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SPECIFIC INTERACTIONS BETWEEN GENES OF THE HEMOSTASIS SYSTEM, FOLATE CYCLE AND BACKGROUND COMORBID PATHOLOGY IN THE PROGNOSIS OF PREECLAMPSIA

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▪ ***Hypothesis/aims of study.*** The search for early predictors of preeclampsia currently remains relevant. There is still a need to study maternal factors affecting the development of preeclampsia such as intergenic interactions in a pregnant woman with single nucleotide polymorphisms (SNPs) in genes associated with hemostasis system and folate cycle, as well as predictors. The aim of this study was to assess the role of comorbid pathology and gene polymorphism associated with the hemostasis system and folate cycle in predicting preeclampsia in a pregnant woman.

Study design, materials and methods. We examined 158 pregnant women in two study groups, including 92 women with preeclampsia and 66 healthy subjects. Somatic anamnesis of the patients was studied, with the course and outcomes of pregnancy analyzed. The carriage of SNPs in genes involved in hemostasis and the folate cycle was studied once by the method of polymerase chain reaction in real time with amplification of polymorphic loci and restriction analysis using specific endonucleases. The analysis of intergenic interactions was performed using the MDR 3.0.2 program.

Results. Seven genes involved in hemostasis and three genes involved in the folate cycle were studied. The highest entropy of the case-control status for preeclampsia is associated with the locus of coagulation factor *F7* 10976G>A — 9.49% and that of methylenetetrahydrofolate reductase *MTHFR* 677C>T (A223V) — 5.35%. The combination of loci of the tissue plasminogen activator inhibitor-1 gene *SERPINE1 (PAI-1)* and the platelet glycoprotein integrin 1α-2 gene *ITGA2* (*SERPINE1 (PAI-1)* (5G>4G) + *ITGA2* (807C> T)) account for 18.28%, and *SERPINE1 (PAI1)* (5G>4G) + *MTHFR* (677C>T) 14.26% of results. A three-locus synergy model *SERPINE1 (PAI-1)* (5G>4G) + *MTHFR* (677C>T) + *ITGA2* (807C>T) responsible for the development of preeclampsia was obtained, which has a reproducibility of 10/10 and an accuracy of predictions of 84.3%.

Conclusion. Our data indicate a high contribution of the *ITGA2*, *SERPINE1 (PAI-1)*, and *MTHFR* mutations combination to the prediction of preeclampsia.

▪ **Keywords:** intergenic interactions; single nucleotide polymorphism; markers; hemostasis; folate cycle; preeclampsia; plasminogen activator inhibitor-1 gene; alpha-2 integrin gene; methylenetetrahydrofolate reductase gene.

ОСОБЕННОСТИ ВЗАИМОДЕЙСТВИЙ ГЕНОВ СИСТЕМЫ ГЕМОСТАЗА, ФОЛАТНОГО ЦИКЛА И ФОНОВОЙ КОМОРБИДНОЙ ПАТОЛОГИИ В ПРОГНОЗЕ РАЗВИТИЯ ПРЕЭКЛАМПСИИ

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▪ ***Актуальность.*** В настоящее время остается актуальным поиск ранних предикторов развития преэклампсии. Возникает необходимость изучения материнских факторов, влияющих на развитие преэклампсии, — межгенных взаимодействий у беременной с однонуклеотидными полиморфизмами генов, ассоциированных с системой гемостаза и фолатного цикла, а также предикторов этих состояний.

Цель — оценить роль коморбидной патологии и полиморфизма генов, ассоциированных с системой гемостаза и фолатного цикла, в прогнозе развития преэклампсии у беременной.

Материалы и методы исследования. Обследованы 158 беременных, разделенных на две группы: 92 женщины с преэклампсией и 66 условно здоровых пациенток. У пациенток изучен соматический анамнез, проведен анализ течения и исходов беременности. Методом полимеразной цепной реакции в реальном времени однократно исследовано носительство однонуклеотидных полиморфизмов генов, ответственных за систему гемостаза и фолатного цикла. Межгенные взаимодействия проанализированы с использованием программы MDR 3.0.2.

