Article

Polymorphism of Genes of Platelets` Integrins and Fibrinogen as a Risk Factor for Homeostatic Disorders in Preeclampsia

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Abstract: The development of perinatal obstetrics is associated with the need for a detailed study of the pathophysiological mechanisms of preeclampsia (PE).

Materials and methods. A prospective cohort study included 173 patients aged 18-45 years with a singleton pregnancy at a gestational age of 22-41 weeks at the Mordovian Republican Central Clinical Hospital. There were 3 groups: group I (n=63) - pregnant women with moderate PE, group II (n=58) - patients with severe PE, group III (control) (n=52) - pregnant women with physiological pregnancy. The assessment of the prevalence of polymorphic variants of genes was by PCR diagnostics. A laboratory study of hemostasis, microcirculation and thromboelastography (TEG) parameters was performed.

Results. In patients with severe preeclampsia, there is a high prevalence of homozygous C/C variants (46.5%) of the ITGB3 gene and heterozygous C/T variants (55.5%) of the ITGA2 gene, hetero- (G/A) and homozygous (A/A) variants of the fibrinogen gene (FGB) - 48.3 and 36.2%, respectively. It is associated with such hemocoagulation disorders as an increase in the prothrombogenic potential of the blood based on a decrease in the number of platelets, prothrombin time and antithrombin III against the background of an increase in fibrinogen and an increase in the strength and volume of the blood clot according to TEG.

Conclusions. The severity of thrombophilia is associated with the severity of preeclampsia; pathological alleles of the studied genes are most often recorded in patients with severe PE and severe hemostasis disorders.

Keywords: Preeclampsia, hemostasis system, polymorphism, genotype, lipid peroxidation.

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1. Introduction

One of the most severe complications in the group of hypertensive disorders of pregnancy is preeclampsia, the frequency of which ranges from 2 to 8%. The classic criteria for the condition is the Zangemeister's triad, which includes increased blood pressure (›140/90 mm Hg), edema, and proteinuria in the second half of pregnancy [1, 2]. However, preeclampsia causes a lot of damage to other organs and organ systems, involving the cardiovascular, central nervous system, kidneys, liver, etc.

It has been established that preeclampsia is a significant risk factor for metabolic, cardiovascular and cerebrovascular complications. According to the American Heart Association, the occurrence of cardiovascular complications increases significantly in the group of women who have had preeclampsia. Thus, the risk of developing chronic arterial hypertension is three to four times higher, and the risk of heart disease and stroke is two times higher than in women with normal gestation. Moreover, early onset and severe course of preeclampsia is associated with a significantly higher incidence of cardiovascular pathology [3]. Therefore, hypertensive disorders of pregnancy are an important predictor of cardiovascular and cerebrovascular complications.

Despite the relevance of the problem, the issues of the etiology of preeclampsia and its complications are still insufficiently studied. The variety of symptoms and clinical manifestations of preeclampsia suggests heterogeneous pathophysiological pathways of its occurrence.

Currently, in the literature, one of the pathogenetic mechanisms for the development of preeclampsia is impaired remodeling of the spiral arteries. Its result is an increase in the sensitivity of blood vessels to vasoconstrictors, which negatively affects the uteroplacental blood flow, leading to hypoxia and ischemia. Endothelial dysfunction arising in response to hypoxic and ischemic processes in the placenta causes the release of inflammatory factors and triggers a cascade of hypercoagulable disorders, including local microthrombosis, which further impairs tissue microcirculation [4].

In addition, endothelial dysfunction leads to a decrease in vasorelaxant factors such as nitric oxide (NO) and an increase in lipid peroxidation activity and, as a result, reactive oxygen species, which exacerbate oxidative stress during pregnancy [5].

The presence of similar pathophysiological aspects of cardiovascular disease and preeclampsia suggests the presence of a genetic predisposition to the hemocoagulation disorders and related complications.

Purpose of the study. To study the contribution of polymorphism of some genes to the occurrence of hemostatic disorders in preeclampsia.

