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GENETIC ANALYSIS OF PREGNANCY WITH FETAL DEVELOPMENT DEFECTS AND EARLY FETAL LOSS

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Abstract: The problem of complicated pregnancy and childbirth occupies the first place in obstetrics and perinatology. Nowadays, there is a lot of research on folate metabolism and its importance in reproductive health, gestational outcomes, and fetal development. Folic acid deficiency caused by diets or lack of enough folic acid in the body, as well as a decrease in the activity of enzymes due to defects in genes involved in folate metabolism, can lead to the development of fetal development defects and complications in pregnancy.

In recent years, mutant homozygous (TT) and heterozygous (ST) genotypes have been found in women with complicated pregnancies. Genetic deficiency of methylenetetrahydrofolate reductase (MTHFR), the key enzyme of the folate cycle, is considered one of the causes of hyperhomocysteinemia, which has a clear toxic effect on the endothelial layer of blood vessels and causes disturbances in the coagulation process. Hyperhomocysteinemia is important in the occurrence of microcirculation-related pregnancy complications, starting with spontaneous abortion in the 1st trimester of pregnancy, and ending with preeclampsia, premature detachment of placenta, and fetal antenatal death. At the same time, as a result of folate cycle disorders, fetal development defects, first of all neural tube defects, may occur. The importance of folic acid in the pathogenetic mechanisms of the origin of anemia has been shown. The study of dysfunctional alleles in genes of folate metabolism in infertility and miscarriage creates interes. The following article is an evidence-based summary of studies which were about folate metabolism, taking into account genetic predisposition and other components.

Key words: folat acid, folate metabolism, hyperhomocysteinemia, 5-methyltetrahydrofolate, 5,10-methylenetetrahydrofolate reductase.

Introduction. One of the important issues of modern medicine is the protection of the pregnant woman and her unborn child health. However, the incidence of pregnancy complications remains high, leading to increased perinatal losses and women's health risks [18].

Complicated pregnancies can be caused by disturbances in the folate cycle caused by endogenous and exogenous factors. Exogenous factors include low socio-economic status, unbalanced nutrition - insufficient intake of micronutrients and vitamins, alcohol intake, smoking, etc. Specific changes in genes, polymorphisms of genes controlling folate metabolism represent endogenous factors. Defects in folic acid metabolism can be included in a separate group that complicates pregnancy.

The folate cycle is a complex process controlled by enzymes that store folate derivatives as coenzymes. This acid is a complex molecule consisting of pteroid acid and one (monoglutamate) or several (polyglutamate) glutamic acid residues. Foods such as cruciferous vegetables, liver, yeast and some fruits mainly contain regenerated polyglutamates, which must be hydrolyzed to monoglutamate by the enzyme pteroylpolyglutamate hydrolase in order to be absorbed in the proximal part of the small intestine. After absorption, folate-monoglutamate is reduced to the biologically active derivative tetrahydrofolate [19, 31]. After methylation, folates enter the bloodstream in the form of 5-methyltetrahydrofolate, and then enter cells through endocytosis with the participation of specific folate receptors. Intracellularly, 5-methyltetrahydrofolate serves as a methyl group donor and a major source of tetrahydrofolate. Tetrahydrofolate becomes a variety of folates and acts as an acceptor of a large number of monocarbonates, which in turn serve as a specific coenzyme in a number of intracellular reactions, such as the synthesis of purines and the pyridine base of thymine.

One reaction that requires the presence of 5,10-methylenetetrahydrofolate and 5-methyltetrahydrofolate is the synthesis of methionine from homocysteine. Remethylation of homocysteine to methionine is catalyzed by the cytoplasmic enzyme methionine synthase (MTR). This enzyme requires methylcobalamin, a derivative of vitamin V12, to function. Methionine synthase catalyzes the remethylation of homocysteine to methionine through a reaction in which methylcobalamin is an intermediate carrier of the methyl group. As a result, oxidation of cobalamin occurs and MTR enzyme becomes inactive. Restoration of enzyme function can be restored with the participation of the enzyme methionine-synthase-reductase (MTRR) in the methylation reaction. In this case, the active form of methionine - S-adenosylmethionine, which is used for methylation of DNA, RNA, proteins and phospholipids, serves as the donor of the methyl group. In the synthesis of methionine from homocysteine, the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which restores 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which contains the methyl group necessary for remethylation of homocysteine, acts as a decisive key [12, 19]. Elevated homocysteine levels are a metabolic consequence of folate deficiency [28]. Genetic defects that ensure the transition of folic acid to the active state, which is necessary for the remethylation of homocysteine to methionine, are also distinguished.

