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THE ROLE OF HYPERHOMOCYSTEINEMIA IN THE DEVELOPMENT OF REPRODUCTIVE LOSSES AND MODERN METHODS OF SOLVING THE PROBLEM

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ABSTRACT

Background. To date, the role of hyperhomocysteinemia as a factor contributing to vascular complications during pregnancy has been well studied [6]. In recent years, special attention has been paid to its embryotoxic effect [3]. According to research, homocysteine is a key cause of neural tube defects, which account for 27.4% of all central nervous system anomalies [6].

Aim. To analyze the prevalence of hyperhomocysteinemia in the Andijan region, to study the structure of reproductive losses associated with elevated homocysteine levels, and to assess the significance of prognostic risk factors in women with hereditary and acquired forms of hyperhomocysteinemia.

Material and methods: to assess the frequency of hyperhomocysteinemia among pregnant women in the period from 2022 to 2024 in the gynecological department of Andijan Maternity Complex No. 2, 150 women were examined in the first trimester of pregnancy using the continuous sampling method with the determination of the level of homocysteine in the blood plasma.

Results. The main and control groups had similar indicators for age, social status and obstetric and gynecological history ($p > 0.05$). The average age in the preeclampsia group was 28.4 ± 0.7 years, in the control group - 29.8 ± 0.7 years. Moderate preeclampsia was noted in 68% of cases, severe - in 32%. Most of the women were employees, had secondary education and were under observation at the antenatal clinic from the 12th week of pregnancy. Analysis of reproductive function showed that most participants in both groups were primiparous ($p > 0.05$), and inflammatory diseases of the pelvic organs occurred with the same frequency ($p > 0.05$).

Conclusions. Prediction of individual risk, it is necessary to take into account the genetic characteristics of a particular ethnic group, which determine the list of candidate genes associated with the risk of diseases, including somatic ones. Therefore, the study of the prognostic role of such genes remains an important task.

Key words: preeclampsia, pregnancy, gene polymorphism.

Introduction. To date, the role of hyperhomocysteinemia as a factor contributing to vascular complications during pregnancy has been well studied [6]. In recent years, special attention has been paid to its embryotoxic effect [3]. According to research, homocysteine is a key cause of neural tube defects, which account for 27.4% of all central nervous system anomalies [6].

Folate therapy is considered a method of pathogenetic prevention of teratogenic effects of homocysteine. Various approaches to the implementation of folate support programs have been developed, but according to statistics, about 500,000 children are born annually in the world with defects associated with elevated homocysteine levels [1,4,8]. The question of the optimal dosage of folates remains open: it has been proven that 400 mcg / day of folic acid reduces the risk of neural tube defects by 70%, while a dose of 5000 mcg reduces the likelihood of fetal anomalies by only 80% [2,5,7].

It is still unclear why folate therapy is not always effective in preventing congenital defects and what additional factors influence their development. This makes it relevant to study the prediction of the risk of perinatal pathology in women with hyperhomocysteinemia.

The aim of the study: to analyze the prevalence of hyperhomocysteinemia in the Andijan region, to study the structure of reproductive losses associated with elevated homocysteine levels, and to assess the significance of prognostic risk factors in women with hereditary and acquired forms of hyperhomocysteinemia.

Materials and methods: to assess the frequency of hyperhomocysteinemia among pregnant women in the period from 2022 to 2024 in the gynecological department of Andijan Maternity Complex No. 2, 150 women were examined in the first trimester of pregnancy using the continuous sampling method with the determination of the level of homocysteine in the blood plasma.

Based on the results of genetic analysis for thrombophilia factors in women with a history of missed abortion, two groups were formed: the first group consisted of 14 women with acquired hyperhomocysteinemia, the second group consisted of 37 patients with hereditary hyperhomocysteinemia caused by polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene.

The comparison group included 16 women with normal homocysteine levels (5.23±0.18 μmol/l), whose pregnancy ended with the birth of healthy children.

StatSoft Statistica 6.0 was used for statistical data processing. Comparison of indicators was carried out using the χ^2 criterion. Differences were considered statistically significant at a significance level of $p < 0.05$.

