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Research Article

**POLYMORPHISMS OF GENES AND THE RISK OF  
PREECLAMPSIA****Evgeny A. Reshetnikov, Inna N. Sorokina, Irina V. Batlutskaya, Evgeny N. Krikun,  
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**Abstract:**

*Objectives: they studied the relations of genetic polymorphisms with the risk of preeclampsia occurrence depending on hereditary complication.*

*Materials and Methods: The study was conducted in two groups of pregnant women: 274 women diagnosed with preeclampsia and 179 women with physiological gestation. They studied seven polymorphisms of folate cycle genes (+677C>T MTHFR (rs1801133), +1298A>C MTHFR (rs1801131), + 66A>G MTRR (rs1801394), + 2756A>G MTR (rs1805087), -1053C>T TYMS (rs699517), IVS 6-68 C>T TYMS (rs1059394), -1122A>G TYMS (rs2790)) by real-time method of polymerase chain reaction (PCR) in DNA synthesis (Real-time-PCR).*

*Results: The frequencies of alleles +2756G MTR and the genotype +2756GG MTR were higher in the group of pregnant women with preeclampsia without hereditary complication, as compared with the pregnant women of control group (OR = 1.61, p = 0.01, OR = 7.26, p = 0.0007, pbonf = 0.0021, respectively).*

*Conclusions: Thus, the polymorphism of methionine synthase gene + 2756A>G MTR is associated with the risk of preeclampsia occurrence depending on the presence of a complicated family anamnesis..*

**Keywords:** *preeclampsia, pregnancy, gene, folate cycle genes.*

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## INTRODUCTION:

Preeclampsia (PE) - is a complication of pregnancy, characterizing by the arterial hypertension, proteinuria, oedemata, as well as by deep disorders of the vascular system, hemostasis, immunity, hemodynamics and microcirculation, fetoplacental insufficiency, kidney, hepatic and lungs malfunctions. (Hayashi *et al*, 2007; Sidorova, Nikitina, 2014).

The prevalence of preeclampsia is 4-18% among all pregnant women (Clark *et al*, 2008), and the perinatal mortality rate is 23-27% (Trunova *et al.*, 2011).

An important role in the etiology and pathogenesis of preeclampsia belongs to the folate candidate genes (Vorozhinceva, 2014, Xiaoming *et al*, 2015, Zhou *et al*, 2016). Mutations in the genes of folate metabolism, causing the decrease in the activity of enzymes of methyltetrahydrofolatereductase and methionine synthase reductase, lead to accumulation of homocysteine in the body of a pregnant woman, and to a deficiency of folic acid (Vorozhinceva, 2014; Xiaoming *et al*, 2015). Deficiency of folic acid affects the proliferation of chorionic cells and the formation of placenta. This complicates the course of gestation, increasing the risk of placental insufficiency, preeclampsia and other disorders of prenatal development. The role of candidate genes of folate metabolism in the formation of PE is actively studied, but these studies often give conflicting results for different populations (Obolenska *et al*, 2011; Pavlova *et al*, 2011; Williams *et al*, 2011; Valenzuela *et al*, 2012; Vorozhinceva, 2014; Reilly *et al*, 2014; Xiaoming *et al*, 2015).

## MATERIALS AND METHODS:

### Object of study

The study group included 274 pregnant women, diagnosed with preeclampsia (105 of them with hereditary burden for preeclampsia, 169 pregnant women without genetic predisposition to preeclampsia) and 179 women with normal course of gestation. The average age of women with PE was  $27.19 \pm 6.4$ , in the control group -  $26.71 \pm 6.36$ . All clinical studies were carried out according to the protocols of ethical committee of the Russian Federation, with the informed consent of patients. The criteria for inclusion in the study were the following: Russian nationality, the absence of kinship, living in the Central Black Earth region of Russia.

The exclusion criteria for the sample formation were the following: uterine pathology, pathology of pregnancy, fetal pathology, multifetal pregnancy.

Preeclampsia was diagnosed by the presence of arterial hypertension, proteinuria and generalized oedemata (Turner, 2010).

### Molecular and genetic methods

Typing of the following polymorphic variants of folate cycle genes was carried out for all pregnant women with preeclampsia and pregnant women from the control group: methylenetetrahydrofolatereductase (+677C>T *MTHFR* (rs1801133), +1298A>C *MTHFR* (rs1801131)), methionine synthase reductase (+66A>G *MTRR* (rs1801394)), methionine synthase (+2756A>G *MTR* (rs1805087)), thymidylatesynthetase (-1053C>T *TYMS* (rs699517), IVS 6-68 C>T *TYMS* (rs1059394), -1122A>G *TYMS* (rs2790)). All polymorphic variants of folate cycle enzymes were analyzed using the method of polymerase chain reaction (PCR) of DNA synthesis in real-time (Real-time-PCR).

