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# Diabetes Mellitus and Pregnancy

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**ABSTRACT**

*Diabetes is associated with high risks of maternal and perinatal mortality, birth injuries, and long-term consequences for the mother and fetus. This article discusses the causes and mechanisms of development of pregestational and GSD, classification, comparison of diagnostic criteria and treatment tactics in different countries. The features of metabolism in pregnant women, risks for pregnant women with diabetes, as well as preconception care of patients are discussed.*

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Diabetes mellitus (DM) is a group of metabolic ski (metabolic) diseases characterized by chronic hyperglycemia, which is the result of impaired insulin secretion insulin or both of these factors [1]. Control and Prevention of Diseases of the United States considers diabetes seventh leading cause of death Estimated International Diabetes Federation, about 20 million intermittency proceeds with hyperglycemia [3].

Generally recognized, according to M. Agarwal, is The fact that hyperglycemia can lead to a number of complications such as miscarriage morbidity, stillbirth, preeclampsia, complications new births; high proportion of caesarean sections, preterm birth and the likelihood of developing diabetes type 2 in the future [4]. S. Mackin et al. held analysis of the history of childbirth over a 15-year period in Scotland diy. The analysis included 813,921 women; of which SD Type 1 was noted in 3,229, type 2 — in 1,452. the lysed period of time significantly increased number of pregnancies complicated by diabetes type 1 - by 44%, type 2 diabetes - by 90%, frequency preterm births increased by 5.3% in women with type 1 DM, by 21.8% — with type 2 DM ($p<0.0001$).

Perinatal mortality and stillbirth rates in women with DM did not show a significant reduction changes over time and were 4-5 times higher compared with the healthy population [5]. M. Hod et al. state that the frequency of gestational diabetes mellitus (GDM) correlated routs with increasing prevalence throughout the world obesity, impaired carbohydrate tolerance and type 2 diabetes, including in women of reproductive age age. Moreover, while the debut age and the pathology of carbohydrate metabolism decreases, age pregnancy, on the contrary, increases. Everybody this leads to the fact that more and more women join pregnant women have predisposing factors susceptibility to gestational hyperglycemia [6].

An important aspect, according to D. Mastrogiannis et al., is that the increase in the incidence of DM also negatively affected during pregnancy in providing medical care. In order to reduce of these indicators, it is proposed to introduce into the practice of telemedicine services, but this is not lo no advantages over the standard management of women [7]. According to L. Guariguata et al., the prevalence of GDM is increasing worldwide. fluctuates between 5.2 and 40.4% in different countries; this wide variability is associated with many factors such as body mass index (BMI), ethnic ocial affiliation, gross national the course of the country, as well as the used diagnostic criteria [8].

Classification

The main classification is the one adopted World Health Organization in 1999, according to which type 1 diabetes is distinguished, type 2 diabetes pa, GDM and other specific types of diabetes with sub- pami. By the same principle, but without division into subtypes, classifies SD American as- diabetes association (2018) [9]. G. Pincus and P. White are isolated during pregnancy8 classes of diabetes by clinical course, duration DM and risk for mother and fetus, by the presence of micros- judiciary complications and their treatment. This classification is used to compare different groups of belt, however, in the Russian Federation in clinical practice, it not used [10].

Etiology

M. Agarwal indicates that the etiology of GDM is related to associated with dysfunction of

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β-cells of the pancreas during pregnancy or delayed response the volume of β-cells on changes in the glycemic level, as well as with severe insulin resistance, secondary to hormonal activity placental tissue [4].

The risk factors for the development of GDM, according to J. Plows et al., are due to

overweight/obesity, excessive weight gain body weight during pregnancy, "Western" diet, ethnicity, genetic polymer- physiology, maternal age, intrauterine environment (low

or high birth weight), families- personal and personal history of GDM and other diseases, such as polycystic ovary syndrome. Neza- depending on the BMI and the total consumption of logia, a diet high in saturates fats, refined sugars, red and processed tanned meat is associated with an increased risk development of GDM [11]. According to R. Rajput et al.ed., a pronounced deficiency of vitamin D in the II trime- str of pregnancy is associated with an increased risk of development of GDM [12]. A. Kautzky-Willer et al. state that in primigravida the fetus is male the risk of developing GDM is 3–4% higher in the older sex; second-parous - by 7% than in pregnant women female [13].