Results. According to the results of the study conducted using the continuous sampling method, the frequency of hyperhomocysteinemia among pregnant women was 3.1%. According to S. G. Lamarre and A. M. Molloy (2011), in the general population this figure varies from 5 to 7%. There is no information in the literature on the prevalence of hyperhomocysteinemia among pregnant women, which did not allow for a comparative analysis. The average homocysteine level was 15.2±0.37 μmol/l, which, according to the classification of Z. S. Barkagan (2002), corresponds to moderate hyperhomocysteinemia. In 85.9% of pregnant women, the homocysteine level was within the normal range (5.9±0.25 μmol/l), corresponding to the gestational age. A retrospective analysis of congenital malformations of the fetus showed that over the past year, 480 pregnancy terminations due to fetal developmental abnormalities were registered in Andijan City Maternity Complex No. 2. The proportion of defects associated with hyperhomocysteinemia was 9.9% of the total. Neural tube defects were predominantly detected (62.5%). The fetotoxic effect of homocysteine is due to impaired migration of the epithelium and ectodermal derivatives, as well as dysfunction of DNA methylation during the formation of organs, the neural tube and the facial skeleton [2]. At the same time, 60.2% of women received folate therapy from the moment of registration, but its low efficiency is explained by the late start of treatment (11.9 ± 0.05 weeks). The critical period for the formation of defects, especially neural tube defects, falls on the 3rd-6th week of pregnancy, and for the neural tube - on the 21st-28th days of gestation. Analysis of the odds ratio for risk factors in women with hyperhomocysteinemia showed that in the acquired form, the main factor was alimentary deficiency of folates and B vitamins, observed in 85.7% of patients. This occurred 3.1 times more often (p=0.0001) than in women with normal homocysteine levels (27.3%), and was associated with a diet dominated by animal proteins, excess fats, and a lack of foods rich in folic acid and B vitamins. The risk of perinatal pathology in such cases increased by 9.7 times (OR=10; 95% CI 2.6–38.3).

Chronic gastrointestinal diseases (chronic gastritis, cholecystitis) were of almost the same importance, being detected in 57.1% of cases. They impaired the absorption and assimilation of folates and B vitamins, increasing the risk of fetal abnormalities by 9 times (OR=9; 95% CI 2.2–32.1). Pathologies of the urinary system (chronic pyelonephritis, cystitis), observed in 35.7% of patients, reduced the excretion of homocysteine, increasing its concentration in plasma and increasing the likelihood of perinatal pathology by 6.7 times (OR=6.7; 95% CI 1.7–15.6). In 42.9% of women with acquired hyperhomocysteinemia, the risk of fetal defects increased by 6.3 times (OR=6.7; 95% CI 1.7–15.6).

A history of reproductive losses in women with acquired hyperhomocysteinemia increased the likelihood of perinatal pathology by almost 5 times (OR = 4.9; 95% CI 1.1–21.3). Early thrombosis in relatives (OR = 4.7; 95% CI 1.22–17.9) and diabetes mellitus (OR = 4.7; 95% CI 1.3–16.9) had the same prognostic significance, in which the risk of embryotoxic effects of homocysteine increased by more than 4.7 times.

Thyroid diseases (hypothyroidism, endemic goiter) and lifestyle factors, such as long-term use of combined oral contraceptives (more than 6 months) and bad habits, had equal prognostic significance. These factors reduced the activity of folate cycle enzymes, increasing the risk of perinatal pathology by 4 times (OR=4.0; 95% CI 1.1–15.1).

When ranking the risk factors for hereditary hyperhomocysteinemia, it was found that the most significant were reproductive losses in the anamnesis, identified in 43.4% of women. In such cases, the risk of perinatal pathology increased by 8.7 times (OR=8.7; 95% CI 2.9–25.1).

Discussion. It can be noted that for women with hereditary hyperhomocysteinemia, an important prognostic factor was a thrombophilic history in close relatives (OR = 5.5; 95% CI 2.1–14.4). Episodes of acute circulatory disorders in relatives of such women were observed significantly more often (39.6%; $p < 0.05$) compared to relatives of women with normal homocysteine levels (10.6%). Bad habits, in particular smoking up to 20 cigarettes per day, had a similar significance,

increasing the risk of fetal abnormalities by 5.5 times (OR = 5.5; 95% CI 2.2–13.9). Chronic gastrointestinal (OR=5.2; 95% CI 2.2–12.1) and kidney (OR=5.2; 95% CI 1.7–15.6) diseases, which were the most significant for prognosis in acquired hyperhomocysteinemia, were less significant in the case of the hereditary form, increasing the probability of fetal defects by 5.2 times. Alimentary deficiency, a key prognostic factor in the acquired form, increased the risk of perinatal pathology by 5.1 times in women with hereditary hyperhomocysteinemia (OR=5.2; 95% CI 2.2–12.1).

The least significant factor for the prognosis of perinatal pathology in hereditary hyperhomocysteinemia was thyroid pathology, increasing the risk of defects by 3.7 times (OR = 3.7; 95% CI 1.5–9.5). In women with hypertension, the probability of fetal abnormalities increased by 3.3 times (OR = 3.3; 95% CI 1.2–8.9), and in diabetes mellitus - by 2.7 times (OR = 2.7; 95% CI 1.1–6.8).

The final ranking of risk factors showed that for acquired hyperhomocysteinemia the most important are alimentary deficiency of folates and B vitamins, chronic gastrointestinal diseases and kidney pathologies. To exclude hereditary hyperhomocysteinemia, it is necessary to take into account the burdened obstetric and thrombophilic history of relatives, long-term use of combined oral contraceptives and smoking. Such patients are recommended to determine the homocysteine level and conduct folate therapy in combination with B vitamins pregravid.

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