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IMPROVING TREATMENT-DIAGNOSTIC MEASURES AIMED AT IDENTIFYING AND CORRECTING LOW OR HIGH LEVELS OF HOMOCYSTEINE

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Abstract

Homocysteine is a sulfur-containing amino acid that is synthesized from methionine under physiological conditions. Normally, the concentration of homocysteine in the blood serum is 5 - 15 μmol/l. During life, the average level of homocysteine can increase by 3 - 5 μmol/l. A serum homocysteine level of more than 16 μmol/l significantly increases the risk of developing cardiovascular diseases. The role of elevated homocysteine levels in the development of endothelial dysfunction and thrombophilic conditions, which are one of the key factors in the development of fetal loss syndrome at different stages of gestation, is described. This article examines homocysteine-related placental and reproductive processes.

Key words: *homocysteine, antenatal fetal death, hyperhomocysteinemia, methionin, prostacyclin decreases, placenta.*

Introduction

Homocysteine is a sulfur-containing amino acid that is formed in the body in the metabolic cycle of methionine. Violation of its metabolism is accompanied by the formation of a large number of radicals containing active oxygen, lead to the accumulation of homocysteine in cells, intercellular space, blood plasma and is realized by hyperhomocysteinemia, which is manifested by a pronounced toxic effect on endothelial cells with a loss of elasticity inside - neovascular layer, the development of systemic endothelial dysfunction (Raijmakers M.T.M. et al., 2001). Damage to the inner layer of the endothelium by homocysteine is accompanied by suppression of the synthesis of NO and sulfated glycosaminoglycans. As a result, platelet aggregation increases. With hyperhomocysteinemia, the synthesis of prostacyclin decreases, and the growth of arterial cells accelerates, which is the cause of thrombovascular pathology [5].

Homocysteine is an amino acid that is formed during the breakdown of methionine, which enters the human body with protein foods (meat, fish, eggs, milk).[9] Normally, this substance is produced in the body in small quantities, and its excess is neutralized by folic acid and the enzymes MTRR, MTHFR and MTR. If the activity of these enzymes is disrupted, excess homocysteine can form in the body, which can cause problems during pregnancy.[11]

Hyperhomocysteinemia, which occurs against the background of an increased content of the abovementioned amino acid in the blood, causes malformations in the fetus. If homocysteine is higher than normal, this threatens anencephaly, in which the fetus dies, or non-closure of the bone marrow canal, which entails serious neurological problems in the child.[12]

In addition, hyperhomocysteinemia can provoke thrombus formation in blood vessels. This can lead to generalized vascular pathology in the second half of pregnancy, gestosis (nephropathy, preeclampsia, eclampsia), and gestational diabetes mellitus.
Homocysteine, which is above normal, is considered a risk factor for autoimmune processes and antiphospholipid syndrome, which negatively affect pregnancy. This substance also freely penetrates the placenta and can harm the fetus.[2-4]

Based on the existing risks, a woman who wants to become a mother in the near future needs to undergo testing to determine the level of this substance in her body. When planning a pregnancy, you can find out what homocysteine level you have using urine and blood tests.[10] This substance should be absent in the urine. In the blood of an adult it should not be more than 15 μmol/l (for women - up to 12 μmol/l). Homocysteine during pregnancy - up to 10 μmol/l.[3-7]

What to do if you have hyperhomocysteinemia? First of all, an elevated level of homocysteine should be confirmed by an analysis, the results of which your attending physician interprets taking into account your age and general condition of the body. As a rule, an excess of this amino acid is not associated with nutrition, but is caused by disturbances in the activity of the enzymes MTRR, MTHFR and MTR due to human genetic characteristics.
Correcting homocysteine levels when planning pregnancy involves taking folic acid supplements and B vitamins, which are prescribed by the attending doctor. Doses, regimen and duration of treatment are determined individually.

During pregnancy, the level of homocysteine physiologically decreases until the term childbirth and in the III trimester is 3.3 - 8.4 μmol/l [1, 4].

