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FEATURES OF THE MEDICAL HISTORY AND PREGNANCY OUTCOMES IN WOMEN WITH ANTIPHOSPHOLIPID SYNDROME DEPENDING ON CORRECTION METHODS

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▪ ***Hypothesis/aims of study.*** The aim of this study was to evaluate the features of the medical history and pregnancy outcomes in women with miscarriage and antiphospholipid syndrome depending on the methods of its correction.

Study design, materials and methods. A prospective cohort study was conducted, in which a total of 137 pregnant women with a history of abortion and antiphospholipid syndrome were examined. The women were divided into two groups according to the principle of the presence or absence of plasmapheresis procedures in the scheme of miscarriage therapy at the pregravid stage. Group I (main) consisted of individuals (n = 73), who were treated with the inclusion of plasmapheresis at the pregravid stage; group II (comparison) included women (n = 64), who were not given efferent therapy.

Results. Antiphospholipid syndrome was more common in patients with a complicated obstetric and gynecological history. As a result of persistent infection, chronic endometritis and salpingo-ooparitis were more often observed in patients with TORCH infection. The titer of antiphospholipid antibodies, regardless of the presence or absence of TORCH infection, decreased after plasmapheresis, such positive dynamics being observed only in patients with a history of gestational losses of less than four.

Conclusion. The level of reduction of antiphospholipid antibodies in relation to the initial values was 60–95%, which indicates the optimal choice of the characteristics of plasmapheresis therapy and its duration.

▪ **Keywords:** antiphospholipid antibodies; antiphospholipid syndrome; miscarriage; plasmapheresis; TORCH infections.

ОСОБЕННОСТИ АНАМНЕЗА И ИСХОДЫ БЕРЕМЕННОСТИ У ЖЕНЩИН С АНТИФОСФОЛИПИДНЫМ СИНДРОМОМ В ЗАВИСИМОСТИ ОТ МЕТОДОВ ЕГО КОРРЕКЦИИ

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▪ ***Цель*** — оценить особенности анамнеза и исходы беременности у женщин с невынашиванием и антифосфолипидным синдромом в зависимости от методов его коррекции.

Материалы и методы. Проведено проспективное когортное исследование. Обследовано 137 беременных с прерываниями беременности в анамнезе и антифосфолипидным синдромом. Обследованные женщины были разделены на две группы по принципу наличия или отсутствия процедур плазмафереза в схеме терапии

невынашивания на прегравидарном этапе. Первую группу (основная) составили женщины (n = 73), которым на прегравидарном этапе проводили комплексную терапию с включением плазмафереза (эфферентная терапия), во второй группе (сравнения, n = 64) эфферентную терапию не проводили.

Результаты. Антифосфолипидный синдром чаще развивался у пациенток с осложненным акушерско-гинекологическим анамнезом. У пациенток с персистирующей TORCH-инфекцией достоверно чаще наблюдались хронические эндометрит и сальпингоофарит. Титр антифосфолипидных антител вне зависимости от наличия или отсутствия TORCH-инфекции снижался после плазмафереза, в то же время такая положительная динамика наблюдалась лишь у пациенток с четырьмя гестационными потерями в анамнезе и менее.

Заключение. Уровень снижения содержания антифосфолипидных антител по отношению к исходным величинам составлял 60–95 %, что указывает на оптимальный выбор характеристик терапии плазмафереза и продолжительности его проведения.

▪ **Ключевые слова:** антифосфолипидные антитела; антифосфолипидный синдром; невынашивание; плазмаферез; TORCH-инфекции.

The diagnosis of antiphospholipid syndrome (APS) is based on clinical and laboratory criteria [1]. It can develop as a complication of an already existing systemic pathology (inflammatory, infectious, and neoplastic diseases in secondary APS) or as an isolated pathology (primary APS) that sometimes precedes the onset of a systemic disease. In APS, two systems are affected, namely, the vascular system, which is manifested by thrombotic complications, and the uteroplacental blood flow, which results in complications of pregnancy [2].