2. Patients and Methods

A prospective cohort study of 173 patients delivered on the basis of the Mordovian Republican Central Clinical Hospital was carried out. Patients were included in the study based on the clinical recommendations “Hypertensive disorders during pregnancy, childbirth and the postpartum period. Preeclampsia. Eclampsia" (2020). The inclusion criteria were the patient's voluntary informed consent to participate in the study, the age of pregnant women from 18 to 45 years, singleton pregnancy, gestational age of 22-41 weeks, and the absence of severe somatic pathology. In accordance with the purpose and objectives of the study, all pregnant women were divided into 3 groups. The first group consisted of 63 patients with moderate preeclampsia. The second group - 58 pregnant women with severe preeclampsia. The third group (control) included 52 patients with a physiological course of gestation. The parameters of the basical blood test and hemostasiogram were evaluated (analyzers "AutomaticAnalyzer 912" (Hitachi, Japan), "CR-10" (Amelung, Germany), "EsyLyte AVL-9180" (AVL, USA), "SYSMEX KX-21N" (Roch, Germany-France)), the level of malondialdehyde, products of nitric oxide metabolism, enzyme activity was determined by standard biochemical methods. We performed thromboelastography (TEG) (TEG® 5000 (USA)), assessment of microcirculation (LAKK - 02 (Russia)), PCR study of some genes of the hemostatic system (CFX96 Touch™ Real-Time PCR DetectionSystem (USA)). All received data were processed by methods of medical statistics Statistics 13.0.

3. Results

We have studied the main indicators of blood coagulation characteristics in pregnant women with preeclampsia of varying severity. The results demonstrate significant changes in the hemostasis system (Fig. 1).

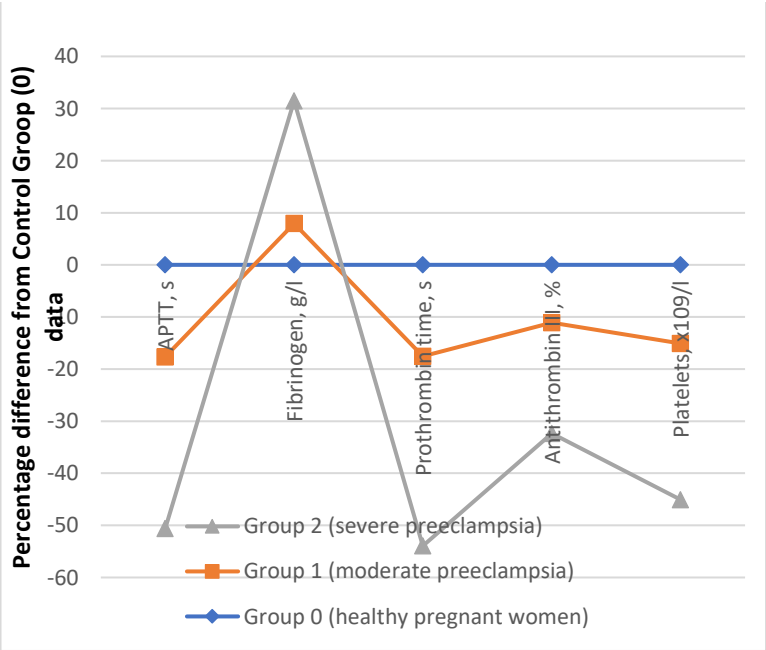

Figure 1. Some indicators difference of hemostasis in pregnant women with PE (M±m)

In the group of pregnant women with moderate preeclampsia, it is recorded a shortening of prothrombin time and aPTT by 17.52% (p<0.05) and 17.65% (p<0.05), relative to the control group. Similar disorders are observed in severe preeclampsia - prothrombin time and APTT are decreased by 36.42% (p<0.05) and 32.98% (p<0.05), relative to the control group and by 22.91% (p<0.05) and 18.62% (p<0.05) relative to similar indicators in moderate PE. At the same time, there is a decrease in the level of antithrombin III and the quantity of platelets in the group of pregnant women with moderate preeclampsia by 11.10% (p<0.05) and 15.11% (p<0.05), respectively, relative to the control group. In second group the level of fibrinogen exceeds that of the control group by 7.94% (p<0.05). In the group of pregnant women with severe preeclampsia, antithrombin III and the quantity of platelet are significantly lower than in the control group by 21.28% (p<0.05) and 29.94% (p<0.05), respectively, and similar indicators in moderate PE by 11.46% (p<0.05) and 17.48% (p<0.05), respectively. Reliably significant changes in hemostatic parameters are indicated by thromboelastography (TEG) (Fig. 2).

