DOI: https://doi.org/10.17816/JOWD59307

Hormone metabolic pattern in the preclinical stage of preeclampsia

© Yury V. Tezikov[1], Igor S. Lipatov[1], Amir R. Azamatov[2]

[1] Samara State Medical University, Samara, Russia;
[2] Samara Regional Clinical Hospital named after V.D. Seredavin, Samara, Russia

BACKGROUND: The imbalance of vascular endothelial cell metabolism determines the clinical manifestations of preeclampsia; however, the molecular mechanisms underlying the vessel destabilization are not fully understood. In recent years, researchers have focused on clarifying the role of dysmetabolic disorders in patients with obstetric pathology, including preeclampsia. This is due to the fact that pregnancy is accompanied by metabolic restructuring aimed at switching the energy supply of the pregnant woman's body from the carbohydrate to the fat component in order to maintain an effective energoplastic supply of the developing fetus. Impairment of this evolutionary adaptation mechanism realized during pregnancy requires additional in-depth study.

AIM: This study was aimed to identify and compare pathogenetic patterns that characterize early and late preeclampsia at the preclinical stage, based on dynamic clinical and laboratory examination of high-risk pregnant women.

MATERIALS AND METHODS: A prospective clinical and laboratory examination of 180 pregnant women with independent factors of high risk of developing preeclampsia was carried out. Comparison groups were identified retrospectively, depending on the period of preeclampsia manifestation: Group I consisted of 31 pregnant women with early preeclampsia; Group II comprised 58 pregnant women with late preeclampsia; and Group III (control) included 30 healthy pregnant women with uncomplicated gestation. Pregnant women were examined twice at the preclinical stage of preeclampsia (11-14 and 18-21 weeks of gestation) and once at clinical manifestation of the disease (28-36 weeks of gestation). The markers of metabolic, hormonal, hemocirculatory, hemostasiological and placental disorders were evaluated.

RESULTS: We found similar pathophysiological changes in pregnant women with both early and late PE, from early gestation periods. Those were characterized by pathological insulin resistance and hyperinsulinemia, as well as associated atherogenic changes in the lipid profile, hyperleptinemia, hyperuricemia, hypersympathicotonia, visceral fat deposition, and contrainsular hormonal deviations. The observed alterations reflected a single hormonal and metabolic pattern of the preclinical stage of preeclampsia. During pregnancy, there was shown an increase in clustering diabetogenic and atherogenic abnormalities and hormonal changes, which were supplemented by associated endothelial and hemostasiological dysfunction and, in early preeclampsia, placental dysfunction, thus accelerating the time of clinical implementation of preeclampsia.

CONCLUSIONS: From the pathogenetic point of view, preeclampsia of various periods of manifestation is an indivisible category with a common basic developmental mechanism characterized by a hormone metabolic pattern from the early stages of pregnancy. These stable changes are the result of the pathologically transformed phylogenetic mechanism of energoplastic supply of the fetus. This transformation is realized via physiological insulin resistance and compensatory hyperinsulinemia development due to the contra-insular activity of placental hormones. The added structural and functional disorders of the embryo (feto) placental system potentiate basic mechanisms (pathological insulin resistance and hyperinsulinemia) and determine the period of preeclampsia clinical manifestation in each particular woman.

Keywords: early preeclampsia; late preeclampsia; pathogenesis; contrainsular placental hormones; insulin resistance; hyperinsulinemia; dyslipidemia; endothelial hemostasiological disorders; placental dysfunction.

To cite this article:
Tezikov YuV, Lipatov IS, Azamatov AR. Hormone metabolic pattern in the preclinical stage of preeclampsia. *Journal of Obstetrics and Women's Diseases.* 2021;70(3):51–63. DOI: https://doi.org/10.17816/JOWD59307

Received: 26.01.2021 **Accepted:** 16.02.2021 **Published:** 30.06.2021

The article can be used under the CC BY 4.0 license
© Eco-Vector, 2021

УДК 618.3-06:616.8-009.24-036.3
DOI: https://doi.org/10.17816/JOWD59307

Гормонально-метаболический паттерн доклинической стадии преэклампсии

© Ю.В. Тезиков[1], И.С. Липатов[1], А.Р. Азаматов[2]

[1] Самарский государственный медицинский университет, Самара, Россия;
[2] Самарская областная клиническая больница им. В.Д. Середавина, Самара, Россия

Обоснование. Доказано, что дисбаланс метаболитов сосудистого эндотелия определяет реализацию клинических проявлений преэклампсии, но молекулярные механизмы, приводящие к самой морфофункциональной дестабилизации эндотелия, в полной мере не ясны. В последние годы внимание исследователей направлено на уточнение роли дисметаболических нарушений в развитии акушерской патологии, в том числе и преэклампсии. Это обусловлено тем, что беременность сопровождается выраженной метаболической перестройкой, направленной на переключение организма беременной с углеводного на жировой компонент для поддержания эффективного энергопластического обеспечения развивающегося плода. Нарушение данного эволюционно закрепленного гестационного механизма адаптации необходимо углубленно изучать.

Цель — на основе динамического клинико-лабораторного обследования беременных высокого риска выделить и сопоставить патогенетические паттерны, характеризующие раннюю и позднюю преэклампсию на доклинической стадии.

Материалы и методы. Проведено проспективное клинико-лабораторное обследование 180 беременных с независимыми факторами высокого риска развития преэклампсии. Ретроспективно в зависимости от срока манифестации преэклампсии выделены группы сравнения: первую группу составили 31 беременная с ранней преэклампсией; вторую группу — 58 беременных с поздней преэклампсией; третью, контрольную, группу — 30 здоровых женщин с неосложненным течением беременности. Женщины были обследованы дважды на доклинической стадии преэклампсии (11–14, 18–21 неделя беременности) и при ее клиническом проявлении (28–36 недель беременности). Оценивали маркеры метаболических, гормональных, эндотелиально-гемостазиологических и плацентарных нарушений.

Результаты. У женщин как с ранней, так и с поздней преэклампсией с ранних сроков беременности выявлены схожие патофизиологические изменения, характеризуемые формированием патологических инсулинорезистентности и гиперинсулинемии, а также связанных с ними атерогенных сдвигов липидного профиля, гиперлептинемии, гиперурикемии, гиперсимпатикотонии, висцерального типа жироотложения брюшной стенки, контринсулярной направленности гормональных изменений и отражающие единый гормонально-метаболический паттерн доклинической стадии преэклампсии. В динамике беременности нарастают взаимосвязанные диабетогенные и атерогенные нарушения, гормональные изменения, которые дополняются ассоциированными с ними эндотелиально-гемостазиологической дисфункцией, а при ранней преэклампсии — плацентарной дисфункцией, ускоряющими сроки клинической реализации преэклампсии.

Заключение. С патогенетических позиций преэклампсия с различными сроками манифестации представляет неделимую категорию с общим базовым механизмом развития, характеризующимся с ранних сроков беременности гормонально-метаболическим паттерном. Данные устойчивые изменения являются результатом патологической трансформации филогенетически закрепленного механизма энергопластического обеспечения плода через формирование физиологической инсулинорезистентности и компенсаторной гиперинсулинемии вследствие контринсулярной активности плацентарных гормонов. Присоединение структурно-функциональных нарушений эмбрио(фето)плацентарной системы потенцирует базовые механизмы (патологические инсулинорезистентность и гиперинсулинемия) и определяет срок клинической манифестации преэклампсии у конкретной женщины.

Ключевые слова: ранняя преэклампсия; поздняя преэклампсия; патогенез; контринсулярные плацентарные гормоны; инсулинорезистентность; гиперинсулинемия; дислипидемия; эндотелиально-гемостазиологические нарушения; плацентарная дисфункция.

