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EVALUATION OF NITRIC OXIDE SYNTHASE LEVELS IN WOMEN WITH HYPERTENSIVE DISORDERS DURING PREGNANCY

Actuality. *Preeclampsia (PE) is a polyetiological hypertensive disorder (HD) that develops in women after the 20th week of pregnancy. It is characterized by elevated blood pressure and proteinuria. This condition adversely affects the health of both the mother and the fetus and can lead to various complications. Despite numerous studies, the pathogenesis of PE remains poorly understood. However, there is compelling evidence that endothelial dysfunction (ED) and endotheliosis (ES) play significant roles in its development. ED impairs the vessels' ability to relax, while ES damages the structure of the endothelium. Both conditions are interrelated in the pathogenesis of PE. Nitric oxide (NO) is a crucial factor in the regulation of vascular tone, and its synthesis is controlled by the enzyme called endothelial NO-synthase (eNOS). In the context of PE, decreased enzyme activity can lead to reduced NO synthesis. This, in turn, impairs the relaxation of the vascular wall and contributes to the development of ED. Although the role of eNOS in the pathogenesis of PE is currently under debate, measuring its concentration could be clinically relevant for women with HD.*

The aim of the research. *To evaluate the level of endothelial NO-synthase in women with hypertensive disorders during pregnancy.*

Materials and methods. *Sixty-five women in the 3rd trimester of pregnancy, who were registered in the Advisory and Diagnostic Department of the Communal Non-profit Enterprise «Regional Perinatal Center» of the Zaporizhzhia Regional Council, participated in the study. The main group consisted of 35 women with singleton pregnancies, the course of which was complicated by gestational hypertension without significant proteinuria (GH), moderate or severe preeclampsia (PE). The control group consisted of 30 women with singleton pregnancies, the course of which was uncomplicated and concluded with physiological delivery. All pregnant women had their serum eNOS concentration measured by enzyme-linked immunosorbent assay (ELISA).*

Research results. *According to the study results, the average eNOS concentration in the main group was 414.44±20.06 pg/ml (σ = 118.69), while in the control group it was 1347.21±72.05 pg/ml (σ = 394.61). This difference is statistically significant ($p < 0.001$). Correlation analysis revealed an inverse relationship between the eNOS level and the severity of PE (ρ = -0.581, $p < 0.001$).*

Conclusions. *The level of eNOS in the peripheral blood serum of women whose pregnancy was complicated by hypertensive disorders was significantly lower compared to that in pregnant women without hypertensive disorders ($p < 0.001$). The average eNOS concentration in pregnant women with clinical manifestations of hypertensive disorders was 414.44±20.06 pg/ml. This was more than three times lower than the corresponding level in pregnant women without clinical manifestations, which was 1347.21±72.05 pg/ml. According to the results of the correlation analysis, an inverse relationship was established between the level of eNOS and the severity of hypertensive disorders (ρ = -0.581, $p < 0.001$).*

Key words: *eNOS, endothelial dysfunction, endothelial NO synthase, endotheliosis, gestational hypertension, hypertensive disorders, nitric oxide, NO, pregnancy, preeclampsia.*

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ОЦІНЮВАННЯ РІВНЯ ЕНДОТЕЛІАЛЬНОЇ NO-СИНТАЗИ У ЖІНОК З ГІПЕРТЕНЗИВНИМИ РОЗЛАДАМИ ПІД ЧАС ВАГІТНОСТІ

Актуальність. *Прееклампсія (ПЕ) – це поліетіологічний гіпертензивний розлад (ГР), який розвивається у жінок після 20-го тижня вагітності і проявляється підвищенням артеріального тиску та протеїнурію. Цей стан негативно впливає на стан здоров'я матері і плода та може призводити до розвитку різноманітних ускладнень. Незважаючи на велику кількість фундаментальних досліджень, патогенез розвитку ПЕ на сьогоднішній день залишається остаточно не з'ясованим, але існують надійні свідчення, що ендотеліальна дисфункція (ЕД) та ендотеліоз (ЕЗ) відіграють важливу роль у ньому. Процеси ЕД знижують здатність судин до релаксації, а ЕЗ пошкоджує структуру ендотелію. Обидва ці стани взаємодіють у патогенезі ПЕ. Оксид азоту (NO) є важливим фактором у регуляції судинного тонусу, а його синтез контролюється ферментом ендотеліальна NO-синтаза (eNOS). У контексті патогенезу ПЕ зниження активності ферменту може призвести до зменшення синтезу NO, що, у свою чергу викликає порушення релаксації судинної стінки та веде до розвитку ЕД. Хоча на сьогодні існує дискусія про роль eNOS у патогенезі ПЕ, визначення його концентрації може бути клінічно доцільним для жінок з ГР.*

