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Роль генетических маркеров тромбофилии в структуре причин развития плацента-ассоциированных осложнений у беременных с тромбоцитопенией

© О.Л. Мысик[1], М.С. Зайнулина[1, 2], В.С. Баранов[3], К.А. Кликунова[4], А.М. Живописцева[5]

[1] Родильный дом № 6 им. проф. В.Ф. Снегирева», Санкт-Петербург, Россия;
[2] Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова, Санкт-Петербург, Россия;
[3] Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта», Санкт-Петербург, Россия;
[4] Санкт-Петербургский государственный педиатрический медицинский университет, Санкт-Петербург, Россия;
[5] Военно-медицинская академия имени С.М. Кирова, Санкт-Петербург, Россия

Актуальность. Нарушения системы гемостаза занимают одно из ведущих мест в структуре причин бесплодия, невынашивания беременности, ассоциированы с репродуктивными потерями и являются значимым звеном в патогенезе плацента-ассоциированных осложнений беременности. Потребление тромбоцитов и факторов свертывания крови могут быть следствием генетической тромбофилии и причиной развития неблагоприятных клинических исходов беременности. Женщины с врожденной и приобретенной тромбофилией составляют группу высокого риска по развитию как тромботических, так и гестационных осложнений беременности.

Цель — оценить частоту встречаемости генетических маркеров тромбофилии у беременных с тромбоцитопенией, определить риск развития акушерских осложнений в зависимости от характера полиморфизмов генов тромбофилии у обследованных женщин.

Материалы и методы исследования. Проведено многоцентровое проспективное исследование с включением 299 женщин в III триместре беременности. Выделено две группы. Основную группу (n = 249) составили пациентки с тромбоцитопенией, контрольную группу (n = 50) — женщины с нормальными показателями тромбоцитов при физиологически протекающей беременности. Всем женщинам проведено полное клинико-анамнестическое и лабораторное обследование. Молекулярно-генетическое исследование крови с целью выявления полиморфизмов генов тромбофилии осуществляли с помощью биочипа, разработанного лабораторией пренатальной диагностики врожденных и наследственных болезней ФГБНУ «НИИ АГиР им. Д.О. Отта» совместно с ФГБУН «Институт молекулярной биологии им. В.А. Энгельгардта» РАН.

Результаты исследования. Данные сравнительного анализа генетических маркеров тромбофилии свидетельствуют о том, что частота встречаемости мутации генов тромбоцитарных рецепторов GPIa у беременных с тромбоцитопенией статистически значимо превышала таковую у беременных с нормальным уровнем тромбоцитов и физиологически протекающей беременностью (42,5 и 14,7 %; p = 0,003). Частота встречаемости полиморфизмов генов, отвечающих за нарушения в системе фибринолиза (*PAI-1, FGB*), также значимо превышала значения в контрольной группе (76,4 % и 47,0; 45,7 и 23,5 % соответственно; p = 0,001 и p = 0,030).

Заключение. Высокая частота встречаемости полиморфизмов генов тромбоцитарных рецепторов и генов, отвечающих за нарушения в системе фибринолиза у беременных с тромбоцитопенией, может служить причиной гиперагрегации тромбоцитов, гиперкоагуляции и выступать значимым фактором риска развития плацента-ассоциированных осложнений при беременности. Многообразие вариантов генетических дефектов, способных привести к неблагоприятному клиническому исходу беременности, определяет необходимость их дальнейшего исследования.

Ключевые слова: генетические тромбофилии; тромбоцитопения; гиперагрегация тромбоцитов; гиперкоагуляция; плацента-ассоциированные осложнения.

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The role of genetic markers of thrombophilia in the structure of the causes of placenta-associated complications in pregnant women with thrombocytopenia

© Olga L. Mysik[1], Marina S. Zaynulina[1, 2], Vladislav S. Baranov[3], Ksenia A. Klikunova[4], Aliya M. Zhivopistseva[5]

[1] Prof. V.F. Snegiryov Maternity Hospital No. 6, Saint Petersburg, Russia;
[2] Academician I.P. Pavlov First St. Petersburg State Medical University, Saint Petersburg, Russia;
[3] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[4] Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russia;
[5] Military Medical Academy named after S.M. Kirov, Saint Petersburg, Russia

