Genetic Determinants of Complicated Pregnancy

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Abstract

Objectives: The connections of polymorphic variants of the gene of vasoactive hormones with the level of arterial pressure in pregnant women, depending on the development of preeclampsia (PE), have been studied. Materials and Methods: The study group included 382 pregnant women diagnosed with PE and 205 women with normal pregnancy. Polymorphisms of the endothelin-1 gene rs5370 (G>T EDN1) and guanine-binding protein β3 subunit gene rs2301339 (G>A GNB3) were studied by real-time polymerase chain reaction (PCR) of DNA synthesis (real-time PCR). Results: Women with PE with genotype TT EDN1 have lower values of systolic, diastolic, and mean arterial pressure at the end of pregnancy compared to those with G EDN1 allele (genotypes GG and GT, \( P = 0.01–0.04 \)). Conclusions: Thus, as a result of this study, significant associations of genetic polymorphisms with blood pressure indicators in pregnant women with PE were established.

Key words: Blood pressure, Genetic polymorphism, Preeclampsia, Pregnancy

INTRODUCTION

Recently, there has been a tendency to increase in the frequency of the pathological course of pregnancy, childbirth, the postpartum period in women, and perinatal morbidity and mortality in newborns.[1]

In this regard, the number of research devoted to molecular genetic studies of the complications of pregnancy has been constantly increasing.[2-4]

Preeclampsia (PE) is a complication of pregnancy, characterized by the development of endothelial dysfunction, multiple organ failure, disruption of coagulation and anticoagulation systems, microcirculation, metabolic processes, and immune response.[5]

According to the world literature and the WHO, the incidence of PE is 2–8%.[6,7] PE remains an important cause of maternal, perinatal, and neonatal morbidity and mortality.[7]

Severe PE and eclampsia cause the risk of complications such as hemorrhages and cerebral edema, placental abruption, disseminated intravascular coagulation syndrome, massive obstetric hemorrhages, HELLP syndrome, hemorrhage and rupture of the liver capsule, pulmonary edema, adult respiratory distress syndrome, and acute renal and hepatic insufficiency.[4,7]

According to a number of studies, this complication of pregnancy has a multifactorial nature.[3,8] Local gene networks of PE include endothelial dysfunction genes, vascular reaction genes, growth factor and cytokine genes, and major histocompatibility genes.[9,15]

MATERIALS AND METHODS

The study involved 587 women living in the territory of Central Russia (Belgorod region). The age of women ranged from 20 to 43 years (mean age 27.98 ± 4.50 years). Clinical and laboratory studies of women were conducted in the Perinatal Center of the Belgorod Regional Clinical Hospital (Department of Pathological Pregnancy). Criteria
for inclusion in the study group were (a) Russian nationality, 
(b) gestational age 37–40 weeks, and (c) informed consent 
for the study. Pregnant women with diabetes and liver or 
kidney failure, as well as pregnant women with diabetes 
with a gestation period of <37 weeks and over 40 weeks, 
were excluded from the study. Blood pressure was measured 
3 times according to the recommendations of the American 
Heart Association. Data on blood pressure before 
pregnancy were obtained from case records of every woman. 
Mean blood pressure (MBP, mmHg) was calculated using 
the Hickam formula: MBP = (SBP + 2DBP)/3, where SBP 
is the systolic blood pressure and DBP is the diastolic blood 
pressure. Among 587 pregnant, 205 patients were with a 
physiological course of gestation and 382 women with a 
pregnancy complicated by PE.

PE was defined as the presence of hypertension, accompanied 
by proteinuria, as defined by a 24 h urine protein excretion 
more 300 mg.

Molecular genetic methods

Venous blood (8–9 ml) was drawn from the ulnar vein of 
each woman. Genomic DNA was isolated using the method 
proposed Miller et al. All women underwent typing of 
molecular genetic markers of endothelin-1 (G>T EDN1 
[rs5370]) and β3 subunits of guanine-binding protein 
(G>A GNB3 [rs2301339]).

The selection of polymorphisms was made in accordance 
with the criteria set forth in the paper by Ponomarenko.[19]

Loci genotyping was produced using real-time polymerase 
chain reaction (PCR) by the method of TaqMan probes 
detection according to relative fluorescence unit values of 
each probe on the thermocycler IQ5 with detecting system in 
real time. “Bio-Rad IQ5-Standart Edition” program was used 
for the alleles discrimination.