Hyperhomocysteinemia is a factor in the occurrence of placental dysfunction and the main etiological factor in the development of pathological hemodynamic and hemostasiological changes in the mother-placentafetus system, the risk of lesions of the vascular endothelium, the occurrence of obstetric and perinatal complications: early onset and severe course of gestation, disruption of placentation, heart attacks and detachment of the placenta [2]. Generalized microangiopathy in the second half of pregnancy is clinically manifested by gestosis: preeclampsia (eclampsia), and therefore - the threat of antenatal death of the fetus. These processes are of fundamental importance for predicting the course of pregnancy [3].

The aim of the study

To determine the content of homocysteine in the blood of pregnant women with a threat of antenatal death of the fetus in connection with the study of family, professional, environmental, genetic, somatic and obstetricgynecological anamnesis, assessment of the blood coagulation system.

Materials and methods

63 pregnant women were examined. Of them, 21 (group A) are practically healthy pregnant women with a physiological course of pregnancy, 21 (group B1) - with a threat of antenatal death of the fetus from 22-30 weeks, and 21 (group B2) - from 31 - 38 weeks of pregnancy. For each patient, generally accepted documentation was drawn up and a general clinical examination was carried out. All subjects were informed about the purpose of the future studies, the method of conducting them, and gave their consent to use the results of the study.

Family-professional, environmental, genetic, somatic and obstetric-gynecological anamnesis was studied. A general clinical examination was conducted at the gynecology department of the Tashkent Medical Academy. General clinical trials were conducted in 2022 and 2023.

The method of quantitative determination of total L-homocysteine in human blood or plasma consisted in the application of an enzyme-linked immunosorbent assay test system. The low level of homocysteine was equal to 5.6-8.4 μmol/l, the average level was 10.0-15.0 μmol/l, and the high level was 20.0-30.0 μmol/l.

Research results and their discussion

Research has confirmed that during the physiological course of pregnancy, the content of homocysteine in the blood decreases by trimester of pregnancy and amounts to 8.4 - 5.7 μmol/l, which is consistent with the literature data [1, 4]. In groups of pregnant women at risk with the development of antenatal fetal death, the concentration of homocysteine increased significantly ($p<0.001$) during gestation.

It was established that with initial concentrations of homocysteine of 18.2±0.3 μmol/l (group B1), the threat of antenatal fetal death actually exists from the 22-29th week. By the time of delivery, this group was diagnosed with high-level hyperhomocysteinemia - 29.1±0.83 μmol/l, which was 1.6 times higher than the initial level, and 5.1 times higher than the control group.

The initial level of homocysteine in group B2 was 14.1±0.7 μmol/l and was significantly higher than the normal values by 1.7 times. In relation to group B1, the initial concentration of homocysteine in the blood of pregnant women of group B2 was 1.3 times lower (the difference is significant - $p<0.001$) and was considered by us as hyper homocysteinemia of moderate severity. Such a level of homocysteine concentration in the 1st trimester can be regarded as a predictor of the development of antenatal fetal death. At the end of the III trimester, before delivery, the level of homocysteine in the blood of pregnant women increased by 1.6 times compared to the initial level and by 3.9 times compared to the control group and amounted to 22.4±0.82 μmol/l, which was regarded as hyper homocysteinemia of a high degree of severity.

The relationship between hyper homocysteinemia and the main anamnestic data and characteristics of the somatic and obstetric-gynecological status, the course of pregnancy, and laboratory data can be traced according to the data shown in Table 1.

Table 1. Relationship of hyper homocysteinemia with basic anamnestic data

Signs	**Groups**					
	А, n=21		Б1, n=21		Б2, n=21	
	Абс	%	Абс	%	Абс	%
The average age of women is 27±2 years	5	16,1	27	87,1	25	80,6
Socially and ecologically unfavorable conditions	3	9,7	29	93,5	27	87,1
Spontaneous miscarriages	-	-	16	51,6	13	41,9
Ectopic pregnancy	-	-	4	12	3	9,7
Miscarriage	-	-	3	9	2	6,5
Violation of MF	3	9,7	21	67	19	61,3