Мета дослідження*. Дати оцінку рівня eNOS у жінок з гіпертензивними розладами під час вагітності.*

Матеріали та методи*. У дослідженні взяли участь 65 жінок в III триместрі вагітності, які знаходились на обліку в консультативно-діагностичному відділенні Комунального некомерційного підприємства «Обласний перинатальний центр» Запорізької обласної ради. Основна група складалася з 35 жінок, з одноплідною вагітністю, перебіг якої був ускладнений гестаційною гіпертензією без значної протеїнурії (ГГ), помірною або важкою ПЕ. Контрольна група складалася з 30 жінок з одноплідною вагітністю, перебіг якої не було ускладнено, і яка завершилась фізіологічними пологами. Всім вагітним було проведено визначення концентрації eNOS у сироватці крові шляхом ферментного імуноферментного аналіз (ELISA).*

Результати дослідження. *За результатами проведеного дослідження встановлено, що середнє значення концентрації eNOS у основній групі сановило 414.44±20.06 пг/мл (σ = 118.69), а у контрольній групі – 1347.21±72.05 пг/мл (σ = 394.61). Ця відмінність є статистично значимою (p < 0,001). Кореляційний аналіз виявив зворотний зв'язок між рівнем eNOS та ступенем тяжкості ПЕ (ρ = -0.581, p < 0.001).*

Висновки. *Рівень eNOS у сироватці периферичної крові жінок, вагітність яких була ускладнена гіпертензивними розладами був достовірно нижчим у порівнянні з вагітними без гіпертензивних розладів (p < 0,001). Середній показник концентрації eNOS у вагітних з клінічними проявами гіпертензивних розладів становив 414.44±20.06 пг/мл, що було в три рази нижчим за відповідний показник у вагітних без клінічних проявів – 1347.21±72.05 пг/мл. Згідно з результатами кореляційного аналізу між рівнем eNOS та ступенем тяжкості гіпертензивних розладів встановлено зворотний зв'язок (ρ = -0.581, p < 0.001).*

Ключові слова: *вагітність, гіпертензивні розлади, гестаційна гіпертензія, ендотеліальна дисфункція, ендотеліальна NO-синтаза, ендотеліоз, оксид азоту, прееклампсія, eNOS, NO.*

Introduction. Actuality. Preeclampsia (PE) is a multifactorial hypertensive disorder (HD) that occurs in pregnant women after 20 weeks of gestation and is characterized by the presence of elevated blood pressure and proteinuria (ACOG, 2020). This condition poses significant risks for both the mother and the fetus because it can lead to serious complications, such as severe disruptions in utero-fetal-placental hemodynamics, fetal growth restriction, premature birth, severe multiple organ failure, and in extreme cases, the development of eclamptic attacks, and even death for both the mother and the fetus (Poon et al, 2019).

Despite the numerous fundamental studies, the pathogenesis of PE remains uncertain today. According to existing studies, there is no doubt that endothelial dysfunction (ED) and endotheliosis (ES) play significant roles in its development. ED is a functional disorder characterized by a reduced ability of vessels to relax and results from an imbalance between vasodilating and vasoconstricting factors produced by the endothelium (Joyner, 2018). In turn, ES is a pathological condition directly characterized by structural damage to the endothelium. It manifests as thickening of vessel walls, deterioration of vascular tone, increased vascular permeability, and thrombus formation (Schuster et al, 2021). Both conditions can coexist and interact in the pathogenesis of diseases like PE.

