АНАЛИЗ ФАКТОРОВ, ОТРАЖАЮЩИХ РАЗВИТИЕ СТЕРИЛЬНОГО ВОСПАЛЕНИЯ, НА ФОНЕ РАЗЛИЧНЫХ СХЕМ ГИПОТЕНЗИВНОЙ ТЕРАПИИ У БЕРЕМЕННЫХ С ПРЕЭКЛАМПСИЕЙ

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Резюме. Считается, что системное воспаление и эндотелиальная дисфункция играют значимую роль в патогенезе ПЭ. Оценить эндотелиальную дисфункцию возможно по степени поражения эндотелиального гликокаликса (эГК). эГК представляет собой поверхностный слой клеток, связанных с эндотелиальной мембраной, и обеспечивает все функции эндотелиальной клетки. Его повреждение можно оценить по уровню циркулирующих его компонентов в материнской крови. Пациентки с ПЭ в основном получают антигипертензивную терапию в объеме только метилдопы («Допегит») или в комбинации с нифедипином («Кордафлекс»). И до сих пор нет данных о влиянии данных препаратов на провоспалительный фон сосудов. Целью нашего исследования было определение уровней IL-6, IL-18, TNFα, галектина-3, гомоцистеина и синдекана-1 (структурного компонента эГК), отражающих развитие системного воспалительного ответа и эндотелиальной дисфункции в крови женщин с ранней и поздней ПЭ, получающих разные схемы антигипертензивной терапии. В данное интервенционное продольное пилотное исследование вошли 82 пациентки. Все пациентки были подобраны методом подбора пар с учетом срока беременности и ИМТ. Группу сравнения составили 15 пациенток до 34 недель и 15 – после 34 недель беременности. Опытная подгруппа 1 состояла из 12 пациенток с ранней ПЭ, получающих только «Допегит», и 16 пациенток с ранней ПЭ, получающих «Допегит» совместно с «Кордафлексом». Опытная подгруппа 2 включала 12 пациенток с поздней ПЭ, получающих «Допегит», и 12 пациенток с поздней ПЭ на комбинированной терапии. В результате исследования оказалось, что уровень только IL-6 был статистически значимо выше у пациенток с ранней ПЭ вне зависимости от типа лечения. Провоспалительный фон был более выражен при поздней ПЭ. Уровень IL-6 был значимо повышен у пациенток с поздней ПЭ на монотерапии «Допегитом». Уровни IL-6 и TNFα были значимо выше у пациенток, получающих «Допегит» + «Кордафлекс» в сравнении

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с контролем. Уровень синдекана-1 был значимо повышен у пациенток с ранней ПЭ, получающих только «Допегит». Не было выявлено статистически значимых различий в уровне синдекана-1 между группами при поздней ПЭ несмотря на его статистически незначимо повышенные уровни у данных пациенток. Уровни галектина-3 и гомоцистеина также значимо не различались между группами, что свидетельствует об отсутствии выраженной воспалительной реакции и эндотелиальной дисфункции у пациенток с ПЭ.

Ключевые слова: преэклампсия, эндотелиальный гликокаликс, эндотелиальная дисфункция, воспаление, антигипертензивные препараты

ANALYSIS OF FACTORS ASSOCIATED WITH STERILE INFLAMMATION IN WOMEN WITH PE RECEIVING DIFFERENT ANTIHYPERTENSIVE TREATMENT STRATEGIES

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Abstract. Systemic inflammation alongside endothelial dysfunction is considered to play a crucial role in PE pathogenesis. Endothelial dysfunction can be assessed by endothelial glycocalyx (eGC) damage. eGC is a superficial layer of cells associated with endothelial membrane that provides all endothelial cells functions. Its damage can be evaluated by the levels of its circulating components in blood. Patients with PE generally receive methyldopa (Dopegyt) solely or in combination with nifedipine (Cordaflex), and there is no understanding of their effect on proinflammatory state of blood vessels. Our study aimed to assess levels of IL-6, IL-18, TNFα, galektin-3 and homocysteine as well as levels of syndecan-1, eCG structural component, representing system inflammatory response and endothelial dysfunction development in blood of women with early- and late-onset PE receiving different antihypertensive treatment strategies. Eighty-two patients were enrolled into this interventional longitudinal pilot study. The comparison group included 15 patients before 34 gestational weeks and 15 patients after 34 weeks. Study subgroup 1 included 12 patients with early-onset PE receiving Dopegyt solely and 16 patients with early-onset PE receiving Dopegyt together with Cordaflex. Study subgroup 2 included 12 patients with late-onset PE receiving Dopegyt solely and 12 patients with late-onset PE receiving combined therapy. As for early-onset PE, only IL-6 demonstrated statistically significant differences in patients receiving both treatment strategies compared to control. Proinflammatory state was more profound in late-onset PE. IL-6 levels were significantly increased in late-onset PE treated with Dopegyt. IL-6 and TNFα levels were significantly higher in late-onset PE patients treated with Dopegyt + Cordaflex compared to control. Syndecan-1 levels were statistically significantly higher in patients with early-onset PE treated with Dopegyt solely. There were no statistically significant differences between the groups despite elevated mean values of syndecan-1 in late-onset PE. Galectin-3 and homocysteine levels did not differ significantly between the groups, representing lack of pronounced inflammatory response and endothelial dysfunction.