HYPOTHESIS/AIMS OF STUDY: Disorders of the hemostatic system continue to occupy one of the leading places in the structure of the causes of infertility and miscarriage. While being associated with reproductive losses, hemostatic disorders are a significant link in the pathogenesis of placenta-associated pregnancy complications. The consumption of platelets and blood clotting factors can be a consequence of inherited thrombophilia and the cause of adverse clinical outcomes of pregnancy. Women with congenital and acquired thrombophilia are at high risk of developing both thrombotic and gestational complications of pregnancy. The aim of this study was to assess the frequency of genetic markers of thrombophilia in pregnant women with thrombocytopenia and to determine the risk of developing obstetric complications depending on thrombophilia gene polymorphisms in the examined women.

STUDY DESIGN, MATERIALS AND METHODS: This multicenter prospective study involved 299 pregnant women in the third trimester of pregnancy. Two groups of patients were included in the study: the main group (n = 249) consisted of individuals with thrombocytopenia, whereas the control group (n = 50) comprised women with normal platelet counts during physiological pregnancy. All patients underwent a complete clinical, anamnestic and laboratory examination. To identify thrombophilia gene polymorphisms, molecular genetic blood testing was conducted using a biochip developed jointly in the Laboratory of Prenatal Diagnostics of Congenital and Hereditary Diseases, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia and the V.A. Engelhardt Institute of Molecular Biology, Moscow, Russia.

RESULTS: The data obtained from a comparative analysis of genetic markers of thrombophilia indicate that the incidence of mutations in the GPIa platelet receptor gene in pregnant women with thrombocytopenia was significantly higher than that in pregnant women with normal platelet counts and physiological pregnancy (42.5% vs. 14.7%; p = 0.003). The frequency of polymorphisms in genes responsible for disorders in the fibrinolytic system (PAI-1, FGB) was also significantly higher than that in the control group (76.4% vs. 47.0%, p = 0.001; 45.7% vs. 23.5%, p = 0.030, respectively).

CONCLUSION: The revealed high frequency of polymorphisms in the platelet receptor genes and genes responsible for disorders of fibrinolysis system in pregnant women with thrombocytopenia may cause platelet hyperaggregation and hypercoagulation, while being a significant risk factor for placenta-associated complications during pregnancy. The variety of genetic defects that may lead to an unfavorable clinical outcome of pregnancy dictates the need for further study.

Keywords: inherited thrombophilia; thrombocytopenia; platelet hyperaggregation; hypercoagulation; placenta-associated complications.

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INTRODUCTION

Thrombocytopenia is one of the most common cytopenic syndromes that complicate the course of pregnancy [1–3]. The main reasons for the decrease in platelet count are increased consumption, destruction, sequestration, or insufficient production of such cells. The most common causes of platelet reduction during pregnancy are associated with the increased platelet consumption resulting from the activation of intravascular blood clotting and in other cases, with background pathology and undiagnosed diseases. In clinical practice, a number of thrombotic microangiopathies are isolated, causing the increase in platelet intake and coagulation factors, which include preeclampsia, eclampsia, and hemolysis, elevated liver enzymes and low platelet count HELLP-syndrome (hemolysis, elevated liver enzymes and low platelet count). The consumption of platelets and clotting factors may also be due to genetic thrombophilia and the circulation of antiphospholipid antibodies. The general population presents a high frequency of genetic and acquired thrombophilia, which according to modern data, reaches 15%–20% [4–6]. Physiological changes in the hemostasis system, predisposing hypercoagulation, contribute to the manifestation of congenital and acquired thrombophilia during pregnancy. The thrombophilia patients are a high-risk group for the development of thrombotic and placenta-associated complications, such as the threat of pregnancy termination, fetal loss syndrome, preeclampsia, and the development of placental insufficiency, and have an increased risk of developing premature detachment of the normally located placenta [7–11]. Congenital and acquired defects of the hemostasis system lead to hyperagregulation and hypercoagulation during pregnancy, disruption of implantation and placental processes, fibrin deposition, and immune complexes on the membrane of syncytiotrophoblast. The cascade of these reactions causes the development of placental insufficiency with fetal growth retention syndrome and fetal hypoxia and is a risk factor for fetal antenatal death [12–14]. In addition to the genetic forms of thrombophilia studied, special attention has been paid to the associative association of gestational complications with the various combinations of polymorphisms of thrombophilia genes [7, 15]. The probability of developing thrombotic and placenta-associated complications increases in patients with numerous genetic defects, comorbid somatic diseases, and history of reproductive losses [16].

