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The Role of Polymorphism of Hereditary Thrombophilia Candidate Genes in the Development of Arterial Hypertension in Women with Preeclampsia.

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ABSTRACT

Preeclampsia is a severe pregnancy complication that has long been one of the leading causes of maternal and perinatal mortality and morbidity worldwide. Despite the achievements of modern medicine, the etiology of this pathology is not known. Multiple risk factors for the development of PE have been identified: arterial hypertension, diabetes mellitus, obesity, a hereditary history of preeclampsia, thrombophilia, etc., but recently, special attention has been paid to genetic determinants, namely, the contribution of individual polymorphic loci of various genes. In the course of our study, we studied the contribution of the rs5918 and rs1126643 polymorphisms of the *GPIII* and *ITGA2* gene, respectively, associated with the development of hereditary thrombophilia, in the development of arterial hypertension, as one of the main symptoms of preeclampsia. The sample included 455 patients with PE; the average age of women was 26.41 ± 4.92 years. It was found that women with PE with CC genotype of rs5918 polymorphism of the *GPIIIa* gene had a more pronounced increase in blood pressure indicators (the distribution of CC, CT, and TT genotypes was 2.25% (n=10), 25.68% (n=114), 72.07% (n=320)), and with the TT genotype of polymorphism rs1126643 of the *ITGA2* gene, a more pronounced increase in SBP and DBP was observed (the frequency of TT, CT genotypes is 19.06% (n=85), 48.43% (n=216), 32.51% (n=145) respectively). Thus, it was found that the CC rs5918 genotypes of the GPIII gene and TT rs1126643 of the *ITGA2* gene are associated with a more pronounced increase in blood pressure in women with pre-eclampsia by the end of pregnancy.

Keywords: preeclampsia, arterial hypertension, hereditary thrombophilia, rs5918, rs1126643.

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INTRODUCTION

Preeclampsia (PE) is a pathological condition that develops in women during pregnancy (after 20 weeks) or a short time after childbirth, and is accompanied by the development of edema, proteinuria, hypertension, up to multiple organ/multisystem failure/ dysfunction. The global prevalence of PE is 3-6% and remains one of the main causes of maternal and perinatal mortality [Dymara-Konopka et al., 2019].

Despite the large number of studies on the etiology of PE, the leading cause of this disease remains unknown, like of most other diseases [Polonikov et al., 2017, Sirotina et al., 2018, Yarosh et al., 2015]. Risk factors for PE include a family history of PE, diagnosed arterial hypertension before pregnancy, type 1 or type 2 diabetes, overweight (high body mass index), infections and excessive weight gain during pregnancy, chronic kidney disease, and others [Clinical recommendations (treatment protocols) of the Russian Federation, 2016]. Recently, more attention has been paid to the study of molecular biomarkers of PE development, which can be detected even before the onset of clinical signs, which will prevent the development of this disease and significantly reduce the adverse effects on the mother and fetus [Polonikov et al., 2015, Ponomarenko et al., 2019]. Thus, the catchiest as key links in the pathogenesis of PE are such molecular mechanisms as: immune maladaptation, endothelial dysfunction [Reshetnikov et al., 2019], thrombophilic disorders [Reshetnikov et al., 2017], angiogenic imbalance, dyslipidemia, etc. [Reshetnikov et al., 2015]. Most of these mechanisms are based on genetic factors [Serebrova et al., 2018], which are responsible for the development of pathogenic changes [Agius et al., 2018]. The presence of hereditary forms of thrombophilia is associated with an increased risk of early development of PE [Mitriuc et al., 2019] and habitual miscarriage [Pritchard, Ashley M. et al., 2016].

OBJECTIVE

To assess the contribution of rs5918 and rs1126643 polymorphisms of the *GPIII* and *ITGA2* gene, respectively, associated with the development of hereditary thrombophilia, in the development of arterial hypertension in women with preeclampsia.

MATERIAL AND METHODS

The sample consists of 455 patients with PE. The average age of women was 26.41 ± 4.92 years. All women are residents of the Central Black Earth Region of the Russian Federation and have no kinship. All women were measured their blood pressure, both before pregnancy and at the time of delivery. These polymorphic rs5918 loci of the GPIII gene and rs1126643 of the *ITGA2* gene were selected for research based on the available data on their involvement in the hemostatic system [Fedorova et al., 2019], as well as in accordance with their significant regulatory potential (HaploReg v4.1). Processing of statistical data was performed using STATISTICA for Windows v. 8.0 (StatSoft, USA).

RESULTS AND DISCUSSION

The frequency of the CC, CT, and TT genotypes of the polymorphic rs5918 locus of *GPIII* gene among women with PE was 2.25% (n=10), 25.68% (n=114), 72.07% (n=320), and the frequency of the TT, CT, and CC of rs1126643 polymorphism of the *ITGA2* gene was 19.06% (n=85),

48.43% (n=216), 32.51% (n=145), respectively. Women with PE with the CC genotype of polymorphism rs5918 of the *GPIIIa* gene had a more pronounced increase in blood pressure indicators (SBP, DBP, MAP, PBP) by the end of pregnancy. It was also found that women with PE with the TT genotype of rs1126643 polymorphism of the *ITGA2* gene had a more pronounced increase during pregnancy for SBP and DBP (Table).