Keywords: preeclampsia, endothelial glycocalyx, endothelial dysfunction, sterile inflammation, antihypertensive drugs

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Introduction

Preeclampsia (PE) remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Alongside with risks that face the mother and fetus, there is proof that women with the history of PE have long-term risk of cardiovascular diseases. Prolonged system inflammation and as a result endothelial dysfunction cause changes in cardiovascular system in PE. Sterile inflammation in contrast to infectious etiological factor is considered to be one of the leading triggers of PE [1, 11].

According to present beliefs, there are two clinical phenotypes of PE, i.e. early-onset PE that manifest before 34 gestational weeks and late-onset PE with its debut after 34 weeks. Generally healthy pregnant women develop early-onset PE with impaired placentation being the main cause leading to formation of proinflammatory milieu in placental tissues [11]. Since extragenital maternal pathology is a risk factor of late-onset PE its rate is higher than that of early-onset PE, i.e. chronic arterial hypertension, inherited and acquired thrombophilia, diabetes mellitus ant other diseases accompanied by proinflammatory state and endothelial activation. Placental stress as a result of hypoxia-ischemic changes of placental tissues [12] leads to formation of molecular patterns associated with damage (DAMPs). DAMPs activate maternal immune system. Thus, vicious circle forms leading to permanent endothelial activation transforming into endothelial dysfunction. Clinically these processes manifest with loss of the ability to hold physiological blood pressure (BP), "capillary leakage" syndrome of different severity and proadgesive, thrombogenic state. According to recent findings, these symptoms are a result of endothelial dysfunction that starts with dysfunction of superficial layer of cells associated with endothelial membrane, endothelial glycocalix (eGC) [16].

Antihypertensive therapy in pregnancy is limited by a small number of drugs that are safe for the mother and the fetus and do not affect feto-placental blood flow. Standard antihypertensive treatment strategies represented by monotherapy with methyldopa (Dopegyt) or alongside with nifedipine (Cordaflex) have demonstrated stabilizing effect on cardiovascular eGC state. However, eGC destruction evaluated by the level of circulating structural components of eGC did not occur only in late-onset PE [8]. It should be noted that effect of these medicines on eGC has not been fully studied yet [14]. In particular, there is no information on their action on proinflammatory state in vessels, especially in terms of evaluation of complex of parameters produced by activated immune cells (cytokines), endothelium (cytokines and homocysteine), eGC components (syndecan-1) and associated molecules (galectin-3).

Aim of this study was an assessment of immune factors and biochemical parameters representing system inflammatory response and endothelial dysfunction development in blood of women with early- and late-onset PE receiving antihypertensive monotherapy and combined treatment.

