CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1324374

Available online at: http://www.iajps.com Research Article

CANDIDATE GENES AND CLINICAL-LABORATORY PARAMETERS IN PREGNANT WOMEN WITH PREECLAMPSIA

Evgeny A. Reshetnikov, Inna N. Sorokina, Evgeny N. Krikun, Lyubov S. Orlova, Valery I. Evdokimov, Alexandr A. Dolgikov

Belgorod State University, Pobedy Street, 85, Belgorod, 308015, Russia

Abstract:

Objectives: They studied the associations of genetic polymorphisms with clinico-laboratory indicators among pregnant women with preeclampsia depending on hereditary complication.

Materials and Methods: The study was conducted among 274 pregnant women with preeclampsia. They studied the polymorphisms of five folate cycle genes (+677C>T MTHFR (rs1801133), +1298A>C MTHFR (rs1801131), -1053C>T TYMS (rs699517), IVS6-68C>T TYMS (rs1059394), -1122A>G TYMS rs2790).

Results: The genotypes -1053CT TYMS and -1053TT TYMS are associated with an increased level of proteinuria among the pregnant women without a complicated family history. The polymorphisms -1053CT TYMS and -1053TT TYMS, IVS6-68CT TYMS and IVS6-68TT TYMS are associated with a higher level of glucose in blood, and the genotypes +1298S MTHFR and + 1298AC MTHFR are interrelated with an increased activated partial thromboplastin time in the group of pregnant women with a family history.

Conclusions: the performed study determined significant associations of folate metabolism genes with an increased level of proteinuria, glucose, and APTT among pregnant women with preeclampsia, depending on the presence of a complicated family history.

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

*** Corresponding author:**

Evgeny A. Reshetnikov,
Belgorod State University,
Pobedy Street, 85, Belgorod, 308015, Russia
E-mail: Reshetnikov@bsu.edu.ru

QR code

Please cite this article in press Evgeny A. Reshetnikov et al., ***Candidate Genes and Clinical-Laboratory Parameters in Pregnant Women with Preeclampsia.,*** *Indo Am. J. P. Sci, 2018; 05(07).*

INTRODUCTION:

Preeclampsia (PE) - is a complication of pregnancy, arisingin the period of late pregnancy and characterizing by the appearance of oedemata, proteinuria, arterial hypertension, as well as by deep disorders of the vascular system, hemostasis, immunity, hemodynamics and microcirculation, fetoplacental insufficiency, decreased kidney function, liver and lungs functions (Williams et al, 2011; Sidorova, 2016). The frequency of PE is 8-20% among all pregnant Suhih, Murashko, 2010). During the last decade, preeclampsia is one of the main factors of perinatal morbidity in the world, and stably ranks № 3-4 in the structure of the causes of maternal morbidity and mortality (Ajlamazyan, Mozgovaya, 2010, Sidorova, 2016).

Genetic component of PE development can account for up to 50% of all risk factors (Baranov, 2009).

An important role in the etiology and pathogenesis of preeclampsia belongs to the candidategenes of folate metabolism (Vorozhinceva, 2014, Zhou et al., 2016). Mutations in the genes of folate metabolism, causing a decrease in the enzymes activity of methyltetrahydrofolatereductase and methionine synthase reductase, lead to excessive accumulation of homocysteinein the blood and, as a consequence, disruption of methylation processes in cells (Vorozhinceva, 2014). Deficiency of folic acid causes the formation of hypertension in pregnant women, the development of total angiopathy, microthrombosis, the increase of insulin resistance. It should be noted, that the role of candidate gens of folate metabolism in the formation of PE is actively investigated, but these studies often give conflicting results in different populations of the world (Obolenska et al., 2011; Pavlova et al, 2011; Williams et al, 2011; Valenzuela et al. al, 2012; Vorozhinceva, 2014; Reilly et al, 2014).

MATERIALS AND METHODS:

Object of study

The study group included 274 pregnant women, diagnosed with preeclampsia. 105 of them had hereditary burden for preeclampsia and 169 pregnant women hadn't genetic disposition to preeclampsia. The average age of women with PE was 27.19± 6.4. All clinical studies were carried out according to the protocols of ethical committee of the Russian Federation, with the informed consent of the patients. The present study includes persons of Russian nationality, born in the Central Black Earth region of Russia, who do not have genetic relationships. Clinical and laboratory examination of women from the main and control groups was performed at the delivery time, in the Perinatal Center of the Belgorod Regional Clinical Hospital of St. Joasaph.