Как цитировать:
Тезиков Ю.В., Липатов И.С., Азаматов А.Р. Гормонально-метаболический паттерн доклинической стадии преэклампсии // Журнал акушерства и женских болезней. 2021. Т. 70. № 3. С. 51–63. DOI: https://doi.org/10.17816/JOWD59307

Рукопись получена: 26.01.2021 **Рукопись одобрена:** 16.02.2021 **Опубликована:** 30.06.2021

ЭКО • ВЕКТОР

Лицензия CC BY 4.0
© Эко-Вектор, 2021

BACKGROUND

Despite the efforts of scientists of various fields, as well as complex and multicenter studies based on the principles of evidence-based medicine, preeclampsia (PE) remains an unresolved interdisciplinary issue and ranks first among causes of maternal and perinatal morbidity and mortality [1, 2]. Moreover, there has been significant progress in the study of the pathogenesis of PE. Several decades ago, the scientific community only made the first convincing attempts to explain the role of the "ovum" in the formation of gestational arterial hypertension and proteinuria; however, at present, the imbalance of vascular endothelial metabolites has been proven to determine the mechanisms of the development of the clinical manifestations of PE [3]. At present, researchers and practitioners encounter problems of the causes and molecular mechanisms of endothelial morphofunctional destabilization.

The search for a clue to the pathogenesis of PE is conducted because this pathology is associated with numerous complications, namely, preterm delivery; premature detachment of the normally located placenta; placental insufficiency (PI) with fetal growth retardation (FGR) and chronic fetal hypoxia; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; and multiple organ failure, which have certain characteristics in their pathogenesis that conceal the basic mechanisms of PE development. This approach is of particular importance in the study of early and late PE. Some researchers suggested the heterogeneity of the pathogenesis of these types of PE, connecting the formation of early PE with impaired placentation processes, various forms of thrombophilia, and autoimmune diseases [4, 5]. Late ("maternal") PE is associated, to a greater extent, with hypertensive disease, metabolic syndrome, diabetes mellitus, modern lifestyle and nutrition, and multifetal pregnancy [6, 7]. Moreover, this provision does not correspond fully to the logic of dividing PE into early and late, which is primarily based on the differences in the frequency of complications and severity of adverse gestational and perinatal outcomes [8]. The choice of gestational age (34 weeks) for the classification of PE variants depending on its manifestation is ambiguous and causes some controversies. Other researchers are convinced that early and late PE have unified basic pathogenetic essence, and they recommend using "early and late manifesting PE" with a gradation of the timing of manifestation before and after week 30 of pregnancy [9]. In this regard, the current search for the true mechanisms of the formation of PE is relevant, which could the enable prediction, prevention, and treatment of this fatal complication of pregnancy much more efficiently.

Recently, the number of publications has increased, which clarifies the role of dysmetabolic disorders in the development of obstetric pathology, including PE [10, 11]. This is because pregnancy is accompanied by a pronounced metabolic restructuring aimed at changing the body of a pregnant woman from taking in carbohydrate to fat components to maintain effective macronutrient support of the developing fetus (by increasing the transplacental supply of glucose, amino acids, and free fatty acids along the density gradient) [12]. Considering the evolutionarily predetermined importance of these changes for the preservation of pregnancy and adequate growth of the fetus, the failure of these gestational adaptation mechanisms can lead to pathological transformation and the development of obstetric complications, which requires further thorough analysis.

This study aimed to identify and compare pathogenetic patterns characterizing early and late PE at the preclinical stage based on dynamic clinical and laboratory examination of women with high-risk pregnancies.

MATERIALS AND METHODS

This observational prospective study performed a detailed examination of 210 pregnant women who received medical care at the antenatal clinics in Samara and delivered in the Samara Regional Perinatal Center of V.D. Seredavin Samara Regional Clinical Hospital in the period from 2016 to 2020. In 180 pregnant women, independent high-risk factors for the development of PE were identified: a history of PE in 40.0% (72/180) of the female patients, PE in the mother or sibling sister in 39.4% (71/180) of cases, and first pregnancy at a late reproductive age in 20.6% (37/180) of patients. The frequency of PE in the subgroups with the presented risk factors was 63.9% (46/72), 50.7% (36/71), and 18.9% (7/37) of the cases, respectively, and 49.4% (89/180) of the total number of women with high-risk pregnancy were examined. Retrospectively, depending on the period of manifestation of PE (before or after week 34 of pregnancy), comparison groups were identified; group 1 included 31 (34.8%, 31/89) pregnant women with early PE, and group 2 included 58 (65.2%, 58/89) women with late PE. Group 3 (control) consisted of 30 healthy women with uncomplicated pregnancy.

The criteria for inclusion in groups 1 and 2 were the presence of PE in pregnant women with independent high-risk factors; pre-pregnancy blood pressure levels <130 and <85 mm Hg, body mass index 18.5–24.9, and absence of metabolic disorders; and provision of consent to participate in a prospective study and publication of the results. The exclusion criteria were impairment of carbohydrate metabolism before pregnancy; PE complicated by HELLP syndrome, acute renal failure, premature detachment of the normally located placenta, respiratory distress syndrome in adults, and acute cerebrovascular accident; gestational diabetes mellitus; severe somatic, infectious, and autoimmune

pathology; polycystic ovary syndrome; genital anomalies and congenital fetal abnormalities; pregnancy after the use of assisted reproductive technologies; and violation of the examination protocol.

Pregnant women of groups 1 and 2 were examined twice at the preclinical stage of PE (weeks 11–14 and 18–21 of pregnancy) and at its clinical manifestation (weeks 28–36 of pregnancy). The women of the control group were examined at the same time. The laboratory parameters were assessed, namely, levels of glucose in venous blood, total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), uric acid, nitric oxide (NO) metabolites, insulin, placental lactogen (PL), leptin, cortisol, norepinephrine (in urine), tumor necrosis factor alpha (TNF-α), fibronectin (FN), circulating endothelial cells, mean platelet volume, platelet–collagen aggregation test, $CD95^+$ lymphocyte count ($LCD95^+$), placental growth factor (PGF), and placental alpha-1-microglobulin (PAMG-1). The insulin resistance index (IR) HOMA-IR and the TG/HDL ratio were calculated. Aspects of the accumulation and distribution of adipose tissue, which are known to have pronounced metabolic and hormonal activity, were also considered.

In the laboratory studies, we used an Architect c4000 biochemical analyzer (Abbott, USA) and test systems corresponding to each indicator, Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Japan), and laser analyzer of platelet aggregation ALAT-2 (Biola Scientific). Characteristics of the distribution of adipose tissue were assessed by the method of Tayama (1999) using a Voluson E6 GE Healthcare ultrasound apparatus (GE, USA). The thickness of the subcutaneous (tSCF) and of the preperitoneal fat (tPPF) were measured, followed by the calculation of the abdominal wall fat index (AWFI = tPPF/tSCF). An index >1.0 indicates a predominantly visceral type of fat deposition in the abdominal wall [13]. The diagnosis of PE and the degree of its severity was established following the criteria of the World Health Organization, approved by the Ministry of Health of the Russian Federation in the clinical protocol [14]. The severity of PI was determined using the classification of Strizhakov et al. [15].