Inflammatory diseases of OS	2	6,5	27	87,1	24	67,7
Smoking	3	9,7	15	48,4	12	38,7
Cardiovascular pathology	-	-	31	100	29	93,5
Diseases of the digestive tract	2	6,5	17	54,8	13	41,9
Pathology of the SVS	-	-	13	41,9	11	35,5
Gestational anemia	-	-	14	45,2	11	35,5
Gestational pyelonephritis	-	-	10	32,3	9	29,0
Ig to cytomegalovirus	12	38,7	29	93,5	26	83,9
A yeast-like fungus	3	9,7	11	35,5	9	29,0
Hypercoagulation	-	-	31	100	31	100
Hypercalcemia	-	-	31	100	31	100
Early toxicosis	-	-	26	83,9	24	67,7
Preeclampsia	-	-	14	45,2	11	35,5
Threat of early miscarriage	-	-	31	100	31	100
Threat of late miscarriage	-	-	31	100	31	100
The threat of premature birth	-	-	31	100	31	100
prematurely peel off placenta	-	-	27	87,1	26	83,9

The average age of women is 27±2 years (the second half of the greatest reproductive activity) was noted in 87.1% of pregnant women of B1 group and in 80.6% - B2. At the same time, only 8 (12.9%) women of the main group had their first pregnancy. 93.5% and 87.1% of the examined groups B1 and B2 lived in socially and ecologically unfavorable conditions.

In the anamnesis, 41 (66.1%) pregnant women noted reproductive losses in the form of spontaneous miscarriages, ectopic pregnancy, abortion that did not occur.

A direct connection between smoking and hyper homocysteinemia and the development of the threat of antenatal fetal death has been established. Before pregnancy, more than 70% of subjects smoked cigarettes, during pregnancy - 48.4% and 38.7% of pregnant women of groups B1 and B2, respectively. Among the total number of pregnant women, 29 (46.7%) women considered themselves to be passive couples.

Hyper homo cysteinemia, in most cases, underlies the development of cardiovascular pathology, digestive tract (TT), urinary system (UT), diseases closely related to dysfunction of the endothelial system. Cardiovascular pathology occurred in 100% of B1 group and in 93.5% of B2. TT and SVS diseases were characteristic in 54.8% and 41.9% of pregnant women of group B1 and in 41.9% and 35.5% of B2.
General infection, a decrease in the immune defense of the mother's body, signs which include a high frequency of detection in clinically significant titers of class G immunoglobulins to cytomegalovirus (93.5%; 83.9%) and yeast-like fungus (35.5%; 29.0%), can be realized by the development of the threat of antenatal death of the fetus against the background of hyper homo cysteinemia.

100% of women with hyper homo cysteinemia have a tendency to hyper coagulation. In 48 (77.4%) women of the main group, indicators of platelet aggregation were higher than normal, plasma concentration of fibrinogen was lower than control, and indicators of activated partial thromboplastin time were decreased. Existing disorders in the hemostasis system lead to the

development of the syndrome of intravascular disseminated blood coagulation. The content of calcium ions (the fourth plasma coagulation factor) was 1.5 times higher than normal in 100% of pregnant women, compared to the data of the control group.

Clinical features of the course of pregnancy with the threat of antenatal death of the fetus against the background of hyper homo cysteinemia were the development of early toxicosis and preeclampsia in 83.9%; 45.2% of pregnant women of group B1 and 67.7%; 35.5% - B2.

Hyper homo cysteinemia was accompanied by the threat of early, late miscarriage, premature birth in 100% of pregnant women of the main group, premature partial or complete detachment of the placenta - in 87.1% and 83.9% of cases and may indicate a real threat of antenatal death of the fetus, which observed was heard in 6 (9.7%) women of the main group.

Conclusions

An increase in the concentration of homocysteine by 1.7 times the normal values in the 1st trimester can be regarded as a predictor of the development of antenatal fetal death. Hyper homocysteinemia is accompanied by hyper coagulation and a high content of calcium ions in the blood, pathological course of pregnancy and can be one of the prognostic tests of antenatal death of the fetus, which requires timely etiopathogenetic correction.
Prospects for further research are to study disorders of folate metabolism and pathogenetic mechanisms of antenatal fetal death.

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