This study aimed to assess the frequency of genetic markers of thrombophilia in pregnant women with thrombocytopenia and the risk of obstetric complications depending on the nature of polymorphisms of thrombophilia genes.

MATERIALS AND METHODS

Between 2013 and 2018, a prospective study was conducted at the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia and Snegirev Maternity, hospital number 6, Saint Petersburg, Russia. The study included 299 women in the third trimester of pregnancy. Two groups were singled out. The main group (n = 249) consisted of patients with thrombocytopenia (platelet level $<150 \cdot 10^9$/l), and the control group (n = 50) comprised women with normal platelets in physiologically proceeding pregnancy. All women underwent a full clinical and laboratory examination. To detect the polymorphisms of thrombophilia genes, we performed a molecular genetic study of blood in the Laboratory of Prenatal Diagnosis of Congenital and Hereditary diseases of the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. The study was carried out with the help of a biochip developed by the Laboratory of Prenatal Diagnosis of Congenital and Hereditary Diseases in cooperation with V.A. Engelhardt Institute of Molecular Biology, Moscow, Russia. At the heart of the principle of working all types of biochips with immobilized DNA is the exact correspondence between direct and complementary DNA in accordance with the rule of Watson–Crick: A<->T and C<->G. The fluorescent signal from microchip cells was recorded using a wide-field fluorescent microscope equipped with a charge-coupled camera device and Imageware (Biochip, V.A. Engelhardt Institute of Molecular Biology, Russia).

The criteria for inclusion into the main group were age 20–40 years and thrombocytopenia (platelet count less than $150 \cdot 10^9$/l) in the third trimester of pregnancy [29 (28; 30) weeks of gestation].

The criteria for exclusion from the study group were immune thrombocytopenia (idiopathic thrombocytopenic purpura), congenital thrombocytopenia, hereditary and acquired coagulopathy, systemic autoimmune diseases, type 1 diabetes with generalized complications, and thrombocytopenia (platelet count less than $50 \cdot 10^9$/l).

The criteria for inclusion into the control group were normal platelet rates and uncomplicated pregnancy in the third trimester.

The criteria for exclusion from the control group were obstetric complications in the third trimester of pregnancy, such as preeclampsia, placental insufficiency, and somatic chronic diseases.

Statistical analysis was performed with Microsoft Excel 2010 and IBM SPSS Statistics 23 software. The description of quantitative data is presented in the form of median (Me) and quartiles (Q_1 and Q_3) in the format Me (Q_1; Q_3). The Shapiro–Wilk criterion was used to test the hypothesis about the normality of distribution. The U-criterion of

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Mann–Whitney test was used to detect differences between samples.

For qualitative indicators, the absolute and relative values of the percentage indicated and statistical hypotheses about the coincidence of observed and expected frequencies were tested using Fischer's exact criterion. For binary traits, the odds ratio (OR) and 95% confidence interval (95% CI) were calculated. The critical level of difference significance (p) was defined as $p < 0.05$.

RESULTS

The average age of the patients in the main group was 31.1 (27.8; 35.0) years, and the control age was 30.7 (28.0; 34.8) years. The groups were comparable in age ($p = 0.68$). The median of thrombocytopenia registration in the main group was 23.1 (22.5; 29.0) in a week. The period of inclusion in the study in the groups did not differ and amounted to 28.8 (28.0; 30.0) in a week in the main group and 29.4 (28.5; 30.0) in the control group ($p = 0.15$). A pregnancy without the use of assisted reproductive technologies occurred in 225 (90.3%) women in the main group and 45 (90%) in the control group ($p = 1$). Table 1 presents the comparative characteristics of reproductive loss in history.

The comparative analysis of data of reproductive losses in history (Table 1) showed that the incidence of preterm birth was significantly higher in the group of pregnant women with thrombocytopenia compared with that of women with physiologically occurring pregnancies, in which such cases were absent (6.4% and 0%, respectively; $p = 0.05$). Cases of antenatal and intranatal fetal death in history were noted in the group of pregnant women with thrombocytopenia. Despite the insignificant statistics, no such cases were recorded in the group of pregnant women with physiologically occurring pregnancies and normal platelet levels. No statistically significant differences were observed in other pregnancy outcomes in history between the groups surveyed.

