidemia. Special risk factors for GSD include: complicated obstetric and gynecological history, multiple pregnancies, polyhydramnios during this pregnancy, the use of high reproductive technologies, pathological weight gain [8,9]. Currently, the risk of developing iatrogenic GSD is increasing due to the use of glucocorticosteroids that have a pronounced counterinsular effect (for example, in the presence of bronchial asthma, adrenal insufficiency, autoimmune thrombocytopenia, systemic lupus erythematosus, hemolytic anemia in a pregnant woman) [10]. Taking into account the progressive increase in the frequency of chronic diseases among the young population, pregnancy in the modern world is a kind of detector of the level of health in women of childbearing age. In the light of modern data, pregnancy is a physiological stress test for beta cells of the pancreas and is a "diabetogenic factor" for the body. A risk factor for the development of GSD is also metabolic syndrome (MS), which is a complex of metabolic, hormonal and clinical disorders based on insulin resistance (IR) and compensatory hyperinsulinemia. The incidence of GSD against the background of MS, according to the literature, is 1-14% [2.11]. The frequency of GSD after in vitro fertilization (IVF), according to V. Krasnopolsky and co-authors, is 12.6%, which is significantly higher than the general population figures for the Russian Federation. In addition, the factors determining the development of pathological insulin resistance include genetic defects leading to changes in insulin sensitivity in insulin–dependent tissues (mutation of genes of the insulin receptor substrate - SIR-1, glycogen synthetase, hormone-sensitive lipase, beta-adrenergic receptors, uncoupling protein UCP-1), as well as molecular defects of proteins that transmit insulin signals – insulin receptor resistance, decreased membrane concentration and activity of intracellular glucose transporters GLUT-4 in muscle tissue. In 1.6– 38% of pregnant women with GSD, specific monoclonal antibodies (AT) – GAD to β-cells, insulin and HLA DR3, DR4 are detected, which are usually inherent in people with a genetic risk of developing type I diabetes (SDI) [2]. The relevance of

modern diagnosis of GSD and the need to achieve the target indicators of carbohydrate metabolism is due to the high frequency (more than 80%) of pregnancy complications and morbidity of newborns [12].The criteria for the diagnosis of GSD were developed through the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study conducted in 2000-2006. In 2012 The Russian Association of Endocrinologists and the Russian Association of Obstetricians and Gynecologists (as well as experts from many other countries) have reached a consensus on the criteria for the diagnosis of GSD. According to the Russian Consensus and the "Clinical Recommendations" of 2013, the diagnosis of carbohydrate metabolism disorders during pregnancy is carried out in two phases [13,14,15]. Borovik N.V. and a group of authors from the D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology conducted a study aimed at analyzing the effectiveness of using new Russian clinical guidelines for the diagnosis and treatment of GSD. 500 birth histories of women with GSD for the period 2013-2014, diagnosed in accordance with new clinical guidelines, were analyzed. Based on the results obtained, the following conclusions can be drawn: 1. The introduction of new Russian clinical guidelines for the diagnosis and treatment of GSD contributes to the earlier detection and initiation of treatment of GSD. 2. The introduction of stricter criteria for target glycemia in GSD leads to a decrease in the frequency of complications of the course and outcomes of pregnancy [16]. The first phase of the diagnosis of carbohydrate metabolism disorders is carried out at the initial visit of all pregnant women to a doctor of any specialty for up to 24 weeks. Fasting venous plasma glucose, glycated hemoglobin (HbA1c) is determined by high-performance liquid chromatography or venous plasma glucose at any time of the day, regardless of food intake. Fasting venous plasma glucose < 5.1 mmol/L is considered normal for pregnant women, after 1 hour during PHTT < 10.0 mmol/L, after 2 hours ≥ 7.8 mmol/L and < 8.0 mmol/L. Obtaining one or more pathological indicators, namely, fasting venous plasma glucose ≥ 7.0 mmol/l, HbA1 ≥ 6.5%, venous plasma glucose, regardless of the time of day and meal in the presence of symptoms of hyperglycemia ≥ 11.0 mmol/ l, allows you to immediately identify women with manifest GSD requiring urgent insulin therapy. Pregnant women with elevated fasting glycemia values, but not corresponding to the parameters of manifest diabetes (more than 5.1, but less than 7.0 mmol/l) should be assigned to the group of gestational diabetes. They need to be prescribed rational diet therapy with dynamic control over the level of glycemia and fetal condition. In the second phase of the diagnosis of gestational diabetes, all women who did not have a violation of carbohydrate metabolism in early pregnancy are recommended to undergo an oral glucose tolerance test (OGTT) with 75 g of glucose between 24 and 28 weeks (up to a maximum of 32

