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THE POSSIBILITIES OF PREDICTING PREECLAMPSIA USING CLINICAL AND GENETIC MARKERS

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Abstract
To date, the search for sensitive and specific biomarkers predicting the development of preeclampsia is extremely important for identifying a high-risk group for this pathology. A case-control study (continuous blind sampling method) was conducted among pregnant women who were delivered in the obstetric hospital of the (sample size 100 people). The use of available clinical and genetic models for predicting the development of preeclampsia is promising, and the data obtained are crucial for the prevention of preeclampsia and related complications.

Keywords: Preeclampsia; pronosis model; genetic polymorphisms.

Introduction

Preeclampsia remains the leading cause of maternal and perinatal morbidity and mortality worldwide. This disease complicates about 3 to 8% of pregnancies [1, 2]. The causes of preeclampsia are still unclear, but modern research indicates a significant role of maternal genetics (genes associated with systemic inflammatory response, endothelial function, angiogenesis and thrombophilic disorders) and epigenetic factors in the development of preeclampsia [3, 4, 5, 6, 7]. At the same time, small sample sizes, genetic heterogeneity of different populations, and diverse environmental factors do not allow us to identify homogeneous genetic associations defined as highly effective biomarkers of preeclampsia. The availability of specific and sensitive predictors is important for the prevention of preeclampsia and its complications affecting the health and life of women and offspring, which determines the relevance of this study [4].

The purpose of the study is to evaluate the effectiveness of a clinical and genetic model for predicting the development of preeclampsia.

Materials and Methods

A case-control study (continuous blind sampling method) was conducted among pregnant women who were delivered in an obstetric hospital (sample size of 100 people). Inclusion criteria: follow-up at a women's clinic, availability of medical documentation, and consent to participate in the study. Exclusion criteria: gestation period of less than 22 weeks, presence of cancer, tuberculosis, severe somatic pathology

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in the stage of decompensation, mental disorders and mental illnesses, alcoholism, drug addiction. Additionally, in order to exclude false positives-

Based on the results of the prognosis of preeclampsia, the study identified women whose pregnancy was not complicated by the development of preeclampsia while using methods to prevent this complication. The research plan complies with the legislation of the Republic of Uzbekistan, international ethical standards and regulatory documents of research organizations. 100 women participated in the study: group 1 (control) – 55 pregnant women without preeclampsia (did not receive preeclampsia prevention), group 2 – 24 patients with moderate and 21 with severe preeclampsia. The family and personal medical history of women, the severity of pregnancy and the outcomes of childbirth were studied. Anamnestic risk factors for preeclampsia (regulated by clinical guidelines [8] and the prognosis scale Hypertension in pregnancy: diagnosis and management (NICE, 2019 [9]), the result-

screening dates for 11-13,6 weeks, measures to prevent the development of preeclampsia. The diagnosis and classifications of nosologies of obstetric pathology were established according to current clinical protocols, the genetic study was performed using reagents from DNA Technology (Russia) on an amplifier detecting DTprime (DNA Technology, Russia), polymorphisms of genes rs1800790 (FGB(-455) G>A, fibrinogen), rs5918 (ITGB3 1565 T>C, integrin beta-3), rs1799889 (PAI-1 (-675) 5G>4G, SERPINE1, plasminogen activator inhibitor-1), rs2010963 (VEGFA (-634) G>C, vascular endothelial growth factor A), rs4762 (AGT 521 C>T, angiotensinogen), rs1403543 (AGTR2 1675 G>A, angiotensin II type 2 receptor), rs1799983 (NOS3 894 G>T, endothelial NO synthase). The distribution of polymorphisms was estimated according to the Hardy-Weinberg law. To predict preeclampsia, we used the clinical and genetic models developed by us, for which the Certificate of state registration of the computer program No. 2024616101 was obtained [10].

Statistical research methods were performed using the licensed statistical software package SPSS Statistica for Windows 17.0. Intergroup differences were assessed using the Mann-Whitney, Kruskal-Wallis, and Pearson hi-squared criteria. The value of $p<0.05$ was considered statistically significant.

Results and Discussion

When analyzing the anamnestic risks of preeclampsia, regulated by current clinical recommendations [8], it turned out that 3 (5.5%) pregnant women in the 1st group had a history of early or severe preeclampsia, 2 (8.3%) - 2nd and 3 (14.3) – 3rd, which became the basis for attribution. These patients are at high risk of developing preeclampsia during their current pregnancy. Additionally, the prediction scale Hypertension in pregnancy: diagnosis and management (NICE, 2019) was used [9]. The most significant predictors of preeclampsia were chronic arterial hypertension and multiple pregnancy. Correct prediction of preeclampsia was performed in 28 (62.2%) cases (66.7% in severe preeclampsia), a false positive prognosis in the control group was given in 17 (30.9%) cases.