In women with a compromised obstetric and gynecological history, increased levels of antiphospholipid antibodies (APA) are detected in 24% of patients with recurrent miscarriage and in 20% of patients with infertility [3]. In most cases, APS (80%) is diagnosed in women of reproductive age. Similarly, this is noted in other autoimmune diseases [4]. Obstetric complications in pregnant women with APS and persistent viral infection are accompanied by hemostatic system disorders [5]. APA have several effects on the formation and development of trophoblast since the establishment of uteroplacental blood flow, and they are often detected in women with a history of three or more unsuccessful attempts of in vitro fertilization [6]. The most common adverse events associated with APS in pregnant women are preterm labor and intrauterine growth retardation. Premature labor is most common in patients who have APS and systemic lupus erythematosus [7].

A. Ruffatti et al. attempted to determine the causes of adverse neonatal outcomes. These factors were the presence of lupus anticoagulant, anticardiolipin antibodies, antibodies to β_2-glycoprotein-1 (β_2GP1), and a history of vascular thrombosis before pregnancy. In the absence of these factors, the neonatal outcome was more favorable [8].

For women with obstetric APS with three or more fetal losses and no history of thrombosis, prophylactic or moderate doses of unfractionated heparin or prophylactic doses of low-molecular-weight heparin (LMWH) in combination with low doses of aspirin [New Drug Application (NDA)] (75–100 mg/day) should be administered without treatment prior to delivery as recommended by the American College of Chest Physicians 9th revision [9]. Therapeutic doses of LMWH adjusted for the patient's weight are recommended in case of a history of thrombosis with regular monitoring of the activity of the anti-Xa indicator [10]. Despite the fact that combination therapy with the use of NDA and LMWH is considered the basic treatment for APS female patients, the efficiency of such therapy remains controversial [11]. The data on the positive effects of treatment with LMWH and NDA in women with clinical criteria for APS and circulation of non-criterial autoantibodies are consistent with the results of Russian authors [12]. The literature also discusses the possibilities of immunomodulatory therapy with intravenous immunoglobulins, namely, multispecific intact immunoglobulins, mainly IgG, obtained from the plasma of healthy donors [13]. Some authors [14] propose to include plasmapheresis (efferent therapy) in combination with anticoagulant, antiplatelet, antioxidant, and immunomodulatory therapy (intravenous immunoglobulin), while other researchers use plasmapheresis in combination with enzyme therapy [15]. The therapeutic basis of plasmapheresis comprises the removal of APA and pro-inflammatory and procoagulant markers, adhesion molecules, vasopressive factors, and

atherogenic lipoproteins to improve the functions of the maternal endothelium, prevent thrombosis, and increase placental perfusion [16].

This study aimed to assess the characteristics of the anamnesis and pregnancy outcomes in women with miscarriage and antiphospholipid syndrome, depending on the methods of its correction.

Materials and methods

A total of 137 pregnant women with a history of abortions and APS were examined. The female patients examined were divided into two groups. Group I (main) comprised women ($n = 73$) who received complex therapy with plasmapheresis at the periconceptional stage, while group II (comparison, $n = 64$) comprised patients who did not receive efferent therapy. The main element of the complex therapy of both groups was the standard protocol for the treatment and prevention of venous thromboembolic complications according to clinical guidelines.

The inclusion criteria were as follows: recurrent miscarriage with a history of antiphospholipid syndrome; availability of an original copy of the written informed consent from the patient and/or her legal representative to participate in the study; age from 22 to 32 years old; pregnant women with singleton pregnancies; absence of severe concomitant therapeutic, infectious, immunological, and surgical diseases and/or complications at the time of inclusion, as well as throughout the study; homozygous physiological set of healthy genes of the hemostasis system; the ability and desire, as well as the absence of any contraindications, to visit the necessary specialists and undergo the procedures provided for by this study (plasmapheresis, injection and invasive methods of diagnosis and treatment, magnetic resonance imaging, computed tomography, laboratory studies, radiography, ultrasound examination, functional tests); and the ability to adequately cooperate in the course of the clinical study.