Table 1: Association of polymorphisms of hereditary thrombophilia *GPIIIa* and *ITGA2* genes with blood pressure values in women with preeclampsia.

Values of blood pressure		Genotypes					
		rs5918 *GPIIIa*			rs1126643 *ITGA2*		
		TT (n=320)	**CT (n=114)**	**CC (n=10)**	TT (n=85)	CT (n=216)	CC (n=145)
SBP, mm Hg	Before pregnancy	110 (110-120)	110 (110-120)	110 (105 -115)	110 (110-120)	110 (110-120)	110 (110-120)
	During pregnancy	130 (110-140)	130 (110-140)	140 (130 -150)	130 (120-140)	130 (110-140)	125 (110-140)
	Friedman ANOVA test, p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
DBP, mm Hg	Before pregnancy	70 (70-80)	70 (70-80)	70 (70-80)	70 (70-80)	70 (70-80)	70 (70-80)
	During pregnancy	80 (70-80)	80 (80-90)	80 (80-100)	80 (80-90)	80 (70-90)	80 (70-90)
	Friedman ANOVA test, p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PBP, mm Hg	Before pregnancy	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)
	During pregnancy	40 (40-50)	42.5 (40-50)	60 (50-60)	40 (40-50)	40 (40-50)	40 (40-50)
	Friedman ANOVA test, p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
MAP, mm Hg	Before pregnancy	83.3 (83.3-86.6)	83.3 (83.3-83.3)	83.3 (83.3-83.3)	83.3(83.3-93.3)	83.3 (83.3-85.0)	83.3(83.3-86.6)
	During pregnancy	96.6 (83.3-106.6)	100 (93.3-106.6)	100 (93.3-116.6)	103.3(83.3-106.6)	96.6 (83.3-106.6)	95.0 (83.3-103.3)
	Friedman ANOVA test, p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Notes: DBP: diastolic blood pressure; MAP: mean arterial pressure; PBP: pulse blood pressure; SBP: systolic blood pressure; ANOVA: analysis of variance; p: value for the Mann-Whitney test. The values of blood pressure level are expressed a median (Me) and interquartile range (Q25 – Q 75).

Many obstetrician-gynecologists regard the presence of hereditary thrombophilia as a risk factor for PE. A sufficient number of studies have been conducted to study the relationship between the Leiden mutation, prothrombin mutation, protein S deficiency, MTHFR C677T and others with late pregnancy complications [Rudzevich et al., 2018]. However, the effect of other mutations leading to a dysfunction in the hemostatic system on the development of PE has not been studied.

We established that the CC genotype of the rs5918 polymorphic locus of the *GPIIIa* gene is associated with a more pronounced dynamics of blood pressure during pregnancy. According to the literature, the genetic polymorphism rs5918 of the platelet fibrinogen receptor *GPIIIa* gene has a significant effect on platelet activity of hemostasis. The GpIIb/IIIa complex is expressed by platelets, which main ligand is fibrinogen. The replacement of thymine with cytosine in exon 2 of the *GPIIIa* gene at position 1565 leads to a replacement in the amino acid sequence of the *GPIIIa* glycoprotein leucine with proline at position 33, which affects the aggregation properties of platelets due to the conformational change in the N-terminal disulfide loop involved in the binding of fibrinogen [Shikhbabaeva et al., 2017].

It was also found that the TT genotype of rs1126643 polymorphism of the *ITGA2* gene is associated with a more pronounced course of SBP and DBP parameters. According to published data, the genetic rs1126643 polymorphism of integrin alpha-2*ITGA2* encoding glycoprotein Ia - one of the components of the blood coagulation system, also affects the thrombotic link of hemostasis. This protein, together with glycoprotein IIa, forms the receptor complex, which is responsible for the interaction of platelets that express it on their surface with the collagen of the vessel wall, which leads to platelet aggregation and the formation of a thrombus. Replacing the cytosine nucleotide with thymine at position 807 in the coding region of the gene, which does not lead to the replacement of the amino acid in the protein, can lead to an increase in the density of receptors on the platelet surface, which will increase the aggregation activity of platelets [Strambovskaya et al., 2014].

CONCLUSION

It was found that the CC rs5918 genotypes of the GPIII gene and TT rs1126643 of the *ITGA2* gene are associated with a more pronounced increase in blood pressure (SBP, DBP, MAP, PBP) in women with pre-eclampsia by the end of pregnancy (Friedman ANOVA test, $p<0.0001$). The frequency of the CC, CT, and TT genotypes of the rs5918 polymorphism of the *GPIIIa* platelet fibrinogen receptor gene among women with PE (the average age of patients is 26.41± 4.92 years) was 2.25% (n=10), 25.68% (n=114), 72.07% (n=320), and the frequency of TT, CT, and CC rs1126643 genotypes of the integrin alpha-2*ITGA2* gene encoding the glycoprotein Ia is 19.06% (n=85), 48.43% (n=216), 32.51% (n=145), respectively.

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