Data were statistically processed using the IBM SPSS Statistics 25 HCIMAGO 5.0 software (IBM Corp., Armonk, NY, USA). The Lilliefors-corrected Kolmogorov–Smirnov criteria and Shapiro–Wilk test were used to assess the normal distribution of the data. All parameters studied had a nonparametric distribution; therefore, the descriptive statistical indicators were represented by the median (*Me*) with an inter-quartile range Q_1 (25%) and Q_3 (75%). For group comparison, the Bonferroni-corrected Mann–Whitney *U* test was used. Considering the conditions for applying this correction, the critical level of significance when comparing the three groups was set as $p < 0.017$. The significance of differences in the qualitative characteristics was determined using the Pearson χ^2 test, and using the Yates correction in the case of a four-field table. The results were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

When comparing women of three age groups (31 [28; 35] years, 30 [26; 33] years, and 28 [25; 32] years, $p = 0.25$), parity [primiparous 35.5% (11/31), 34.5% (20/58), and 46.7% (14/30), multiparous 64.5% (20/31), 65.5% (38/58), and 53.3% (16/30), respectively, $\chi^2 = 1.35$, $p = 0.51$)], marital status [registered marriage 67.7% (21/31), 65.5% (38/58), and 70.0 % (21/30), unregistered marriage 32.3% (10/31), 34.5% (20/58), and 30.0% (9/30), respectively, $\chi^2 = 0.18$, $p = 0.91$], professional status [employed 71.0% (22/31), 70.7% (41/58), and 73.3% (22/30), housewives 29.0% (9/31), 29.3% (17/58), and 26.7% (8/30), respectively, $\chi^2 = 0.07$, $p = 0.96$], no significant differences were revealed in any of the parameters. The frequency of occurrence of independent high-risk factors of PE in pregnant women of groups 1 and 2 was as follows. A history of PE was revealed in 54.8% (17/31) and 50.0% (29/58) of the cases ($\chi^2 = 0.04$, $p = 0.83$), family history of PE was detected in 38.7% (12/31) and 41.4% (24/58) of the cases ($\chi^2 = 0.01$, $p = 0.98$), and first pregnancy at a late reproductive age was in 6.5% (2/31) and 8.6% (5/58) of the cases ($\chi^2 = 0.01$, $p = 0.95$), respectively. Analysis of the incidence of PE, depending on the severity, showed that with early PE, a more severe course was more often noted (by 1.6 times), but no differences were found in pregnant women of group 2 [severe PE in 48.4% (15/31) and 31.0% (18/58) of the cases, moderate PE in 51.6% (16/31) and 69.0% (40/58) of the cases ($\chi^2 = 1.91$, $p = 0.16$) with early and late clinical manifestations, respectively].

In the comparative analysis of the clinical and laboratory aspects of early and late PE, it is important to assess the frequency of structural and functional disorders of the fetoplacental complex with PI implementation, which play a leading role in the mechanisms of early PE formation [4]. Indeed, PI was more often diagnosed in group 1 with early PE [45.1% (14/31) versus 37.9% (22/58) in group 2], but no significant differences were found ($\chi^2 = 0.19$, $p = 0.66$) (Table 1). Furthermore, data on the severity of PI indicate the formation of more severe morphological and functional disorders of the fetoplacental complex in group 1, which is probably substantiated by the establishment of the pathomorphological changes at the earlier stages of the development of the embryo(feto)placental system. The frequency of the occurrence of grade II–III PI in early PE is 1.4 times higher than that in late PE, namely, in 41.9% (13/31) and 31.0% (18/58) of pregnant women, respectively ($\chi^2 = 0.63$, $p = 0.42$). In parallel, a disorder of the trophic function of the placenta, manifested in the FGR,

Table 1. Incidence of placental insufficiency and fetal growth retardation in groups 1 and 2, % (*n*)

Pathology	Group 1 (*n* = 31)	Group 2 (*n* = 58)	χ^2	*p*
Chronic placental insufficiency	**45.1 (14)**	**37.9 (22)**	**0.19**	**0.66**
Grade I (placental dysfunction)	3.2 (1)	6.9 (4)	0.05	0.81
Grade II (decompensated PI)	29.0 (9)	20.7 (12)	0.39	0.53
• Grade IIA	3.2 (1)	6.9 (4)	0.05	0.81
• Grade IIB	9.7 (3)	6.9 (4)	<0.01	0.95
• Grade IIC	16.1 (5)	6.9 (4)	0.31	0.58
Grade III (progressive decompensated PI)	12.9 (4)	10.3 (6)	<0.01	0.99
Grade IV (critical PI)	0 (0)	0 (0)	–	–
Fetal growth retardation	**35.5 (11)**	**20.6 (12)**	**1.60**	**0.21**
Grade I	3.2 (1)	6.9 (4)	0.05	0.81
Grade II	22.6 (7)	10.3 (6)	1.54	0.21
Grade III	9.7 (3)	3.4 (2)	0.53	0.46

Note. PI, placental insufficiency. Calculation of statistical significance was made using Pearson χ^2 with Yates correction ($p < 0.05$).

was assessed. Grade II FGR was found 2.1 times more often ($\chi^2 = 1.54$, $p = 0.21$) and grade III FGR was detected three times more often ($\chi^2 = 0.53$, $p = 0.46$) in group 1 than in group 2 (Table 1). Moreover, the presence of a significant predominance in early PE is established only for the total assessment of grade II and III FGR ($\chi^2 = 4.27$, $p = 0.04$). The identified patterns indicate the absence of a specific and primary role of morphofunctional disorders of the fetoplacental complex in the mechanisms of early PE, despite their greater pathogenetic effect at a given term of manifestation.

Considering the obtained results of laboratory examination at 11–14 weeks of pregnancy, we revealed similar hormonal and metabolic changes in pregnant women at the preclinical stage of early and late PE. One of the fundamental mechanisms of gestation and energy supply to the fetus is the phenomenon of physiological IR, which redirects energy and plastic substrates from the mother to the developing embryo(feto)placental complex [16]. In addition, the results of the study (Table 2) show that from the early stages of pregnancy, the levels of insulin and HOMA-IR, which characterize the severity of IR and compensatory/pathological hyperinsulinemia (HI), are significantly higher than the reference values in groups 1 and 2, with no significant differences between groups with early and late PE ($p_{ins} = 0.37$, $p_{HOMA\text{-}IR} = 0.63$). In this regard, numerous studies [7, 17] have reported that pathological IR is considered one of the leading mechanisms of the formation of chronic arterial hypertension, a variant of which is PE [18]. In response to the emerging IR and HI during pregnancy, changes in the lipid spectrum occur, leading to an increase in atherogenic fractions that provide the maternal organism with energy and maintain physiological IR [11]. The levels of TC, TG, and TG/HDL were significantly higher and the level of HDL was significantly lower in groups 1 and 2 than in the control group (p_{TC}, p_{TG}, $p_{TG/HDL}$, and $p_{HDL} < 0.001$), which indicates pronounced atherogenic disorders in PE, regardless of the term of manifestation. Based on inclusion and exclusion criteria, the glucose level was not beyond the reference values and did not differ significantly in the study groups at all examination periods ($p > 0.05$).

At the first laboratory testing, among hormonal parameters, significant differences between the PE groups and control group were noted in terms of the levels of leptin, cortisol, and PL. The concentration of leptin in pregnant women of groups 1 and 2 was more than 1.5 times higher than the control parameters (p_{1-3} and $p_{2-3} < 0.001$), which indicates the involvement of leptin in the mechanisms of PE formation, while no differences were found at the preclinical stage between the early and late PE ($p = 0.45$). In literature, this hormone is involved in the development and maintenance of pathological IR, endothelial dysfunction, proinflammatory changes, and sympathicotonia [19]. Pregnancy is an enormous stress factor for a woman's body, which increases the production of cortisol, the most important adaptive hormone [20]. In pregnant women with early and late PE, a significant excess in the physiological levels of cortisol was found from the early stages of pregnancy (p_{1-3} and $p_{2-3} < 0.001$), which also leads to an increase in pathological IR and HI. Moreover, no significant differences were found in the blood levels of cortisol in groups 1 and 2 ($p_{1-2} = 0.37$).