Nitric oxide (NO) is one of the important vasodilating factors that ensure endothelial relaxation and the regulation of vasomotor tone. It also has pronounced antioxidant and anti-inflammatory effects (Pautz et al, 2021). Some studies link the development of ED and ES to oxidative stress (OS), which manifests as an increase in the production of reactive oxygen species (ROS) and nitrogen species (RNS). An excess of these species can disrupt interactions between endothelial cells and activate proliferation and inflammation processes. This disruption hinders the synthesis and action of vasodilating factors like NO, leading to increased synthesis of vasoconstrictors (Aouache et al, 2018). These changes contribute to vasoconstriction, impaired blood flow, and are typical manifestations of ED. Additionally, ROS and RNS can directly damage endothelial cells, causing apoptosis and thus becoming one of the contributing factors to the occurrence of ES itself [Belenichev et al, 2015; Chen et al, 2017).

Endothelial NO-synthase (eNOS) is one of the enzymes responsible for NO synthesis. There is evidence of a significant decrease in the levels of eNOS and NO in the placenta of women who suffered from PE during pregnancy (Kim et al, 2018; Motta-Mejia et al, 2017). According to some studies, changes in the concentration of eNOS may be associated with a decrease in the enzyme's expression or an alteration in its phosphorylation due to the overproduction of soluble tyrosine kinase-1 (sFlt-1) (Viveka et al, 2021). In the context of the pathogenesis of PE, a decrease in enzyme activity, attributed to reduced concentration, can lead to decreased NO synthesis. This, in turn, impairs the relaxation of the vascular wall and contributes to the development of ED (Boulanger et al, 2019; Shaheen et al, 2021). Additionally, a low concentration of eNOS can contribute to the intensification of OS and the associated phenomenon of damage to endothelial cells, as well as the development of ES. These phenomena can lead to vascular disorders and hypertension, symptoms that are characteristic of PE (Melchiorre et al, 2022).

There are several studies that show the concentration of eNOS in peripheral blood can be significantly reduced in pregnant women with PE compared to healthy pregnant women. This reduction may be associated with ED, leading to impaired synthesis and release of NO, which may contribute to the development of hypertension and other vascular disorders characteristic of this condition (Guerby et al, 2019; Guerby et al, 2021; Shaheen et al, 2020). However, some studies have not confirmed such a connection. According to these studies, no significant differences in eNOS concentration levels were detected between similar groups of pregnant women. This inconsistency may be due to elevated levels of NO in the blood of PE patients, potentially caused by the activation of other pathways for NO synthesis, aside from eNOS (Dymara-Konopka et al, 2019).

Thus, the concentration of eNOS in peripheral blood may be associated with the clinical manifestations of PE, indicating the feasibility of its determination in this group of women.

The aim of the research. To evaluate the level of endothelial NO-synthase in women with hypertensive disorders during pregnancy.

Materials and methods. Sixty-five women in the 3rd trimester of pregnancy, who were registered in the Advisory and Diagnostic Department of the Communal Non-profit Enterprise «Regional Perinatal Center» of the Zaporizhzhia Regional Council, participated in the study.

The main group consisted of 35 women with a singleton pregnancy, the course of which was complicated by gestational hypertension without significant proteinuria (GH), moderate or severe PE. The diagnosis was established in accordance with the current clinical guidelines of the Ministry of Health of Ukraine. Criteria for establishing diagnoses: GH – arterial hypertension (AH) (systolic pressure ≥ 140 mm Hg and diastolic pressure ≥ 90 mm Hg), which occurred after 20 weeks of pregnancy without pathological proteinuria or other organic disorders, and blood pressure normalizes during the 6 weeks of the postpartum period. GH can progress to PE. Moderate PE is a multi-systemic syndrome manifested after 20 weeks of pregnancy by an increase in blood pressure in the range of: systolic pressure – 140-159 mm Hg, diastolic pressure – 90-109 mm Hg and proteinuria. Severe PE is defined as severe hypertension (systolic pressure ≥ 160 mm Hg or diastolic pressure ≥ 110 mm Hg) and proteinuria, or hypertension of any degree and one or more of the following

symptoms: severe headache; visual impairment; edema of the optic disc; pain in the epigastric region, nausea or vomiting; pain in the right hypochondrium or tenderness on palpation of the liver; increased tendon reflexes; generalized edema; oliguria (diuresis < 0.5 ml/kg/hour); the number of platelets is below 100 x 10^9/l; increased level of transaminases (AST and/or ALT > 70 IU/l); fetal growth restriction (Ministry of Health of Ukraine, 2022).