During pregnancy, the following hemostatic reactions developed: increased coagulation potential of the blood, suppressed fibrinolysis, reduced content and activity of natural blood anticoagulants, and increased functional activity of platelets. In the presence of congenital thrombophilia, these processes contribute to the emergence of serious vascular disorders, promoting the violation of uterine–placental blood flow and the development of chronic placental insufficiency. Thus, pregnancy is a kind of test for hidden thrombophilia, in which the disease manifests in the form of typical gestational complications. Table 2 presents the comparative characteristics of the genetic profiles of the women surveyed.

From Table 2, in pregnancy with thrombocytopenia, the frequency of mutations of GpIa receptor gene, GpIa, was significantly higher than that in the control group (42.5% and 14.7%, respectively; $p = 0.003$). The incidence of polymorphisms of genes responsible for violations in the fibrinolysis system (PAI-1 and FGB) also significantly exceeded the values in the control group (76.4% and 47%; 45.7% and 23.5%, respectively, $p = 0.001$ and $p = 0.03$). The frequency of other polymorphisms did not reveal reliable differences between groups of pregnant women with thrombocytopenia and the control group. Clinical manifestations in the presence of genetic thrombophilia against the background of pregnancy are diverse. Table 3 presents the comparative characteristics of gestational complications in the women surveyed.

As shown in Table 3, the incidence of pregnancy edicts in the main group was significantly higher than that in the control group (66.3% and 14%; $p < 0.001$). When comparing the data obtained, proteinuria in pregnant women with thrombocytopenia was likely to determine the values

Table 1. Distribution of surveyed pregnant women on the frequency of reproductive losses in history

Characteristic	Study group, $n = 249$		Control group, $n = 50$		Statistical analysis		
	n	%	n	%	p, Fisher's exact criterion	OR	95% CI
Non-developing pregnancy	64	25.7	8	16	0.20	1.82	0.81–4.07
Spontaneous miscarriage	32	12.9	4	8	0.48	1.70	0.57–5.03
Birth	114	45.8	24	48	0.88	0.91	0.50–1.68
Artificial abortion	47	18.9	4	8	0.07	2.68	0.92–7.80
Preterm birth	16	6.4	0	0	0.05	7.14	0.42–120.8
Antenatal fetal death in history	9	3.6	0	0	0.37	3.99	0.23–69.66
Intranatal fetal death in history	2	0.8	0	0	1.00	1.02	0.05–21.57

Note. $p \leq 0.05$: statistically significant differences between groups. OR: odds ratio; CI: confidence interval.

Table 2. Frequency of detection of mutations in thrombophilia genes in pregnant women with thrombocytopenia and the control group

Polymorphism	Pregnant women with thrombocytopenia		Control group		Statistical analysis		
	n (127)	%	*n* (34)	%	*p*, Fisher's exact criterion	OR	95% CI
F V Leiden	8	6.3	1	2.9	0.67	2.22	0.27–18.38
F II Protrombin	3	2.36	0	0	1.00	1.94	0.10–38.46
MTHFR	71	55.9	14	41.2	0.18	1.81	0.84–3.90
PAI-1	97	76.4	16	47	0.001	3.64	1.65–8.00
FGB	58	45.7	8	23.5	0.03	2.73	1.65–6.49
GPIIIa	40	31.5	9	26.4	0.68	1.28	0.55–2.98
PLAT	21	16.5	3	8.82	0.42	2.05	0.57–7.32
GpIa	54	42.5	5	14.7	0.003	4.29	1.56–11.81
GpIb	10	7.9	2	5.8	1.00	1.37	0.29–6.56
MTRR	29	22.8	6	17.6	0.64	1.38	0.52–3.66
MTR	11	8.6	2	5.88	0.74	1.52	0.32–7.20

Note. $p \leq 0.05$: significant differences between groups. OR: odds ratio; CI: confidence interval.