The pathogenetic mechanisms of PE are inextricably linked with the formation of the placenta, a new provisional organ with a powerful hormonal potential [16]. One of the most important placental hormones is PL, which exhibits

Table 2. Values of laboratory parameters at 11–14 and 18–21 weeks of pregnancy in women of the compared groups (*Me* [Q_1; Q_3])

Gestational age, weeks	Group 1 *n* = 31	Group 2 *n* = 58	Group 3 *n* = 30	*p*
		Glucose, mmol/l		
11–14	4.3 [3.8; 4.7]	4.4 [3.9; 4.8]	4.5 [4.0; 4.8]	0.64
18–21	4.2 [3.7; 4.6]	4.2 [3.8; 4.7]	4.4 [4.0; 4.8]	0.67
		HOMA-IR		
11–14	1.91[x] [1.68; 2.22]	1.76[x] [1.54; 2.06]	1.40 [1.12; 1.58]	<0.001
18–21	3.37[x] [2.98; 3.54]	2.76[x, yy] [2.51; 3.08]	1.62 [1.18; 1.96]	<0.001
		Insulin, pmol/ml		
11–14	74.8[x] [65.6; 85.3]	66.2[x] [54.8; 75.1]	50.6 [40.7; 58.1]	<0.001
18–21	129.4[x] [118.9; 137.7]	112.3[x, yy] [103.5; 121.6]	59.8 [50.3; 68.5]	<0.001
		Total cholesterol, mmol/l		
11–14	5.63[x] [5.45; 5.88]	5.48[x] [5.31; 5.72]	4.99 [4.58; 5.28]	<0.001
18–21	6.94[x] [6.58; 7.09]	6.75[x] [6.39; 7.02]	5.46 [5.21; 5.78]	<0.001
		Triglycerides, mmol/l		
11–14	2.08[x] [1.95; 2.17]	1.91[x] [1.82; 2.03]	1.69 [1.45; 1.82]	<0.001
18–21	2.92[x] [2.70; 3.09]	2.83[x] [2.59; 3.01]	2.03 [1.87; 2.20]	<0.001
		High-density lipoproteins, mmol/l		
11–14	1.19[x] [1.12; 1.26]	1.24[x] [1.17; 1.31]	1.35 [1.29; 1.40]	<0.001
18–21	1.12[x] [1.05; 1.18]	1.15[x] [1.10; 1.21]	1.23 [1.18; 1.29]	<0.001
		Triglycerides/high-density lipoproteins		
11–14	1.68[x] [1.50; 1.86]	1.55[x] [1.36; 1.74]	1.25 [1.06; 1.41]	<0.001
18–21	2.52[x] [2.27; 2.75]	2.43[x] [2.17; 2.66]	1.63 [1.45; 1.83]	<0.001
		Uric acid, μmol/l		
11–14	201.4 [176.6; 219.3]	195.2 [167.7; 213.9]	184.7 [163.4; 207.9]	0.18
18–21	299.6[x] [276.1; 328.4]	265.1[x, y] [241.3; 292.8]	217.3 [188.7; 238.5]	<0.001
		NO metabolites, μmol/l		
11–14	16.2 [14.1; 17.8]	17.6 [15.8; 19.4]	18.8 [16.5; 21.2]	0.26
18–21	20.1[x] [17.5; 21.9]	22.9[x, y] [20.1; 24.2]	33.7 [31.3; 36.4]	<0.001
		Placental lactogen, mg/l		
11–14	6.1[x] [4.5; 7.4]	5.5[x] [4.0; 6.7]	2.1 [0.9; 3.1]	<0.001
18–21	9.5[x] [7.8; 10.4]	9.1[x] [7.3; 9.9]	4.2 [3.3; 5.6]	<0.001
		Leptin, ng/ml		
11–14	35.5[x] [28.8; 39.4]	30.2[x] [22.4; 34.1]	18.9 [13.6; 23.2]	<0.001
18–21	66.6[x] [59.4; 73.9]	59.4[x, y] [52.7; 64.6]	22.4 [17.1; 28.3]	<0.001
		Tumor necrosis factor alpha, pg/ml		
11–14	13.6[x] [11.3; 15.7]	11.9[x] [18.8; 14.5]	4.9 [3.6; 6.1]	<0.001
18–21	26.7[x] [23.4; 30.2]	20.8[x, yy] [17.6; 24.4]	9.7 [7.2; 11.2]	<0.001
		Fibronectin, μg/ml		
11–14	235 [213; 252]	221 [199; 238]	219 [197; 242]	0.29
18–21	397[x] [372; 422]	359[x, y] [331; 384]	288 [264; 307]	<0.001
		Placenta growth factor, pg/ml		
11–14	213[x] [182; 236]	219[x] [189; 238]	237 [204; 270]	0.15
18–21	284[x] [258; 312]	325[x, y] [296; 348]	421 [385; 467]	<0.001

End of Table 2

Gestational age, weeks	Group 1 *n* = 31	Group 2 *n* = 58	Group 3 *n* = 30	*p*
Placental alpha-1 microglobulin, ng/ml				
11–14	25.2^{x} [19.8; 30.1]	21.4^{x} [16.3; 26.9]	10.1 [7.5; 13.2]	<0.001
18–21	39.6^{x} [34.9; 43.9]	32.8$^{x, y}$ [28.2; 36.8]	17.4 [13.2; 21.1]	<0.001
Cortisol, μg/dl				
11–14	28.1^{x} [22.2; 36.9]	23.8^{x} [17.7; 32.1]	13.2 [9.3; 18.7]	<0.001
18–21	48.6^{x} [41.1; 56.2]	45.2^{x} [38.3; 52.9]	27.4 [19.8; 32.2]	<0.001
Norepinephrine, μg/day (in urine)				
11–14	24.8 [18.2; 32.1]	21.9 [16.7; 28.4]	21.4 [15.4; 27.3]	0.34
18–21	60.3^{x} [51.4; 72.2]	57.5^{x} [49.1; 68.9]	31.2 [25.5; 38.2]	<0.001
Circulating endothelial cells, cells/100 μl				
11–14	19 [15; 22]	17 [14; 21]	16 [13; 20]	0.21
18–21	39^{x} [34; 43]	34$^{x, y}$ [28; 37]	20 [15; 24]	<0.001
Aggregation of platelets with collagen, %				
11–14	39.9 [36.1; 43.2]	38.5 [35.0; 41.9]	37.7 [34.6; 40.1]	0.19
18–21	58.7^{x} [56.1; 61.0]	53.3$^{x, y}$ [51.2; 57.6]	41.7 [37.5; 44.3]	<0.001
Mean platelet volume, fl				
11–14	7.21 [6.85; 7.47]	7.15 [6.78; 7.39]	7.12 [6.85; 7.31]	0.52
18–21	8.54^{x} [8.25; 8.96]	8.13$^{x, y}$ [7.72; 8.40]	7.34 [7.15; 7.59]	<0.001
Lymphocytes CD95^{+}, %				
11–14	19.9 [18.1; 23.0]	19.3 [17.6; 21.9]	18.2 [16.3; 21.2]	0.48
18–21	34.8^{x} [29.5; 39.2]	29.2$^{x, y}$ [23.3; 32.8]	21.6 [19.3; 24;8]	<0.001

Note. Significance was calculated using the Kruskall–Wallis rank analysis of variance, and intergroup comparisons were performed using the Mann–Whitney *U* test with Bonferroni adjustment ($p < 0.017$); *x,* differences are significant compared with the control (*x* — $p < 0.001$); *y,* differences are significant compared with the group 1 (*y* — $p = 0.01$, *yy* — $p < 0.001$).

pronounced counter-insular activity and ensures the formation of physiological IR during pregnancy. In addition, the levels of PL were significantly higher in groups 1 and 2 than in the control group ($p_{1–3}$, $p_{2–3} < 0.001$). Significant differences were found between the group of pregnant women with PE and the control group, in the level of PAMG-1 synthesized by the placenta and exerting a counter-insular effect. From weeks 11–14 of pregnancy, the concentration of PAMG-1 in groups 1 and 2 was more than two times higher than that in the control group ($p_{1–3}$ and $p_{2–3} < 0.001$), while no differences were found between early and late PE ($p_{1–2} = 0.35$). In the first trimester of pregnancy, the level of TNFα was higher in the PE group than in the control group ($p_{1–3}$ and $p_{2–3} < 0.001$, $p_{1-2} = 0.46$). This cytokine is actively synthesized in the placenta and, according to recent data, is not only an important marker of inflammation but also a mediator of IR, leading to the formation of arterial hypertension [21]. The generalized results of stage 1 of laboratory monitoring of women in the comparison groups indicate that in patients with early and late PE, a single hormonal–metabolic pattern is formed at the early stages of pregnancy, leading to the development of pathological IR and HI.

