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ИММУНОЛОГИЧЕСКИЕ И ПАТОМОРФОЛОГИЧЕСКИЕ АСПЕКТЫ РАННЕЙ И ПОЗДНЕЙ ПРЕЭКЛАМПСИИ

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Резюме. Одно из самых распространенных осложнений беременности – преэклампсия (РЕ) может возникать начиная с 20 недель гестации и завершается только с полным удалением последа. Традиционно РЕ принято подразделять на раннюю, возникающую до 34 недель беременности включительно (EOPE), и позднюю – после 34 недель гестации (LOPE). Клинические проявления в том и другом случае одинаковы, однако факторы риска и степень тяжести ПЭ различны. Установлено, что EOPE определяется нарушением инвазии трофобласта и трансформации спиральных артерий матки в ранние сроки беременности, а позднее начало РЕ связывают со оксидативным стрессом синцитиотрофобласта, возникающим вторично, при ограниченном газообмене и недостаточном поступлении питательных веществ. Многочисленные исследования отмечали значительный вклад иммунных реакций в патогенез преэклампсии, однако состояние В-лимфоцитов при EOPE и LOPE не исследовалось. Проводилась комплексная оценка состояния женщин при раннем (до 34 недель беременности включительно) и позднем (после 34 недель) развитии преэклампсии с учетом клинических и анамнестических характеристик, особенности формирования структурных компонентов плаценты, а также определением характера дифференцировки и функциональной активности В-лимфоцитов. В периферической венозной крови исследовали содержание $CD19^+$, $CD20^+$, $CD19^+CD27^+IgD^\pm$, $CD19^+CD20^-CD38^+$, $CD20^+CD5^+$-клеток и сывороточный уровень IL-5, IL-9, IL-13. Морфологическое исследование включало макроскопическое описание, органометрию, обзорную гистологию и трансмиссионную электронную микроскопию. В группе женщин с ранней преэклампсией в анамнезе чаще имелись перинатальные потери, преждевременные роды и медицинские аборты, а в текущей беременности внутриутробное инфицирование, маловодие, плацентарная недостаточность и задержка роста плода. При поздней преэклампсии чаще отмечался метаболический синдром, анемия, а в анамнезе артериальная гипертензия. В периферической крови всех женщин с преэклампсией отмечалось повышение содержания $CD20^+CD5^+$-клеток по сравнению с показателями при неосложненной беременности, более выраженное при позднем начале преэклампсии. Только у женщин с ранней преэклампсией в крови повышалось содержание $CD19^+CD20^-CD38^+$ и $CD19^+CD27^+IgD^\pm$-клеток, IL-5,

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IL-9 и IL-13. Исследования последа при ранней преэклампсии свидетельствовали о нарушении имплантации и патологической плацентации с развитием первичной плацентарной недостаточности, переходящей в хроническую форму. При поздней преэклампсии развитие фетоплацентарной недостаточности определяли хронические расстройства материнской и плодовой гемоциркуляции с повышенным отложением фибрина и фибриноида в базальной пластинке и в зонах некроза эпителия ворсин. Проведенное исследование показало, что сроки манифестации преэклампсии определяются действием факторов клинического анамнеза, структурной перестройкой в плаценте и иммунными реакциями В-лимфоцитов тесно взаимосвязанными между собой.

Ключевые слова: ранняя преэклампсия, поздняя преэклампсия, плацента, периферическая кровь, В-лимфоциты