In the work of A.A. Vasilyeva notes that change after the application of auxiliary productive technologies is associated with high risk of GDM and fetal macrosomia (18.2 and 5.88%, respectively, $p<0.05$) [14].

meta- analysis of 11 studies in which8,085 women showed that women who received hydroxyprogesterone caproate, marked by increased risk of developing GDM (relative risk(RR) 1.73; 95% confidence interval (CI) 1.32—2.28). In women treated with intravenous progesterone ginally, there was a low risk of developing GDM, though

these differences did not reach statistical significance. due to incorrect estimation of CI (RR 0.82; 95% CI0.50–1.12) [15].

According to P.V. Popova et al., risk of development GDM rises 3-fold if pregnant women have arterial hypertension (OR=3.04, 95% CI 1.5—6.3) compared with women without arterial hypertension hypertension ($p=0.005$) [16].

Thanks to the widespread introduction into practice of sex genome veneering reveals more and more new types of DM.

Thus, in the course of a recent study (2019) in the Mosul presented a case of DM in pregnant women p.I271T mutations in the HNF4A gene and p.L148F, p.Y265C, p.G288W in the HNF1A gene [17].

To date, it is known that MODY-diabetes associated with a defect in 13 genes (previously in the classification from 1999, 3 types were distinguished) [18].

Pathogenesis

Type 1 diabetes is caused by various factors such as heredity, viral infections, autoimmune processes, etc., leading to damage to pancreatic β-cells and line insufficiency. Genetic predisposition susceptibility to type 1 diabetes is due to the presence of certain haplotypes of genes of the main complex histocompatibility and other genes [19, 20].

The etiopathogenesis of type 2 diabetes is different: external factors such as obesity, age, physical inactivity and genetic predisposition women develop insulin resistance and insufficient function of β-cells with different

stump of expression [19].

According to the literature, in the etiopathogenesis of DM1st and 2nd types, the role of disturbances in the monal signaling systems of the brain and peripheral tissues. Previously,

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attention was paid to the signal system that is regulated by insulin, insulin

like growth factor type 1, adipok- nom, leptin [21].

At present, according to Botam A.O. Shpakov and K.V. Derkach, leading role assigned to adenylate cyclase signaling system(ACSS), which includes as a sensory compo- nent G-protein-coupled receptors [22]. GDM is closer in developmental mechanisms to type 2 diabetes pa [23].

According to the description of J. Plows et al., on the molecule lar level of insulin resistance in GDM usually manifested by a signaling failure insulin, which leads to inadequate translocation tion of the plasma membrane of the glucose transporter zy 4 (GLUT4) - the main transporter, which is responsible for the delivery of glucose into the cell for use vanity as energy. The level of insulin-stimulation lyated glucose uptake is reduced by 54% during pregnancy accompanied by GDM, compared to with normal pregnancy. While the abundance of insulin receptors, as a rule, does not touched decreased levels of tyrosine or increased phosphorylation of serine / threonine in the receptor insulin re attenuates insulin signaling.

In addition, the expression and/or phosphorylation changes. downstream regulators for signal transmission insulin levels, including the substrate of the insulin receptor lin (IRS)-1, phosphatidylinositol-3-kinase (PI3K) and GLUT4. Many of these molecular changes persist after pregnancy. It's believed that some of the previously discussed risk factors development of GDM have an impact, interfering with insulin signaling.

For example, saturated fatty acids increase intracellular concentration of diacylglycerol in myocytes, activating protein kinase C (PKC) and by inhibiting tyrosine kinase, IRS-1 and PI3K. Pro-inflammatory cytokines and adi- ponectins also modify this process [11].

It is known that processes are activated in DM oxidative stress.

According to the results of the study research conducted by Iraq scientists (2017), a change in biomarkers in the blood of pregnant women was detected with diabetes and placenta: excessive secretion of radicals, toxic derivatives, specific proteins and enzymes cops, but at the same time a decrease in the synthesis of antioxidant tov (superoxide dismutase, glutathione peroxidase, uric acid). These violations contribute pathological course of pregnancy, abnormal mu formation of the placenta and adverse effects natal outcomes in maternal DM, as well as the phenomenon of congenital malformations in the fetus [24].

Diagnostics

H. Berger et al. state that the control of gli- kemia during pregnancy reduces the likelihood adverse outcomes for mother and newborn however, no absolute threshold has been identified at which This risk arises [25].