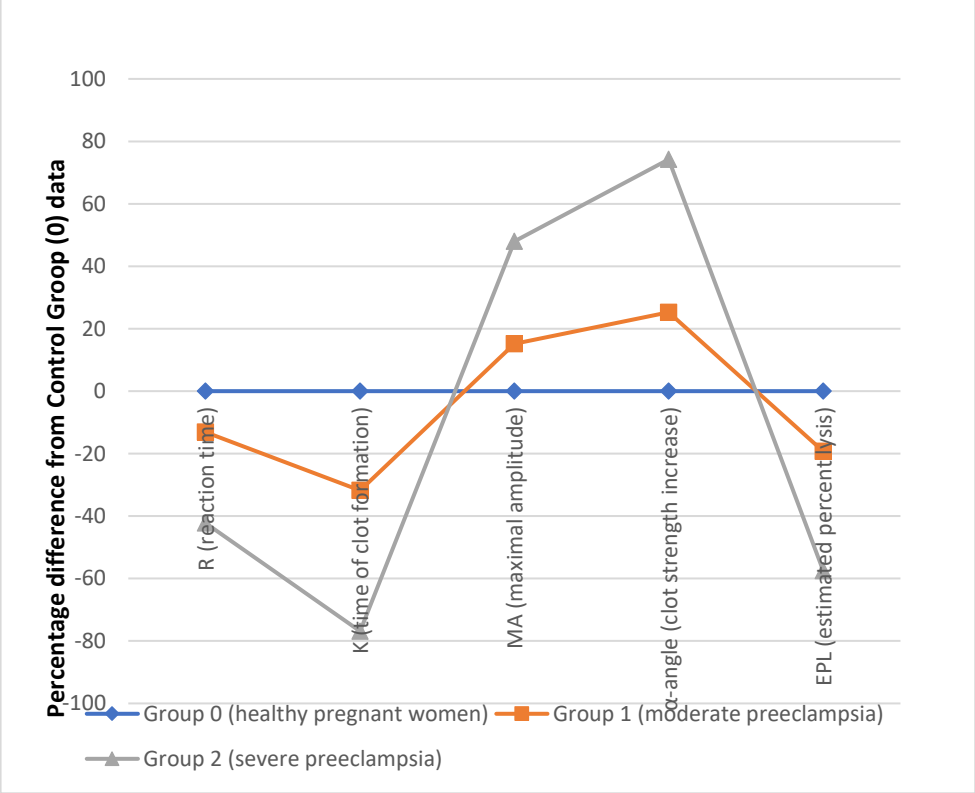

Figure 2. Some indicators of hemostasis in pregnant women with PE according to thromboelatography (M±)

In the group of pregnant women with a moderate course of preeclampsia, it is indicated a decrease in microcirculation, neurogenic tone and index of microcirculation efficiency by 11.97% (p<0.05), 19.66% (p<0.05) and 14.78% (p<0.05) relative to the control group. There is a statistically significant increase in the bypass rate by 25.23% (p<0.05) relative to group 3. In a severe course of preeclampsia, more pronounced changes in the above indicators are most specific against the background of an increase in the activity of myogenic mechanisms of regulation of vascular tone and a decrease in the influence of the neurogenic component.

We analyzed the molecular polymorphisms of the genes of the hemostasis system ((T1565C) ITGB3, (C807T) ITGA2, (G(-455) A) FGB) in pregnant women with varying degrees of preeclampsia.

In the group of women with moderate preeclampsia, the distribution of beta-3 integrin gene (ITGB3) genotypes is: TT genotype - 42.9%, TC genotype - 34.9%, CC genotype - 22.2% ($\chi 2$ = 4.21, p=0.04 and OR=3.0 (1.0–8.7)). Polymorphic variants (C/C, C/T, T/T) of the integrin alpha gene -2 (ITGA2) distributed as follows – 55,5, 27,0 и 17,5% ($\chi 2$=3,4, p=0,06 и OR=2,83 (0,91–8,77)) respectively, and genotype (G/G, G/A, A/A) fibrinogen gene (FGB) – 50,8, 31,7 и 17,5% ($\chi 2$=8,04, p=0,05 и OR=4,43 (1,53–12,8)).

There is a high prevalence of polymorphic variants of the genes of the hemostasis system in case of aggravation of the pathology. Thus, polymorphic variants of the beta-3 integrin gene (T1565T, T1565C and C1565C) account for 20.7%, 32.8% and 46.6% at $\chi 2$=5.84, p=0.01, OR=5.29 (1 .26–22.25), respectively. The prevalence of genetic variants (C807C, C807T and T807T) of the alpha-2 integrin gene is 20.7, 44.8 and 34.5% ($\chi 2$=20.0, p=0.001, OR=12.5 (3.82–42 ,45)) respectively, fibrinogen gene (G(-455) G, G(-455)A and A(-455)A) - 15.5, 48.3 and 36.2% ($\chi 2$=24.3, p=0.001, OR=42.0 (5.1–357.1)). Thus, in the group of patients with pregnancy complicated by preeclampsia, there is an increase in the frequency of occurrence of pathological alleles of the genes of the hemostasis system. Moreover, the maximum frequency of pathological alleles is associated with the aggravation of the pathology.