Statistical analysis

Allele frequencies of the genes polymorphism were estimated 
by the gene counting method, and the Chi-square test was 
used to identify significant departure from Hardy–Weinberg 
equilibrium. The distribution of allele and genotype frequencies 
between the study groups was compared by the Chi-square test 
for 2 × 2 contingency tables. The distribution of the quantitative 
traits such as SBP, DBP, MAP, and pulse pressure (the pressure 
difference between the systolic and diastolic pressures, PPB) 
before and at the end of pregnancy was analyzed by the Shapiro– 
Wilks test. Since the values of the quantitative traits did not 
follow the normal distribution, median (Me) and interquartile 
range (Q25-Q75) were used for their description and intergroup 
comparisons were done using the Mann–Whitney U-test. All 
statistical analyses were performed using STATISTICA for 
Windows v. 6.0 (StatSoft, USA).

RESULTS

The biomedical and clinical characteristics of the study 
women are shown in Table 1.

As a result of studying the relationship of polymorphism 
of endothelin gene 1 G>T EDN1 rs5370 with BP levels in 
women at the end of pregnancy, significant associations 
were established only for pregnant women with PE [Table 2]. 
Women with PE with genotype TT EDN1 have lower values 
of systolic, diastolic, and mean arterial pressure at the end of 
pregnancy compared to those with G EDN1 allele (genotypes 
GG and GT, P = 0.01–0.04).

The study of the relationship between the polymorphism 
of the guanine-binding protein β3 subunit of rs2301339 and 
the blood pressure levels in pregnant women revealed no 
significant associations.

DISCUSSION

The results of this study suggest that G>T EDN1 rs5370 
polymorphism is associated with the level of arterial pressure 
in pregnant women with PE (37–40 weeks). The genotype TT 
EDN1 is associated with lower rates of systolic, diastolic, and 
MBP.

Gene EDN1 is located on the chromosome 06p24. The 
polymorphism studied is due to the replacement of guanine with 
thymine at position 5665 in exon 5 and leads to the replacement 
of the amino acid lysine with asparagine in the 198th codon of
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Table 2: Association rs5370 polymorphism of the endothelin 1 gene with indicators of blood pressure in women at the end of pregnancy, Me (Q25-Q75)

<table>
<thead>
<tr>
<th>Values of blood pressure</th>
<th>Genotypes</th>
<th>TT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>195</td>
<td>10</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>110.0 (110.0–120.0)</td>
<td>110.0 (110.0–115.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>70.0 (70.0–80.0)</td>
<td>70.0 (70.0–75.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>PBP, mmHg</td>
<td>40.0 (40.0–45.0)</td>
<td>40.0 (30.0–40.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>85.0 (83.3–90.0)</td>
<td>83.3 (83.3–83.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>∆MAP, mmHg</td>
<td>3.3 (0.0–8.3)</td>
<td>0.8 (0.0–6.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>∆SBP, mmHg</td>
<td>5.0 (0.0–10.0)</td>
<td>0.0 (0.0–10.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>∆DBP, mmHg</td>
<td>0.0 (0.0–10.0)</td>
<td>0.0 (0.0–5.0)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Pregnant women without preeclampsia (PE) (n=205)

| N                       | 382       |
| SBP, mmHg               | 140.0 (135.0–150.0) | 130.0 (130.0–140.0) | 0.04 |
| DBP, mmHg               | 90.0 (85.0–100.0) | 80.0 (80.0–80.0) | 0.02 |
| PBP, mmHg               | 50.0 (50.0–60.0) | 50.0 (50.0–55.0) | 0.8 |
| MAP, mmHg               | 106.7 (103.3–116.7) | 100.0 (96.7–103.3) | 0.01 |
| ∆MAP, mmHg              | 20.0 (13.3–28.3) | 20.0 (6.7–20.0) | 0.2 |
| ∆SBP, mmHg              | 25.0 (20.0–40.0) | 20.0 (20.0–20.0) | 0.1 |
| ∆DBP, mmHg              | 20.0 (10.0–25.0) | 15.0 (5.0–20.0) | 0.2 |

Pregnant women with PE (n=382)

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PBP: Pulse blood pressure, MAP: Mean arterial pressure, ∆MAP: Change of mean arterial pressure, ∆SBP: Change of systolic blood pressure, ∆DBP: Change of diastolic blood pressure

CONCLUSIONS

Thus, as a result of the study, the relationships of the genetic polymorphisms of vasoactive hormones with the level of blood pressure in women with PE were revealed. Women with genotypes GG and GT EDN1 (rs5370) have higher values of systolic, diastolic, and mean arterial pressure at the end of pregnancy.

Data obtained as a result of the research broaden the understanding of the mechanisms of preeclampsia development, and also allows prediction the nature of the clinical course of the disease, which will ensure the optimization of the treatment and diagnostic process for each patient.

REFERENCES

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