Результаты исследования. Изучено семь генов, ответственных за систему гемостаза, и три гена фолатного цикла. Развитие преэклампсии наиболее часто, по данным исследования случай – контроль, связано с однонуклеотидными полиморфизмами генов коагуляционного фактора *F7* 10976G>A (9,49 %) и метилентетрагидрофолатредуктазы *MTHFR* 677C>T (A223V) (5,35 %). На долю комбинаций однонуклеотидных полиморфизмов гена антагониста тканевого активатора плазминогена *SERPINE1 (PAI-1)* и гена фактора тромбоцитарного гликопротеина интегрина 1α-2 *ITGA2* (*SERPINE1 (PAI-1)* (5G>4G) + *ITGA2* (807C>T)) приходится 18,28 %, а на долю *SERPINE1 (PAI-1)* (5G>4G) + *MTHFR* (677C>T) — 14,26 %. Получена трехлокусная модель синергизма развития преэклампсии *SERPINE1 (PAI-1)* (5G>4G) + *MTHFR* (677C>T) + *ITGA2* (807C>T), которая характеризуется воспроизводимостью 10/10 и точностью предсказаний развития преэклампсии 84,3 %.

Заключение. Полученные данные свидетельствуют о большом значении комбинации однонуклеотидных полиморфизмов в генах *ITGA2*, *SERPINE1 (PAI-1)*, *MTHFR* при формировании преэклампсии.

▪ **Ключевые слова:** межгенные взаимодействия; однонуклеотидный полиморфизм; гены — маркеры системы гемостаза и фолатного цикла; преэклампсия; ингибитор плазминогена I типа, ген интегрина альфа-2; ген метилентетрагидрофолатредуктазы.

Background

Preeclampsia remains one of the leading complications of pregnancy and is classified as Great Obstetrical Syndrome complicating gestation. Although it affects only 3%–8% of pregnant women, preeclampsia is a significant contributor to maternal and infant mortality and affects the health of both the mother and child [1]. According to the World Health Organization, every seventh or eighth maternal death (13%–14%) during gestation, labor, and postpartum is associated with this formidable pathology [2].

Although numerous studies are devoted to searching for important etiological risk factors for preeclampsia due to its medical and social significance, the root cause of this formidable complication of pregnancy was not clarified. Many scientists believe that most reasons, including both environmental and genetic factors, only predispose to the complications of pregnancy, but the trigger mechanism of preeclampsia remains unclear in evidence-based medicine [3, 4].

According to the scientific concept of the last decade, a combination of two conditions is required for initiating preeclampsia, that is, a synergistic effect of maternal factors (genetic, alimentary, and metabolic) and reduced placental blood flow [5, 6]. Because of this concept, a direct correlation between several female diseases and hypertension risk in pregnant women was confirmed.

Thus, an association between preeclampsia and urinary tract infection in pregnant women was identified. In one of the evidence-based studies of American scientists devoted to monitoring 2607 women with urinary tract infections during gestation, preeclampsia was recorded four times more often compared with pregnant women without urinary tract infection (31.1% *vs.* 7.8%) [7]. When studying the risk factors for the clinical prediction of preeclampsia, 3176 and 1010 pregnant women showed a high correlation between the above complication with diabetes mellitus, obesity, arterial hypertension in relatives, and blood pressure level in a woman herself [8, 9].

Preeclampsia is a highly inherited disease. However, the clinical significance of a particular gene, its contribution to preeclampsia, and the possibility of using this marker as a screening test were not established [10].

With the exception of identical twins, the genome of each individual is unique. Gene

polymorphism is characterized by ethnic and individual differences in the genome within the human population [11]. The inheritance of polymorphic gene mutations determines the uniqueness of each individual and the predisposition to certain multifactorial diseases and complications of pregnancy [12, 13]. Since the mechanism of preeclampsia appears to be based on inflammatory processes and endothelial and microcirculatory disorders, which are closely associated with the risk of thrombosis, it is reasonable to search for risk factors causing hypertension during pregnancy in the genomic part responsible for hemostasis [3, 14].