The non-inclusion criteria were as follows: noncompliance with the established age criteria at the time of possible inclusion in a clinical trial (aged less than 22 and over 32 years old); severe endocrine diseases, including polycystic ovary syndrome and type 1 and 2 diabetes mellitus; physically demanding job, professional sports, and occupational hazards; tendency to be diagnosed with hemophilia and thrombophilia or the presence of a gene mutation in the hemostasis system [factor V Leiden mutation, prothrombin gene mutation, methylene tetrahydrofolate reductase (MTHFR) mutation; methionine synthase reductase (MTRR) mutation, plasminogen activator inhibitor I mutation]; a history or occurrence in the course of a clinical study of abortion with genetic mutations of the abortive material, indicating the impossibility of a safe completion of the current pregnancy; hormonal therapy (including the intake of combined oral contraceptives with contraceptive and/or therapeutic purposes), signs of moderate and severe ovarian pathology, pathology of the thyroid gland, adrenal glands, pituitary gland, and hypothalamus that requires hormone replacement therapy; therapeutic moderate or severe pathology and any pathology for which surgical intervention is required during the study, in the next year after the study, or in history; and addiction to tobacco, alcohol, and other types of drug addiction in the course of the study.

The exclusion criteria were as follows: onset of multiple pregnancy; the development of a serious illness and/or complications, patients undergoing surgical treatment and receiving hormonal therapy; refusal of the patient and/or her legal representatives from further monitoring; laboratory and clinical signs of anhornomia; persistence and/or aggravation of infectious pathology; tobacco smoking, alcoholism, and other types of unhealthy habits; surgical interventions on the organs of the endocrine system; and trauma to the abdominal cavity or skull.

Each of the groups was divided into two subgroups according to the presence or absence of laboratory signs of active Toxoplasma; Other infections, namely, syphilis, hepatitis B, varicella-zoster virus, and other infections affecting the fetus; Rubella; Cytomegalovirus; Herpes (TORCH) infection.

In subgroups 1 of each group, according to the results of clinical examination and laboratory tests, no signs of TORCH infection activity were observed. On the contrary, in subgroups 2, both clinical and laboratory signs of TORCH infection activation were noted. Simultaneously, the incidence of a certain infectious concomitant pathology in both subgroups was comparable. In both subgroups (I_2 and II_2), before the onset of

pregnancy, the therapy was performed, aimed at deactivating the TORCH infection, based on clinical guidelines. After the elimination of signs of activity of the infectious process, planning of pregnancy was started, and in group I, plasmapheresis was performed. The number of miscarriages was comparable between the groups and the subgroups.

To identify the infectious process, to track the dynamics of its development and the efficiency of treatment, and to verify clinical and laboratory recovery, immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies, their avidity, presence/absence of antigens of infectious agents, and their titer were determined. The studies were conducted on automatic analyzers Architect 2000 (Abbott, USA) and Immulite 2000 (Siemens, Germany) using standardized original reagents. Subsequently, markers of the infections of syphilis, Epstein-Barr virus, herpes simplex virus types 1 and 2, cytomegalovirus, toxoplasmosis, chlamydia, human immunodeficiency virus, and hepatitis A, B, and C were determined.

The key parameters of the hemostasis components were studied using platelet and plasma components. For this purpose, a multiplate impedance aggregometer (Roche, France) was used. Fibrinogen concentration, activity, and content of blood coagulation factors, heparin, plasmin inhibitor, plasminogen, and proteins C and S were determined using an ACL-700 automatic coagulometer (Laboratories Instrumentals, USA). In all women examined, the most common polymorphisms of genes of the hemostasis system were identified, namely, the Leiden mutations; gene of prothrombin, MTHFR; MTRR; and mutation of a plasminogen activator inhibitor. The study included only those patients who did not have laboratory signs of the above mutations. Molecular studies of venous blood were performed by polymerase chain reaction using RotorGene (QIAGEN, Germany) and DT-96 (DNA-Technology, Russia) amplifiers. Laboratory diagnostics of APS was conducted by identifying the autoantibodies of lupus anticoagulant and antibodies to phospholipids (IgG, IgM, IgA to cardiolipin, phosphatidylserine, glycoprotein, annexin, prothrombin) and/or to the β-subunit of human chorionic gonadotropin (IgM and IgG). Antibodies were detected using a MultiSkan EX analyzer. Their content was determined before treatment, after plasmapheresis sessions, and throughout the entire period of pregnancy. Moreover, an isolated or combined increase in the concentration of a certain type of antibodies was mandatorily recorded.