Oedemata, arterial hypertension and proteinuria were the base for the diagnosis of preeclampsia (Turner, 2010). Exclusion criteria for the formation of the sample were the following: the presence of uterine pathology (uterine fibroids, internal genital abnormalities), pathology of pregnancy (anomalies of placentation and location of placenta, rhesus-conflict), fetal pathology (congenital malformations), multifetal pregnancy.

All pregnant women were examined in laboratory conditions, including: general blood test, coagulogram, biochemical blood test, general urine test (protein, specific gravity, epithelium, leukocytes, cylinders), Nechiporenko test, Zimnitskiy test (leukocytes, erythrocytes).

Molecular and genetic methods

Typing of polymorphic variants of folate cycle genes of methylenetetrahydrofolatereductase (+677C>T *MTHFR* (rs1801133), +1298A>*CMTHFR* (rs1801131)), thymidylatesynthetase (-1053C>T *TYMS* (rs699517), IVS 6-68 *C>TTYMS* (rs1059394), -1122A>G *TYMS* (rs2790)) was carried out for all pregnant women with preeclampsia, and pregnant control group, on the basis of the research laboratory "Human molecular genetics" of Belgorod State National Research University. The material for the study was venous blood, obtained in a volume of 8-9 ml from the ulnar vein of pregnant women. 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

Formation of the database and statistical calculations were carried out using the program "STATISTICA 6.0". 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. In order to minimize the errors of the first kind (false positive results), the Bonferronicorrection was used when carrying out multiple comparisons.

The study of the connections of polymorphic variants with pathogenetically significant continuous characters of PE (blood pressure level, fibrinogen level, prothrombin index, etc.) was carried out using nonparametric statistics (Rebrova, 2006).

RESULTS:

The studied clinical and laboratory parameters (proteinuria, the content of fibrinogen, total protein, urea and creatinine in blood, activated partial thromboplastin time, thrombin time) in pregnant women with preeclampsia are presented in Table 1.

Table 1: The distribution of clinical and laboratory parameters in the study group of women with preeclampsia

Parameters	Lower quartile, (Q25)	Median, (M_e)	Upper quartile, (Q75)	Shapiro-Wilk statistics	Level of significance (p)
Proteinuria, g/l	0.03	0.06	0.12	0.48	0.000000
The content of fibrinogen in blood, g/l	3.70	4.20	5.00	0.98	0.00004
APTT, s	29.00	35.00	37.00	0.97	0.000001
TT, s	14.00	15.00	15.00	0.88	0.000000
The total protein content in blood, g/l	61.00	65.15	69.00	0.99	0.01
Urea content in blood, mmol/l	3.57	4.40	7.10	0.89	0.000000
Creatinine level in blood, μmol/l	64.00	72.00	84.00	0.98	0.0001

Note: APTT - activated partial thromboplastin time, TT - thrombin time.

As a result of the study, it was found, that women with PE, without hereditary burden, with genotypes -1053CT *TYMS* and -1053TT *TYMS,* have higher level of proteinuria (M_e= 0.066 g/l, Q10-Q90 = 0.33-0.163 g/l), than women with the genotype -1053CC *TYMS* for the given locus (M_e= 0.085 g/l, Q10-Q90 = 0.033-0.124 g/l, p = 0.04, respectively).

In pregnant women with PE, having burdened familial history, with genotypes -1053TT *TYMS* and -1053CT *TYMS*, the glucose level in blood (M_e= 4.30 mmol/l, Q10-Q90 = 3.86-4.90 mmol/l) is statistically significantly higher, than that of women with the genotype-1053CC *TYMS* (M_e= 3.8 mmol/l, Q10-Q90 = 3.55-4.25 mmol/l, p = 0.004). In women with PE, with hereditary burden, having the genotypes +1298AC *MTHFR* и +1298CC*MTHFR*, the level of APTT (M_e= 35.0 s, Q25-Q75 = 30.0-36.0 s) is higher, than that of individuals with genotype + 1298AA *MTHFR* (M_e= 30.0 s, Q25-Q75 = 27.50-35.0 s, p = 0.03).