It has been now established that defects in many human genes can lead to disorders in the blood coagulation system. Among these, genes associated with the hemostasis system and folate cycle and classified as single-nucleotide polymorphisms (SNPs) or point mutations are of great importance. Currently, there are numerous publications on the contribution of particular SNP point mutations to multifactorial diseases [15–17]. However, because of the lack of clear mathematical methods for calculating predisposition to certain multifactorial diseases depending on gene polymorphisms, difficulties still remain in the interpretation of a particular result of genetic testing. This is particularly true for diseases mediated by genes and metabolic and environmental factors. These include pathology of the cardiovascular system and hypertension, in particular, hypertensive disorders during pregnancy, as well as preeclampsia [1, 18, 19].

The diagnosis of clinical signs of preeclampsia is usually straightforward, but it is often late. Therefore, the current search for predictors of early screening for this complication of pregnancy currently remains relevant. The investigation of maternal factors influencing preeclampsia, comorbid pathology (to identify risk groups), and gene polymorphism associated with the hemostasis system and folate cycle is necessary to determine the probability of hypertensive disorders during pregnancy.

Aim. The study aimed to assess the role of comorbid pathology and gene polymorphism associated with the hemostasis system and folate cycle in predicting preeclampsia in a pregnant woman.

Study design, materials, and methods

We examined 158 pregnant women residing in the Khanty-Mansi Autonomous Okrug (KMAO), Yugra, who completed their pregnancy in 2018–2019 in Surgut Clinical Perinatal Center (healthcare organization, level 3). Based on the analysis of pregnancy outcomes, labor, and postpartum, all those examined were divided into two groups, including 92 women in the main group with preeclampsia and 66 healthy patients in the control group without any complications.

The criteria for inclusion into the main group were an increase in blood pressure of ≥140/90 mmHg and daily proteinuria of >0.3 g/L, first detected after the week 20 of gestation.

The criteria for noninclusion (exclusion) in the study were human immunodeficiency virus infection, pregnancy after the use of assisted reproductive technologies, and multiple pregnancies.

All patients were tested once before completion of pregnancy for the carriage of SNPs in genes involved in hemostasis and the folate cycle by the method of polymerase chain reaction in real time using a DT-96 detecting amplifier and commercial sets of CardioGenetics Thrombophilia and Genetics of Folate Metabolism produced by DNA-Technologies (Russia). The SNPs in the following genes associated with the hemostasis system and folate cycle were determined in the examined women: *F5*: 1691G>A (Leiden mutation); *F7*: 10976G>A; *F13A1*: 103G>T; *FGB*: –455G>A, *ITGA2*: 807C>T; *ITGB3*: 1565T>C; *SERPINE1 (PAI1)*: –675_5G>4G; *MTHFR*: 677C>T; 1298A>C; *MTR:* 2756A>G; *MTRR*: 66A>G.

The difference in allele frequency between groups was assessed using the Fisher's angular transformation criterion (φ). The values of $p < 0.05$ were considered statistically significant. The odds ratio (OR) with 95% confidence interval (CI) was used to determine the association of preeclampsia with gene alleles involved in hemostasis and the folate cycle. The sensitivity (Se), specificity (Sp), predictive value positive (PVP), predictive value negative (PVN), and diagnostic efficiency (DE) of common somatic factors were determined to search for predictors of preeclampsia.

Intergenic interactions were analyzed by multifactor dimensionality reduction (MDR) using the MDR 3.0.2 open source program.

Table 1 / Таблица 1

Somatic diseases in women with preeclampsia who are carriers of single nucleotide polymorphisms in genes involved in hemostasis and the folate cycle, absolute values (%)

Анализ соматических заболеваний у женщин с преэклампсией, носителей однонуклеотидного полиморфизма генов системы гемостаза и фолатного цикла, абс. знач. (%)