### Statistical methods

Gene and phenotypic frequencies were calculated using the standard methods. The conformity of the observed distribution of genotypes to the expected one, according to the Hardy-Weinberg equilibrium, was performed using the  $\chi^2$  criterion. The Bonferroni correction was used when carrying out multiple comparisons.

The associations of alleles and genotypes of the studied polymorphic variants with the formation of preeclampsia were assessed using 2x2 conjugation tables, with calculation of  $\chi^2$  criterion, with the Yates correction for continuity and odds ratio (OR), with 95% confidence interval (Schlesselman J., 1982).

## RESULTS:

Significant differences were not revealed in the process of comparative analysis of the frequency distribution of alleles and genotypes of polymorphic markers of folate cycle genes in the group of pregnant women with PE, having hereditary burden, and in the group of healthy pregnant women (taking into account the Bonferroni correction).

In the group of pregnant women with preeclampsia, without hereditary burden, high frequencies of alleles + 2756G *MTR* (33.73%), IVS6-68T *TYMS* (29.01%) and the genotype + 2756GG *MTR* (15.53%) were found, in comparison with the pregnant women from the control group (21.30%, OR=1.61; 95%CI 1.12-2.31;  $\chi^2=6.87$ ; p=0.01; 21.50%, OR=1.49; 95%CI 1.02-2.18;  $\chi^2=4.31$ ; p=0.04; 2.47%, OR=7.26; 95%CI 2.32-25.29;  $\chi^2=15.29$ ; p=0.0007,  $p_{\text{bonf}}=0.0021$ ).

When using Bonferronicorrection, the differences

between pregnant women with PE, without a burdened familial history, and pregnant women from the control group were statistically not significant for the genotype IVS6-68TT *TYMS*.

### DISCUSSION:

The results of this study show, that polymorphism of the methionine synthase gene +2756A>G *MTR* has significant pathogenetic importance for the occurrence of preeclampsia. The allele +2756G *MTR* and the genotype +2756GG *MTR* are associated with a risk of preeclampsia in pregnant women without a burdened familial history.

Methionine synthase (*MTR*) is one of the most important enzymes of folate metabolism. This cytoplasmic enzyme catalyzes the reaction of homocysteine methylation, with its conversion to methionine, using 5-methyltetrahydrofolate as a donor of the methyl group, thereby reducing the concentration of homocysteine in blood. The polymorphism of the gene +2756A>G *MTR* is associated with the replacement of asparagine to glycine at the 919 position of the protein, that may affect its secondary structure, and therefore has a functional significance (Furness et al, 2008).

In other studies on the search for associations of folate cycle genes with the risk of preeclampsia, opposite results were obtained. Thus, in the studies on the Polish, Spanish and South American populations, there was no association of polymorphism of gene +2756A>G *MTR* with the risk of preeclampsia development (Also-Rallo et al, 2005, Pérez-Sepúlveda et al, 2013, Seremak-Mrozikiewicz et al, 2017).

The inconsistency of the results, obtained in various studies, may be related to the differences in the ethnic and, respectively, genetic background of the studied populations (Churnosov et al., 2005; Sorokina et al., 2007; Xiaoming et al, 2015). Even the population of certain regional groups of Russians (Belgorod region, the south of Central Russia, the center of Central Russia) is so genetically diverse, as some of the nations of Western Europe (Germans, Norwegians, etc.) and is significantly higher, than the variability of most ethnic Slavic groups (Bulgarians, Czechs, Poles) (Churnosov et al., 2005; Sorokina et al., 2007). This feature of the Russian gene pool determines the need to take into account the population sample, for which the results are obtained.

### SUMMARY:

Thus, as a result of this study, significant associations of polymorphism of the gene +2756A>G *MTR* with

the risk of preeclampsia were established, depending on the burdened familial history.

### CONCLUSION:

The data, obtained in the process of the research, will make it possible to form risk groups of preeclampsia at the preclinical stage, and to carry out effective preventive measures in these groups. On the other hand, it will allow to predict the nature of the clinical course of disease among patients, that will optimize the therapeutic-diagnostic process for each patient.

### Conflicts of interest

The authors confirm that there are no conflicts of interest.

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