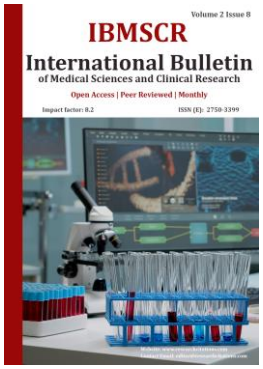

METHODS FOR CORRECTION OF ANTIPHOSPHOLIPID SYNDROME

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Relevance. Antiphospholipid syndrome (APS) is diagnosed according to clinical and laboratory criteria [1]. It can develop as a complication of an already existing systemic pathology (inflammatory, infectious, neoplastic diseases - secondary APS) or as an isolated pathology (primary APS), which sometimes precedes the onset of a systemic disease. In APS, two systems are affected: the vascular system, which is manifested by thrombotic complications, and the uteroplacental blood flow, which leads to pregnancy complications [2].

In women with a burdened obstetric and gynecological history, elevated levels of antiphospholipid antibodies (APA) occur in 24% of cases with recurrent miscarriage and in 20% of cases with infertility [3]. In most cases, APS (80%) is diagnosed in women of reproductive age. The same trend is observed in other autoimmune diseases [4]. Obstetric complications in pregnant women with APS and persistent viral infection are accompanied by disorders in the system hemostasis [5]. Antiphospholipid antibodies have a multifaceted effect on the processes of formation and development of the trophoblast since the establishment of uteroplacental blood flow, they are often detected in women with three or more unsuccessful attempts at in vitro fertilization in history [6]. The most common adverse events associated with APS in pregnant women - preterm birth and intrauterine growth retardation. Preterm delivery is most common in patients with combined APS and systemic lupus erythematosus [7]. A. Ruffatti et al. attempted to determine the causes of adverse neonatal outcomes.

Such factors were the presence of lupus anticoagulant, anticardiolipin antibodies, antibodies to β2-glycoprotein-1 (β2GP1), 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, according to the American College of Thoracic Physicians (ACCP) Revision 9 guidelines, prophylactic or intermediate doses of unfractionated heparin or prophylactic doses of low molecular weight heparin (LMWH) should be given before delivery in combination with low-dose aspirin (LDA) (75–100 mg/day) without treatment [9]. Therapeutic doses of LMWH adjusted for the patient's weight are recommended in case of a history of thrombosis with regular monitoring of anti-Xa activity [10]. Despite the fact that combination therapy using LDA and LMWH is the mainstay of the treatment of women with APS, the reliability of evidence for the effectiveness of such therapy remains controversial [11]. Good experience data treatment with LMWH and NDA preparations in women with clinical criteria for APS and circulation of non-criteria autoantibodies are consistent with the results of Russian authors [12]. The literature also discusses the possibility of immunomodulatory therapy with intravenous immunoglobulins,

polyspecific intact immunoglobulins, predominantly IgG, made from the plasma of healthy donors [13].

Some authors [14] propose to include plasmapheresis (efferent therapy) in the scheme of anticoagulant, antiaggregant, antioxidant and immunomodulatory therapy (intravenous immunoglobulin), others researchers use plasmapheresis in combination with enzyme therapy [15]. The therapeutic basis of plasmapheresis is the removal of APA, as well as proinflammatory and procoagulant markers, adhesion molecules, vasopressive factors, and atherogenic lipoproteins in order to improve the functions of the maternal endothelium, prevent thrombosis, and increase placental perfusion [16].

Purpose of work: evaluate methods for correcting antiphospholipid syndrome in pregnant women.

Materials and methods. A total of 37 pregnant women with a history of miscarriage and APS were examined. The examined women were divided into two groups: group I (main) consisted of women (n = 18), who underwent complex therapy with the inclusion of plasmapheresis at the pregravid stage, in group II (comparison, n = 19) patients did not receive efferent therapy. The main element of complex therapy for both groups was the standard protocol for the treatment and prevention of venous thromboembolic complications in accordance with clinical guidelines.

Each group was divided into two subgroups based on the presence or absence of laboratory evidence of active 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. In subgroups 2, on the contrary, both clinical and laboratory signs of activation of TORCH infection were noted. At the same time, the frequency of occurrence of a certain infectious comorbidity in both subgroups was comparable. In both subgroups (I2 and II2), prior to the onset of pregnancy, therapy aimed at deactivating TORCH infection was performed based on clinical recommendations, after the disappearance of signs activity of the infectious process, they started planning pregnancy, in group I — plasmapheresis. The number of miscarriages was comparable in groups and subgroups.