Groups/somatic diseases/statistics	Control group, *n* = 66	Group of women with preeclampsia, *n* = 92
Arterial hypertension	0	50 (54.3%)
Se	54.3; 100%	
PVP	100; 51.2%	
DE	36.8%	
φ; *p*	10.3; <0.01*	
OR, 95% CI	24.90 (1.6–392.0)*	
Renal disorders	3 (4.5%)	30 (32.6%)
Se	32.6; 95.5%	
PVP	93.7; 40.4%	
DE	52.9%	
φ; *p*	4.8; <0.01*	
OR, 95% CI	10.16 (2.95–35.02)*	
Moderate-severe anemia	0	26 (28.3%)
Se	28.3; 100%	
PVP	100; 40%	
DE	51.5%	
φ; *p*	6.9; <0.01*	
OR, 95% CI	13.21 (0.82–212.62)*	
Gestational diabetes mellitus	3 (4.5%)	24 (26.1%)
Se	26.1; 95.5%	
PV	92.3; 38.2%	
DE	48.5%	
φ; *p*	3.98; <0.01*	
OR, 95% CI	7.41 (2.13–25.82)*	
Hepatic disorders	6 (9.1%)	6 (6.5%)
Se	6.5; 90.9%	
PVP	60.0; 31.8%	
DE	33.8%	
φ; *p*	0.60; >0.05	
OR, 95% CI	0.70 (0.22–2.27)	
Thyroid disorders	6 (9.1%)	12 (13.0%)
Se	13.0; 90.9%	
PVP	75.0; 33.3%	
DE	38.2%	
φ; *p*	0.78; >0.05	
OR, 95% CI	1.50 (0.53–4.23)	
Obesity	9 (13.6%)	24 (26.1%)
Se	26.1; 86.4%	
PVP	80.0; 35.9%	
DE	45.5%	
φ; *p*	1.96; >0.05	
OR, 95% CI	2.23 (0.96–5.19)	

N o t e: * The significance of differences is between the preeclampsia patient group and control group. Se, sensitivity; Sp, specificity; PVP, prognostic value positive; PVN, prognostic value negative; DE, diagnostic efficiency; φ, the Fisher's angular transformation criterion; OR, odds ratio; CI, confidence interval.

The study was conducted in accordance with the ethical standards set out in the Declaration of Helsinki and the EU Directives (8/609EC), with voluntary informed consent of the patients to participate in the complex study and approval provided by the local ethics committee.

Results

Age, menarche onset, and residence period in the KMAO did not have statistically significant differences in the study groups. The anamnesis of pregnant women with preeclampsia was found to contain a high percentage of patients with arterial hypertension (54.3%), urinary tract infection (32.6%), moderate-severe anemia (28.6%), gestational diabetes mellitus (26.1%), and obesity (26.1%). Although the above cases revealed low Se (36.8%) and predictive value (52.9%) of the diseases for the interpretation of possible preeclampsia in a true pregnancy, but with high Sp (51.5%) and PVP (48.5%), the DE of these signs of preeclampsia was insufficient (Table 1).

In 69.7% ($\varphi = 8.4$; $p < 0.01$; OR = 35.70; 95% CI [2.3–556.3]) of patients in the main group, the clinical signs of preeclampsia were preceded by hemodynamic disorders in the uterine and fetal blood flow (hemodynamic disorders of degrees IA, IB, and II). This pathology was not found in the control group.

When analyzing the data of the genetic study, a combined carriage of SNPs in genes involved in hemostasis and the folate cycle was found in all patients (100%) of the main and control groups. We identified an association of SNP–675_5G>4G of the plasminogen activator inhibitor [*SERPINE1 (PAI1)*] and 66A>G of the methionine synthase reductase (*MTRR*) gene with preeclampsia. Their frequency in the study group was 78.3% and 82.6% compared with 54.5% and 50.0% in the control group ($p < 0.01$). The 4G allele of the *SERIPNE1 (PAI1)* gene leads to impaired plasminogen production, whereas the G allele of the *MTRR* gene may phenotypically manifest as hyperhomocysteinemia and thrombotic disorders (Table 2).

Table 2 / Таблица 2

Frequency of polymorphisms in genes involved in hemostasis and the folate cycle in women with preeclampsia and in healthy pregnant women, absolute values (%)

Частота полиморфизмов генов — маркеров системы гемостаза и фолатного цикла у женщин с преэклампсией и условно здоровых беременных, абс. знач. (%)