Plasmapheresis was performed in patients included in the study group, while observing the clinical recommendations on the use of this procedure in preparation for pregnancy to remove autoantibodies from the blood (decrease in the concentration) and also taking into account the indications and contraindications for efferent therapy. Plasmapheresis was performed using an intermittent technique using the mandatory standardized premedication, which included antihistamines and hormonal drugs. All women received traditional pre-perfusion preparation aimed at complete elimination (significant reduction in concentration) of autoantibodies that cause and indicate the development of antiphospholipid syndrome. The average amount of plasma collected during one procedure was 976.5 ± 112.3 ml. In this regard, all women underwent pre-perfusion preparation in the form of infusion therapy in the mode of moderate hemodilution with electrolyte and protein balance correction. The surgery was completed with gradual (within 30–40 min) replenishment of the plasma deficit with fresh frozen donor plasma of at least 80% of the volume of exfusion plasma, protein blood substitutes, and crystalloids. The blood was exfused into sterile plastic containers with an anticoagulant of the Gemakon type and centrifuged in an OS-6M centrifuge for 20 min at a speed of 1,500 rpm. After centrifugation, the plasma was removed, and the erythrocyte concentrate was diluted with isotonic sodium chloride solution at a ratio of 1:1.5 with a temperature of 37°C. Such extracorporeal "washing" of erythrocytes was performed three times in succession without time intervals.

Statistical processing of the data was performed using the Statistica 6 program. The normality of distribution of the results obtained in the variational series was assessed using the Kolmogorov–Smirnov test and according to the rule of two and three sigmas (σ). When comparing the quantitative characteristics of two sets of unconjugated samples, under the law of normal distribution, the Student's *t*-test was used. The Mann–Whitney *U* test was used if the compared populations of unconjugated samples did not meet the normal distribution law.

The Wilcoxon's test was used when comparing two linked samples. When comparing qualitative characters, χ^2 was used. In this study, the critical level of significance of statistical hypotheses was equal to 0.05.

Results

The average age of the patients enrolled in the study was 26.1 ± 2.7 years. There were no statistically significant differences in age between the patients of the main groups, the comparison groups, and the subgroups ($p > 0.05$). Antiphospholipid syndrome was often observed in patients with a complicated obstetric and gynecological history. In patients with habitual fetal loss, chronic salpingo-oophoritis and menstrual dysfunction were recorded significantly more often (Table 1), which is probably due to repeated hormonal stress, which, in addition to reproductive dysfunction, contributed to a decrease in immunoresistance; occurrence and/or progression of infectious pathology, including the TORCH infection; and the aggravation of the APS course. Hormonal changes caused by the loss of pregnancy (specifically repeated one) superimposed or independently provoked the development of secondary immunosuppression, which contributed to the long-term persistence of the infectious agent, the progression of APS with excessive stress, and distortion of the immune response, thereby forming a vicious circle, the relationship in which intensified with each new loss of pregnancy, stress, or emergence/activation of an infectious agent.

According to the change in the APA level, depending on the number of gestational losses, a gradual (more significant from the fourth loss of pregnancy) increase was revealed in both the initial antibody titer and the antibody titer retained after efferent therapy (Table 2). When comparing the indicators of the APA content in subgroups with $TORCH^-$ and $TORCH^+$ in the main group and the comparison group, regardless of the amount of reproductive losses, the level of APA increased significantly, specifically the level of IgG to cardiolipin and IgG to β_2GP1 in subgroups with $TORCH^+$. One of the key points was a decrease in the APA titer using plasmapheresis, regardless of the presence or absence of TORCH infection (as evidenced by comparable APA levels in both subgroups of the main group after therapy). At this stage of the study, the effectiveness of the

Table 1 / Таблица 1

Frequency of gynecological pathology depending on the number of reproductive losses
Частота гинекологической патологии в зависимости от количества репродуктивных потерь