Exclusion criteria from the main group: multiple pregnancy; chronic arterial hypertension; type 1 or type 2 diabetes; acute kidney diseases and chronic kidney failure; autoimmune diseases (systemic lupus erythematosus or antiphospholipid syndrome); pregnancy due to assisted reproductive technologies; concomitant severe gynecological pathology; severe extragenital pathology (EGP).

The control group consisted of 30 women with a singleton pregnancy in whom no hypertensive complications were noted, and their course and delivery were physiological (Ministry of Health of Ukraine, 2022).

The average examination term was 29.94±0.24 weeks (σ = 1.39) in the main group and 29.40±0.23 weeks (σ = 1.25) in the control group, with no statistically significant difference ($p > 0.05$). The average age of pregnant women was 30.31±0.96 years in the main group and 28.53±0.80 years in the control group, and the difference was not statistically significant ($p > 0.05$). Based on anamnestic data, no statistically significant differences were found between the main and control groups in terms of social and professional status ($p > 0.05$).

In both study groups, obstetric history, concomitant diseases, and the course of current and previous pregnancies were considered. All subjects also underwent a comprehensive clinical and biochemical examination, including the determination of serum eNOS concentration using enzyme-linked immunosorbent assay (ELISA).

Ultrasound examinations were performed using the "MyLab50" device ("Esaote", Italy) with Doppler to assess condition of the fetus and feto-placental hemodynamics.

All subjects gave birth at the Communal Non-profit Enterprise "Regional Perinatal Center" of the Zaporizhzhya Regional Council. Management and delivery for the women in the studied groups were conducted in accordance with the current guidelines from the Ministry of Health of Ukraine. Initial assessments of the newborns, early physiological adaptation and medical care were administered in compliance with these guidelines. All newborns were evaluated using the Apgar scale, and the degree of respiratory failure was determined based on the Downes scale.

The research adheres to modern ethical and moral guidelines, including the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP), the Declaration of Helsinki (1964), and the Conference of the Council of Europe on Human Rights and Biomedicine, as well as current legislative acts of Ukraine. All women provided informed consent to participate in the study.

Statistical data analysis was conducted using licensed software packages Microsoft Excel and STATISTICA 13. The hypothesis about the normal distribution of the studied variables was tested with the Shapiro-Wilk test. The statistical significance of differences was assessed using the Student's t-test for independent samples and the non-parametric Mann-Whitney U-test. Pearson's Chi-square test was used for categorical variables within groups. Spearman's correlation coefficient was utilized for calculating correlations.

Research results. According to medical history data, 31.43% of participants in the main group were experiencing their first pregnancy, compared to 56.67% in the control group. This difference was not statistically significant ($p > 0.05$). In the main group, 60% of women were expecting their first child, compared to 66,67% in the control group; this difference was also not statistically significant ($p > 0.05$).

All women in the main group experienced elevated blood pressure. The average time at which elevated blood pressure was first noted was 30.71±0.82 weeks ($\sigma = 4.84$). No cases of hypertension were observed in the control group.

According to the study results, the distribution of the severity HD in the main group was as follows: GH was observed in 31.43% of the participants, moderate PE in 42.86%, and severe PE in the remaining 25.71% (Fig. 1).