The MTHFR gene is located on the short arm of chromosome 1 (1p36.3) and consists of 11 exons. The entire coding region is approximately 1980 base pairs long. The most studied is the C677T mutation of the MTHFR gene, which is associated with the exchange of cytosine to thymine at position 677, which leads to the exchange of alanine to valine (p.Ala222Val) in the catalytic domain of the enzyme protein. As a result, its activity decreases by 70% in the homozygous variant of the polymorphic allele, and by 35% in the heterozygous genotypes. Homozygosity for the C677T allele leads to a significant increase in homocysteine, especially against the background of low levels of folate in the blood plasma. A decrease in the activity of this enzyme is one of the important reasons for the accumulation of homocysteine in the body [5, 7, 16, and 17].

In recent years, there has been a lot of evidence that more homozygous and sometimes heterozygous genotypes are found in women with complicated pregnancies. Deficiency of folic acid and group B vitamins, which is related to dietary characteristics or due to insufficient digestion in the body, as well as defects in folate metabolism genes, which lead to a decrease in enzyme activity, leads to the accumulation of large amounts of homocysteine in the blood and disruption of methylation processes in cells [26].

Homocysteine has a strongly expressed toxic property and its negative effects are manifested in different ways. Homocysteine is a derivative of methionine, an essential amino acid. Methionine in the protein obtained through food, participates in all reactions that require the participation of a methyl group for the synthesis of biologically active substances (nucleic acids, adrenaline, creatinine, etc.). The active form of methionine is S-adenosylmethionine, which becomes S-adenosylhomocysteine after losing the methyl group as a SN3- group donor for this process. Subsequent hydrolysis of S-adenosylhomocysteine yields homocysteine [19]. Homocysteine is a cytotoxic amino acid, and the increase in its amount in cells is provided in two ways: a) by re-methylation to methionine; b) by trans-sulfanization to cysteine [11].

The first method uses 5-methyltetrahydrofolate (5-MTHF), the active form of folic acid, as the donor of the methyl group needed to convert homocysteine to methionine. This reaction is catalyzed by the enzyme methionine synthetase, and vitamin V12 acts as a coenzyme in this process. In the second case, betaine is used as a methyl group donor, and the conversion of homocysteine to methionine is catalyzed by the enzyme betaine-homocysteine-methyl-transferase. Re-methylation along the first folate-dependent pathway occurs in all tissues of the human body, while the enzymes of the betaine-dependent reaction are concentrated almost exclusively in the liver and kidney. During trans-sulfonation, the enzyme cystathionine-β-synthetase catalyzes the conversion of homocysteine and serine to cystathionin, which is then hydrolyzed by the enzyme cystathionine to form cysteine and α-ketobutyrate. Vitamin V6 is used as a coenzyme in both reactions. Excess cysteine is oxidized to taurine and inorganic sulfates or excreted in the urine [19].

Homocysteine damages the endothelial layer of blood vessels and triggers the coagulation process. Endothelium is not only a barrier between the vascular wall and circulating blood, but also a tissue that produces vasoactive substances, mediators and their inhibitors. With the help of these biologically active substances, the endothelium plays a leading role in controlling the tone of blood vessels. One such substance is nitric oxide. It is continuously produced by the endothelium and has a number of protective properties, including vasodilation, inhibition of smooth muscle cell proliferation, and inhibition of platelet and other blood cell aggregation [20, 21]. In addition, under normal conditions, nitric oxide has the property of reacting with homocysteine and thereby "neutralizing" it. As a result of this interaction, S-nitro homocysteine is formed, which is an additional powerful vasodilator and prevents platelet aggregation. However, these protective properties of nitric oxide are not realized in conditions of hyperhomocysteinemia, because homocysteine in high concentration has a negative effect on its activity and synthesis. Release of oxygen free radicals caused by homocysteine, internal and peroxidation of lipids occurs, and as a result, the activity of endothelial nitric oxide synthase decreases. Thus, in conditions of hyperhomocysteinemia, the synthesis of the most important factor of vasodilation and endothelial protection is reduced [21]. At the same time, we must not forget that there are other important vasoactive substances in the body that are out of balance due to oxidative stress and endothelial dysfunction caused by homocysteine. These compounds include prostacyclin PGI2 and thromboxane A2. Both of them are synthesized from arachidonic acid under the action of cyclooxygenase, but they have different properties. Thromboxane induces platelet aggregation and thrombus formation, while it has the strongest vasoconstrictor properties of all prostaglandins. Prostacyclin is mainly synthesized in vascular endothelium. Unlike thromboxane, prostacyclin relaxes the smooth muscles of blood vessels and induces platelet disaggregation, causing fibrinolysis.