IMMUNOLOGICAL AND PATHOMORPHOLOGICAL ASPECTS OF EARLY AND LATE PREECLAMPSIA

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Abstract. Preeclampsia (PE) is one of the most common complications of pregnancy, and it can be after 20 weeks of gestation. It ends only with a complete dissection of afterbirth. Traditionally, PE is subdivided into the early one, taking place through 34 weeks of pregnancy (EOPE) and the late one, which is after 34 weeks of gestation (LOPE). Clinical manifestations are similar in both cases however, risk factors and the severity of PE are different . It has been established that EOPE is determined by impaired trophoblast invasion and transformation of the spiral arteries of the uterus in early pregnancy, and late onset of PE is associated with oxidative stress of syncytiotrophoblast, which occurs secondarily, with limited gas exchange and insufficient intake of nutrients. Numerous studies have noted a significant contribution of immune responses to the pathogenesis of preeclampsia, however, the state of B-lymphocytes in EOPE and LOPE has not been studied. A comprehensive assessment of the condition of women with early (up to 34 weeks of pregnancy inclusive) and late (after 34 weeks) development of preeclampsia was carried out, taking into account clinical and anamnestic characteristics, the peculiarities of the formation of the structural components of the placenta, as well as determining the nature of differentiation and functional activity of B-lymphocytes. In peripheral venous blood, the content of $CD19^+$, $CD20^+$, $CD19^+CD27^+IgD^\pm$, $CD19^+CD20^-CD38^+$, $CD20^+CD5^+$-cells and serum levels of IL-5, IL-9, IL-13 were examined. Morphological examination included gross description, organometry, survey histology, and transmission electron microscopy. In the group of women with early preeclampsia in history, there were more often perinatal losses, premature births and medical abortions, and in the current pregnancy, intrauterine infection, oligohydramnios, placental insufficiency and fetal growth retardation. With late preeclampsia, metabolic syndrome, anemia, and a history of arterial hypertension were more often observed. In the peripheral blood of all women with preeclampsia, there was an increase in the content of $CD20^+CD5^+$-cells in comparison with those in uncomplicated pregnancy, more pronounced in the late onset of preeclampsia. Only in women with early preeclampsia blood levels of $CD19^+CD20^-CD38^+$ and $CD19^+CD27^+IgD^\pm$-cells, IL-5, IL-9 and IL-13 increased. Studies of the placenta in early preeclampsia indicated impaired implantation and pathological placentation with the development of primary placental insufficiency, which becomes chronic. In late preeclampsia, the development of placental insufficiency was determined by chronic disorders of maternal and fetal hemocirculation with increased deposition of fibrin and fibrinoid in the basal lamina and in the zones of villous epithelium necrosis. The study showed that the timing of the manifestation of preeclampsia is determined by the action of factors of the clinical history, structural rearrangements in the placenta and immune responses of B-lymphocytes are closely interrelated.

Keywords: early and late preeclampsia, placenta, peripheral blood, B-lymphocytes

Introduction

Being a unique physiological state, pregnancy causes changes in the functioning of multiple host systems. Continuously exchanging antigen material connects the two body systems triggering a cascade of immune reactions giving the most favorable development conditions for the fetus. Nevertheless, there are instances where the balance of the immune regulatory processes is disturbed under the influence of various factors such as genetic, contagious, hormonal, etc., and the reserve capacity of the immune system becomes insufficient in response to adverse reactions. Most of the gestational process complications result from such conditions, but the timeframe for clinical symptoms varies considerably. Preeclampsia (PE) is one of the most common complications of pregnancy occurring after 20 weeks of gestation that disappears only after birth. Traditionally, PE is subdivided into the early PE occurring through 34 weeks of pregnancy (EOPE) and the late PE observed after 34 weeks of gestation (LOPE). Clinical manifestations are similar in both cases, but PE risk factors [8] and the severity of differ [13]. The cause of PE is characterized by syncytiotrophoblast stress, systemic inflammatory reaction and maternal endothelial dysfunction [9] However, detailed analytical reviews have demonstrated that EOPE is diagnosed by trophoblast invasion dysplasia and the transformation of the uterine spiral artery in early pregnancy [5, 9]. This leads to the development of adverse reactions due to perfusion changes and increased placental stress [9]. Late-onset PE is associated with syncytiotrophoblast oxidative stress, which emerges secondarily in case of limited gas exchange and inadequate nutritional intake [9]. On the one hand, LOPE is associated with boosted apoptotic damage to the placenta, a massive inflow of syncytiotrophoblast microparticles (STBM) into the maternal bloodstream. As STBM ligands, they activate immune system cells. This leads to the release of inflammatory cytokines, coagulation factors and superoxide radicals, contributing to development of systemic inflammation associated with preeclampsia [9]. On the other hand, this condition may be determined by maternal hypersensitivity to factors of placental origin due to genetic predisposition, somatic problems associated with endothelial dysfunction, cardiovascular disease [5]. Numerous studies, including those performed in our laboratory, have noted a significant contribution of immune reactions to preeclampsia-related pathogenic mechanism. Some features of developing inflammatory reactions and immune regulatory processes were revealed both at the systems level and in the placenta under various PE forms. At the same time, the information on B-lymphocyte state transition is sparce, paying virtually no attention to role during EOPE and LOPE.