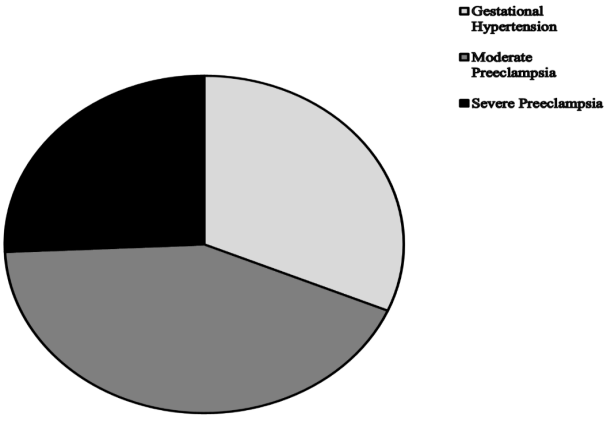

Fig. 1. Distribution of severity of hypertensive disorders in the main group

The average systolic blood pressure in the main group was 155.14±2.47 mm Hg (σ = 14.63), compared to 111.67±1.5 mm Hg in the control group (σ = 8.24). This difference was statistically significant ($p < 0.001$). The average diastolic blood pressure in the main group was 101.71±1.04 mm Hg (σ = 6.18), compared to 70.17±1.6 mm Hg in the control group (σ = 8.76). This difference was also statistically significant ($p < 0.001$). The average level of proteinuria in the main group was 1.71±0.33 g/l (σ = 1.94), compared to 0.0093±0.0108 g/l in the control group (σ = 0.01). The difference between the groups was statistically significant ($p < 0.001$).

The analysis of the research data revealed the presence of various forms of EGP in all pregnant women in the main group, compared to 43.33% in the control group – a difference that was statistically significant ($p < 0.001$). Importantly, a moderate positive correlation was found between the presence of EGP and the severity of PE ($\rho = 0.591$, $p < 0.001$).

HD during previous pregnancies were observed in 34.29% of women in the main group; no such cases were found in the control group.

Regarding the course of pregnancy, threatened abortion was recorded in 17.14% of women in the main group and in 3.33% in the control group; this difference was not statistically significant ($p > 0.05$). Cervical insufficiency was noted in 5.71% of women in the main group and 3.33% in the control group ($p > 0.05$). The threat of premature birth was seen 2.89 times more frequently in the main group (77.14%) compared to the control group (26,67%), a difference that was statistically significant ($p < 0.05$).

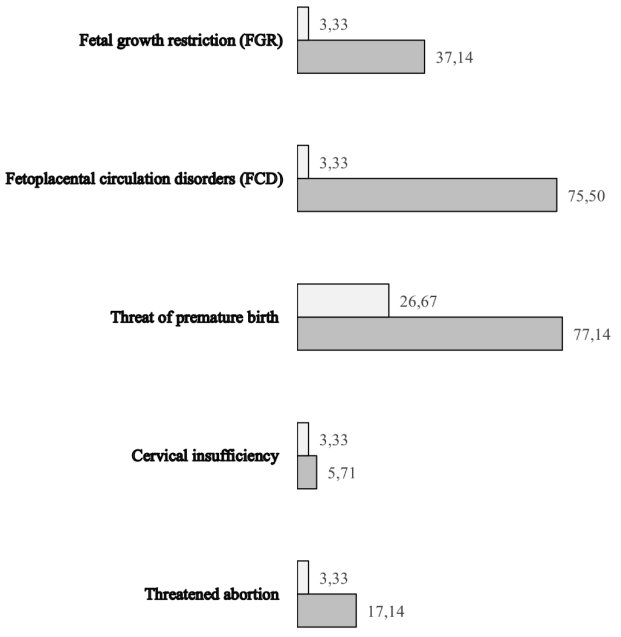

Fig. 2. Characterization of the course of pregnancy in the study groups

Fetoplacental circulation disorders (FCD) were recorded in 80% of cases in the main group. In contrast, such conditions were noted in only 3.33% of cases in the control group, a difference that was statistically significant ($p < 0.001$). Fetal growth restriction (FGR) was observed in 37.14% of pregnant women in the main group and in 3.33% in the control group; this difference was also statistically significant ($p < 0.05$) (Fig. 2).

According to the results of the immunoenzymatic analysis conducted using the ELISA, the average concentration of eNOS in the main group was 414.44±20.06 pg/ml (σ = 118.69), while in the control group, the average eNOS concentration was approximately three times higher, at 1347.21±72.05 pg/ml (σ = 394.61). This difference was statistically significant ($p < 0.001$) (fig. 3).

Correlation analysis revealed an inverse relationship between the level of eNOS and the severity of PE ($\rho = -0.581$, $p < 0.001$).