A number of studies [11, 19] dedicated to determining the effect of homocysteine show that this amino acid significantly reduces the synthesis of prostacyclin in endothelial cells and increases the formation of thromboxane A2 (TkA2). Thus, in hyperhomocysteinemia, the TkA2/PGI2 ratio increases, which is manifested by increased vascular tone and increased thrombogenesis [19]. Many studies show that one of the effects of high concentrations of homocysteine is increased blood vessel density due to increased collagen synthesis and accumulation in blood vessels. This effect is explained by the fact that homocysteine increases the synthesis of collagen by vascular smooth muscle cell fibroblasts, and the accumulation of collagen in the cell layer occurs in parallel with the increase in the amount of homocysteine [21, 29]. Further studies have shown that the thiol group of homocysteine plays an important role in this process. Thus, as a result of the accumulation of collagen and the proliferation of smooth muscle cells of the vascular wall, blood vessels are deformed, thickened and stiffened. Some studies have proven the ability of homocysteine to activate elastase, which causes the degradation of elastin and inflammation of the endothelium, as a result of which the main components that cause the deformation of the vascular wall are easier to deposit on the vascular walls of calcium, cholesterol, and lipids.

It has also been found that homocysteine inhibits the production of endothelin-1. Endothelin-1 is a 21-amino acid protein produced by vascular endothelium. By binding to specific transmembrane receptors of smooth muscles, endothelin-1 stimulates their proliferation and has a strong vasoconstrictor effect. These properties of endothelin determine its importance in the development of vascular pathologies. But endothelin-1 can act on the transmembrane receptors of endothelial cells and cause a depressor reaction on the contrary. Normally, endothelial cells have antithrombotic and fibrinolytic properties and prevent the adhesion of circulating blood cells to the surface of blood vessels. Damage to the endothelium caused by hyperhomocysteinemia is accompanied by activation of the endothelium-dependent link of hemostasis and increased platelet aggregation.

In the literature [12, 19] there is information that homocysteine disrupts the function of tissue plasminogen activator, promotes the binding of lipoprotein to fibrin, which reduces fibrinolysis. Also, at high concentrations, homocysteine inhibits the function of natural anticoagulants such as antithrombin III and protein. In addition, homocysteine is able to change the normal antithrombotic properties of the endothelium, which leads to an increase in the activity of blood clotting factors V, X and XII [11, 19, 21].

Among other effects of homocysteine is its ability to activate nuclear factor κβ (NF-kb), which regulates the transcription of many genes in many tissues. Homocysteine in high concentrations damages the structure and function of mitochondria and has a negative effect on the expression of mitochondrial genes. Unfortunately, pregnancy itself is a condition that increases the risk of venous thrombosis 5-6 times. Several pathogenetic mechanisms have been proposed to explain this relationship, including: compression of the inferior vena cava and iliac arteries by the pregnant uterus, increased blood volume during pregnancy, insufficiency of venous valves. Also risk factors such as tendency to stasis due to hormonal changes, changes in rheological and coagulation properties of blood and physiological hypercoagulability due to inhibition of fibrinolysis [11, 12]. As a result of hyperhomocysteinemia during pregnancy, blood clots are formed in the tissues, as well as in the uterine wall and placenta, and microcirculation is disturbed. This can cause a number of complications in the early stages of pregnancy (defects in embryo implantation, normal miscarriage), and in the later stages of pregnancy (chronic fetoplacental insufficiency, fetal growth retardation, fetal death). Hyperhomocysteinemia is a risk factor for the development of conditions that prevent normal pregnancy, such as autoimmune processes and antiphospholipid syndrome. In addition, homocysteine can pass through the placenta and have a direct embryotoxic effect. Folic acid deficiency can cause birth defects in the fetus. One of the most serious defects caused by folic acid deficiency is neural tube defect (NTD). Fetal growth and development is characterized by increased cell production. Inadequate folate intake is critical in DNA and RNA synthesis. NTN is a sometimes fetal development defect that

presents with anencephaly or spina bifida. Defects occur between days 21 and 27 of pregnancy. During this period, many women do not even know that they are pregnant. Against the background of folate deficiency, hyperhomocysteinemia can cause severe and fatal neurological pathologies such as spinal cord malformation (spina bifida) and anencephaly, as well as failure to close the upper lip and palate [2, 6, 13, and 26]. A decrease in methylation in the cell due to a decrease in the activity of folate metabolism enzymes or a lack of methyl groups leads to a change in the methylation profile of the centromeric regions of the chromosomes, a violation of the compatibility of chromosomes during oogenesis, and the risk of having a child with Down syndrome (chromosome trisomy 21) increases. Disruption of DNA methylation profile is also associated with chromosome 18 segregation disorder.