4. Discussion

It is known that a normal pregnancy is characterized by a hypercoagulable state of the blood, due to an increase in the procoagulant potential, suppression of endogenous anticoagulants and inhibition of the fibrinolytic system. These changes during normal gestation provide a low risk of blood loss during a cytotrophoblast invasion, a childbirth and a postpartum period. [6]. The risk of thrombotic complications increases with the addition of complications in the form of preeclampsia. We note a statistically significant decreasing of prothrombin time and aPTT. Thus, the average prothrombin time in a physiologically proceeding pregnancy, moderate and severe preeclampsia is 15.98±0.87, 13.18±0.54 and 10.16±0.49 sec. respectively. The APTT is shortening to 28.14±1.38 and 22.90±1.41 sec in groups 2 and 3, respectively, in contrast to the normal values in the control group (34.17±1.55). Our data are consistent with the results of the BhutaniN and others study, which shows a shortening of the prothrombin time as the pathology worsens (10.9 s, 10.1 s and 9.8 s, respectively), while the average APTT in the control group and in preeclampsia of varying severity was 26.68 s, 26.71 and 26.25 s. respectively. A decrease in the quantity of platelets, a shortening of the prothrombin time and aPTT indicate significant violations of the coagulation cascade. Moreover, similar changes in the above hemostasiological parameters are characteristic of DIC.

In our study, laboratory changes in hemostasis are confirmed by TEG. The clot formation time (K), α-angle and maximum amplitude (MA) reflect the physical properties of the blood clot - its relative density and size - and correlate with the level of fibrinogen and the quantity of platelets. In the group of pregnant women with moderate preeclampsia, there is a statistically significant decrease in clot formation time (K) and reaction time (R) compared with the control group - by 31.79% ($p<0.05$) and 13.11% ($p<0.05$), respectively. At the same time, α-angle, maximum amplitude (MA) and clot strength (G) are increased by 25.26% ($p<0.05$), 15.17% ($p<0.05$) and 30.72 % ($p<0.05$), respectively.

The data obtained, together with a laboratory-recorded increase in the level of fibrinogen and a decrease in the quantity of platelets, suggest the presence of significant hypercoagulable changes, as well as an increase in the size and density of the blood clot in women with preeclampsia of varying severity. Our study is consistent with the results of other studies [7, 8, 9]. However, in the work of Wang, M. et al. opposite results of studies are showed - in pregnant women with preeclampsia, the average values of R and K were higher than in the control group, at the same time, there was a decrease in the average values of MA and α-angle [10]. Thus, pathophysiological changes in hemostasis in preeclampsia require further research.

The deterioration of microcirculation closes the vicious circle of pathogenesis. In the study, there is an increase in the myogenic component of regulation against the background of a decrease in neurogenic tone with a decrease in the index and the efficiency of microcirculation, which ultimately leads to a deterioration in uteroplacental blood flow. In our study, the genetic aspects of the development of preeclampsia are studied too. It is known that the receptor responsible for platelet adhesion to the surface of subendothelial collagen is alpha-2 integrin (ITGA2). Polymorphism of the C807T gene of the ITGA2 gene causes structural changes in the above receptor, which leads to an increase in the platelet adhesion rate and, as a result, the development of thrombotic complications [11]. In the group of pregnant women with moderate and severe preeclampsia, there is a high frequency of prothrombogenic alleles of the genes of the hemostasis system affecting plasmic and platelet hemostasis, which is consistent with the study by Borodina I. E. et al. [12]. In addition, our results are consistent with the studies of Bakirov B. A. et al., and confirm the increase in the adhesive properties of platelets in patients with mutations in the ITGA2 and ITGB3 genes [13]. Moreover, in modern literature there is information that the presence of a homo- or heterozygous mutation of the ITGB3 gene is associated with resistance to the antiplatelet effect of aspirin [14].

5. Conclusions

Preeclampsia is characterized by pronounced changes in the coagulation properties of blood, which leads to disruption of microcirculation in tissues and deterioration of uteroplacental blood flow. Moreover, the aggravation of the pathology is associated with more pronounced changes in these disorders. The degree of changes in these pathophysiological components is associated with polymorphism of the genes of the hemostasis system. Thus, a comprehensive assessment of hemostatic factors in the carriage of mutant alleles of the (T1565C) ITGB3, (C807T) ITGA2, (G(-455) A) FGB) genes can be an effective predictor of adverse obstetric and perinatal outcomes.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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