Analysis of laboratory testing data at 18–21 gestational weeks revealed additional pathogenetic aspects of the preclinical stage of the formation of early and late PE. For all the above parameters, similar significant differences were noted between the control group and groups 1 and 2 with PE ($p < 0.001$ for all indices). In addition, the values of HOMA-IR, insulin, and leptin, characterizing a single hormonal and metabolic pattern, began to increase in group 1, which naturally determines the earlier clinical manifestation of PE (p_{ins}, $p_{HOMA-IR}$, and $p_{FN0}\alpha < 0.001$, p_{PAMG-1}, and $p_{lep} = 0.01$).

Diabetogenic and atherogenic disorders detected at the preclinical stage of PE were naturally supplemented by the characteristics of the accumulation and distribution of adipose tissue in the comparison groups (Fig. 1). In women with early and late PE at 11–14 gestation weeks, no significant differences were found in the values of tPPF, tSCF, and AWFI when compared with the control group (p_{tPPF}, p_{tSCF}, and $p_{AWFI} < 0.05$). However, from the second

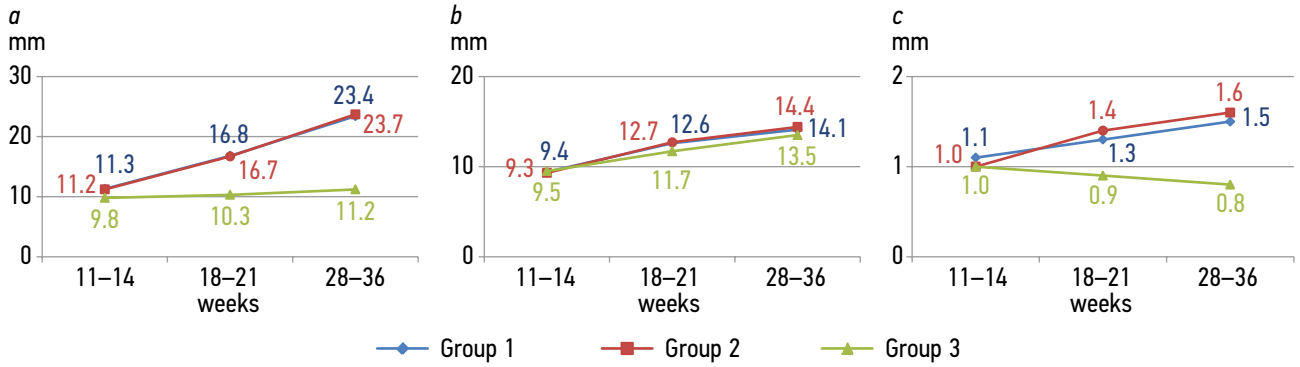

Fig. 1. Dynamics of preperitoneal fat thickness (*a*), subcutaneous fat thickness (*b*), abdominal wall fat index (*c*) in pregnant women of the comparison groups

laboratory testing, in the PE groups, a significant increase in preperitoneal (visceral) fat was observed (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.86$), which has a pronounced hormonal activity and plays an important role in the formation of pathological IR [7]. A similar pattern was revealed in the analysis of AWFI value (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.65$), which indicates a predominantly visceral type of fat deposition in the abdominal wall in groups 1 and 2 and confirms the similarity of the pathological changes within the hormonal–metabolic pattern in early and late PE at the preclinical stage of the formation of this pathology.

The formation of pathological IR and HI through central regulatory mechanisms leads to an increase in sympathetic activity, which contributes to the formation of arterial hypertension in PE and further potentiates IR and HI [7]. An increase in the concentration of norepinephrine, reflecting sympathoadrenal activity, was registered in the early and late PE groups (Table 2), while this indicator was significantly higher than the level in the control group (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.42$).

At stage 2 of the examination, a significant increase in the concentration of uric acid in pregnant women with PE was revealed, and it was higher in group 1 than in group 2 (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.01$). The physiological increase in uric acid levels during pregnancy provides the natural antioxidant defense of the body. However, in pregnant women with PE, a pronounced increase in the level of uric acid is noted, which in pathological concentrations acquires an alternative activity, leads to a potentiation of IR, functional destabilization of endothelial cells, and activation of platelets, and increases blood pressure through an increase in the synthesis of angiotensin II [22, 23].

The TNFα concentration at 18–21 weeks of gestation was also significantly higher in groups 1 and 2 (p_{1-3} and $p_{2-3} < 0.001$), while a significant difference was noted between early and late PE ($p_{1-2} < 0.001$). The formation of proinflammatory changes in PE is also evidenced by an increase in the LCD95$^+$ level, which indicates the trophoblast-induced apoptotic readiness of lymphocytes (Table 2).

During the study, the PGF level was assessed, which belongs to the family of proteins of the vascular endothelial growth factor and indicates the morphofunctional state of the fetoplacental complex [24, 25]. No significant differences were found in this indicator between the comparison groups at 11–14 weeks of gestation ($p = 0.15$), which indicates the dominance of hormonal and metabolic disorders in the pathophysiological mechanisms of the formation of early and late PE. At the second laboratory testing, the PGF level was significantly lower in the PE groups (p_{1-3} and $p_{2-3} < 0.001$), while the indicators were lower in pregnant women with early PE than in group 2 ($p_{1-2} = 0.01$). This is consistent with the results of the clinical examination and is explained by the earlier addition of morphofunctional dysfunction of the embryo(feto)placental complex as a pathogenetic component to increasing metabolic disorders, which additionally potentiates pathological IR and HI and consequently accelerates the clinical implementation of PE.

The increase in diabetogenic disorders, atherogenic changes in the lipid profile, and hormonal and pro-inflammatory changes leads to structural and functional destabilization of the endothelium, which plays an important role in the subsequent stages of the pathogenesis of PE. Thus, by weeks 18–21 of pregnancy, in groups 1 and 2, the counts of circulating endothelial cells begin to increase significantly (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.01$), the desquamation of which is an objective sign of the severity endothelial damage. In parallel, the production of NO, which functions as the most important vasodilator and vasoprotector, decreases in the damaged intima of the vascular wall [26]. The level of NO metabolites is more than 1.5 times lower in pregnant women with PE than in the control group (p_{1-3} and $p_{2-3} < 0.001$), while the significant differences between groups 1 and 2 ($p_{1-2} = 0.01$) are due to the accelerated onset of pathogenetic events in early PE. Endothelial damage in PE is accompanied by an increase in the concentration of FN (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.01$), which reflects procoagulation shifts in hemostasis as a general indicator. These changes in hemostasis are accompanied by an

