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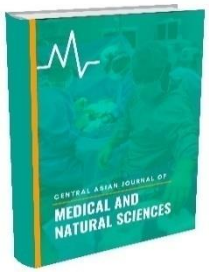

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The Role of Folate Cycle Genes in the Developing of Fetal Disorders

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Abstract: The prevention problem of complicated course of pregnancy and childbirth takes a leading place in modern obstetrics and perinatology. The authors conducted a profound analysis of numerous clinical studies in the area of folate metabolism in general, its role in the reproductive health of women, gestational complications, and in the formation of fetal pathology.

Key words: congenital malformations of the fetus, folate metabolism, genetics, homocysteine.

Introduction. Protecting the health of a pregnant woman and unborn baby are one of the key points of contemporary medicine, however the prevalence of pregnancy complications is significantly improving, and leading to negative effects on a woman's health and perinatal loss[5]. Folate cycle disorders which was occurred due to endogenous and exogenous factors is the reason for the complicated course of pregnancy. Exogenous risk factors include low socioeconomic status, unbalanced diet, insufficient intake of trace elements and vitamins, alcohol consumption, smoking, etc. Endogenous factors are represented, first of all, by the specificity of the genome, including

polymorphisms of genes regulating folic acid metabolism. Defects in folic acid metabolism in the body can be divided into a separate group of causes that complicate pregnancy. The folate cycle is a complex process controlled by enzymes with folic acid derivatives as coenzymes. This acid is a complex molecule consisting of pteroid acid and one (monoglutamate) or several (polyglutamate) glutamic acid residues. Food, especially fresh herbs, liver, yeast, and some fruits contain mainly reduced polyglutamates, which in the proximal part of small intestine they turned to monoglutamate with the help of pteroylpolyglutamate hydrolase enzyme for absorption in the. After absorption, folate-monoglutamate is reduced to tetrahydrofolate, which has biological activity [6, 8]. After methylation, folates enter the blood in the form of 5-methyltetrahydrofolate, simultanious it enters cells through endocytosis with the participation of specific folate receptors. Inside the cell, 5-methyltetrahydrofolate serves as a donor of methyl groups and the main source of tetrahydrofolate. Moreover, it acts as an acceptor of a large number of mono-carbon fragments, turning into various types of folates, which serve as specific coenzymes in a number of intracellular reactions, especially, the synthesis of purines and thymine pyrimidine base. One reaction that requires 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 synthas. Methylcobalamin, which is a derivative of vitamin B12, is needed for the enzyme work. Methionine synthase catalyzes the remethylation of homocysteine to methionine by a reaction in which methyl cobalamin acts as an intermediate carrier of the methyl group. In this case, cobalamin is oxidized and MTR enzyme becomes inactive. Enzyme function can be restored during the methylation reaction involving the enzyme methionine synthase-reductase (MTRR). In this case, the donor of the methyl group is methionine - the activated form of s-adenosylmethionine, which is also used for methylation of other compounds: DNA, RNA, proteins and phospholipids. The main role in the synthesis of methionine from homocysteine plays the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate ant it contains the methyl group necessary for the remethylation of homocysteine. [3, 6]. The metabolic result of folic acid deficiency is an increase in homocysteine levels [7]. Moreover, genetic defects in the production of enzymes that catalyze the conversion of folic acid to its active form, which is necessary for the remethylation of homocysteine to methionine, are also distinguished. The most studied mutation c677t of the MTHFR gene is associated with the replacement of cytosine with thymine at position 677. This leads to the replacement of alanine with valine in the catalytic domain of the enzyme protein (Ala222Val), in the homozygous variant for the polymorphic allele, its activity is reduced by 70% , leading to a 35% decrease in heterozygous genotypes. Homozygosity for the C677t allele leads to a significant increase in homocysteine levels, especially against the background of low plasma folate levels. This decrease in enzyme activity is one of the important reasons for the homocysteine accumulation in the body [1, 2, 4]. In recent years, there is a lot of evidence that homozygous (TT) and even heterozygous (CT) genotypes are significantly more common among women with complicated pregnancies. The lack of folic acid and b vitamins due to the their insufficient absorption by the body or specific characteristics of the diet, as well as the decrease of enzyme activity because of defects in folate metabolism genes, lead to excessive accumulation of homocysteine in the blood and disruption of methylation processes in the cell. [9]. Homocysteine is clearly toxic, but its negative effects are very diverse. Homocysteine is a derivative of the essential amino acid- methionine. Methionine obtained with food in the protein content is involved in all reactions, where the methyl group is used for the synthesis of biologically active substances (nucleic acids, adrenaline, creatinine, etc.).