Materials and methods

Eighty-two patients were enrolled into this interventional longitudinal pilot study. The comparison group included 30 pregnant women: i. 15 patients before 34 gestational weeks, and ii. 15 patients after 34 weeks (NP1 and NP2 groups, respectively). Study group comprised 52 patients that were stratified by gestational age and type of antihypertensive treatment. Study subgroup 1 included 28 patients before 34 weeks: 12 patients with early-onset PE receiving Dopegyt solely (subgroup PE 1); and 16 patients with early-onset PE receiving Dopegyt together with Cordaflex (subgroup PE 2). Study subgroup 2 included 24 patients after 34 weeks: 12 patients with late-onset PE receiving Dopegyt solely (subgroup PE 3); and 12 patients with late-onset PE receiving combined therapy (subgroup PE 4). The study was conducted on the basis of NSBI "National Medical research center for obstetrics, gynecology and perinatology named after academician V.I. Kulakov" (further in the text Center) in accordance with the principles of WMA Declaration of Helsinki. Study design was approved at local ethical committee (protocol № 5, May, 27th, 2021). Preeclampsia was diagnosed according to the clinical recommendations of Ministry of Health of Russian Federation criteria [11]. Inclusion criterion for the study group was PE and for the comparison group – healthy pregnancy. Non-inclusion criteria were as follows: ART pregnancy, severe extragenital disease, history of organ transplantation, immunotherapy in pregnancy. Exclusion criteria were HELLP-syndrome, acute viral and infectious diseases during pregnancy. Patients were matched by age, BMI, gestational term. All patients signed informed consent. Antihypertensive therapy comprised of drug of central action, Dopegyt (mean daily dose 1500 mg). When there was insufficient hypotensive effect, additional Ca-channel blocker, Cordaflex, was prescribed (mean daily dose 40 mg). Mean therapy duration was at least 11 days. In order to assess effectiveness of given therapy 24-hor BP monitoring was performed (BPLab® device, Peter Telegin, Nizhniy Novgorod, Russia).

Fasting blood samples were collected into vacuum test-tubes. Preparation of blood serum was performed according to standard operation procedure of Center Biobank where probes were stored at -80°C till factors analysis. Humoral factors were studied by ELISA using commercial test-systems. We used test-systems for identification of desquamated forms of eGC structural component, syndecan-1 (SEB966Hu, Cloud-Clone Corp., USA); identification of cytokines – IL-18 (BMS267-2, Bender MedSystem, Austria), IL-6 (A-8768, Vector-Best, Russia), TNFα (BMS223-4, Bender MedSystem, Austria), galektin-3 (BMS279-4, Bender MedSystem, Austria) and homocysteine (FHCY100, Axis-Shield, United Kingdom).

We used the program MedCalc version 16.4 (MedCalc, Belgium) for statistical analysis of obtained data. The normality of distribution of studied characteristics was assessed using Shapiro–Wilk test. The nonparametric Mann–Whitney U test was used. Data are represented as median and interquartile range for continuous variables. Differences were considered significant when p-value was less than 0.5. We included data with p-value less than 0.1 considered as a trend in changes into our pilot study.

Results and discussion

Typical feature of inflammatory response, including that caused by non-infectious agents, is an increase in proinflammatory cytokines and factors, thus proving endothelium activation. An increase in gene expression of cytokines in placenta and in blood levels of IL-18, IL-6, and TNFα was reported in PE [1, 6, 7, 10]. Proinflammatory milieu induces eGC destabilization which in turn reduces protective layer of endothelium proteoglycans and destroys composition of their carbohydrate chains [16]. Meanwhile, blood levels of circulating proteoglycans and molecules normally bound to glycocalyx rise.

An elevation of shed forms of eGC proteoglycans in blood of patients with PE was demonstrated [15], as well as an increase in galectin-3, secreted car-