For example, in countries with low and medium income level (India, China, Nigeria, Pakistan, Indonesia, Bangladesh, Brazil, Mexico) most women are not screened for the presence of diabetes during pregnancy, although there is an annual but up to 85% of deliveries occur from world- number and, as it turned out, 80% of them are prevent delivery of pregnant women with diabetes [6].

In France, Norway and the UK, selective screening based on the detection of risk factors, in Finland it is a universal screening with glucose 50 g, in Austria and Hungary - universal oral glucose tolerance test (OGTT) with 75 g of glucose. In the UK, at the coast patients with a high risk of developing GDM are used glucose tolerance test (GTT) with 75 g glucose immediately when registering, and with a negative result again at 24-28 weeks.

At 16-18 weeks pregnant to interpret the results of OGTT using WHO criteria are used

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[26].

According to A. Egan et al., there are no available randomized clinical trials, under-asserting any benefit from the treatment of GDM, diagnosed before 24 weeks of gestation [27].

According to E. Huhn et al., the goal of early testing - to identify women with low or high high risk of developing GDM, which will reduce spending on universal screening and diagnostics from 24 weeks of pregnancy, as well as identify women with GDM and start treatment as early as possible to reduce the adverse effects of long-term intrauterine exposure to hyperglycemia [28].

In our country, in the diagnosis of GDM, it is used a two-stage approach — up to 24 weeks and at 24–28 weeks [29].

Biochemical markers of pregnancy in the first trimester stre can change with DM, which must be taken into account in order to avoid an increase in the number of false positive results. So, the study of M. Savvidou et al. demonstrated that the level of PAPP-A at 11-13 weeks of pregnancy decreased by 25% in type 2 DM and by 9% in type 1 DM [30].

Pregnant women with diabetes are observed by an obstetrician-gynecologist log together with an endocrinologist, therapist and the need for other professionals. When bad well-being and glucose level> 11 mmol / l is necessary to determine the level of ketones in the blood and carry out urine monitoring (glucose, ketones, protein). The patient performs self-monitoring of glycemia at least 6-7 times.

System of continuous monitoring of glycemic mii is used for hypoglycemic episodes.

The Cochrane Review (2019) of clinical studies tests in Europe, the USA and Canada, a comparison was made methods of monitoring hyperglycemia. investigators concluded that it was not enough evidence of the advantage of one method over others [20].

The main methods for diagnosing the condition of the fetus are ultrasound examination (ultrasound), dopplerometry of the vessels of the fetoplacental- complex, cardiotocography. All these methods are are complementary. Data available Ultrasound with changes in the fetus and placenta, which that occur against the background of hyperglycemia, it is possible their timely and adequate correction. When researching research use devices of high and expert class, equipped with a multi-frequency convex

sensor with a frequency of 2-6 or 2-8 MHz. In addition to the darny triple screening in terms of 10—14, 20—24 and 31-34 weeks, fetal ultrasound can be performed in different personal periods of pregnancy [31]. Yes, according to according to F.F. Burumkulova, in patients with GDM crosomia may be suspected at 22–24 weeks and accurately diagnosed already in the period of 27-28 weeks. By- This category of patients needs additional additional studies between the 2nd and 3rd scenarios using ultrasonography [32]. Typical signs of diabetic feto-pathia (DF), according to V.I. Krasnopolsky and co- ed., are: - detection of macrosomia (not only take into account fetal weight, but also carry out a percentile assessment ku, i.e. exceeding the 90th percentile on the G.M. De- mentieva); visceral signs (double contour of the go-dexterity, an increase in the subcutaneous fat layer at the yes in the neck and abdomen, cardiomegaly, cardiotia, hepatomegaly, splenomegaly, hyperplasia of co- fetal adrenal glands, enlargement of the pancreas glands of the fetus, an increase in the width of the scapula of the fetus); - signs of fetoplacental insufficiency: polyhydramnios, placental hyperplasia, dilated intervillous spaces, calcification, increase venous-arterial coefficient of pu- guilt >2.7 and violation of the fetal-placental hemodynamics);determination of the degree of maturity of the