In our study, we decided to conduct a comprehensive assessment of women with EOPE and LOPE, taking into account their clinical and anamnestic characteristics, features of placenta structural component formation, and determining the nature of B-lymphocyte differentiation and functional activity.

Materials and methods

The anamnesis and clinical course of preeclampsia were analyzed in the groups of women with early-onset preeclampsia (218 women within 24-34 weeks of gestation) and late-onset preeclampsia (92 women with more than 34 weeks of gestation). Immunoassay was performed in 38 women with PE during 24-34 weeks of pregnancy and 44 women with PE during 34 up to 40 weeks of pregnancy. The control group consisted of women with uncomplicated pregnancy, including 30 women during 24-34 weeks of gestation and 24 women during 34-40 weeks of gestation. Laboratory tests were performed on a FACSCantoII flow cytometer with the FACSDiva software (BectonDickinson) by analyzing percentage of $CD19^+$- and $CD20^+$-lymphocytes in peripheral venous blood, $CD27^+IgD^{\pm}$, CD20-$CD38^+$ cells in the $CD19^+$ population, $CD5^+$-cells in the $CD20^+$ population were estimated. We used Beckman Coulter monoclonal antibodies CD19, CD20, CD38, CD27, IgD; eBioscience CD5, CD20. Serum IL-5, IL-9, IL-13 from bio-plex 27 kits (Bio-Rad) were examined on a Luminex 200 analyzer (Luminex Corporation). Serum levels of immunoglobulins G, A, M were measured on a microplate reader in Immunoscreen test systems (VECTOR-BEST JSC). Morphological examination of 35 placentas in early PE and 40 placentas in late PE was performed, including macroscopic examination, organometry, observational histology, and transmission electron microscopy. The results were statistically processed using a package of licensed software packages: Microsoft Office 2010, Statisticafor Windows 13.0. Values were quantified and presented as median with the 25^{th} and 75^{th} percentiles (Me ($Q_{0.25}$-$Q_{0.75}$) %). The significance of differences between variables was assessed by the nonparametric criteria of the Mann–Whitney U test.

Results and discussion

The analysis revealed that the mean age of the patients did not depend on the onset of PE and was 32.0 (26.0-35.0) years in the subgroup with early-onset PE (EOPE) and 30.0 (26.0-35.0) years ($p > 0.05$) in the subgroup with late PE (LOPE). The

