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### Features Of The Reproductive System In Women With Type 2 Diabetes Mellitus

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<sup>1</sup>Candidates of Medical Science Department of Endocrinology and Internal Diseases No. 3 <sup>2</sup>Master student Department of Endocrinology and Internal Diseases №. 3 (Samarkand, Uzbekistan) **ABSTRACT:** Diabetes mellitus is one of the most common diseases in the world. Currently, there is a tendency to increase the number of patients every year. Metabolic and endocrine disorders occurring against the background of diabetes mellitus affect the reproductive health of women, increase the risk of developing various obstetric complications during gestation: preeclampsia and eclampsia, disseminated intravascular coagulation syndrome, severe forms of preeclampsia, bleeding in the early postpartum period, and others. are also associated with high perinatal mortality rates.

**Key words:** Gestational diabetes mellitus, Placental insufficiency, Infertility, Pregnancy miscarriage.

#### **Purpose of the work**

Analysis of literature sources devoted to modern ideas about the influence of diabetes mellitus on reproductive health and fertility of women, disclosing the role of neuroendocrine disorders in the occurrence of gynecological diseases and infertility in female patients.

Diabetes mellitus (DM) is the main pathology associated with damage to the cells of the islet apparatus of the pancreas, and is a group of metabolic diseases accompanied primarily by a violation of carbohydrate and lipid metabolism and united by one common constant feature - hyperglycemia, which is caused by absolute or relative insufficiency insulin [1]. Diabetes mellitus ranks third in the structure of mortality and leads to the development of severe complications from the cardiovascular, nervous, genitourinary and other systems [2].

The first mentions of this disease were discovered in 1500 BC. in Ancient Egypt. The ancient Greek physician Demetrios introduced the term "diabetes", which literally translates to "pass through", since he considered the inability of the body to retain fluid at the basis of this pathological condition. The concept of "diabetes mellitus" was first used by the British

scientist T. Willis, who, on the basis of an increased glucose content in the urine and blood of a patient, isolated diabetes mellitus and insipidus (or "tasteless") diabetes [3].

Modern histological studies of pancreatic tissue in patients with diabetes mellitus have revealed changes in its structure. In patients with hyperglycemia, there is a decrease in the number of pancreatic cells, dystrophic changes in beta cells, changes in the composition and number of specific granules, degranulation of insulocytes. There is an alternation of atrophic and compensatory hypertrophied islets of Langerhans – Sobolev [1].

#### Main part

Edema is found around the vessels and small capillaries, and congestion in the vessels. Macroscopically, patients with diabetes may experience a decrease in the size of the pancreas, lipomatosis and sclerosis. However, in many cases, the tissue is not changed, and only electron microscopy and immunohistochemical studies can detect signs of a pathological process.

Since this disease is associated with metabolic disorders, changes are also found in other tissues and target organs: hepatomegaly, lipid deposition in liver cells, generalized macroangiopathy (atherosclerosis of the vessels of the kidneys, retina, brain, peripheral nervous system, etc.), microangiopathies caused by plasma sweating through damaged areas of the basement membrane, combined with endothelial proliferation and infiltration of the vascular walls by immunocompetent cells. These changes in the vessels contribute to the development of diabetic glomerulosclerosis and nephropathy, as well as the thickening of the basement membranes of the lung hemocapillaries and narrowing of their lumen [4, 5].

The pathological process also affects the thyroid gland, in which a local or diffuse increase in connective tissue elements, dystrophic and atrophic processes, a decrease in the number and flattening of thyrocytes, deformation of their nuclei, an increase in the viscosity of the colloid, atherosclerosis and calcification of large blood vessels (macroangiopathy), plasma impregnation vessels of the microvasculature and perivascular edema (microangiopathy).

These pathomorphological changes indicate the suppression of the thyroid gland function [6–8].

Today, there is a tendency towards an increase in the number of persons of reproductive age with chronic diseases. According to statistics, diabetes mellitus is one of the most common chronic diseases on the planet. According to the estimates of the International Diabetes Federation, more than 425 million people worldwide have this diagnosis, that is, diabetes occurs in 1 out of 11 adults, while about 70% of them are of working age [9].

Currently, there is an increase in the number of patients with diabetes mellitus: for example, in 1980, 108 million people all over the world were exposed to this disease, in 2014 - 422 million, that is, the number of patients has quadrupled and continues to grow steadily. By 2030, the incidence is expected to rise to 366 million [1]. In the WHO Global Report on Diabetes, the disease was ranked as one of the 4 priority noncommunicable diseases [2].