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fetus [31]. In order to assess the functional maturity of the fetus S.N. Lysenko et al. propose to measure the following general indicators: interhemispheric size of the cerebellum, the largest size of the Beklar nucleus (point of ossification- of the distal epiphysis of the femur), the ratio connection between the cortical and medulla of the supra- fetal kidneys (adrenal coefficient) depending on gestational age. From the 35th week of gestation tion, the width of the fetal adrenal gland does not depend on the time ka pregnancy, but the ratio of thickness changes cortex and medulla. For mature fruit characteristic value of the adrenal ratio ent not exceeding 0.99. It reflects gestational ionic changes in the fetal adrenal gland in the form of predominance lyation of the medulla and the beginning of involution adrenal cortex. For functional but a mature fetus is characterized by the magnitude of the interhemispheric the size of the cerebellum is 53 mm or more. Dot size ossification of the distal epiphysis of the femur fetus>5 mm can be considered a criterion for the maturity of the internal triuterine fetus [33]. M.A. Lebedev and Ch.G. Gagaev (2019) found that the average diameter of the umbilical cord can be additionally marker for suspected macrosomia. Mouth- updated statistically significant differences (p=0.006) when comparing the diameter of the umbilical cord in pregnant women with diabetes and without it, as well as a positive correlation the relationship between the body weight of newborns and the diameter of the umbilical guilt according to ultrasound data [34]. Maternal hyperglycemia is known to cause there is an increase in the load on the pancreas fetal teeth, namely on the exocrine part, causing her hypertrophy.

Conducted by S.N. Lysenko and co- ed. analysis of ultrasound data showed that in fetuses belt with diabetes pancreatic hyperplasia zy occurred 5 times more often than with physiological early course of pregnancy. Enlargement fetal pancreas, namely its thickening can serve as an additional recognition com DF and a reflection of the severity of the process.

These authors noted the highest correlation relational relationship of pancreatic hyperplasia fetal lesions with hypoglycemia on the 1st day of life but congenital [35]. Dopplerometry allows you to assess the condition uteroplacental blood flow and therefore have there is an important diagnostic and prognostic value treatment in pregnant women with hyperglycemia. Prognosis- the calic value of such a Doppler parameter, as volumetric blood flow in the umbilical artery in the term34-37 weeks, to clarify the severity of DF hall in his work S.N. Lysenko et al. Fruits with fetopathy, this indicator is statistically significant higher than in the fetuses of the control group ($p<0.05$) [36].

Cardiotocography is a research method that ry allows you to objectively assess the nature of the heart fetal activity and contractile activity uterus. The interpretation of the result is carried out according to the score Fisher scale.

Clinic

The development of type 1 diabetes occurs more often in young

house age that as seniority progresses disease leads to disorders in various organs nah and tissues of the body, including in the reproductive noah system. So, researchers E.V. Siberian et al. revealed a direct dependence of violations menstrual cycle on the duration of type 1 diabetes, the time of the onset of the disease and the severity of the given pathology and doses of insulin therapy. Out of 100 patients A child aged 11 to 17 with type 1 diabetes measured 60% had menstrual dysfunction tions. These patients are 3 times more likely than healthy short and scanty menstruation was observed, in 63% girls had anovulatory menstrual cycle, and only 10% of patients did not have any gynecological pathology [37]. Among the reasons for the decline in

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fertility in women are chin with SD, according to V.M. Guryeva et al. cheny violations of the functions of the hypothalamic-pituitary- system: reducing the release of luteinizing hormone (LH) in response to a decrease in the level of gonadotropin-releasing hormone (GnRH), basal concentrations of LH and follicle-stimulating hormone on (FSH), concentrations of thyroid-stimulating hormone. This leads to a decrease in the production of thyroxine and disruption to the synthesis of prolactin. In addition, with DM, insulin-dependent processes in the cells of the egg are nicks due to a decrease in the influence of gonadotropins on the ovaries. However, the mechanism of these processes is up to the end ca has not been studied [38].

The work of E.V. Siberian et al. testifies that autoaggression and autoimmune oophoritis are contribute to the formation of functional disorders gonads with the development of normogonadotropic hypogonadal dysma in girls and girls with type 1 diabetes, which also associated with varying duration and degree the severity of this disease.

Antibody concentration to ovarian tissue is statistically significantly higher in pa-patients with severe DM compared with patients patients with moderately severe diabetes and women of the control group. When evaluating menstrual functions of girls with severe DM type 166.6% had irregular menstrual cycle, 50% - anovulatory and only 33.33% - regular [39].