Parameter		Group (subgroup)			
		I_1 (n = 36)	I_2 (n = 37)	II_1 (n = 34)	II_2 (n = 30)
Single pregnancy loss	Total amount	7	7	6	6
	Chronic endometritis, %	28.6	14.3	16.7	16.7
	Chronic salpingo-oophoritis, %	28.6	42.9	33.3	33.3
	Ectopia of the uterine cervix, %	14.3	14.3	16.7	16.7
	Menstrual disorder, %	42.9	57.1	50.0	50.0
	Genital infection (herpes, chlamydial and ureaplasma infections), %	28.6	14.3	16.7	33.3
Habitual pregnancy loss (2 times or more)	Total amount	29	30	28	24
	Chronic endometritis, %	31.0	36.7*	32.1	33.3
	Chronic salpingo-oophoritis, %	55.2*	60.0*	71.4*	75.0*
	Ectopia of the uterine cervix, %	10.4	16.7	17.9	12.5
	Menstrual disorder, %	75.9*	83.3*	85.7*	83.3*
	Genital infection (herpes, chlamydial and ureaplasma infections), %	51.7*	66.7*	75.0*	54.2*

N o t e: * $p < 0.05$ when comparing identical parameters in women with single and multiple loss of pregnancy.

Table 2 / Таблица 2

Blood levels of antiphospholipid syndrome markers depending on the number of reproductive losses after efferent therapy, Me (HQ; LQ)

Содержание в крови маркеров антифосфолипидного синдрома в зависимости от количества репродуктивных потерь после эфферентной терапии, Me (HQ; LQ)

Parameter	Subgroup							
	I_1 (n = 36)		I_2 (n = 37)		II_1 (n = 34)		II_2 (n = 30)	
	in.	ther.	in.	ther.	in.	ther.	in.	ther.
Number of reproductive losses — 1								
Lupus anticoagulant	2.4 (2.2; 3.4)	1.1 (0.9; 1.5)	3.6 (3.1; 4.0)	1.2^ (0.8; 1.7)	2.2 (2.1; 3.6)	1.9 (1.3; 2.3)	3.7 (3.2; 4.1)	2.4 (2.2; 2.7)
Cardiolipin IgG	18.0 (17.6; 19.0)	4.4^ (2.6; 6.5)	23.2$^{\#}$ (21.6; 25.1)	4.1^ (2.2; 5.8)	19.1 (17.7; 21.0)	10.7 (8.1; 12.3)	22.4 (20.3; 24.9)	15.2$^{\#}$ (14.2; 16.7)
β_2-glycoprotein-1 IgG	12.5 (8.3; 14.3)	4.8^ (3.1; 5.4)	16.2$^{\#}$ (15.2; 17.1)	3.3^ (2.7; 3.6)	11.4 (10.2; 12.8)	6.6 (5.9; 7.4)	17.3$^{\#}$ (15.8; 18.1)	10.4$^{\#}$ (8.5; 11.7)
Number of reproductive losses — 2								
Lupus anticoagulant	2.7 (2.5; 3.4)	1.3^ (0.9; 1.4)	3.5 (3.0; 4.2)	1.4^ (0.9; 1.5)	2.1 (2.0; 3.3)	1.7 (1.5; 2.2)	3.7 (3.1; 4.0)	2.1 (2.0; 2.5)