Groups/genes/alleles	Control group, *n* = 66 (%)	Group of women with preeclampsia, *n* = 92 (%)	φ; *p*	OR, 95% CI
F5: 1691G>A (Leiden mutation)				
G/G	66 (100%)	91 (98.9%)	1.29; $p > 0.05$	2.44 (0.12–48.91)
G/A	0	1 (1.1%)		
A/A	0	0		
F7: 10976 G > A				
G/G	59 (89.4%)	80 (86.9%)	1.22; $p > 0.05$	1.50 (0.58–3.86)
G/A	7 (10.6%)	10 (10.9%)		
A/A	0	2 (2.2%)		
F13A1: 103G > T				
G/G	46 (69.7%)	60 (65.2%)	0.59; $p > 0.05$	1.23 (0.63–2.42)
G/T	16 (24.2%)	24 (26.1%)		
T/T	4 (6.01%)	8 (8.7%)		
FGB: –455G > A				
G/G	30 (45.5%)	54 (58.7%)	0.52; $p > 0.05$	1.10 (0.58–2.01)
G/A	27 (41.0%)	30 (32.6%)		
A/A	9 (13.6%)	8 (8.7%)		
SERPINE1 (PAI1): –675_5G > 4G				
5G/5G	30 (45.5%)	20 (21.7%)	**5.00; $p < 0.01$**	**2.58 (1.28–5.20)**
5G/4G	20 (30.3%)	38 (41.3%)		
4G/4G	16 (24.2%)	34 (37.0%)		

End of table 2 / Окончание табл. 2

Groups/genes/alleles	Control group, *n* = 66 (%)	Group of women with preeclampsia, *n* = 92 (%)	φ; *p*	OR, 95% CI
ITGA2: 807C > T				
C/C	36 (54.6%)	44 (47.8%)	0.83; *p* > 0.05	1.31 (0.69–2.47)
C/T	15 (22.7%)	34 (37.0%)		
T/T	15 (22.7%)	14 (15.2%)		
ITGB3: 1565T > C				
T/T	54 (81.8%)	66 (71.7%)	1.48; *p* > 0.05	1.77 (0.82–3.84)
T/C	12 (18.2%)	24 (26.1%)		
C/C	0	2 (2.2%)		
MTHFR: 677C > T				
C/C	36 (54.5%)	54 (58.7%)	0.52; *p* > 0.05	0.84 (0.45–1.60)
C/T	24 (36.4%)	34 (37.0%)		
T/T	6 (9.1%)	4 (4.3%)		
MTHFR: 1298A > C				
A/A	34 (51.5%)	56 (60.9%)	1.55; *p* > 0.05	0.68 (0.36–1.29)
A/C	25 (37.9%)	26 (28.2%)		
C/C	7 (10.6%)	10 (10.9%)		
MTRR: 66A > G				
A/A	33 (50.0%)	16 (17.4%)	**4.04; *p* < 0.01**	**4.75 (2.30–9.79)**
A/G	24 (36.4%)	46 (50.0%)		
G/G	9 (13.6%)	30 (32.6%)		
MTR: 2756A > G				
A/A	36 (54.5%)	58 (63.1%)	1.07; *p* > 0.05	0.70 (0.37–1.34)
A/G	24 (36.4%)	32 (34.7%)		
G/G	6 (9.1%)	2 (2.2%)		

N o t e: φ, the Fisher's angular transformation criterion; OR, odds ratio; CI, confidence interval.

No statistically significant differences were found between the groups in the frequency of carriage of SNPs in other genes involved in the hemostasis system and folate cycle. The development of preeclampsia is affected by intergenic interactions. Therefore, combinations of different loci should be studied. Thus, we simulated the effect of intergenic interactions of various SNPs in genes involved in hemostasis and the folate cycle on preeclampsia using the MDR method. The highest entropy of the case-control status for preeclampsia is associated with the locus of coagulation factor *F7* 10976G>A—9.49% and that of methylenetetrahydrofolate reductase *MTHFR* 677C>T (A223V) — 5.35%. Simultaneously, the intergenic interaction of these loci was weak (1.55%). The combination of SNPs of the *SERIPNE1 (PAI1)*: –675_5G>4G + *ITGA2:* 807C>T account for 18.28% and *PAI1*: –675_5G>4G + *MTHFR*: 677C>T for 14.26% of results (Figure 1). The glycoprotein A2 integrin, which is a subunit of the platelet collagen receptor, von Willebrand factor, and other coagulation factors, is present in this locus combination and increases the rate of platelet adhesion to type 1 collagen and the risk of thrombosis, stroke, and myocardial infarction.