Ovarian dysfunction associated with diabetes not only with a low chance of pregnancy, but also with you high risk of pathological termination of pregnancy ness. In a study on mice, Y. Su et al. on- insulin has been shown to impair ovarian function during implantation of embryos due to dis- functions of ovarian autophagy processes. In the group mice receiving subcutaneous injection of human eternal recombinant insulin, there was a decrease estrogen E2, progesterone, LH, FSH, and transcription proteins (growth factor 9), control lyating the process of mRNA synthesis. Histologically found more immature follicles fishing and a decrease in luteinization in them [40].

Changes that occur in the body of a pregnant woman noah, predispose to ketosis, especially in patients current with LED type 1. Starting from the second trimester, increase there is resistance to insulin under the action of central lactogen, prolactin and cortisol due to their antagonistic properties. progesterone, decreasing motility of the gastrointestinal tract, contributing to there is increased absorption of carbohydrates and the development of gi-perglycemia. Most maternal glucose due to easy flow along the gradient of con- centration enters the fetus and placenta.

As a result the mother's body, experiencing a relative deficit insulin converts free fatty acids in the liver acids to ketones. However, the exact mechanism by which maternal diabetic ketoacidosis affecting the fetus is unknown. Possibly due to decrease in the production of 2,3-diphosphoglycerate delivery of oxygen to the child is reduced [41].

Clinically, diabetic ketoacidosis manifests itself with the following symptoms: tachycardia, hypotension nia, the smell of acetone from the mouth, dry skin wa, in severe cases, disorientation and coma. Provo- leading factors in the development of this condition there may be infections, especially the genitourinary system we, dehydration, vomiting. Negatively affects non-compliance with the recommendations of the endocrinologist for in- sulinotherapy and nutrition. There is a risk of preterm birth due to ketoacidosis due to inability to use tocolysis with β-agonists and prevention of respiratory th fetal distress syndrome with glucocorticoids, so how these groups of drugs lead to hyperglycaemia chemia [41]. In the development of hypertensive complications in pregnant in patients with DM, disorders play a certain role lipid metabolism and

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the complement system. In work M.E. Yablokov et al. compared the level of general cholesterol, triacylglycerides, total activity complement systems in 102 patients, including those with GDM there were 27, with type 1 DM — 28, with type 2 DM — 18. Cholesterol levels in pregnant women did not differ various forms of DM and in control, as well as in the presence of arterial hypertension and preeclampsia, and urotriacylglyceride vein was statistically significant higher in all forms of DM than in controls (p=0.03), and also statistically significantly higher in the presence of preeclampsia (p=0.02).

Women with DM have the highest. The highest concentration of triacylglycerides occurred in type 2 DM (p=0.00001). The presence of hypertensive complications in pregnant women with DM was accompanied by an increase in total complement activity, most expressed in women with type 2 DM (p=0.01) [42]. V.V. Kovalev et al. revealed the association sinogen (AGT) with the risk of developing hypertensive disorders in women with GDM (OR 3.28; 95% CI1.64-6.59; p=0.003). Presence of the 704C allele of the AGT gene in the genotype (704TC+CC) increases the risk by 3.87 times development of hypertensive disorders against the background of GDM(OR 3.87; 95% CI=1.60–9.35; p=0.002), in turn red genotype 704TT has a protective effect volume regarding the development of this pathology (OR0.26; 95% CI 0.62–0.11; p=0.002) [43].

Medical treatment Depending on the duration of pregnancy in patients The patient with diabetes changes the need for insulin, it not the same during the day: low at night, with more or less pronounced rise at dawn - symptom of "dawn", followed by post- foamy drop during the day. First trimester - the period of the most frequent hypoglycemic events and insulin therapy should be especially carefully monitored and adjusted during this period. From the second trimester, the need for insulin increases.