Table 3. Comparison of the incidence of obstetric complications in the surveyed patient groups

Characteristic	Main group, *n* = 249		Control group, *n* = 50		Statistical analysis		
	n	%	*n*	%	*p*, Fisher's exact criterion	OR	95% CI
Swelling of pregnant women	165	66.3	7	14	<0.001	12.07	5.20–27.98
Proteinuria ≤0.15 g/l	217	87.15	49	98	0.02	0.14	0.02–1.04
Proteinuria >0.15 g/l	32	12.6	1	2	0.02	7.23	0.96–54.17
Moderate preeclampsia	16	6.43	0	0	0.05	7.14	0.42–120.93
Severe preeclampsia	14	5.6	0	0	0.05	2.70	0.35–48.63
Development of chronic placental insufficiency	70	28.1	0	0	<0.001	39.67	2.41–651.77
Development of chronic renal failure with impaired hemodynamics	61	24.5	0	0	<0.001	32.95	2.00–542.09
Thrombotic complications after childbirth	3	1.2	0	0	1.00	1.43	0.07–29.20
Childbirth through natural birth paths	139	55.8	30	60	0.64	0.84	0.45–1.56
Delivery by cesarean section	98	39.3	10	20	0.01	2.60	1.24–5.43

Note. $p \leq 0.05$: significant differences between groups. OR: odds ratio; CI: confidence interval.

of protein in the urine ≥0.15 g/l (12.6% and 2%; $p = 0.02$). Meanwhile, women with physiologically occurring pregnancies were most likely to have minimal numbers of proteinuria or no protein at all ($p = 0.02$). Cases of the development of moderate-to-severe preeclampsia were noted only in pregnant women with thrombocytopenia ($p = 0.05$). The comparative analysis of signs of placental insufficiency showed that pregnant women with thrombocytopenia more often develop placental insufficiency with and without hemodynamic disorders ($p < 0.001$). This condition proves the hyperagregation of platelets and the development of microcirculatory disorders, leading to the violation of uterine–placental blood flow. The frequency of cesarean delivery in pregnant women with thrombocytopenia significantly exceeded the rates in the control group (39.3% and 20%; $p = 0.01$).

DISCUSSION

To date, genetic thrombophilia and antiphospholipid syndrome are associated with a high risk of miscarriage and remain one of the main causes of gestational complications. These conditions directly lead to the activation of the hemostasis system, intravascular blood clotting, increased consumption of thrombocytes, and the development of secondary thrombocytopenia and contribute to the development of serious obstetric, thromboembolic, and hemorrhagic syndromes [17–19]. Thrombotic complications, according to various authors, affect 0.3%–3.5% of pregnant women and are found in 7%–10% of cases in pregnant women over 40 years. Thus, special attention has been paid to the study of thrombotic and non-thrombotic effects of thrombophilia [20–22]. The manifestation of clinical manifestations of thrombophilia in pregnancy is multifaceted and includes a variety of disorders from macrothrombosis in large vessels to micro-thrombosis, leading to a violation of microcirculation primarily in the uterine–placental blood flow and in vital organs. Thrombosis of the main vessels is accompanied by a violation of placenta perfusion, aggravates uterine–placental circulation and fetus [23, 24]. The importance of hyperfibrinogenemia in the development of thrombosis is evident and increases three times in the presence of pathological allele 455A [7, 25].

Our study identified significant differences between the main and control groups when analyzing the frequency of mutations in *FGB* genes (455 G > A); *PAI1* (675 5G > 4G); *ITGA2* (807 S > T). The *FGB* gene encodes the amino acid sequence β-chain of fibrinogen. The plasminogen inhibitor is a major component of the blood anti-clotting system and plays a significant role in the process of fibrinolysis control during pregnancy as an important factor in uterine–placental circulation. Carriers of the pathological allele of this gene are associated with the development of the pathology of trophoblast infestation in the early stages of pregnancy, preeclampsia of severe degree, and placental insufficiency with delayed fetal growth and are a risk factor for fetal antenatal death and deep vein thrombosis [9, 10, 25]. The comparative analysis of gestational complications in our study showed that pregnant women with thrombocytopenia often develop placental insufficiency with or without hemodynamic disorders ($p < 0.001$). The homozygous carrier *PAI-1* (4G/4G) in combination with any pathological allele of the genes of the hemostasis system and folate cycle can serve as a genetic marker of propensity to develop placental insufficiency caused by thrombophilia in pregnancy [25].