In 2017, more than 8.5 million patients were registered in Russia, and in the USA, China, India and Indonesia - more than 20 million people in each of the countries. Diabetes mellitus occurs with different frequencies in different ethnic groups: persons with white skin are 1.5–2 times less susceptible to this disease than representatives of the Negroid race and the peoples of the Iberian Peninsula [10]. Diabetes mellitus occurs in about 1% of women of reproductive age before pregnancy, and the incidence of all types of diabetes during gestation

is 3.5–4%, in some countries reaching 20%, with type 1 and 2 diabetes occurring in average 0.7-1%, and for gestational diabetes - about 3% [5].

The development of modern methods of diagnosis and treatment, as well as the development of preventive measures to combat complications, contribute to a decrease in the number of pregnant women with this disease. Moreover, every 6th child is born to a mother with chronic hyperglycemia during the gestational period, and more than 1 million children subsequently have type 1 diabetes mellitus [11]. Pregnancy and childbirth in patients with diabetes have an adverse effect on the course of the underlying disease, and hyperglycemia leads to impaired growth and development of the fetus and is associated with an increased risk of obstetric complications.

A successful course of pregnancy and childbirth is observed only in 20% of women with diabetes, which indicates the need for careful monitoring of the condition of the expectant mother by an obstetrician-gynecologist and endocrinologist [12].

According to the generally accepted classification, the following types of diabetes are distinguished: type 1 and type 2 diabetes identified before pregnancy, gestational diabetes, which is understood as any impairment of glucose tolerance that does not meet the manifestation criteria.

At the same time, type 1 diabetes is about 10% and is common among young people (up to 20 years). Type 2 diabetes occurs in about 90% of cases and was previously considered "adult diabetes", but now there is an increase in the incidence of type 2 diabetes among children and adolescents [13, 14]. Risk factors for developing diabetes during gestation are the woman's age over 30-35 years, overweight before pregnancy (BMI over 30 kg / m2), significant weight gain during pregnancy, a burdened family history of diabetes, impaired glucose tolerance during the previous pregnancy, perinatal death, the birth of children with intrauterine malformations, glucosuria [13, 15].

Today, gestational diabetes mellitus is considered a predictor of the development of type 2 diabetes and further cardiovascular complications [16]. In many cases, the diagnosis of gestational diabetes mellitus is not based on the clinical picture and complaints of the patient due to the lack of expression and nonspecificity of symptoms, but on laboratory parameters detected during screening studies. Among different population groups, gestational diabetes remains undetected in 10–25% of cases. In the first trimester of pregnancy, diabetes is found in 2% of cases, in the second - in 6%, and in the third - in 3%. Every year in the world more than 200 thousand births are complicated by the development of gestational diabetes mellitus [10, 15].

The reasons for the development of diabetes mellitus are varied: it is the destruction of beta cells of the pancreas due to autoimmune reactions, and their genetic defects (mutations of the nuclear factor of hepatocytes  $4\alpha$ ,  $1\alpha$ ,  $1\beta$ , glucokinase, insulin gene, mitochondrial DNA, which is manifested as inherited through the mother diabetes and deafness syndrome, etc.), as well as chronic pancreatitis, hemochromatosis of the pancreas, infections (cytomegalovirus, Coxsackie B virus), impaired tissue sensitivity to the action of insulin, and many others [13, 17, 18].

Despite the differences in etiological factors and pathogenetic mechanisms, obstetric and other complications arising in all types of diabetes are similar, as are the causes of disability and death of patients. Pregnancy and childbirth are associated with changes in all types of metabolism, which cannot but affect the course of the underlying disease in patients with diabetes. The need for all substances necessary for plastic processes increases, which is manifested by the intensification of protein, lipid and carbohydrate metabolism.

Glucose is the main energy substrate that is used for synthetic reactions in the body of the fetus and mother [4]. With an increase in gestation, energy requirements are constantly increasing, which requires changes in the regulatory mechanisms in order to maintain sufficient glucose levels. From the 12th week of pregnancy, the placenta begins to actively function, which is accompanied by an increase in the level of estrogen, progesterone, prolactin and placental lactogen, as well as an increase in the synthesis and secretion of cortisol and growth hormone [13].

These hormones have a counterinsular effect and cause physiological hyperglycemia in women by increasing gluconeogenesis in the liver. In response to an increase in blood glucose, insulin production increases, but in pregnant women the sensitivity of cells and tissues to the action of insulin is reduced, that is, insulin resistance is observed, which is considered an adaptive mechanism designed to provide the fetus with the necessary nutrients [1].

Thus, changes in carbohydrate metabolism during pregnancy are of a physiological nature, but they are similar to the pathogenesis of diabetes, which is why the gestational period is considered a diabetogenic factor [16].

In the first trimester of pregnancy, there is an increase in glucose tolerance, an increase in the synthesis and secretion of insulin by beta cells, as well as an increase in tissue sensitivity to the action of insulin [19]. These changes are caused by a decrease in the concentration of glucose in the blood of a pregnant woman due to an increase in its utilization by the fetus, as well as an increase in the level of estrogen. In the second trimester, the production of placental hormones increases, which have a counterinsular effect and cause a decrease in glucose tolerance. Insulin production increases in response to hyperglycemia.