All pregnant women who participated in the study underwent prenatal screening at 11-13.6 weeks with the calculation of the risk of preeclampsia based on the software product "Astraia" developed by Fetal Medicine Foundation. Thus, the results of preeclampsia risk screening at 11-13.6 weeks using the Astraia proogram were correct only in 55.6% of cases and proved to be less effective

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compared to the anamnestic prognosis scale Hypertension in pregnancy: diagnosis and management (NICE, 2019) [9]. The prevalence of preventive measures using acetylsalicylic acid from 12-16 weeks in patients with preeclampsia was inadequately low. It should be noted that in patients with moderate preeclampsia, the time to start taking aspirin was significantly shorter, and the frequency of use of the drug was higher than in patients with severe preeclampsia. To test the preeclampsia prognosis models we developed [10], the software product was used in pregnant women who participated in the study. A number of parameters containing anamnestic data, SAD and DBP results during the initial examination at up to 12 weeks of gestation were used for the analysis.

When using an anamnestic model for predicting the development of preeclampsia (moderate/severe), its high sensitivity (86.7%) was noted, but its specificity was rather low (50.9%). The next step to improve the quality of the prognosis of preeclampsia was to additionally use the data on the molecular and genetic characteristics of the patients who participated in the study.

When using the clinical and genetic model for predicting the development of preeclampsia (moderate/severe), its high sensitivity was noted to 96.6% and with a specificity of up to 70%.

Additionally, a model for the prognosis of severe preeclampsia for women without a history of preeclampsia is proposed. The sensitivity of the clinical and genetic model for the prognosis of severe preeclampsia in patients without a history of this pathology was 75%, while the specificity of the model reached 100%. It should be noted that the model allowed to identify an additional 61.5% of patients with moderate preeclampsia.

Today, one of the preferred directions in obstetrics is the search for effective early predictors of preeclampsia for the timely appointment of preventive measures in order to reduce the frequency of its development, shift the timing of manifestation or severity pathology. However, anamnestic prognostic tests of preeclampsia are not always successful, and modern effective biomarkers are often technically and financially inaccessible for use in clinical practice. [3, 5, 7, 11]. Models combining several indicators remain promising for predicting preeclampsia, including body mass index, mean blood pressure, uterine vessel pulsation index, placental growth factor (PlGF), placental protein 13 (PP13), endothelin-1, extracellular microvesicles of endothelial origin CD-144, erythropoietin production adequacy ratio, and others. [3, 5, 7, 11, 12]. We have proposed anamnestic and clinical-genetic models for the prognosis of preeclampsia. At the first visit of a pregnant woman in the first trimester, it is recommended to use an anamnestic prognostic model, which, with high sensitivity (86.7%), makes it possible to identify a risk group for preeclampsia. To improve the quality of prognosis in the selected risk group, it is necessary to conduct molecular genetic research in the volume of AGT C521T (rs4762), AGTR2 G1675A (rs1403543), NOS3 G894T (rs1799983), ITGB3 T1565C (rs5918), FGB G (-455) A (rs1800790), PAI-1 5G (-675) 4G (rs1799889), VEGFA C (-634) G (rs2010963). The productivity of the proposed model can reach 96.6% and surpasses the results obtained in the study of prognostic models Hypertension in pregnancy: diagnosis and management (NICE, 2019) and regulated by current clinical protocols [8]. A special feature of the proposed model is the identification of the clinical and genetic characteristics of pregnant women with no history of preeclampsia.: The sensitivity of this scale was 75%, while the specificity reached 100%. Modern methods of preventing preeclampsia in the

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high-risk group include the use of acetylsalicylic acid at a dose of 150 mg/day from 12-16 weeks and calcium supplements in a continuous regime from the stage of pre-pregnancy preparation until the end of breastfeeding [1, 5, 8]. According to the results of this study, the inadequate use of regulated preventive measures in patients with preeclampsia should be noted.

It should be noted that in women with moderate preeclampsia, the time to start taking acetylsalicylic acid was significantly shorter, and the frequency of use of the drug was higher than in severe preeclampsia, which certainly had a beneficial effect on pregnancy outcomes in these pregnant women.

Conclusion

Modern studies confirm the involvement of a number of predisposition genes in the development of preeclampsia: genes of endothelial NO synthase (eNOS), proteins of the renin-angiotensin-aldosterone system, prothrombin (FII-20210GA), V factor (FVL-1691GA), the enzyme methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor (PAI-)1, the gene vascular endothelial growth factor (VEGF), the leptin gene [4, 7, 13, 14]. These genes are associated with a number of somatic diseases, including metabolic syndrome, which are proven risk factors for preeclampsia [13].

The use of the proposed software products for calculating individual risks of preeclampsia will make it possible to identify high-risk women in a timely manner and ensure adequate preventive measures to improve maternal and perinatal pregnancy outcomes.

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