We also generated a three-locus synergy model *SERIPNE1 (PAI1)*: –675_5G>4G + *MTHFR*: 677C>T + *ITGA2*: 807C>T responsible for developing preeclampsia, which has a reproducibility of 10/10, prediction accuracy of 84.3%, and Sp of 97.2%, $X^2 = 11.05$ ($p = 0.0009$).

For the control group, a two-locus synergy model *ITGA2*: 807C>T + *MTHFR*: 1298AC was obtained with a reproducibility of 9/10, prediction accuracy of 74.1%, Se of 66.7%, and Sp of 83.3%, $X^2 = 5.0451$ ($p = 0.0247$). The highest entropy was found in associations of polymorphisms

ITGA2-CT + *MTHFR*: 1298AC — 7.28% and *PAI1*-5G5G + *ITGB*-3TT — 4.43% (Figure 2), which may indicate a protective effect of the combination of these polymorphisms against preeclampsia. For clarification, the second version of locus model contains the glycoprotein A3 integrin, which is also associated with an increased risk of thrombosis leading to cardiovascular pathology and early termination of pregnancy due to thrombotic lesions of the placenta.

At the same time, it should be noted that, according to the literature, the greatest contribution to the impaired blood flow to the placenta and the placental disorders in the decompensation stage is also made by mutations/SNPs — MTHFR: 677C>T — 100% and SERIPNE1 (PAI1): 675_5G>4G — 87% contributing to the development of preeclampsia in equal proportions of both homozygous and heterozygous forms [20]. However, we did not study the contribution of SNP point mutations — ITGA2: 807C>T and the combined effect of the above genes as predictors of the placental disorders.

Discussion of the results

The relevance and complexity of studying the genetic architecture of preeclampsia as a multifactorial disease are beyond doubt. Today, there are approximately 30 theories of the onset of preeclampsia, in which the genetic determinants of disease development are of great importance [21].

Congenital and acquired thrombophilia contribute to preeclampsia as a severe pregnancy complication. The activity of *SERIPNE1 (PAI1)* increases from physiological preparation to ovum implantation, but the endothelial damage can lead to hemostasis disorders and thrombosis. The association between SNPs in *MTHFR* genes and thrombotic disorders during pregnancy was described [3, 20].

According to the latest scientific data, preeclampsia is associated with impaired placentation, incomplete transformation into spiral arteries, impaired vascular remodeling, and endothelial dysfunction development [3, 5]. Here, maternal factors in preeclampsia and placental disorders are a potentiating background for pregnancy pathology. Several studies have reported that endocrine, metabolic, genetic, and alimentary disorders are among the most significant factors preceding the onset of preeclampsia [3, 14, 20]. Since the above disorders/diseases, as well as preeclampsia, are caused by

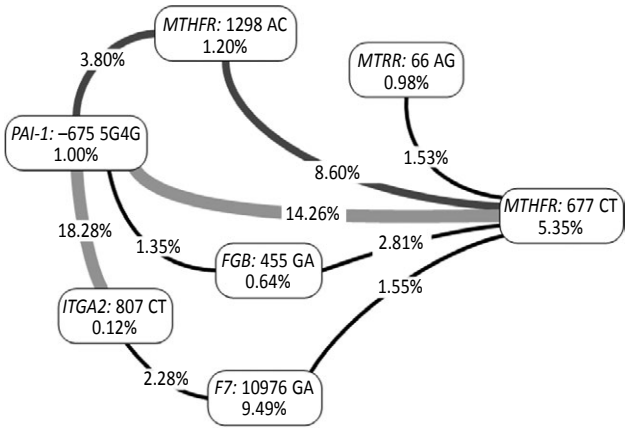

Fig. 1. Intergenic interactions of polymorphic loci of genes involved in hemostasis system and the folate cycle in preeclampsia. Strong synergy (light gray), moderate synergy (dark gray), additive interaction (black); interaction strength and direction is expressed in entropy, %

Рис. 1. Межгенные взаимодействия полиморфных локусов ряда генов системы гемостаза и фолатного цикла на фоне преэклампсии: светло-серый цвет — выраженный синергизм; темно-серый — умеренный синергизм; черный — аддитивное взаимодействие; сила и направленность взаимодействия выражены в процентах