incidence of bronchial asthma was higher in pregnant women with early-onset PE found in 2.75% of cases, while it was not recorded in another subgroup (p = 0.01). Metabolic syndrome manifested as obesity and arterial hypertension was significantly more frequently diagnosed in the subgroup with late PE – in 45.12% of cases compared to the another subgroup (23.03%, p = 0.04). At the same time, in hypertensive patients with the early PE development, the duration of this disease lasted for 8.0 (4.0-12.0) years, which was significantly longer than in late-onset PE – 6.0 (3.0-9.0) years (p = 0.03). Analysis of obstetric and gynecological status showed that subjects examined in the subgroup with early PE were significantly more likely to have perinatal loss (5.96%), premature delivery (16.51%), and medical abortions (7.80%) in the history compared to another subgroup (1.2%, 7.61%, and 1.09% respectively; p = 0.02 in all cases). During pregnancy, early-onset PE was more often associated with intrauterine infection from the trimester 1 (6.88% *vs* 2.17%; p = 0.04), placental insufficiency and VTE developed in the trimester 2 (74.31% and 57.80% *vs* 53.26% and 32.61%, respectively; p = 0.01 for all cases), and small-viscosity (13.76% and 4.35%; p = 0.01) compared to the subgroup with late-onset PE. The subgroup with late-onset PE had a higher incidence of anemia in pregnant women reaching 40.22%, compared to another subgroup (22.48%, p = 0.01). Patients with early PE on admission had higher mean BP than those with late-onset: 118.3 (113.3-126.3) mm Hg *vs* 116.7 (110.0-120.0) mm Hg (p = 0.01); they had proteinuria of 3 g/l per urine sample significantly more frequently (26.8% *vs* 16.2%). (p = 0.01); proteinuria higher than three g/l in a urine sample was found at significantly higher rate (26.8% *vs* 16.2%, p = 0.04); they required ICU treatment significantly more often (p = 0.01). In this subgroup, labor was occurred at 33.0 (30.1-34.2) weeks, which was significantly earlier than in the late-onset PE being at 37.0 (35.9-37.5) weeks (p = 0.00). Accordingly, the number of premature deliveries in this category of patients was higher than in another subgroup – 92.2% *vs* 46.7% (p = 0.00).

Laboratory assays showed no differences in percentage of $CD19^+$- and $CD20^+$-lymphocytes between the control groups matched gestational age and the groups with PE (control 24-34 weeks pregnancy $CD19^+$ 4.75% (3.38-6.90), $CD20^+$ 5.90% (4.20-8.20), EOPE $CD19^+$ 4.70% (3.18-7.25), $CD20^+$ 4.60 (2.68-7.60); control more after 34 weeks of pregnancy $CD19^+$ 4.70% (3.55-5.75), $CD20^+$ 4.00% (2.50-5.60), LOPE $CD19^+$ 4.05 (2.75-6.98), $CD20^+$ 4.85% (2.78-7.10); p > 0.05 in all cases). Irrespective of the gestational age of PE clinical manifestations, increased $CD5^+$-cell frequency in the $CD20^+$B-lymphocyte population was observed in such patient peripheral blood samples (Table 1) compared to those in the control group of the corresponding gestational age. Furthermore, in LOPE vs. EOPE the level of $CD20^+CD5^+$-lymphocytes was higher. Only women

TABLE 1. CONTENT OF B-LYMPHOCYTE POPULATIONS IN THE PERIPHERAL BLOOD AND THE SERUM LEVEL OF CYTOKINES IN UNCOMPLICATED PREGNANCY, EARLY AND LATE PREECLAMPSIA, Me ($Q_{0.25}$-$Q_{0.75}$)

Parameter	24-34 weeks pregnancy		More when 34 weeks pregnant	
	Control	Early preeclampsia	Control	Late preeclampsia
$CD27^+IgD^±$ in $CD19^+$, %	25.10 (17.45-30.15)	39.00 (26.30-43.90) p = 0.003	27.70 (23.90-39.40)	33.95 (22.95-37.95)
$CD20^-CD38^+$ in $CD19^+$, %	0.55 (0.33-1.35)	3.70 (1.73-8.20) p = 0.000	2.60 (0.90-3.60)	3.60 (1.80-8.60)
$CD5^+$ in $CD20^+$, %	11.35 (9.48-13.23)	13.85 (10.10-22.03) p = 0.045	8.85 (6.98-12.08)	21.20 (14.95-24.18) p = 0.000
IL-9, pg/ml	50.32 (41.28-92.77)	102.11 (66.56-126.08) p = 0.03	54.09 (48.99-94.84)	74.67 (50.31-89.08)
IL-13, pg/ml	0.07 (0.00-0.37)	1.76 (0.68-6.63) p = 0.004	0 (0-10.52)	2.27 (0.68-4.74)
IL-15, pg/ml	70.90 (58.18-87.33)	45.82 (9.11-69.38) p = 0.006	81.26 (61.61-86.98)	38.61 (6.69-56.38) p = 0.015