After childbirth, the use of drugs that reduce glucose levels should be monitored especially but carefully in order to prevent the development of gi- hypoglycemia, especially when breastfeeding. Breastfeeding women are prone to hypoglycemia how carbohydrates are excreted in milk, so before feeding recommended food intake, and its energy the tical value is increased by 500 kcal [44]. There are different forms of insulin that are divided according to the time of onset of action, duration ness, and also differ in origin. So, in the Cochrane Review (2017) with a sample of 554 women

women and 554 newborns compared various
types of insulin, namely human Insulin lys-
about two-phase short-acting with conventional in-
sulin (n=33), human insulin with insulin
animal origin (n=43), insulin aspart
ultra-short-acting with human insulin
(n=223), long-acting insulin detemir

action with Hagedorn insulin of medium duration action (n=162). No clear differences found between types of insulin and methods of their administration [45]. According to Russian recommendations, pregnant women nym allowed the use of insulin preparations per person short and medium duration action, analogues of ultrashort insulin (lis- pro, aspart) and prolonged (detemir, glargine100 U/ml) action [1]. In pregnant women, insulin administration is through multiple injections (MII), and using a pump by continuous subcutaneous insulin infusion (CSII) in different modes. At The choice of insulin regimen is guided by possible pathological

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variability of glucose PS, since there is a high risk of developing hypoglycemic conditions and ketoacidosis. skin infusion of insulin in combination with continuous glucose monitoring is the optimal small regimen of insulin therapy in achieving target values of glycemia without increasing the frequency hypoglycemic conditions and variability glucose levels [46]. O.A. Pankratova and V.V. Rimashevsky proved we have the advantages of using a pump- linotherapy in pregnant women with type 1 diabetes based on ve results of examination of newborns. 117 women were examined prospectively, 21 of them were belt with SD type 1 with PPII. In children from wives patients with CSII are statistically significantly less frequently observed neurological, respiratory disorders, myocardial lesions, hypoproteinemia, polycythemia mia, hypertrophic cardiomyopathy, 2.8 times edematous syndrome was detected less frequently, 6 times less phenotypic signs of DF began, 2.5 times less episodes of hypoglycemia were recorded on the 1st day life compared to children whose mothers high levels of MIS ($p<0.05$) [47]. A.U. Kazimova et al. data overview

literature on the possibility of using phytotera- pii to reduce oxidative damage with diabetes, namely the use of the flavonoid quercetina - extract of Hibiscus rosa-sinensis flowers. But for the use of herbal remedies for the purpose of phytothe- treatment of diabetes during pregnancy as an alternative th method of treatment requires long and thorough nye preclinical and clinical studies [48]. According to E.V. Shikh and L.Yu. Comb- kovoy, early appointment of vitamin and mineral complexes leads to a decrease in the amount of belt-type with a high risk of the birth of a large fetus yes, mainly due to the share of alimentary-dependent Sim factors and social risks of macrosomia fetus on the mother's side: obesity, older age35 years, high parity. When diagnosing the risk of crosomia at the 23-24th week in order to increase both sintering with folic acid and zinc is preferred nie should be given to a complex of vitamins produced given the interactions of its components [49]. According to the data of three randomized con- controlled trials (RCTs) involving 1,099 belt obese, evidence in favor of changing Metformin to prevent GDM few [50]. According to A.I. Sazonova et al., chief reason for the prohibition of the use of Metformin during pregnancy in many countries of the world and Russia This is the fact that this drug almost unchanged crosses the placenta that into the blood of the fetus [51].

Based on 45 RCTs involving 20,909 pregnant women, when taking Aspirin in doses of 50-150 mg in a period of 16 weeks and previously there was a significant decrease in the risk for preeclampsia (RR 0.57; 95% CI 0.43–0.75, $p<0.001$, R2 44%; $p=0.036$), severe preeclampsia these (RR 0.47; 95% CI 0.26–0.83; $p=0.009$; R2 100%; $p=0.008$) and fetal malnutrition (RR 0.56; 95% CI 0.44–0.70; $p<0.001$; R2 100%; $p=0.044$), with higher lower doses of aspirin were more effective [52].

According to the American Diabetes association, prophylactic use low doses of Aspirin (60-150 mg/day) after the 12th non- dividing pregnancy to birth will reduce morbidity, mortality and drug costs software [9].

CONCLUSION

Improving the methods of laboratory and in- instrumental research over the past decade allowed to achieve good outcomes in pregnancy with diabetes. Achieving optimal glycemia became possible due to the wide application change in synthetic analogues of insulin and daily regular glucose monitoring. Used- administration of tableted hypoglycemic drugs is the subject of discussion in the world community stve, and in the Russian Federation is prohibited. The use of vitamin mineral complexes helps to reduce the number la pregnant women with macrosomia,

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as well as congenital fetal malformations.

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