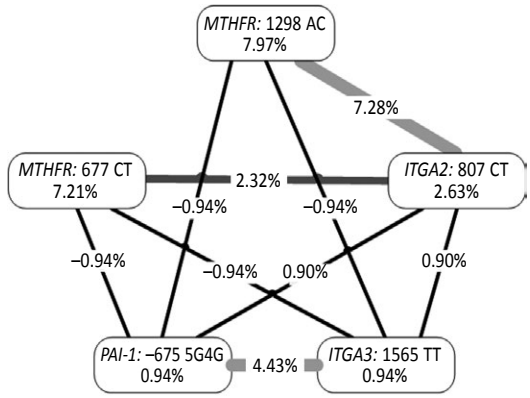

Fig. 2. Intergenic interactions of polymorphic loci of genes involved in hemostasis system and the folate cycle in healthy patients. Strong synergy (light gray), moderate synergy (dark gray), additive interaction (black); interaction strength and direction is expressed in entropy, %

Рис. 2. Межгенные взаимодействия полиморфных локусов ряда генов системы гемостаза и фолатного цикла у условно здоровых пациенток: светло-серый цвет — выраженный синергизм; темно-серый — умеренный синергизм; черный — аддитивное взаимодействие; сила и направленность взаимодействия выражены в процентах

inflammation, endothelial dysfunction, microcirculatory disorders, and defects in the hemostasis system and endothelial cells, this association becomes obvious.

Our study confirmed that somatic diseases such as arterial hypertension (54.3%), renal infection (32.6%), anemia (28.3%), gestational diabetes mellitus (26.1%), and obesity (26.1%) were common in women with preeclampsia in the descending order of frequency. At the same time, the pregnancy was complicated by impaired uterine and fetal blood flow (69.7%), that is, placental disorders. However, the DE of comorbid pathology (arterial hypertension, renal disease, anemia, and gestational diabetes mellitus) in predicting preeclampsia was characterized by low Se (up to 54.3%) and high Sp (up to 100%), and the predictive value was approximately 50% or less for the above diseases.

When analyzing the data of the genetic study for the carriage of genes associated with the hemostasis system and folate cycle, the following SNPs were detected with high frequency in the development of preeclampsia: 675_5G>4G of the plasminogen activator inhibitor gene *SERPINE1 (PAI1)* — 78.3% and 66A>G of the *MTRR* gene — 82.6%. The combinations of *PAI1* SNPs in genes are also common: –675_5G>4G + *ITGA2*: 807C>T, *PAI1*: –675_5G>4G + *MTHFR*: 677C>T, *SERIPNE1 (PAI1)*: –675_5G>4G + *MTHFR*: 677C>T + *ITGA2*: 807C>T. Probably, the combined carriage of SNPs in genes associated with the hemostasis system and folate cycle and responsible for the impairment of the plasminogen activator synthesis, endothelium state, and increased platelet aggregation activation serve as a trigger factor leading to vascular endothelial wall damage, microcirculatory disorders, thrombus formation in the intervillous and vascular space, and impaired trophoblast invasion.

This genotype can be qualified for an early predictor of preeclampsia and, possibly, placental insufficiency. At the same time, all the above genes are considered to be factors with a moderate risk of thrombosis [14].

Conclusion

Assessment of the contribution of comorbid pathology to the development of preeclampsia cannot serve as a method for predicting hypertensive disorders because of low Se and high Sp of clinical signs.

The study of SNPs in genes associated with the hemostasis system and folate cycle [*SERIPNE1 (PAI1)*, *ITGA2*, and *MTHFR*] using a three-locus model can be performed as a screening test for predicting preeclampsia from early pregnancy, since the results obtained indicate a high contribution of SNPs combination in these genes to the formation of preeclampsia.

Since the mechanisms of preeclampsia and cardiovascular pathology are similar, there is a need to further investigate the gene polymorphisms of the renin-angiotensin and kinin-bradykinin systems as well as the combinations of the above SNPs in genes as possible predictors of placental disorders. This will allow the development of a multicomponent screening model for predicting not only preeclampsia but also other pregnancy complications.

The use of the results obtained can be recommended for the prevention of severe forms of placental disorders and preeclampsia during the preconception period after additional studies.

Additional information

Conflict of interest. The authors declare no conflict of interest.

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