To ensure the supply of a sufficient amount of glucose to the fetoplacental system, insulin resistance develops due to the action of progesterone, estrogen, prolactin and placental lactogen. In the third trimester, the concentration of contrainsular hormones gradually decreases, and the utilization of glucose by the fetus increases, which helps to reduce the level of glucose in the blood of a pregnant woman [12].

It should be noted that maternal insulin does not cross the placental barrier to the fetus. Thus, maternal hyperglycemia stimulates the growth and differentiation of fetal pancreatic cells. It has been established that in women with diabetes, the islets of Langerhans of the fetus are enlarged, their number in the tissue of the pancreas increases, which is explained by compensatory hyperplasia [19]. Fetal hyperglycemia, which develops before the 10-12th week of intrauterine development, when the islet apparatus is not formed, activates lipid peroxidation (LPO) under the influence of reactive oxygen species, the products of which are malondialdehyde, 4-hydroxynonenal.

The negative consequences of LPO are fragmentation and destruction of the lipid bilayer of membranes, dysfunction of ion channels due to changes in membrane viscosity, destruction of organelles, changes in the activity of receptors and enzyme systems of cells, activation of mutations, which disrupts the normal course of embryogenesis and leads to the development of diabetic embryopetopathy [20]. These disorders develop in 75% of newborns

whose mother had type 1 diabetes, and in 25% if gestational diabetes was recorded during pregnancy.

At the same time, 2/3 of newborns have a hypertrophic variant, which is characterized by overweight fetus, moon-shaped face, hypertrichosis, cardiomegaly, hemodynamic disturbance and hepatomegaly; in one third there is a hypotrophic variant - children are short, low birth weight, later there is a delay in physical and neuropsychic development. Incorrect laying of organs and systems leads to the birth of a child with intrauterine developmental anomalies: hydrocephalus, anencephaly, meningocele, renal agenesis, transposition of great vessels, atrial and / or interventricular septal defects, etc.

In diabetic embryopetopathy, fetal mortality is 3–5 times higher than the average [13, 21].

Diabetes mellitus poses a threat to the life and health of a woman during pregnancy. It is known that both diabetes and gestational age are associated with an increased risk of developing disseminated intravascular coagulation syndrome (DIC) [13].

Violation of the rheological properties of blood is manifested by hypercoagulation and hyperaggregation, which, on the one hand, are due to the activation of the platelet link characteristic of diabetes, and on the other, the occurrence of DIC syndrome is associated with a decrease in the effect of anticoagulant mechanisms: antithrombin AIII and the fibrinolytic system, which is observed in physiological conditions during pregnancy [22].

Maternal hyperglycemia interferes with placental formation and angiogenesis. Patients with diabetes mellitus have hyperplasia of the placenta with the formation of additional lobes or annular placenta, which leads to its premature maturation, calcification and aging, and, consequently, to a violation of its functions: barrier, transport, synthetic, endocrine, gas exchange, excretory. Violation of blood flow in the system "mother - placenta - fetus" is due to the formation of a single a. umbilicalis, formation of arterio-arterial anastomoses and impaired transformation of aa.spirales [13, 21].

The consequence of this is chronic fetal hypoxia with redistribution of blood flow to the central nervous system and the formation of an asymmetric variant of intrauterine growth retardation. Changes in hemodynamics and abnormalities in the formation of the placenta lead to the development of placental insufficiency and miscarriage. It was found that in 20% of patients of fertile age with diabetes, pregnancy does not occur for 2 years or more, which is associated with dysfunction of the hypothalamic-pituitary system (decreased production of FSH, LH, thyroid stimulating hormone and prolactin), impaired carbohydrate metabolism, decreased thyroid function and the development of obesity [7, 8, 23]

Other common complications in women with diabetes during gestation are preeclampsia and eclampsia, severe forms of preeclampsia, exacerbation of the underlying disease with the development of progressive diabetic retinopathy, glomerulosclerosis, polyneuropathy, ketoacidosis, weakness of labor, early postpartum delivery, and heavy bleeding period, inflammatory diseases of the genitourinary system, and death is also possible [24–26].

#### Conclusion

Thus, we can conclude that diabetes mellitus is a threat to the life and health of the mother and fetus. Patients should be informed about the need for pregravid preparation, which consists in referring to an endocrinologist's consultation to resolve the issue of the possibility of carrying a pregnancy, stabilizing the level of glycemia and clarifying the complications of

diabetes, repeated comprehensive examination and hospitalization in case of pregnancy, which will reduce the risk of complications and perinatal death.

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