Discussion. The conducted study demonstrates a statistically significant decrease ($p < 0.001$) in eNOS levels in women with hypertensive disorders during pregnancy compared to the control group. This observation supports the hypothesis that the concentration and activity of eNOS play an important role in the pathogenesis of hypertensive states in pregnant women, aligning with the findings of several similar studies. For instance, Kim S. et al. highlight the molecular mechanisms regulating eNOS synthesis (Kim et al, 2018). Their research focuses on the role of inflammatory cytokines, particularly TNFα, whose activity contributes to the increased concentration of microRNA-31-5p, leading to a decrease in the mRNA stability of the enzyme and causing post-transcriptional reduction in the concentration and activity of eNOS. While our study concentrates on the clinical aspects of the consequences of reducing this enzyme's concentration, both studies can complement each other.

It should be noted that the study by Laskowska M. et al., similar to ours, focused on the enzyme's concentration in maternal peripheral blood, showed no significant differences in eNOS levels between pregnant women with hypertensive disorders and uncomplicated pregnancies. However, this study found increased levels of asymmetric dimethylarginine (ADMA) in this group. This may indicate that the mechanisms behind the development of endothelial dysfunction and hypertensive disorders during pregnancy are multifactorial, and various biochemical pathways can lead to reduced NO bioavailability (Dymara-Konopka et al, 2019).

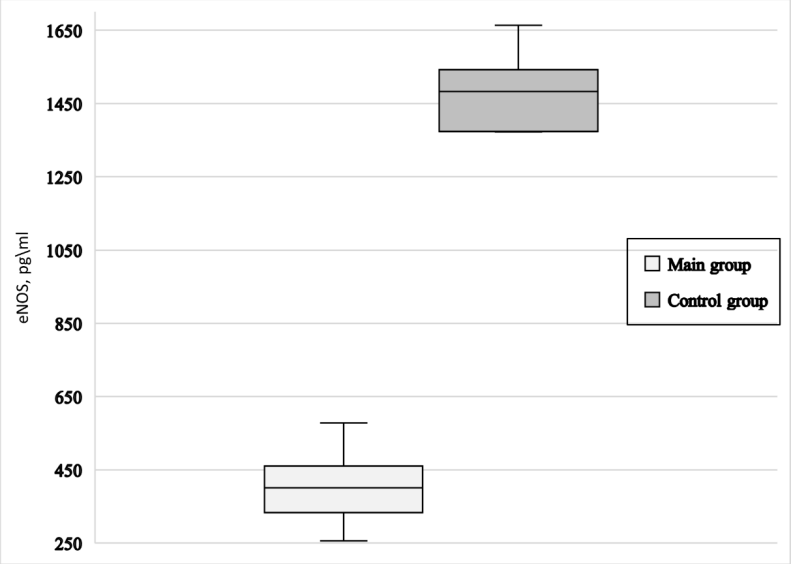

Fig. 3. Average value of eNOS concentration in study groups

Our study identified an inverse correlation between the level of eNOS and the severity of hypertensive disorders, suggesting the potential role of eNOS as a marker in the diagnosis of hypertensive disorders in pregnancy. This is supported by the results of other studies, which also showed a relationship between decreased NO bioavailability and increased blood pressure in pregnant women.

The results of our study highlight the role of eNOS in the pathogenesis of hypertensive disorders during pregnancy, yet emphasize the need for further comprehensive research to develop effective prevention and treatment strategies for this complication.

Conclusions

The course of pregnancy in women with hypertensive disorders is characterized by a statistically significant decrease in the level of endothelial Nitric Oxide Synthase (eNOS) compared to pregnant women without hypertensive disorders ($p < 0.001$). The average concentration of eNOS in the main group, consisting of pregnant women with clinical manifestations of hypertensive disorders, was 414.44±20.06 pg/ml. This was three times lower than the corresponding level in the control group of pregnant women without clinical manifestations of hypertensive disorders, which was 1347.21±72.05 pg/ml. These findings are further supported by correlation analysis, which reveals a significant relationship between the level of eNOS and the severity of hypertensive disorders ($\rho = -0.581$, $p < 0.001$)

Prospects for further research. In the further development of this research, it appears promising to deepen the understanding of the pathogenetic mechanisms of preeclampsia, with a focus on the significance of oxidative and nitrosative stress. It is essential to thoroughly investigate how the imbalance between pro-oxidants and antioxidants, along with changes in the concentration of nitrosylated proteins, affects endothelial function, contributing to the development of hypertensive conditions during pregnancy.

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