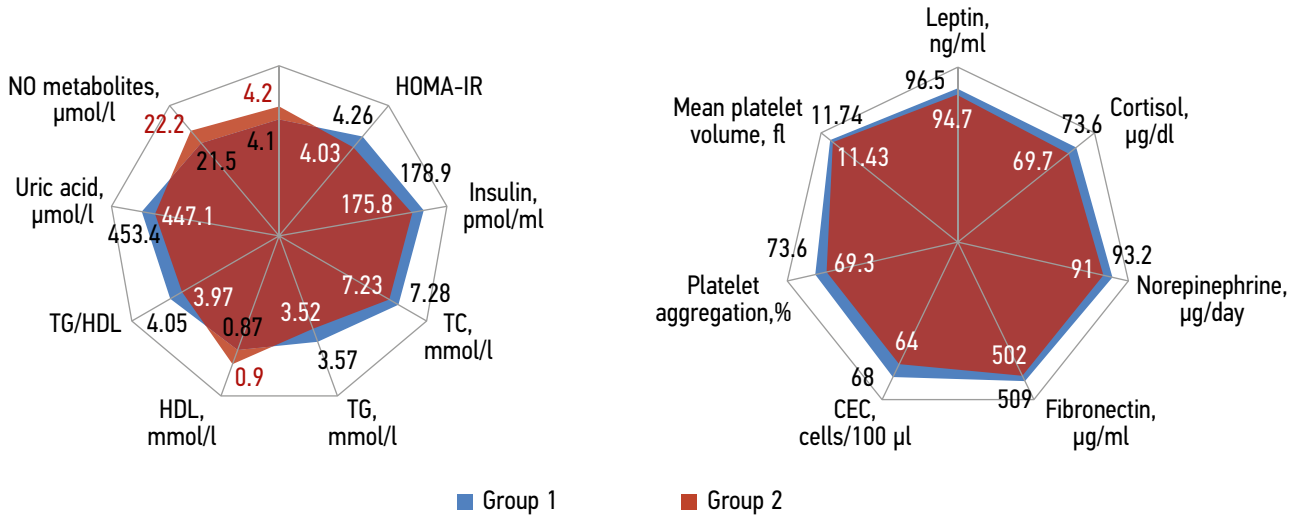

Fig. 2. Values of laboratory parameters in pregnant women of groups 1 and 2 with clinical manifestation of preeclampsia: TG, triglycerides; HDL, high-density lipoprotein; TC, total cholesterol; CEC, circulating endothelial cells; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance

increase in the functional activity of platelets. By the second laboratory testing, in pregnant women with PE, the mean platelet volume increased significantly, which characterizes the increase in the number of young and activated forms when compared with the control (p_{1-3} and $p_{2-3} < 0.001$, $p_{1-2} = 0.01$). A similar pattern was detected in the analysis of the platelet–collagen aggregation test. The results of the laboratory examination at 18–21 weeks of gestation indicate the preservation and growth of a hormonal–metabolic pattern common for the preclinical stage of early and late PE, which is complemented by the associated endothelial–hemostasiological dysfunction.

The results of the laboratory examination during the period of clinical manifestations of PE (Fig. 2, Table 3) enabled clarifying the degree of involvement of placental morphofunctional disorders in the pathogenetic mechanisms of early and late PE.

The absence of significant differences in metabolic, hormonal, and pro-inflammatory indicators and markers of hemostasiological and endothelial dysfunction ($p_{1-2} > 0.05$), presented in Fig. 2, indicates the unity of pathophysiological changes, which rate of increase determines the period of clinical manifestation of PE. In addition, significant differences were noted between pregnant women with early and late PE for a number of placenta-associated indicators (i.e., PGF, PAMG-1, PL, TNF-α, and LCD95⁺). A detailed analysis of these markers of the fetoplacental complex state showed that these differences are related to the

Table 3. Values of laboratory parameters indicating significant differences between pregnant women with early and late preeclampsia of varying severities, with clinical manifestation of preeclampsia (*Me* [Q_1; Q_3])

Group 1 (n = 31)		Group 2 (n = 58)		$p_{moderate}$	p_{severe}
Moderate PE (n = 16)	Severe PE (n = 15)	Moderate PE (n = 40)	Severe PE (n = 18)		
Placental lactogen, mg/l					
14.9 [14.1; 16.0]	20.6 [17.5; 23.8]	14.5 [13.7; 15.7]	18.1 [15.3; 20.5]	0.68	0.04
Placental alpha-1 microglobulin, ng/ml					
83.7 [77.3; 89.1]	107.5 [98.2; 118.8]	82.1 [75.8; 87.4]	98.3 [91.2; 107.4]	0.74	0.04
Placenta growth factor, pg/ml					
230 [215; 252]	170 [145; 191]	235 [220; 259]	187 [166; 208]	0.71	0.03
Lymphocytes CD95⁺, %					
53.9 [47.4; 58.1]	61.7 [57.6; 66.2]	50.6 [45.2; 56.7]	55.2 [51.5; 59.0]	0.68	0.02
Tumor necrosis factor alpha, pg/ml					
31.2 [28.4; 33.4]	44.6 [41.2; 47.4]	29.4 [26.8; 31.7]	37.1 [34.0; 40.5]	0.79	<0.001

Note. PE, preeclampsia. The calculation of the significance of intergroup differences was performed using the Mann–Whitney *U* test ($p < 0.05$).

severe forms of PE, regardless of the time of its manifestation. Table 3 presents that early and late moderate PE did not differ significantly in the markers indicated ($p > 0.05$), while significant differences were revealed in severe PE ($p_{PGF} = 0.03$, $p_{PAMG-1} = 0.04$, $p_{PL} = 0.04$, $p_{TNF\alpha} < 0.001$, $p_{LCD95+} = 0.02$). This aspect is due to the earlier establishment of morphofunctional disorders of the embryo(feto)placental complex in early PE, which naturally leads to the development of more severe forms of PI and FGR and thereby aggravate the course of PE, and an increase in markers of the state of the fetoplacental complex, accelerating and potentiating hormonal and metabolic changes existing in the early stages. This characterizes the pathogenetic aspects of early PE with the formation of a hormonal–metabolic pattern with the addition of endothelial–hemostasiological and placental dysfunctions.

CONCLUSIONS

In the clinical and laboratory examinations of women with early and late PE, from early pregnancy, similar pathophysiological changes occur, reflecting a single hormonal and metabolic pattern of the preclinical stage of PE. Decompensation of the mechanisms of physiological gestational adaptation in pregnant women with PE is accompanied by the formation of pathological IR and HI as well as associated atherogenic changes in the lipid profile, hyperleptinemia, hyperuricemia, hypersympathicotonia, visceral type of fat deposition of the abdominal wall, and counter-insular hormonal changes, which is the basic (dysmetabolic) pathogenetic component of PE.

The examination results at 18–21 weeks of gestation revealed that with early and late PE, interrelated diabetogenic and atherogenic disorders intensify, including hormonal changes with the addition of pro-inflammatory status, oxidative stress, activation of the immune system, and imbalance of angiogenic factors, which induces the formation of prothrombotic disorders and endothelial dysfunction that manifest clinically as arterial hypertension and proteinuria with PE. Consequently, in the preclinical stage of pregnancy, the hormonal–metabolic pattern common for early and late PE is enhanced, which is complemented by the associated endothelial–hemostasiological dysfunction.

When analyzing the frequency of PI of varying severities, no significant differences were revealed between groups 1 and 2, which indicates the involvement of embryo(feto) placental complex pathology in the pathogenetic mechanisms of the formation of both early and late PE. Furthermore, the tendency toward the formation of more severe forms of PI and consequently FGR in pregnant women with early PE, as well as significant differences in the levels of placenta-associated indicators (such as PGF, PL, PAMG-1, TNF-α, and LCD95$^+$), indicate a greater participation placental dysfunction in the development of early PE. Earlier morphofunctional placental disorders, as an additional alternative factor, accelerate and potentiate hormonal and metabolic changes pre-existing in the early stages; therefore, the peculiarity of the preclinical stage of early PE consists in the formation of a hormonal and metabolic pattern with the addition of endothelial–hemostasiological and placental dysfunction.

Thus, from the pathogenetic point of view, early and late PE represent an indivisible category with a common basic developmental mechanism, which is characterized by the formation of a hormonal–metabolic pattern from early pregnancy caused by the disruption of gestational adaptation mechanisms due to the counter-insular activity of placental hormones and aimed at macronutrient provision of the growing fetus. The addition of an alternative component (i.e., placental dysfunction, genetic polymorphisms, epigenetic changes, pre-gestational, and periconception aggravating factors) potentiates the basic mechanisms (pathological IR and HI) and determines the term of clinical manifestation of PE in a particular woman.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.
Funding. The study had no external funding.
Author contributions. *Yu.V. Tezikov* created the study concept and design and edited the text; *I.S. Lipatov* collected and processed the material; *A.R. Azamatov* performed statistical data processing and the literature analysis.