In pregnant women with genotypes IVS6-68CT *TYMS* and IVS6-68TT *TYMS*, the glucose level in blood (M_e= 4.40 g/l, Q25-Q75 = 3.88-4.90 g/l) is higher than in women with genotype IVS6-68CC *TYMS* (M_e= 3.80 g/l, Q25-Q75 = 3.50-4.30 g/l, p = 0.006).

DISCUSSION:

As the results of this study indicate, polymorphisms of folate metabolism genes (+1298A>*CMTHFR*, -1053C>T *TYMS*, IVS 6-68 *C>TTYMS*) have an important pathogenetic significance in the formation of clinical and laboratory parameters in pregnant women with PE. Genetic variants -1053CT *TYMS* and -1053TT *TYMS* are associated with the increased level of proteinuria in the group of pregnant women with PE, without a burdened familial history. Polymorphic variants -1053CT *TYMS* and -1053TT *TYMS*, IVS6-68CT *TYMS* and IVS6-68TT *TYMS* are connected with higher level of glucose in blood, and the genotypes +1298CC *MTHFR* and +1298AC *MTHFR* are associated with an increased APTT, in the group of pregnant women with PE, having a burdened familial history.

The following medical and biological mechanisms can be the base of revealed by us associations of genetic polymorphisms of folate cycle genes with clinical-laboratory parameters of women with PE. The decrease in the activity of folate cycle enzymes (in individuals with genetic variants +1298CC *MTHFR,* +1298AC *MTHFR*) leads to the disruption in the delivery and metabolism of folic acid, the accumulation of homocysteinein the blood plasma and the development of hyperhomocysteinemia (Suhovolskaya et al, 2012). Herewith, homocysteine begins to show its toxic properties, which primarily concern the vessel wall. According to the literature, a high level of homocysteinemia (HC) is a risk factor for the development of both atherosclerotic and thrombogenicvascular diseases. An increase in the concentration of homocysteineincreases oxidative stress, stimulates the production of smooth muscle cells, and alters the elastic properties of the vessel wall (Makacariya, 2004; Zajnulina et al, 2005). The malfunction of microcirculation increases permeability of blood vessels, that leads to deterioration of rheological properties of blood, slowing of blood flow in the microvasculature, increasing of peripheral resistance and, consequently, to hypertension; that, in turn, increases the risk of preeclampsia and the severity of its manifestations (proteinuria, hypoproteinemia) (Bolshakova, 2004; Baranova, 2006).

In various studies on the search for associations of folate cycle genes with clinical-laboratory parameters in pregnant women, conflicting results were obtained. Thus, in the Portuguese population, the genotype +677TT *MTHFR* was associated with a decrease in SBP and DBP, in women with gestational hypertension (Matos et al, 2013). And in the study of Yakut, Buryat and Russian populations, the associations of polymorphism +677C>T *MTHFR*with blood pressure, proteinuria and hypoproteinemiawere not revealed in pregnant women with preeclampsia (Vorozhishcheva, 2014). In a similar study, conducted on the Russian population of Central Russia, there were also no associations of polymorphic marker of gene *MTHFR* with proteinuria and arterial hypertension, in case of preeclampsia (Halford-Knyazeva, 2013).

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). 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 folate metabolism genes with increased levels of proteinuria, glucose, and APTT in pregnant women with preeclampsia were established, depending on the burdened familial history.

CONCLUSION:

The results of this study broaden the concept of molecular and genetic determinants of preeclampsia development. The obtained data can be used in the work of women's consultation clinics and obstetric-gynecologic hospitals, with the purpose to identify the groups with an increased risk of preeclampsia development, among women in preconception period andat the early stages of pregnancy.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

REFERENCES:

1. Ajlamazyan, E.K., Mozgovaya, E.V., 2008. Gestational toxicosis: theory and practice. M.: Publishing house MEDpress-inform.
2. Bailey, L., Gregory, J., 1999. Polymorphisms of methylenetetrahydrofolatereductase and other enzymes: metabolic significance, risks and impact on folate requirement. J Nutr, 129:919-922.
3. Baranov, V.S., 2009. Genetic passport is the basis of individual and predictive medicine. SPb.: Publishing House N-L.
4. Baranova, E.I., Bolshakova, O.O., 2004. Clinical relevance of homocysteinemia (literature review). Arterial hypertension, 1: 12-15.
5. Churnosov, M.I., Pesik, V.Yu., Rudyh, N.A., 2005. Materials on the study of gene pool structure of the Russian population in Central Russia. Medical Genetics, 6 (4): 289a-289.
6. Friedman, G., Goldschmidt, N., Friedlander, Y., Ben-Yehuda, A., Selhub, J., Babaey, S., Mendel, M., Kidron, M., Bar-On, H., 1999. Acommon mutation A1298C in human methylenetetrahydrofolatereductase gene: association with plasma total homocysteineand folate concentrations. J Nutr, 129: 1656-1661.
7. Halford-Knyazeva, I.P., 2013. Genetic markers for the prediction of preeclampsia: extended abstract of Cand. Sci. (Medicine) Dissertation.M., 16p.
8. Matos, A., da Silva, A.P., Maia, H., Ferreira, J., Clode, N., Areias, M.J., Bicho, M.C., Bicho, M., Rebelo, I., 2013. The polymorphism C677T of methylenetetrahydrofolatereductase (MTHFR)