Cardiolipin IgG	17.3 (17.1; 18.7)	4.7^ (2.9; 5.2)	24.1$^{\#}$ (22.3; 25.0)	4.8^ (3.4; 5.1)	21.0 (18.8; 22.6)	9.5 (8.0; 10.1)	25.6$^{\#}$ (23.1; 27.2)	16.8$^{\#}$ (13.5; 16.9)
β_2-glycoprotein-1 IgG	12.2 (9.1; 13.4)	4.9^$^{\#}$ (3.8; 5.1)	16.0$^{\#}$ (15.1; 17.0)	3.5^ (3.1; 3.7)	12.7 (11.5; 12.9)	6.9 (5.9; 7.2)	16.4$^{\#}$ (15.5; 17.3)	11.2$^{\#}$ (9.9; 11.8)
Number of reproductive losses — 3								
Lupus anticoagulant	4.3* (3.6; 4.4)	1.9*$^{\#}$ (1.5; 2.4)	3.5 (3.0; 4.2)	1.4^ (0.9; 1.5)	2.1 (2.0; 3.3)	1.7 (1.5; 2.2)	3.7 (3.1; 4.0)	2.1 (2.0; 2.5)
Cardiolipin IgG	18.4 (14.2; 19.7)	4.0^$^{\#}$ (2.9; 5.1)	21.6$^{\#}$ (20.0; 23.8)	3.7^ (2.0; 3.9)	20.4 (18.4; 21.6)	12.1 (9.1; 13.5)	20.2 (19.3; 23.2)	16.4$^{\#}$ (14.1; 17.1)
β_2-glycoprotein-1 IgG	13.4 (8.9; 13.6)	4.5^ (3.2; 5.0)	15.1$^{\#}$ (15.0; 16.1)	3.0^ (2.2; 3.3)	11.6 (10.4; 12.9)	6.7 (5.8; 7.2)	18.1$^{\#}$ (17.0; 18.9)	11.2$^{\#}$ (9.6; 11.9)
Number of reproductive losses — 4								
Lupus anticoagulant	6.2*^ (5.7; 6.6)	2.3* (2.1; 3.0)	8.3* (6.2; 9.1)	1.9* (1.9; 2.5)	7.1* (6.0; 7.3)	2.5 (2.2; 2.9)	8.9* (7.1; 9.0)	2.9$^{\#}$ (2.4; 3.3)
Cardiolipin IgG	23.4* (22.5; 25.6)	3.2^ (2.7; 5.5)	29.4*$^{\#}$ (27.1; 30.5)	4.0^ (3.2; 5.1)	22.6 (20.7; 24.0)	13.4 (10.9; 15.5)	27.8$^{\#}$ (24.2; 29.1)	16.7 (15.2; 17.9)
β_2-glycoprotein-1 IgG	18.9* (17.3; 19.5)	5.9^$^{\#}$ (4.5; 6.4)	22.4*$^{\#}$ (19.8; 23.8)	3.0^ (2.5; 3.4)	17.7* (16.5; 19.7)	11.1* (9.9; 12.4)	22.8 (17.8; 23.7)	12.4 (9.6; 13.9)
Number of reproductive losses — 5 or more								
Lupus anticoagulant	8.3* (7.8; 8.6)	2.9*^ (2.3; 3.3)	10.9*$^{\#}$ (9.1; 11.3)	1.5 (1.1; 3.6)	8.2* (7.5; 8.8)	3.7* (3.5; 4.2)	10.8*$^{\#}$ (9.7; 12.0)	3.2*$^{\#}$ (2.7; 3.5)
Cardiolipin IgG	23.4* (22.5; 25.6)	3.2^ (2.7; 5.5)	29.4*$^{\#}$ (27.1; 30.5)	4.0^ (3.2; 5.1)	22.6 (20.7; 24.0)	13.4 (10.9; 15.5)	27.8$^{\#}$ (24.2; 29.1)	16.7 (15.2; 17.9)
β_2-glycoprotein-1 IgG	28.1* (27.0; 29.7)	5.1^$^{\#}$ (4.2; 5.4)	29.8* (26.8; 31.3)	3.8^ (2.7; 3.9)	29.6* (26.8; 30.7)	15.2* (12.9; 16.3)	31.4* (29.1; 33.2)	19.2*$^{\#}$ (19.0; 22.9)