Note. p, difference from the control.

with EOPE had $CD19^+$-cell population characterized by increased percentage of $CD20\text{-}CD38^+$ plasmacytes and increased frequency of $CD27^+IgD^\pm$ B-memory cells. Analysis of cytokines regulating B-cell maturation and differentiation showed that the level of IL-5, IL-9 and IL-13 increased only with EOPE. Various clinical manifestations of PE groups differed among those with lower serum IL-9 level compared to women with LOPE.

Morphological examination of the placenta showed that all PE types had implantation disorders such as marginal umbilical cord insertion and placenta hypoplasia. However, the detection and manifestation rate depended on the age of clinical manifestations for pregnancy complication. Thus, marginal cord insertion in EOPE and LOPE was diagnosed in 32.3% and 19.4% ($p = 0.04$) cases, respectively. Placenta hypoplasia, defined as grade 3, was more frequently diagnosed in EOPE (68% in EOPE, 6.3% in LOPE, $p = 0.04$) and accompanied by fetal growth restriction (FGR) in 74% of cases. Placentas of women with LOPE were twice as often diagnosed with placental villous infarcts compared with placentas with EOPE (EOPE -31.3%, LOPE – 67.4%, $p < 0.005$) combined with obliterating angiopathy of the stem villous arteries. Premature detachment of typically situated placenta PDNSP (19.4%, $p = 0.04$) and intradecidual hemorrhages (9.68%, $p = 0.04$) were characteristic to EOPE placentas, inducing development of acute placental deficiency, while in LOPE, these disorders were not identified. Disorders of differentiation of the vascular-stromal component in villi were more frequently diagnosed in placentas with EOPE (EOPE-12.9%, LOPE-2.3%, $p = 0.04$). At EOPE, enlarged stromal canals, the peripheral orientation of vessels in the intermediate villi and hypoplasia of the muscular layer with deformed stem villi lumen were defined. In EOPE, placentas with increased deposition of fibrin and fibrinoid in areas of necrosis of the villous epithelium, in the basal lamina stroma, and intercellular areas peripheral cytotrophoblast (CTB) predominated. At the ultrastructural level, a twofold decrease in the number of mitochondria in the perinuclear zones and between the cisterns of the granular endoplasmic reticulum was observed in the cells of peripheral CTB of LOPE placentas compared with the group of EOPE placentas. However, the mean mitochondrial area of peripheral CTB was two times higher than that of EOPE ($p < 0.000$), reaching 3.91 ± 1.82 mcIU^2. Mitochondria of the peripheral STB in placentas at EOPE were not in contact with the granular endoplasmic reticulum (GER), and there was an increase in the cytoplasm not only in the number of loose lysosomes but also in the number of necrotized mitochondria in contact with amorphous structures. The effect of pathological processes in the placenta is closely related to the severity of compensatory and adaptive reactions. Hyperplasia of acroteric villi (35.5%), capillaries in terminal villi (41.9%), and syncytial capillary membranes were significantly more frequent ($p = 0.04$) in LOPE placentas. While comparing the placental pathomorphological changes with the intensity of compensation and adaptation processes, the chronic placental deficiency was diagnosed in 83.6% of cases with EOPE and 73.12% with LOPE.