may increase risk for future higher blood pressure in women with previous hypertension in pregnancy. Pregnancy Hypertens., 3(2):69.
9. Obolenska, M.I., Rodrihes, R.R., Martseniuk, O.P., 2011.Folate-relatedprocesses in humanplacenta: gene expression, aminothiols, proliferationandapoptosis. Ukr.Biokhim.Zh., 83(1):5-17.
10. Pavlova, K.K., Trifonova, E.A., Gotovceva, L.V., Maksimova, N.R., Nogovicyna, A.N., Stepanov, V.A., 2010. The role of polymorphisms of genes eNOS, ACE and MTHFR in the development of gestational toxicosisin the Yakut population. Yakut Medical Journal, 3 (31): 28-31.
11. Rebrova, O.Yu., 2006. Statistical analysis of medical data. Application of program package STATISTISA. Moscow: Publishing House Media Sfera.
12. Reilly, R., McNulty, H., Pentieva, K., Strain, J.J., Ward, M., 2014. MTHFR 677TT genotypeanddisease risk: is there a modulating role for B-vitamins? Proc. Nutr. Soc., 73(1):47-56.
13. Sidorova, I.S., 2016. Preeclampsia.M.: Publishing house "Meditsinskoe informatsionnoe agenstvo".
14. Sorokina, I.N., Churnosov, M.I., Balanovskaya, E.V., 2007. Genetic resources of the population of Belgorod region II."Familial portraits" in groups of regions with different levels of division, and the role of migrations in their formation. Genetics, 8 (43): 1120-1128.
15. Strizhakov, A.N., Makacariya, A.D., Timohina, E.V., Bajmuradova, S.M., Kozlova U.A., 2009. Clinical significance of acquired and hereditary forms of thrombophilia in the pathogenesis of intrauterine growth restriction syndrome. Questions of gynecology, obstetrics and perinatology, 8 (2): 16-21.
16. Suhih, G.T., Murashko, L.E., 2010. Preeclampsia.M.: Publishing house GEOTAR-media.
17. Suhovolskaya, M.A., Subbotina, T.N., Olhovskiy, I.A., Bazarin, K.P., 2012. Mutations in the genes of methylenetetrahydrofolatereductase (MTHFR) and methionine synthase (MTR), and risk factors for hyperhomocysteinemiain athletes. Clinical laboratory diagnostics, 9:65.
18. Turner, J.A., 2010. Diagnosis and management of preeclampsia: an update. Int. J. Womens Health, 2: 327-337.
19. Valenzuela, F.J., Pérez-Sepúlveda, A., Torres, M.J., Correa, P., Repetto, G.M., Illanes, S.E., 2012. Pathogenesis of preeclampsia: the genetic component. J Pregnancy, 2012:632732.
20. Vorozhishcheva, A.Yu., 2014. Genetic factors for development of preeclampsia in populations of different ethnic origins: extended abstract of Cand. Sci. (Medicine) Dissertation. Tomsk; 24p.
21. Williams, P.J., Broughton Pipkin F., 2011. The genetics of preeclampsia and other hypertensive disorders of pregnancy. Best Pract Res ClinObstetGynaecol, 25(4):405-417.
22. Zajnulina, M.S., Glotov, A.S., Kornyushina, M.L., 2009. Thrombophilia in obstetric practice. SPb.: Publishing House N-L.
23. Zhou, L., Cheng, L., He, Y., Gu, Y., Wang, Y., Wang, C., 2016. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10, and TNFalpha with preeclampsia in Chinese women. Inflamm Res, 65(9): 717-724.