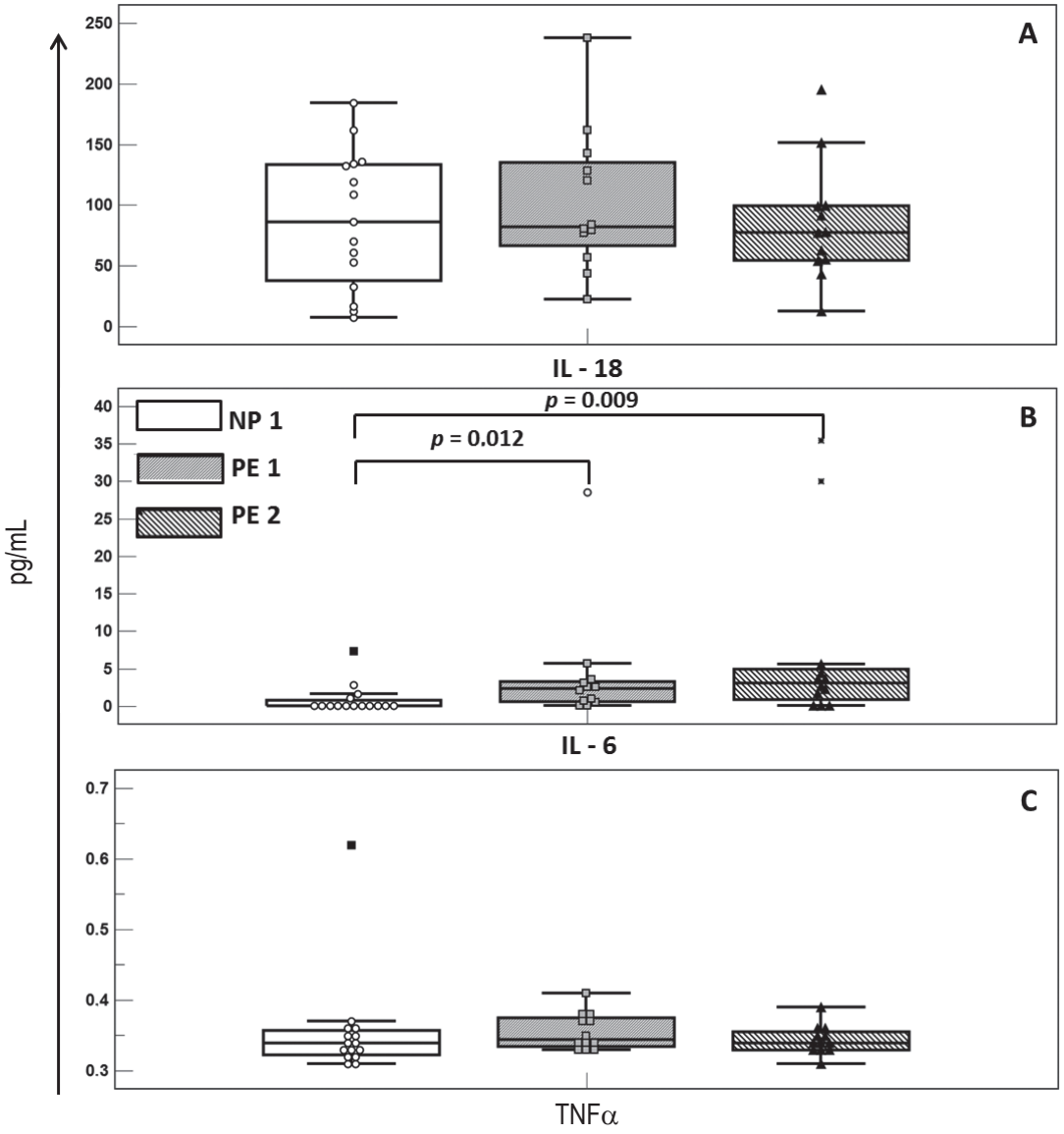

Figure 1. IL-18 (A), IL-6 (B), and TNFα (C) levels in peripheral blood of patients with early-onset PE, receiving Dopegyt and Dopegyt + Cordaflex

Note. Differences are given at p < 0.1.