Our study data are broadly consistent with the generally accepted characteristics of EOPE and LOPE [5, 9]. Thus, clinical data confirm the greater severity of the pathological process in EOPE, which is combined with more pronounced changes in B-lymphocyte differentiation and cytokine status in women with EOPE. Because this group had an increased rate of medical abortions, premature delivery, perinatal miscarriages and signs of intrauterine infection in the current pregnancy, it seems most likely that trophoblast invasion disorders, spiral artery remodeling, and development of initial placental deficiency in EOPE are due to initial hypoplasia of endometrium. Pathomorphological studies of the placenta indicate implantation disorders and pathological placentation with developing initial placental deficiency. Premature detachment of the normally located placenta and intradecidual hemorrhage are indicative of acute KD in EOPE at the implantation stage. Subsequently, this process turns into a chronic form, as evidenced by disorders of maturation of the villous chorion, trophoblast mitochondrial dysfunction, syncytiotrophoblast dystrophic and necrotic changes. Such events may contribute to the enhanced release of different sized syncytiotrophoblast microparticles (STBM) into the maternal bloodstream compared to uncomplicated pregnancy [4, 10]. B-lymphocytes are known to be able to bind and phagocytize STBM [11]. This early and prolonged activation of B-lymphocytes in EOPE could determine their enhanced differentiation into memory B-cells ($CD19^+CD27^+IgD^\pm$, B-mems). IL-9 could play an essential role in this process, and its level was elevated in EOPE and IL-5 and IL-13. In this combination, it should be noted that increased production of IL-9, IL-5, IL-13 by the Th17-cell population is noted in some pathological conditions [1]. Excessive Th17 activity underlies many immunoregulatory disorders in PE. Takatsuka S. et al. (2018) showed that IL-9R is selectively expressed on memory B-cells, which can produce IL-9 in a secondary response [12]. IL-9/IL-9R signal transduction initiates development of B-mems and promotes their differentiation into

plasma cells upon repeated exposure to antigen [12]. This agrees well with our data on the increased peripheral blood plasma cells ($CD19^+CD20^-CD38^+$) in EOPE. Stimulation of B-lymphocytes by IL-5 could also have contributed to this. Experimental studies have proven that IL-5 is a critical cytokine for the homeostatic proliferation of B1-lymphocytes and their immunoglobulin production [7]. We found that both types of PE were characterized by elevated levels of B1-cells ($CD20^+CD5^+$). Most studies link their pathological effects in PE with the production of agonistic angiotensin II type 1 receptor autoantibody (AT1-AA) [6], anti-endothelial cell antibodies [15]. These antibodies induce signaling pathways leading to blood vessel constriction, secretion of anti-angiogenic factors, circulation of endothelial microparticles, etc. [2, 3, 14]. Autoimmunity involving such antibodies affect the vascular endothelium in target organs, including the placenta. According to our data, the level of B1-cells ultimately increased in woman peripheral blood with LOPE. Perhaps the dystrophic and necrotic changes noted in the placenta in LOPE syncytiotrophoblast of villi with increased deposition of fibrin and fibrinoid, with a reduced volume of intervillous space and the development of placental hypoperfusion reflect these autoimmune reactions. Data from pathomorphological studies suggest that in LOPE, development of fetoplacental insufficiency is defined by chronic disorders of maternal hemocirculatory tract combined with obliteration angiopathy of the stem villous arteries, increased fibrin and fibrinoid deposition in the basal bed, in the peripheral cytotrophoblast and areas of villous epithelial necrosis. The formation of compensatory processes in LOPE ensures the prolongation of pregnancy with the appearance of clinical signs of placental deficiency only at the phase of late fetalization of the placenta.

The study showed that the effect of clinical history factors determines the timing of PE manifestation, disorders in development of various placental structures, and B-lymphocyte immune reactions closely interrelated.