This association was not shown for other autosomes (2, 7, 10, 13, 14, 15, 16, 22) and sex chromosomes. Deficiency of methyl group in fast-dividing fetal cells can lead to the addition of dUMP to dTMP in the synthesized DNA chain, resulting in the loss of nucleotide pairs, DNA chain breakage, and activation of the apoptosis mechanism [9, 24, 28]. Folic acid deficiency plays an important role in the development of fetal growth retardation syndrome, whose main function of this vitamin is coenzyme for the formation of purine and pyrimidine bases in the formation of DNA and RNA. Disruption of folic acid participation in DNA synthesis leads to changes in the process of cell division [11]. Cells that divide rapidly, especially hematopoietic tissue cells, are the most sensitive to DNA synthesis disruption. Therefore, one of the first signs of folic acid deficiency is the hyper segmentation of neutrophils, which is followed by an increase in megaloblastic cells and macrocytes in the bone marrow, and eventually microcytic anemia with leukopenia and thrombocytopenia develops. This worsens the condition of the fetus and increases its hunger for oxygen. Thus, folic acid, group B vitamins and homocysteine play important roles in the developing embryo and dividing cells [11, 12, 19, 25].

There is information in the literature that the MTHFR 677T/T genotype, together with low folate levels, may serve as a potential risk factor for the development of conditions such as decreased DNA methylation and neoplastic processes. The importance of low functional allele of folate metabolism genes in reproductive function disorders such as infertility [1], miscarriage [1, 8, 11, 16, 22], fetoplacental disorders and hypertensive disorders [8, 10, 11, 16, 24] fetal development defects arouses interest especially. A number of mechanisms of fertility disorders, as well as disturbances in the process of DNA methylation in somatic and germ cells, can be defined as effects of hyperhomocysteinemia.

In hyperhomocysteinemia, vascular stenosis, fibrinolysis and imbalance in fibrin formation, vasoconstriction, trophoblast invasion and placental dysfunction, observed with disruption of placentation, lead to the occurrence of obstetric pathologies. The significance of the MTHFR C677T polymorphism in the occurrence of normal miscarriage and early fetal growth retardation has not been fully investigated [1, 27]. One of the main causes of normal miscarriage in the first trimester is genomic mutations in the fetus, which occur due to the non-separation of chromosomes during parental gametogenesis. Research in this area suggests that the presence of low-functioning alleles of folate metabolism, resulting from changes in the DNA methylation profile of the cell, can lead to poly and aneuploidy in the fetus during gamete formation. In addition, in the rapidly dividing cells of the embryo, the deficiency of the methyl group leads to the addition of a uridyl nucleotide instead of a thymidyl nucleotide to the DNA strand being synthesized. As a result, anomalously fragile DNA is formed, and its synthesis slows down dramatically. This causes cell cycle disruption in rapidly dividing fetal cells and possibly triggers apoptosis mechanisms. In scientific research conducted with abortive materials, it was proven that the risk of spontaneous termination of pregnancy increases by 14 times when homozygous or heterozygous status of MTHFR S677T gene alleles is detected in the embryo [25].

Folic acid is directly involved in the development of placental blood vessels, and angiogenesis disorders in this area are associated with the pathogenesis of preeclampsia, fetoplacental insufficiency, fetal growth

retardation, and fetal death [4, 23, 24, 27,]. Adequate intake of folic acid may help prevent other types of developmental defects, including heart defects and birth defects. In addition, low folate intake during pregnancy is associated with preterm births and low birth weight [3, 14, 15, 28, 29].

Conclusion. The information presented in the review of the literature shows the importance of carrying out research on the assessment of folate metabolism, its pathogenetic role in pregnancy and the development of fetal organs and systems. It is not enough to study the polymorphism of the methylenetetrahydrofolate reductase gene (MTHFR S677T), a comprehensive study of this issue with genotyping of other indicators of the folate cycle and their components is necessary. In conclusion, in order to reduce the risk of complications in pregnancy and the development of fetal defects, the development of pathogenetically based early diagnosis and the development of qualified assistance in the stages of pregravid preparation and early ontogeny shows the need to continue research in this area.

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