The *ITGA2* gene encodes the protein integrin alpha-2, a membrane glycoprotein that is expressed on the membranes of various cells including platelets. Pathological allele T (homozygote type T/T) is associated with an increase in platelet aggregation rate and is thus a risk factor for thrombophilia. Pathological alleles of *ITGA2* and *ITGV3* genes (associated with changes in the properties of platelet receptor fibrinogen) can lead to resistance to aspirin therapy [10, 16]. A comparative analysis of the genetic profile in our study showed that in the group of pregnant women with thrombocytopenia, the frequency of mutations of platelet receptor gene GpIa significantly exceeded that in the control group (42.5% and 14.7%; $p = 0.003$). These data support the possible role of the *ITGA2* gene in the development of platelet hyperagregulation and activation of thrombotic risk in pregnancy.

CONCLUSION

The study of genetic profiles of the women examined enabled the identification of a group of pregnant women with a high thrombotic risk. In pregnant women with thrombocytopenia against the background of activation of the hemostasis system, multigenic carrying of a combination of pathological genes, namely, *PAI-1*, *FGB,* and *GpIa*, which are associated with a high thrombotic risk,] represent a significant risk factor for the development of placenta-associated complications of pregnancy. Polymorphism of genes *PAI-1*, *FGB,* and *GpIa* can be used as molecular predictors of placental insufficiency, leading to adverse outcomes of pregnancy. Genetic examination and diagnosis of thrombotic risks in pregnant women with thrombocytopenia against the background of activation of intravascular blood clotting, subject to the use of anticoagulant therapy, can significantly affect the clinical outcomes of pregnancy.

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ОБ АВТОРАХ

***Ольга Леонидовна Мысик**;
адрес: Россия, 192014, Санкт-Петербург, ул. Маяковского, д. 5;
ORCID: https://orcid.org/0000-0002-8895-6845;
e-mail: olga_mysik88@mail.ru

Марина Сабировна Зайнулина, д-р мед. наук;
ORCID: https://orcid.org/0000-0002-2622-5000;
Scopus Author ID: 37076359000; ResearcherID: B-5746-2018;
e-mail: zainulina@yandex.ru

Владислав Сергеевич Баранов, д-р мед. наук,
профессор, член-корр. РАН, засл. деят. науки РФ;
ORCID: https://orcid.org/0000-0002-6518-1207;
Scopus Author ID: 56057974100; eLibrary SPIN: 9196-7297;
e-mail: baranov@vb2475.spb.edu

Ксения Алексеевна Кликунова, канд. физ.-мат. наук, доцент;
ORCID: https://orcid.org/0000-0002-5978-5557;
e-mail: kliksa@gmail.com

Алия Мирзаевна Живописцева, канд. мед. наук, доцент;
ORCID: https://orcid.org/0000-0002-1360-1652;
eLibrary SPIN: 2881-5149; e-mail: aliamir@list.ru

AUTHORS INFO

***Olga L. Mysik**;
address: 5, Mayakovsky str., Saint Petersburg, 192014, Russia;
ORCID: https://orcid.org/0000-0002-8895-6845;
e-mail: olga_mysik88@mail.ru

Marina S. Zaynulina, MD, PhD, DSci (Medicine);
ORCID: https://orcid.org/0000-0002-2622-5000;
Scopus Author ID: 37076359000; ResearcherID: B-5746-2018;
e-mail: zainulina@yandex.ru

Vladislav S. Baranov, MD, PhD, DSci (Medicine), Professor,
Corresponding Member of the Russian Academy of Sciences,
Honoured Scientist of the Russian Federation;
ORCID: https://orcid.org/0000-0002-6518-1207;
Scopus Author ID: 56057974100; eLibrary SPIN: 9196-7297;
e-mail: baranov@vb2475.spb.edu

Ksenia A. Klikunova, PhD, Assistant Professor;
ORCID: https://orcid.org/0000-0002-5978-5557;
e-mail: kliksa@gmail.com

Aliya M. Zhivopistseva, MD, PhD, Assistant Professor;
ORCID: https://orcid.org/0000-0002-1360-1652;
eLibrary SPIN: 2881-5149; e-mail: aliamir@list.ru