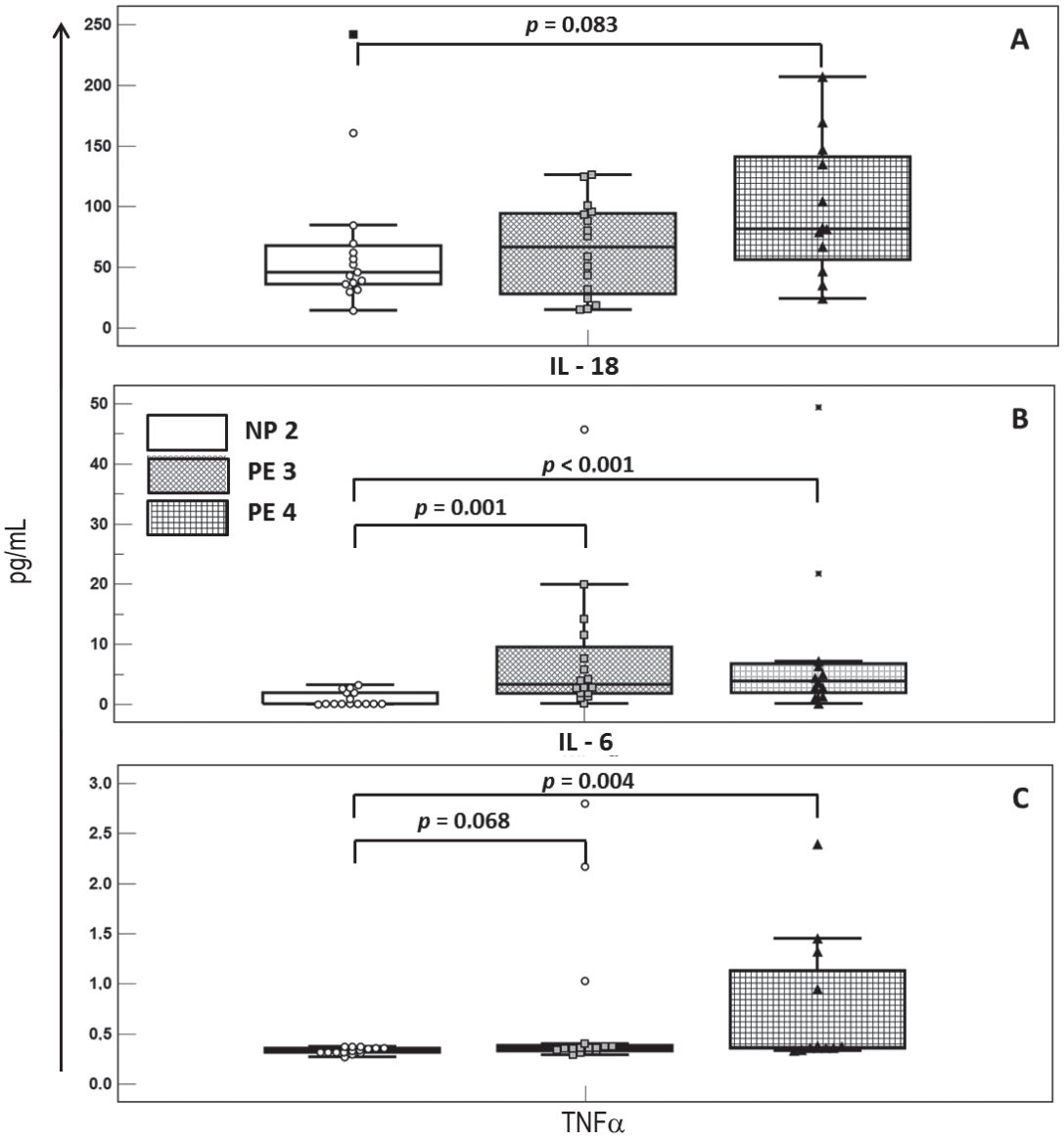

Figure 2. Cytokines IL-18 (A), IL-6 (B), and TNFα (C) levels in peripheral blood of patients with late-onset PE receivng Dopegyt and Dopegyt + Cordaflex

Note. Differences are given at p < 0.1.

TABLE 1. COMPARATIVE ANALYSIS OF SYNDECAN-1, GALECTIN-3, AND HOMOCYSTEINE LEVELS IN PATIENTS WITH PE RECEIVING DOPEGYT AND DOPEGYT + CORDAFLEX

Parameter	NP 1 (n = 15)	PE 1 (n = 12)	PE 2 (n = 16)	NP 2 (n = 15)	PE 3 (n = 12)	PE 4 (n = 12)
SDC-1, pg/mL	930 (753-3640)	3065# (1595-5385)	1715## (1130-5265)	1290 (820-11288)	5070 (2095-9835)	2570 (1475-3490)
Galectin-3, ng/mL	11.96 (10.91-19.17)	17.04 (9.49-29.26)	12.97 (11.56-16.90)	15.17 (10.52-32.00)	13.09 (9.74-15.63)	14.82 (11.48-20.16)
Hcy, umol/L	10.00 (8.84-11.15)	9.16 (6.18-10.79)	8.67 (6.62-9.69)	8.61 (6.90-10.04)	8.99 (7.05-9.91)	9.67 (7.84-11.89)

Note. #, p = 0.019 comparing groups NP1 and PE1; ##, p = 0.075 comparing groups NP1 and PE2.

bohydrate-binding protein bound to glycocalyx [9]. Amino acid homocysteine (Hcy) is a factor associated with inflammation. Higher levels of Hcy were demonstrated in PE (above 10 mkMol/L), being considered as hyperhomocysteinemia associated with elevated risk of cardiovascular, cerebral, and peripheral arteries pathology leading to endothelial dysfunction [5].

Comparative analysis revealed elevated levels of proinflammatory factors in patients with PE receiving Dopegyt and Dopegyt + Cordaflex compared to control. However, only IL-6 demonstrated statistically significant differences reflecting increased proinflammatory state in blood vessels of patients with early-onset PE receiving both treatment strategies (Figure 1B).

