American Journal of Medicine and Medical Sciences 2025, 15(5): 1597-1599
DOI: 10.5923/j.ajmms.20251505.63

The Possibilities of Predicting the Development of Severe Preeclampsia in Low-Risk Women

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Abstract Molecular genetic and clinical predictors have been studied, which can serve as the basis for the development of personalized prediction methods and be used as additional measures for the prevention of severe preeclampsia in somatically healthy patients who do not have known risk factors for preeclampsia.

Keywords Severe preeclampsia, Gene polymorphism, and predication in low-risk women

1. Introduction

According to the United Nations (UN) (2015), 52% of maternal deaths in the modern world are caused by three preventable causes - bleeding, sepsis, and hypertension. According to experts from the WHO (World Health Organization) (2011), the RCOG (Royal College of Obstetricians and Gynaecologists) (2014), and the UN (2015), an appropriate interdisciplinary approach to the treatment and management of patients with hypertensive disorders and preeclampsia can prevent most adverse outcomes for mothers and fetuses.

Currently, there is sufficient information confirming the multifactorial nature of preeclampsia, which results from the combined effects of various factors, including molecular genetic, environmental, and epigenetic factors.. To predict the risk of developing hypertensive disorders and preeclampsia, scientists have been investigating polymorphisms of genes that are involved in the regulation of blood vessel tone and endothelial function. These include:

- alpha-adducin (ADD1-1378G>T)
- angiotensinogen (AGT-704T>C and AGT-521C>T)
- the angiotensin type 1 receptor (AGTR1-1166A>C)
- type 2 angiotensin receptor (AGTR2-1675G>A)
- endothelial nitric oxide synthase (eNOS3-786T>C and eNOS3-894G>C) [4,5,6,7].

At present, there are no specific molecular genetic markers that can be used to accurately predict PE.

The clinical recommendations of professional obstetric and gynecological communities from around the world identify clinico-biological and anamnestic risk factors for hypertensive disorders in pregnant women based on evidence-based medicine. However, in some cases, severe preeclampsia and related obstetric complications develop in mothers without known risk factors.

Our previous studies have shown that preeclampsia is the main cause of critical obstetric conditions among young fertile women, and in over 50% of cases, it occurs in low-risk mothers. This complication can lead to severe consequences for both the mother and the baby.

The purpose of the study was to identify predictors of severe preeclampsia in women with no known risk factors.

2. Materials and Methods

To identify predictors of severe preeclampsia, studies of genetic polymorphisms were conducted and the clinical, anamnestic and laboratory data of 80 somatically healthy patients with confirmed severe preeclampsia (the main group) and 60 women with uncomplicated pregnancy (the control group), comparable in age, social status, parity, obstetric and family history, delivered in maternity hospitals, were analyzed. Tashkent Main criteria for inclusion in the study: maternal age 18-35 years, spontaneous singleton pregnancy, body mass index < 35 kg/m2 in the first trimester of pregnancy, absence of bad habits (alcohol and narcotic drugs), extragenital diseases, family (mother or sister) or individual history of preeclampsia, thrombosis, burdened obstetric history and factors the risk of preeclampsia in the 1st trimester of gestation [9], the woman's consent to participate in the study. The diagnosis of severe preeclampsia was made according to the criteria set out in current national clinical protocols and was based on symptoms such as severe arterial hypertension (systolic blood pressure >160 mmHg, diastolic blood pressure >110 mmHg), proteinuria, as well as one or more criteria for severe preeclampsia, indicating the development of multiple organ failure. insufficiency (HELLP(ELLP) syndrome; persistent headaches, vomiting or other cerebral or visual disorders; oliguria < 500 ml/day, increased creatinine levels;