N o t e: in. — initially; ther. — after therapy; * $p < 0.05$ when comparing identical parameters in women with single and multiple loss of pregnancy; ^ $p < 0.05$ between identical indicators of the comparison subgroup and the main group; $^{\#}$ When comparing identical parameters in the presence and absence of TORCH infection.

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use of efferent therapy as a method to reduce the APA level was clearly demonstrated. Regardless of TORCH⁻ and TORCH⁺ and the amount of reproductive losses, in all cases, there is a significant decrease in the level of IgG to cardiolipin and IgG to β_2GP1 after the plasmapheresis procedure. With five or more reproductive losses, plasmapheresis, in addition to reducing the level of IgG to cardiolipin and IgG to β_2GP1, contributed to a decrease in the level of lupus anticoagulant.

Regardless of the initial concentrations of APA, their amount after the course of efferent therapy was comparable in women, with a history of no more than three gestational losses. Simultaneously, the content of APA in relation to the initial values decreased by 60%–95%, which indicates the optimal choice of the characteristics of therapy and the duration of its implementation. Based on the post-therapy APA levels, women with more than three reproductive losses responded to efferent therapy to a lesser extent. The concentration of antibodies after plasmapheresis was 40%–70% of the initial value.

According to the correlation analysis (Table 3), the strongest direct relationship with the number of reproductive losses in the history was revealed for IgG β_2GP1, which was moderate only in TORCH infection. This correlation was least typical for lupus anticoagulant (moderate to average). The IgG level to cardiolipin correlated with the amount of reproductive losses only in the absence of TORCH infection. It was also noted that as the gestational age increased, the correlation increased.

Probably, with an increase in the number of gestational losses and gestational age, at least two factors affect the effectiveness of plasmapheresis therapy. First, a significant number of abortions undoubtedly lead to the inclusion of other, non-hemostasiological and immunological, mechanisms of miscarriage. Second, as the time interval from the plasmapheresis increases, its eliminating effect is gradually leveled and the concentration of antibodies increases again.

In the main group of female patients with a history of a single gestational loss, in 100% of cases, pregnancy ended in childbirth. Premature birth was observed in 1 (7.1%) woman, and term delivery was observed in 13 women (92.9%). In patients of the main group, whose history included 2 or more gestational losses, in subgroup I_1, pregnancy ended in childbirth in 96.6% of women and in 86.7% of women in subgroup I_2. In subgroup I_1, one (4.5%) case of spontaneous miscarriage was recorded, while in subgroup I_2, there were three (13.3%) such cases. Term delivery in these patients was noted in 26 (78.8%) cases, and premature delivery was observed in 7 cases (21.2%). In 33% of patients, delivery was performed by cesarean section.

In the comparison group, pregnancy ended with childbirth in 50% of cases only in women with a history of one gestational loss. Pregnancy ended in childbirth in 13 (46.4%) cases in women in subgroup II_1, with a history of 2 or more gestational losses. In 12 (75%) cases, in pregnant women in subgroup II_1, delivery was performed by cesarean section. In the range of indications for operative delivery by cesarean section, severe preeclampsia, hemorrhage, hypoxia, and fetal growth retardation were observed. In patients in subgroup II_2, with 2 or more gestational losses in the history, childbirth

Table 3 / Таблица 3

Correlation between the number of reproductive losses and the presence of antiphospholipid antibodies depending on the number of reproductive losses (*r*; *p*)

Корреляционные связи между количеством репродуктивных потерь и наличием антифосфолипидных антител в зависимости от количества репродуктивных потерь (*r*; *p*)

Indicators compared	Subgroup			
	I_1 (*n* = 36)	I_2 (*n* = 37)	II_1 (*n* = 34)	II_2 (*n* = 30)
Number of reproductive losses/lupus anticoagulant	0.41 *p* = 0.001	0.32 *p* = 0.022	0.54 *p* = 0.017	0.77 *p* = 0.002
Number of reproductive losses/Cardiolipin IgG	0.73 *p* = 0.001	0.30 *p* = 0.001	0.85 *p* = 0.022	0.12 *p* = 0.033
Number of reproductive losses/β_2-glycoprotein-1 IgG	0.82 *p* = 0.035	0.76 *p* = 0.011	0.90 *p* = 0.002	0.53 *p* = 0.034

N o t e: * $p < 0.05$ when comparing identical parameters in women with single and multiple loss of pregnancy.

Table 4 / Таблица 4

Antiphospholipid syndrome markers and pregnancy outcomes after efferent therapy depending on reproductive losses and antiphospholipid antibody levels
Маркеры антифосфолипидного синдрома и исходы беременностей после эфферентной терапии в зависимости от гестационных потерь и уровня антифосфолипидных антител