Proinflammatory state was more profound in late-onset PE. In particular, IL-6 levels were significantly increased in patients treated with Dopegyt ($p = 0.001$), as well as a trend to increase in TNFα levels, $p = 0.068$ (Figure 2B, C). Generally proinflammatory state was seen in patients treated with Dopegyt + Cordaflex: IL-6 (Figure 2B) and TNFα (Figure 2C) levels were significantly higher compared to control ($p < 0.001$ and $p = 0.004$, respectively). Same trend was seen for IL-18, $p = 0.083$ (Figure 2A).

Syndecan-1 levels were statistically significantly higher in patients with early-onset PE treated with Dopegyt solely, $p = 0.019$, and non-significantly higher in those receiving combined therapy, $p = 0.075$ (Table 1). There were no statistically significant differences between the groups despite elevated mean values of syndecan-1 in late-onset PE. Galectin-3 and homocysteine levels did not differ significantly between the groups (Table 1), representing lack of pronounced inflammatory response and endothelial dysfunction.

Symptoms of system inflammatory response are known to be seen in healthy pregnant women, however, as pregnancy progresses those symptoms become more prominent due to penetration of allogenic fetal cells, debris and fetal DNA into mother blood as well as physiological "placenta aging" [3]. More pronounced proinflammatory state is observed in patients of elder age because of blood vessel aging due to cardiovascular and metabolic, i.e. obesity, diseases [8]. Given this fact we enrolled patients matched by age, BMI and gestational age to eliminate confounders that intervene with study results.

IL-6 plays vital role in chronic inflammatory response and TNFα controls its production. Our results demonstrate that despite antihypertensive therapy key proinflammatory cytokines levels are increased, especially in late-onset PE and in those receiving combined therapy. What is more, not only IL-6 and TNFα levels are elevated in patients treated with Dopegyt + Cordaflex but strong direct correlation between their blood levels was observed ($r_s = 0.72$, $p = 0.003$). This finding proves their pathogenic role and demonstrates absence of positive effect of therapy on inflammatory response in this group of patients. Strong direct correlation between IL-6 and galectin-3 levels was revealed in patients with early-onset PE receiving Dopegyt + Cordaflex ($r_s = 0.75$, $p = 0.005$). Though galectin-3 levels did not differ significantly between these patients and control group, identified correlation may imply its potential pathogenic role in long-term changes of vessels as galectin-3 is a biomarker of heart failure in cardiology [2]. It is believed that main source of galectin-3 in maternal blood is placenta and not endothelium [9]. Nevertheless, vessels molecular changes as a result of PE may bear long-term consequences and galectin-3 is a promising candidate for long-term prognosis of risk of cardiovascular diseases.

It is known that antihypertensive drugs affect cytokine production by immune cells of placenta and peripheral blood. In particular, dose-dependent effect, i.e. inhibition of cytokine production by placental cells and mononuclear cells in preeclamptic patients, was demonstrated *in vitro* for clonidine, diazoxide, hydralazine and furosemide [13]. Combined antihypertensive treatment affects cytokines state in patients with arterial hypertension. Therapy with enalapril + hydrochlorothiazide and enalapril + indapamide significantly decreased IL-6 and TNFα levels as well as mean blood pressure. These effects were accompanied by clinical improvement of heart failure parameters according to scale of patient's clinical state assessment [4]. As for Dopegyt and Cordaflex, we have not found similar articles. Limitation of our study is having no data on baseline levels of studied molecules before the start of therapy, sometimes because of urgent need for delivery of some patients with severe PE. This point limits therapy duration and explains retrospective analysis of antihypertensive treatment. However, obtained data allow us to evaluate proinflammatory state in blood vessels of patients with early- and late-onset PE receiving different treatment options.

Conclusion

Immune and biochemical factors reflecting development of system inflammatory response and

endothelial dysfunction in patients with early- and late-onset PE receiving Dopegyt solely and Dopegyt + Cordaflex were studied. It was demonstrated that proinflammatory state was more profound in late-onset PE patients treated with combined therapy. This finding may be explained by the presence of comorbidities that require additional prescription of Cordaflex. In early-onset PE more prominent eGC destruction alongside with higher IL-6 levels was observed. Our results demonstrate necessity for differential approach to therapy of different PE clinical phenotypes and perspectives of anti-inflammatory drugs prescription in patients with late-onset PE to negate symptoms of sterile inflammation.

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