Received: Mar. 16, 2025; Accepted: Apr. 12, 2025; Published: May 30, 2025
Published online at http://journal.sapub.org/ajmms

edema of the optic disc; increased ALT, AsAT, LDH enzymes; thrombocytopenia and/or its progression; epigastric pain/ upper right quadrant of the abdomen, etc. [8]. Genotyping to identify the polymorphisms of interest was performed on DNA obtained from peripheral blood leukocytes. The polymerase chain reaction with real-time detection of the amplification product was used as a method. The genotype frequencies of the examined patients were checked for compliance with the Hardy-Weinberg law. Statistical processing of the results was performed using the Statistica 10 software package. The reliability of the difference between the two averages was assessed by the Student's criterion (t); between the shares – by the criterion x2. The values were considered statistically significant at $\chi 2>3.84$, at $p<0.05$. The strength of the relationship between the studied polymorphism and the frequency of preeclampsia was assessed by the value of the V-Kramer index and the odds ratio (OR). The confidence intervals (CI) given in the work were constructed for a confidence probability of p=95%.

3. Results and Discussion

The average age of the mothers included in the study ranged from 20 to 35 years and had no significant differences in the compared groups: 31.5±3.3 years (severe PE group) vs. 31.1±3.9 years (control group, p=0.126). Women also had similar body mass indexes (23.6±4.2 kg/m2 vs 24.1±3.2 kg/m2, p=0.093) and an obstetric history: 50% and 44% were primiparous, 50% and 56% had uncomplicated births in the past (px2=0.396), uncomplicated artificial abortion. 48% and 42% (px2=0.688), respectively. When analyzing the frequency of genetic polymorphisms associated with hypertension and the frequency of alleles in the compared clinical groups, we did not find a molecular marker that could claim to be a predictor of severe preeclampsia. Modern research has shown that the probability of developing perinatal and obstetric complications increases with the combination of minor alleles of different genes [5]. At the same time, homozygosity for one functionally defective allele is a high risk factor for gestational complications, and the presence of two or more unfavorable polymorphism alleles of various genes in a heterozygous state may increase the chance of developing this complication [7]. Based on the assumption that the cause of severe PE in young somatically healthy mothers may be a combination of unfavorable alleles of known polymorphisms associated with hypertension, the second stage of the study assessed the combinations of the claimed polymorphisms and the relative risk of developing preeclampsia. Combinations of potentially predictive polymorphisms of the candidate genes of arterial hypertension (px2<0.001; V= 0.287) were registered more often in women with severe preeclampsia, which significantly increased the risk of developing this complication (OR= 9.12; CI 2.63- 31.60).

When entering clinical, anamnestic and laboratory data from patients of the compared groups into the Excel database table, the following variables were obtained: severe preeclampsia, bacteriuria, gestational pyelonephritis, acute respiratory viral infections, cytomegalovirus infection (CMVI), acute nonspecific vaginitis, acute vulvovaginal candidiasis, bacterial vaginosis, trichomoniasis, the presence of chlamydia in cervical samples – dichotomous variables (they take two values), polymorphisms of vasoactive genes (ADD1-1378G>T, AGT-704T>C, AGT-521C>T, AGTR1-1166A>C, AGTR2-1675G>A, eNOS3-786T>C, eNOS3-894G>C) – rank variables, which births are ordinal variables, gestation period and a history of abortions are quantitative variables. The matrix of statistically significant nonparametric correlation coefficients (according to Spearman), constructed at this stage of the work, demonstrates significant relationships ($p<0.05$) between the studied independent variables: a combination of AGTR2-1675AA + eNOS3-786CC genotypes, a history of abortions, bacteriuria, acute respiratory viral infections in the 2-3 trimester of pregnancy, acute vulvovaginitis in the 2-3 trimester of pregnancy and a dependent trait there is "severe preeclampsia" in the equation. Thus, established co-factors can claim to be predictors of severe preeclampsia in young somatically healthy women who do not have known risk factors for this pregnancy complication associated with a high risk of maternal and perinatal morbidity and mortality.

4. Conclusions

The identified molecular-genetic and clinical predictors can serve as the basis for the development of personalized prediction methods and be used as additional preventive measures for severe preeclampsia in somatically healthy patients with no known risk factors for preeclampsia.

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