Reference

1. Cosmi L., Maggi L., Santarlasci V., Capone M., Cardilicchia E., Frosali F., Querci V., Angeli R., Matucci A., Fambrini M. Identification of a novel subset of human circulating memory $CD4^+$ T cells that produce both IL-17A and IL-4. *J. Allergy. Clin. Immunol., 2010, Vol. 125, pp. 222-230.e1.*

2. Cunningham M.W., Williams J.M., Amaral L., Usry N., Wallukat G., Dechend R., LaMarca B. Agonistic autoantibodies to the angiotensin II type 1 receptor enhance angiotensin II-induced renal vascular sensitivity and reduce renal function during pregnancy. *Hypertension, 2016, Vol. 68, no. 5, pp. 1308-1313.*

3. Erez O., Romero R., Espinoza J., Fu W., Todem D., Kusanovic J.P. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age. *J. Matern. Fetal. Neonatal. Med., 2008, Vol. 21, pp. 279-287.*

4. Germain S.J., Sacks G.P., Soorana S.R., Sargent I.L., Redman C.W. Systemic inflammatory priming in normal pregnancy and preeclampsia: the role of circulating syncytiotrophoblast microparticles. *J. Immunol., 2007, Vol. 178, pp. 5949-5956.*

5. Huppertz B. The critical role of abnormal trophoblast development in the etiology of preeclampsia. *Curr. Pharm. Biotechnol., 2018, Vol. 19, Iss. 10, pp. 771-780.*

6. Lamarca B., Parrish M.R., Wallace K. Agonistic autoantibodies to the angiotensin II type i receptor cause pathophysiologic characteristics of preeclampsia. *Gender Med., 2012, Vol. 9, pp. 139-146.*

7. Moon B., Takaki S., Miyake K., Takatsu K. The role of IL-5 for mature B-1 cells in homeostatic proliferation, cell survival, and Ig production. *J. Immunol., 2004, Vol. 172, no. 10, pp. 6020-6029.*

8. Panova I.A., Rokotyanskaya E.A., Malishkina A.I., Kudryasova A.V. Scientific substantiation of personalized choice of antihypertensive therapy and management tactics for pregnant women with hypertensive disorders. *Obstetrics and Gynecology, 2020, no. 1, pp. 110-118.* (In Russ.)

9. Redman C.W., Staff A.C. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. *Am. J. Obstet. Gynecol., 2015, Vol. 213, Suppl. 4, pp. S9.e1, S9-11.*

10. Salomon C., Guanzon D., Scholz-Romero K., Longo S., Correa P., Illanes S.E., Rice G.E. Placental exosomes as early biomarker of preeclampsia – potential role of exosomal microRNAs across gestation. *J. Clin. Endocrinol. Metab., 2017, Vol. 102, no. 9, pp. 3182-3194.*

11. Southcombe J., Tannetta D., Redman C., Sargent I. The immunomodulatory role of syncytiotrophoblast microvesicles. *PLoS ONE, 2011, Vol. 6, no. 5, e20245.* doi: 10.1371/journal.pone.0020245.

12. Takatsuka S., Yamada H., Hanniuda K., Saruwatari H., Ichihashi M., Renauld J., Kitamura D. IL-9 receptor signaling in memory B cells regulates humoral recall responses. *Nat. Immunol., 2018, Vol. 19, pp. 1025-1034.*

13. Vodneva D.T., Romanova V.V., Dubova E.A., Pavlov K.A., Shmakov R.G., Schegolev A.I. Clinical and morphological features of early and late preeclampsia. *Obstetrics and Gynecology, 2014, no. 2, pp. 35-40.* (In Russ.)

14. Yang S., Zhong Q., Qiu Z., Chen X., Chen F., Mustafa K., Ding D., Zhou Y. Angiotensin II receptor type 1 autoantibodies promote endothelial microparticles formation through activating p38 MAPK pathway. *J. Hypertens., 2014, Vol. 32, no. 4, pp. 762-770.*

15. Ziganshina M.M., Amiraslanov E.Y., Yarotskaya E.L., Dolgushina N.V., Sergunina O.A., Nikolaeva M.A., Kan N.E., Tyutyunnik V.L., Mantrova D.A., Loginova N.S., Konradi A.O., Sukhik G.T. Autoantibodies to endothelial cells in patients with hypertensive disorders during pregnancy. *Pregnancy Hypertens., 2018, Vol. 12, pp. 65-70.*

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