Parameter		Subgroup							
		I_1 (n = 36)		I_2 (n = 37)		II_1 (n = 34)		II_2 (n = 30)	
		combined	isolated	combined	isolated	combined	isolated	combined	isolated
Lupus anticoagulant, n. (%)	in.	4 (11.1%)	5 (13.9%)	4 (10.8%)	7 (18.9%)	5 (14.7%)	5 (14.7%)	2 (6.7%)	5 (16.7%)
	ther.	2 (5.6%)*	2 (5.6%)*	2 (5.4%)*	3 (8.1%)*	5 (14.7%)	4 (11.8%)	2 (6.7%)	3 (10.0%)
Cardiolipin IgG, n. (%)	in.	7 (19.4%)	3 (6.5%)	10 (27.0%)	4 (10.8%)	6 (17.6%)	4 (11.8%)	9 (30.0%)	5 (16.7%)
	ther.	5 (13.9%)	2 (5.6%)	9 (24.3%)	4 (10.8%)	5 (14.7%)	4 (11.8%)	9 (30.0%)	5 (16.7%)
β_2-glycoprotein-1 IgG, n. (%)	in.	18 (50.0%)	6 (16.7%)	17 (45.9%)	11 (29.7%)	16 (47.0%)	9 (26.4%)	17 (56.6%)	8 (26.7%)
	ther.	6 (16.7%)*	2 (5.6%)*	6 (16.2%)*	1 (2.7%)*	12 (35.3%)	6 (17.6%)	17 (56.6%)	7 (23.3%)
Number of gestational losses, n. (%)	1	3 (8.3%)	4 (11.1%)	3 (8.1%)	4 (10.8%)	3 (8.8%)	3 (8.8%)	2 (6.7%)	4 (13.3%)
	≥2	19 (52.8%)	10 (27.8%)	13 (35.1%)	17 (48.6%)	13 (38.2%)	15 (44.1%)	10 (33.3%)	14 (46.7%)
Pregnancy outcomes	Childbirth	21 (95.5%)^	14 (100%)	13 (81.3%)^	20 (95.2%)^	–	16 (88.9%)	2 (16.7%)	8 (44.4%)
	Reproductive losses	1 (4.6%)^	–	3 (18.8%)^	1 (4.8%)^	16 (100%)	2 (11.1%)	10 (83.3%)	10 (55.6%)

N o t e: in. — initially; ther. — after therapy; * $p < 0.05$ when comparing identical parameters in women with single and multiple loss of pregnancy; ^ $p < 0.05$ between identical indicators of the comparison subgroup.

was observed in 7 (29.2%) cases. Moreover, in 70.8% of cases, spontaneous miscarriages were noted in early pregnancy stage. In total, in the comparison group, pregnancy ended in childbirth in 26 (40.6%) cases, of which premature birth was observed in 14 (53.8%) cases and reproductive losses were noted in 38 (59.4%) cases.

The most common causes of the "first" spontaneous miscarriage include hormonal dysfunction, genetic mutations, and infections. Probably, the primary cause was also APS, which, with an increase in the number of reproductive losses and with the involvement of TORCH infection and thrombophilia, became an increasingly significant pathogenic factor that no longer depended only on the dysfunction of the immune system, but many other vicious circles were intertwined in it.

It follows from the data presented in Table 4 that the isolated APA of any class has a significantly less pathogenic effect on the course and outcome of pregnancy than their combined interaction. The combined presence of APA in the main group was found in 38 patients, while pregnancy termination was observed in 4 (10.5%) women and in 28 patients in the comparison group, and reproductive losses were registered in 26 patients (92.9%). With the isolated determination of APA, reproductive losses were noted in 1 (2.9%) patient out of the 35 pregnant women and in 12 (33%) patients out of the 36 patients in the comparison group.

Conclusion

Antiphospholipid syndrome often developed in female patients with a complicated obstetric and gynecological history. In patients with persistent TORCH infection, chronic endometritis and salpingo-oophoritis were significantly more frequent.

Regardless of the presence or absence of TORCH infection, APA titer decreased after plasmapheresis, while such a positive trend was registered only in patients with a history of gestational losses of less than four. The APA level in relation to the initial values decreased by 60%–95%, which indicates the optimal choice of the characteristics of plasmapheresis therapy and the duration of its conduct.

Correlation analysis revealed the strongest direct association in women with a history of large number of reproductive losses to IgG β_2GP1, which was moderate only with TORCH infection. This

correlation was least typical for lupus anticoagulant (moderate to average). The IgG level to cardiolipin correlated with the amount of reproductive losses only in the absence of TORCH infection. Probably, at least two factors affect the decrease in the plasmapheresis therapy efficiency with an increase in the number of gestational losses and gestational age. First, a significant number of abortions lead to the activation of other, non-hemostasiological and immunological, mechanisms of miscarriage, and second, as the time interval from the plasmapheresis increases, its eliminating effect is gradually leveled, and the concentration of antibodies increases again.

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