The aim. Determination of the polymorphic variants role of folate cycle genes in disorders of the early stages of human embryonic development.

Materials and methods. 1 group was formed from 30 pregnant women with various developmental anomalies in the fetus. Group 2 consisted of 30 women with no history of pregnancy. The comparison

group consisted of 30 patients with normal fetal development. All women were under control in the maternity complex of the Tashkent Medical Academy clinic, they formed. The researched groups did not differ in terms of age, parity, onset of menstrual function, presence of genital and extragenital pathology. Levels of homocysteine and folic acid in blood plasma of all pregnant women were determined, molecular genetic examination of peripheral blood was performed (DNA isolation; detection of genetic mutations in MTHFR, MTRR, MTR folate cycle genes).

Results and their discussion. The level of homocysteine in the plasma of women in the 1 and 2 groups was higher than patients in the comparison group by 20.8 and 17.5 mkmol/l, respectively. 11 (36.7%) and 8 (26.7%) of women in the 1 and 2 groups had homozygous and 8 (60%) and 16 (53%) — heterozygous mutation of the MTHFR C677T gene. 4 women in the control group had only ma A heterozygous mutation of a certain gene has been identified. The level of homocysteine in the plasma of women of groups 1 and 2 was higher than that of patients in the comparison group by 20.8 and 17.5 mkmol/l, respectively. In the study of the MTRR gene, the mutation was detected in 14 (46.6%) and 13 (43%) women in groups 1 and 2, respectively, which is 7.7 and 6.5 times higher than the results of the control group. The level of folic acid is 5.3 ng/ml in group 1 and 9.8 and 13.5 in group 2 and control groups, respectively, which is not lower than normal values (>3 ng/ml). Analysis of fetal malformations showed the presence of multiple malformations and feto-placental insufficiency in 7 (27%) fetuses. Brain defects in 5 fetuses (19% of cases); defects of the urinary system in 4 fetuses (15% of cases); - defects of the cardiovascular system in 3 fetuses (12% of cases). Down syndrome in 3 fetuses (12%); placental hypoplasia (in 15% of cases) combined with hypotrophy and fetal immaturity was detected in 4 fetuses.

In women with a history of fetal growth retardation, fetal developmental defects, and hyperhomocysteinemia - 51% of cases had a complex thrombotic history (heart attack, vascular thrombosis, thromboembolism in close relatives), and 46% had a family reproductive history (pregnancy, fetal growth retardation, preterm abruption of normally located placenta).

It can be assumed that the basis of these complications may be hyperhomocysteinemia and genetic thrombophilia.

Studies have shown that after treatment in women with a history of fetal growth retardation and fetal developmental defects, clear dynamics were observed in the decrease of homocysteine and hemostasis indicators..

For 3 months, women received preventive treatment with methylfolate and group B vitamins. Semi-unsaturated Omega-3 fatty acids, vitamin E 400 XB. To correct hemostasis once a day was prescribed, subcutaneously, low molecular weight heparin "Fraxiparin" (calcium nadroparin) in the amount of 0.6 ml. After a month on the background of treatment, the concentration of homocysteine in patients decreased to 10.5 mmol/l, and after 2 weeks, the homocysteine level approached normal limits and was 7.5 mmol/l

The negative effect of hyperhomocysteinemia on vascular endothelium and stimulation of thrombosis leads to the development of a number of pregnancy complications. In the early stages of pregnancy, it can lead to disruption of placentation and disruption of fetoplacental blood circulation, resulting in infertility and miscarriage.

Conclusion. Thus, results of research showed that mthfr gene mutations and hyperhomocysteinemia in the anamnesis are more common in women with fetal defects and underdeveloped pregnancies**.** It is not enough to study the polymorphism of only one methylenetetrahydrofolate reductase gene (MTHFR C677T), and it required comprehensively study the issue with genotyping of other indicators of the folate cycle and their components. The presence of hyperhomocysteinemia in these women, despite normal folic acid levels, suggests that folate metabolism is insufficient due to mutations in

folate cycle genes. To reduce the risk of pregnancy complications, early diagnosis and timely correction of imbalances with an individual approach at the stages of pregravid preparation and early ontogeny is pathogenetically based.

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