REFERENCES

1. Bezhenar VF, Adamyan LV, Filippov OS, et al. Maternal mortality in the Northwestern Federal Region of the Russian Federation: a comparative analysis 2018–2019, conceptual approaches to reduction. *Russian Journal of Human Reproduction*. 2020;26(6–2):33–41. (In Russ.). DOI: 10.17116/repro20202606233

2. Stevens AB, Brasuell DM, Higdon RN. Atypical preeclampsia — gestational proteinuria. *J Family Med Prim Care.* 2017;6(3):669–671. DOI: 10.4103/2249-4863.222029

3. Echeverria C, Eltit F, Santibanez JF, et al. Endothelial dysfunction in pregnancy metabolic disorders. *Biochim Biophys Acta Mol Basis Dis.* 2020;1866(2):165414. DOI: 10.1016/j.bbadis.2019.02.009

4. Strizhakov AN, Timokhina EV, Ibragimova SM, et al. New possibilities for differential prediction of early onset and late onset preeclampsia. *Obstetrics, Gynecology and Reproduction.* 2018;12(2):55–61. (In Russ.). DOI: 10.17749/2313-7347.2018.12.2.055-061

5. Makatsariya AD, Serov VN, Gris JCh, et al. Catastrophic antiphospholipid syndrome and thromboses. *Obstetrics and Gynecology.* 2019;(9):5–14. (In Russ.). DOI: 10.18565/aig.2019.9.5-14
6. Aulamazyan EK, Evsyukova II, Yarmolinskaya MI. The role of melatonin in development of gestational diabetes mellitus. *Journal of Obstetrics and Women's Diseases.* 2017;67(1):85–91. (In Russ.). DOI: 10.17816/JOWD67185-91
7. Nolan CJ, Prentki M. Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift. *Diab Vasc Dis Res.* 2019;16(2):118–127. DOI: 10.1177/1479164119827611
8. Savel'eva GM, Shalina RI, Konoplyannikov AG, Simuhina MA. Pre-eclampsia and eclampsia: new approaches in diagnosis and evaluation of severity. *Akusherstvo i ginekologiya: novosti, mneniya, obuchenie.* 2018;6(4):25–30. (In Russ.). DOI: 10.24411/2303-9698-2018-14002
9. Redman CW. Early and late onset preeclampsia: Two sides of the same coin. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health.* 2017;7:58. DOI: 10.1016/j.preghy.2016.10.011
10. Tezikov YuV, Lipatov IS. Results of carbogenotherapy for the prevention of placental insufficiency. *Rossiiskii vestnik akusherа-ginekologa.* 2011;11(5):71–77. (In Russ.)
11. Chen X, Stein TP, Steer RA, Scholl TO. Individual free fatty acids have unique associations with inflammatory biomarkers, insulin resistance and insulin secretion in healthy and gestational diabetic pregnant women. *BMJ Open Diabetes Res Care.* 2019;7(1):e000632. DOI: 10.1136/bmjdrc-2018-000632
12. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol.* 2019;15(5):275–289. DOI: 10.1038/s41581-019-0119-6
13. Tayama K, Inukai T, Shimomura Y. Preperitoneal fat deposition estimated by ultrasonography in patients with non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract.* 1999;43(1):49–58. DOI: 10.1016/s0168-8227(98)00118-1
14. Gipertenzivnye rasstrojstva vo vremja beremennosti, v rodah i poslerodovom periode. Prejeklampsija. Jeklampsija. Klinicheskie rekomendacii (Protokol lechenija). 2016. (In Russ.). [cited 22 Jan 2021]. Available from: http://www.rokb.ru/sites/default/files/pictures/gipertenzivnye_rasstroystva_vo_vremya_beremennosti_v_rodah_i_poslerodovom_periode._preeklampsiya._eklampsiya.pdf
15. Strizhakov AN, Tezikov YuV, Lipatov IS, et al. Standardization of diagnostics and clinical classification of chronic placental insufficiency. *Gynecology, Obstetrics and Perinatology.* 2014;13(3):5–12. (In Russ.)
16. Napso T, Yong HEJ, Lopez-Tello J, Sferruzzi-Perri AN. The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation. *Front Physiol.* 2018;9:1091. DOI: 10.3389/fphys.2018.01091
17. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis.* 2017;11(8):215–225. DOI: 10.1177/1753944717711379
18. Algoritmy vedenija pacienta s arterial'noj gipertenziej gipertonicheskim krizom. Obshherossijskaja obshhestvennaja organizacija "Sodejstvija profilaktike i lecheniju arterial'noj gipertenzii "Antigipertenzivnaja Liga". Saint Petersburg; 2019. (In Russ.). [cited 2021 Apr 25]. Available from: https://scardio.ru/content/documents/algorythmy.pdf
19. Ökdemir D, Hatipoğlu N, Kurtoğlu S, et al. The role of rrisin, rnsulin and leptin in maternal and fetal interaction. *J Clin Res Pediatr Endocrinol.* 2018;10(4):307–315. DOI: 10.4274/jcrpe.0096
20. Katkova NY, Bodrikova OI, Sergeeva AV, Andosova LD, Shahova KA, Bezrukova IM, et al. The state of the local immune status, the content of neopterin and cortisol in different variants of preterm labor. *Journal of Obstetrics and Women's Diseases.* 2017;66(3):60–70. (In Russ.). DOI: 10.17816/JOWD66360-70
21. Romantsova TI, Sych YP. Immunometabolism and metainflammation in obesity. *Obesity and metabolism.* 2019;16(4):3–17. (In Russ.). DOI: 10.14341/omet12218
22. Belinina AA, Mozgovaya EV, Remneva OV. Spectrum of genetic thrombophilia in pregnant women with varying severity of preeclampsia. *Bulletin of Medical Science.* 2020;1(17):28–32. (In Russ.)
23. Bezbabicheva TS. Contradictory properties of uric acid and aspects of the biochemistry of arterial hypertension. *Natural resources of the Earth and environmental protection.* 2020;l(10–11–12):78–80. (In Russ.). DOI: 10.26787/nydha-2713-203X-2020-1-10-11-12-78-80
24. Lipatov IS, Tezikov YuV, Santalova GV, Ovchinnikova MA. Prevention of recurrent herpetic infection in pregnant women and intrauterine infection of the fetus with the herpes simplex virus. *Rossiiskii vestnik akushera-ginekologa.* 2014;14(4):63–68. (In Russ.)
25. Ngala RA, Fondjo LA, Gmagna P, et al. Placental peptides metabolism and maternal factors as predictors of risk of gestational diabetes in pregnant women. A case-control study. *PLoS One.* 2017;12(7):e0181613. DOI: 10.1371/journal.pone.0181613
26. Yuyun MF, Ng LL, Ng GA. Endothelial dysfunction, endothelial nitric oxide bioavailability, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? *Microvasc Res.* 2018;119:7–12. DOI: 10.1016/j.mvr.2018.03.012

СПИСОК ЛИТЕРАТУРЫ

1. Беженарь В.Ф., Адамян Л.В., Филиппов О.С. и др. Материнская смертность в Северо-Западном федеральном округе Российской Федерации: сравнительный анализ 2018–2019 гг., концептуальные подходы к снижению // Проблемы репродукции. 2020. Т. 26. № 6–2. С. 33–41. DOI: 10.17116/repro20202606233
2. Stevens A.B., Brasuell D.M., Higdon R.N. Atypical preeclampsia — gestational proteinuria // J. Family Med. Prim. Care. 2017. Vol. 6. No. 3. P. 669–671. DOI: 10.4103/2249-4863.222029
3. Echeverria C., Eltit F., Santibanez J.F. et al. Endothelial dysfunction in pregnancy metabolic disorders // Biochim.