weeks). OGTT with 75 g of glucose is a safe stress diagnostic test for detecting disorders of carbohydrate metabolism during pregnancy. Interpretation of the results of OGTT can be carried out by an obstetrician-gynecologist, internist, general practitioner, endocrinologist. It is important to note that a special consultation with an endocrinologist is not required to establish the fact of carbohydrate metabolism disorders [17,18]. The role of HbA1c in assessing glycemic control in DM patients has been confirmed by the results of the United Kingdom Prospective Diabetes Study (UKPDS) and The Diabetes Control and Complications Trial (DCCT). HbA1c is a reliable predictor of micro— and macrovascular complications of diabetes, an indicator of the risks of pathology of pregnancy and fetus [19]. However, these predictors are not always informative enough. Thus, the definition of HbA1c has a distortion of the result in hemoglobinopathies, anemia, blood loss, massive hemotransfusion. The average HbAlc level does not fully reflect the degree of hyperglycemia, therefore, other indicators of the degree of diabetic compensation should be taken into account, which do not manifest themselves in changes in HbAlc levels. In most cases, there is a clear correlation between blood glucose levels and the clinical condition of the pregnant woman. At the same time, there may be a situation when a pregnant woman has some symptoms of diabetes mellitus, despite normal blood glucose levels. Cardiotocography and ultrasound examination (ultrasound) of the fetoplacental complex with incipient decompensation are not always informative enough, often the information received is local in nature [20]. In this regard, it is relevant to search for alternative markers of GSD. One of these markers is glycated albumin (GA). The HA content, unlike HbA1c, does not depend on iron deficiency during pregnancy. Accordingly, the HA level better reflects the average glucose content [21]. In a cross-sectional study by Pan et al., 713 pregnant women had HbA1c and HA levels measured with a positive hourly OGTT from 50 g of glucose. An independent association of GA with glucose levels was revealed within 120 minutes after exercise [22]. Another promising biomarker for the diagnosis of GSD is fructazamine. Fructazamines are glycated serum proteins formed by the reaction of glucose mainly with albumin. Unlike glycated hemoglobin, the level of fructosamine correlates with an increase in glucose 3 weeks before the necessary analysis, since the half-life of serum proteins is less than the lifetime of erythrocytes [23]. However, the results of recent studies evaluating the diagnostic potential of fructazamine in GSD are contradictory. In a study by Khan et al. Fasting plasma glucose and serum fructosamine levels were measured in 165 pregnant women. It was found that fasting plasma glucose and fructosamine made it possible to identify patients at high risk of developing GSD, who were necessarily prescribed OGTT screening [24]. However,

according to the results of the study by Li et al., the following conclusions can be reached: this biomarker is effective in identifying patients with a higher risk of developing GSD, but is ineffective in predicting the development of GSD in early pregnancy due to the absence of a statistically insignificant correlation with OGTT [25]. Moreover, the level of fructosamine in serum correlates with maternal and gestational age [26], which, on the one hand, limits the use of this marker at present, and on the other hand, opens up new relevant directions in the study of GSD biomarkers, the main task of which will be to determine the threshold values of fructazamine to increase its diagnostic effectiveness. From all of the above, it follows that the debate regarding the methods and criteria for diagnosing GSD does not stop. Thus, the National Institutes of Health (NIH) and the American College of Obstetricians and Gynecologists (American College of Obstetricians and Gynecologists) have not adopted new criteria for the diagnosis of GSD. Although the American Diabetes Association has adopted the criteria proposed by the IADPSG for the diagnosis of GSD during PGTT at the 24th to 28th week of pregnancy, it recommends that fasting glycemia at the first pregnancy referral be determined only for the diagnosis of manifest diabetes mellitus (≥7.00 mmol/l). Caution in adopting new criteria for the diagnosis of GSD is due both to the understanding that this will lead to a significant increase in cases of GSD and the burden on healthcare, and to concerns about the "medicalization" of pregnancy [13, 27].

Conclusion

At the present stage, the scope of predisposing factors is expanding, and the proportion of pregnant women with risk factors leading to the development of gestational diabetes mellitus is increasing. The new diagnostic criteria allow us to try to distinguish the conditions of gestational diabetes mellitus, manifest diabetes mellitus and insulin resistance.

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