Biophys. Acta Mol. Basis. Dis. 2020. Vol. 1866. No. 2. P. 165414. DOI: 10.1016/j.bbadis.2019.02.009

4. Стрижаков А.Н., Тимохина Е.В., Ибрагимова С.М. и др. Новые возможности дифференциального прогнозирования ранней и поздней преэклампсии // Акушерство, гинекология и репродукция. 2018. Т. 12. № 2. С. 55–61. DOI: 10.17749/2313-7347.2018.12.2.055-061

5. Макацария А.Д., Серов В.Н., Гри Ж.К. и др. Катастрофический антифосфолипидный синдром и тромбозы // Акушерство и гинекология. 2019. № 9. С. 5–14. DOI: 10.18565/aig.2019.9.5-14

6. Айламазян Э.К., Евсюкова И.И., Ярмолинская М.И. Роль мелатонина в развитии гестационного сахарного диабета // Журнал акушерства и женских болезней. 2018. Т. 67. № 1. С. 85–91. DOI: 10.17816/JOWD67185-91

7. Nolan C.J., Prentki M. Insulin resistance and insulin hypersecretion in the metabolic syndrome and type 2 diabetes: Time for a conceptual framework shift // Diab. Vasc. Dis. Res. 2019;16(2):118–127. DOI: 10.1177/1479164119827611

8. Савельева Г.М., Шалина Р.И., Коноплянников А.Г., Симухина М.А. Преэклампсия и эклампсия: новые подходы к диагностике и оценке степени тяжести. Акушерство и гинекология: новости, мнения, обучение. 2018. Т. 6. № 4. С. 25–30. DOI: 10.24411/2303-9698-2018-14002

9. Redman CW. Early and late onset preeclampsia: Two sides of the same coin // Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017. Vol. 7. P. 58. DOI: 10.1016/j.preghy.2016.10.011

10. Тезиков Ю.В., Липатов И.С. Результаты применения карбогенотерапии для профилактики плацентарной недостаточности // Российский вестник акушера-гинеколога. 2011. Т. 11. № 5. С. 71–77.

11. Chen X., Stein T.P., Steer R.A., Scholl T.O. Individual free fatty acids have unique associations with inflammatory biomarkers, insulin resistance and insulin secretion in healthy and gestational diabetic pregnant women // BMJ Open Diabetes Res. Care. 2019. Vol. 7. No. 1. P. e000632. DOI: 10.1136/bmjdrc-2018-000632

12. Phipps E.A., Thadhani R., Benzing T., Karumanchi S.A. Pre-eclampsia: pathogenesis, novel diagnostics and therapies // Nat. Rev. Nephrol. 2019. Vol. 15. No. 5. P. 275–289. DOI: 10.1038/s41581-019-0119-6

13. Tayama K., Inukai T., Shimomura Y. Preperitoneal fat deposition estimated by ultrasonography in patients with non-insulin-dependent diabetes mellitus // Diabetes Res. Clin. Pract. 1999. Vol. 43. No. 1. P. 49–58. DOI: 10.1016/s0168-8227(98)00118-1

14. Гипертензивные расстройства во время беременности, в родах и послеродовом периоде. Преэклампсия. Эклампсия. Клинические рекомендации (Протокол лечения). 2016. [дата обращения 22.01.2021]. Доступ по ссылке: http://www.rokb.ru/sites/default/files/pictures/gipertenzivnye_rasstroystva_vo_vremya_beremennosti_v_rodah_i_poslerodovom_periode._preeklampsiya._eklampsiya.pdf

15. Стрижаков А.Н., Тезиков Ю.В., Липатов И.С. и др. Стандартизация диагностики и клиническая классификация хронической плацентарной недостаточности // Вопросы гинекологии, акушерства и перинатологии. 2014. Т. 13. № 3. С. 5–12.

16. Napso T., Yong H.E.J., Lopez-Tello J., Sferruzzi-Perri A.N. The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation // Front. Physiol. 2018. Vol. 9. P. 1091. DOI: 10.3389/fphys.2018.01091

17. Rochlani Y., Pothineni N.V., Kovelamudi S., Mehta J.L. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds // Ther. Adv. Cardiovasc. Dis. 2017. Vol. 11. No. 8. P. 215–225. DOI: 10.1177/1753944717711379

18. Алгоритмы ведения пациента с артериальной гипертензией и гипертоническим кризом. Общероссийская общественная организация «Содействия профилактике и лечению артериальной гипертензии «Антигипертензивная лига». Санкт-Петербург, 2019. [дата обращения 25.04.2021]. Доступ по ссылке: https://scardio.ru/content/documents/algorythmy.pdf

19. Ökdemir D., Hatipoğlu N., Kurtoğlu S. et al. The role of irisin, insulin and leptin in maternal and fetal interaction // J. Clin. Res. Pediatr. Endocrinol. 2018. Vol. 10. No. 4. P. 307–315. DOI: 10.4274/jcrpe.0096

20. Каткова Н.Ю., Бодрикова О.И., Сергеева А.В. и др. Состояние локального иммунного статуса, содержание неоптерина и кортизола при различных вариантах преждевременных родов // Журнал акушерства и женских болезней. 2017. Т. 66. № 3. С. 60–70. DOI: 10.17816/JOWD66360-70

21. Романцова Т.И., Сыч Ю.П. Иммунометаболизм и метавоспаление при ожирении // Ожирение и метаболизм. 2019. Т. 16. № 4. С. 3–17. DOI: 10.14341/omet12218

22. Белинина А.А., Мозговая Е.В., Ремнёва О.В. Спектр генетических тромбофилий у беременных с различной степенью тяжести преэклампсии // Бюллетень медицинской науки. 2020. № 1 (17). С. 29–33.

23. Безбабичева Т.С. Противоречивые свойства мочевой кислоты и аспекты биохимии артериальной гипертензии // Natural resources of the Earth and environmental protection. 2020. Т. 1. № 10–11–12. С. 78–80. DOI: 10.26787/nydha-2713-203X-2020-1-10-11-12-78-80

24. Липатов И.С., Тезиков Ю.В., Санталова Г.В., Овчинникова М.А. Профилактика рецидивов герпетической инфекции у беременных и внутриутробного инфицирования плода вирусом простого герпеса // Российский вестник акушера-гинеколога. 2014. Т. 14. № 4. С. 63–68.

25. Ngala R.A., Fondjo L.A., Gmagna P. et al. Placental peptides metabolism and maternal factors as predictors of risk of gestational diabetes in pregnant women. A case-control study // PLoS One. 2017. Vol. 12. No. 7. P. e0181613. DOI: 10.1371/journal.pone.0181613

26. Yuyun M.F., Ng L.L., Ng G.A. Endothelial dysfunction, endothelial nitric oxide bioavailability, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? // Microvasc. Res. 2018. Vol. 119. P. 7–12. DOI: 10.1016/j.mvr.2018.03.012

AUTHORS INFO

***Yury V. Tezikov**, MD, Dr. Sci. (Med.), Professor;
address: 89 Chapaevskaya Str., Samara, 443099, Russia;
ORCID: https://orcid.org/0000-0002-8946-501X;
eLibrary SPIN: 2896-6986; e-mail: yra.75@inbox.ru

Igor S. Lipatov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0001-7277-7431;
eLibrary SPIN: 9625-2947; e-mail: i.lipatoff2012@yandex.ru

Amir R. Azamatov, MD;
ORCID: https://orcid.org/0000-0003-0372-6889;
eLibrary SPIN: 9261-9264; e-mail: azamatov.amir@yandex.ru

ОБ АВТОРАХ

***Юрий Владимирович Тезиков**, д-р мед. наук, профессор;
адрес: Россия, 443099, Самара, ул. Чапаевская, д. 89;
ORCID: https://orcid.org/0000-0002-8946-501X;
eLibrary SPIN: 2896-6986; e-mail: yra.75@inbox.ru

Игорь Станиславович Липатов, д-р мед. наук, профессор;
ORCID: https://orcid.org/0000-0001-7277-7431;
eLibrary SPIN: 9625-2947; e-mail: i.lipatoff2012@yandex.ru

Амир Русланович Азаматов;
ORCID: https://orcid.org/0000-0003-0372-6889;
eLibrary SPIN: 9261-9264; e-mail: azamatov.amir@yandex.ru