IgG and IgM antibodies, their avidity, the presence/absence of antigens of infectious agents, and their titer were determined in order to identify the infectious process, monitor the dynamics of its development, the effectiveness of treatment, and verify the clinical and laboratory cure.

Key parameters of hemostasis links were studied using platelet and plasma components. Laboratory diagnosis of APS was carried out by identifying autoantibodies: lupus anticoagulant, 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). 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 one or another type of antibody was necessarily recorded.

Plasmapheresis was performed in patients included in the main group, following the clinical recommendations for the use of this procedure in preparation for pregnancy in order to remove autoantibodies from the blood (reducing the concentration), and also taking into account the indications and contraindications for efferent therapy.

Plasmapheresis was performed in patients included in the main group, following the clinical recommendations for the use of this procedure in preparation for pregnancy in order to remove autoantibodies from the blood (reducing the concentration), and also taking into account the indications and contraindications for efferent therapy. Plasmapheresis was performed according to an intermittent technique against the background of mandatory standardized premedication, which included antihistamines and hormonal drugs. All women received traditional preperfusion preparation aimed at complete elimination (significant reduction in concentration) of autoantibodies that cause and indicating the development of antiphospholipid syndrome. The average amount of plasma extracted during one procedure was 866.3 ± 102.7 ml. Due to this preperfusion preparation for all women was carried out in the format of infusion therapy in the mode of moderate hemodilution with correction of electrolyte and protein balance.

The operation was completed by gradual (within 30–40 min) replenishment of the plasma deficiency with fresh frozen donor plasma of at least 80% of the volume of exfused plasma, protein blood substitutes, and crystalloids.

Statistical data processing was carried out using the Statistica 6 program. The normality of the distribution of the results obtained in the variation series was assessed using the Kolmogorov-Smirnov test, as well as according to the rule of two and three sigma (σ). When comparing the quantitative characteristics of two sets of unrelated samples obeying the normal distribution law, Student's t-test was used.

Results. The mean age of the patients who took part in the study was 27.3 ± 1.4 years. There were no statistically significant differences in age between the patients of the main groups, the comparison group and subgroups ($p > 0.05$). Antiphospholipid syndrome often developed in patients with a complicated obstetric and gynecological history. In patients with recurrent fetal loss, chronic salpingo-oophoritis and menstrual dysfunction were significantly more often recorded, which is probably due to repeated hormonal stress, which, in addition to reproductive dysfunction, contributed to a decrease in immunoresistance, the addition and / or progression of infectious pathology, including TORCH infection, as well as aggravation of the course of APS. Hormonal changes caused by pregnancy loss (especially multiple ones) 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 perversion of the immune response, thereby forming a vicious circle, the connection in which increased with each new loss pregnancy, stress, or attachment/activation of an infectious agent.

According to the change in the content of APA depending on the amount of gestational losses, a gradual, more significant - from the fourth pregnancy loss, an increase in both the initial antibody titer and the antibody titer that persists after efferent therapy was revealed. When comparing the levels of APA in subgroups with TORCH– and TORCH+, in the main group and the comparison group, regardless of the number of reproductive losses, the level of APA significantly increased, especially the level of IgG to cardiolipin, IgG to β2GP1 in subgroups with TORCH+.

One of the key points is the reduction of APA titer with the help of plasmapheresis, regardless of the presence or absence of TORCH infection (as evidenced by comparable levels of APA after therapy in both subgroups of the main group). At this stage of the study, the effectiveness of using efferent therapy as a way to reduce the content of APA was clearly

shown. Regardless of TORCH– and TORCH+ and the number of reproductive losses, in all cases there is a significant decrease in the level of IgG to cardiolipin, IgG to β2GP1 after the plasmapheresis procedure.

Regardless of the initial concentrations of APA, their number after a course of efferent therapy was comparable in women with a history of no more than three gestational losses. At the same time, 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 levels of APA after therapy, 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, the strongest direct relationship with the number of reproductive losses in history was found for IgG β2GP1, which was moderate only in case of TORCH infection. Least of all, such a correlation was typical for lupus anticoagulant (from moderate to moderate). The level of IgG to cardiolipin correlated with the number of reproductive losses only in the absence of TORCH infection. It was also noted that as the gestation period increased, the correlations intensified.

It is likely that with an increase in the number of gestational losses and gestational age, at least two factors influence the effectiveness of plasmapheresis therapy. First, a significant number of abortions, no doubt, leads to the inclusion of other, non-hemostatic and immunological, mechanisms of miscarriage. Secondly, as the time interval increases from the moment of plasmapheresis, its elimination effect is gradually leveled and the concentration of antibodies increases again.

In the main group of women with a history of a single gestational loss, in 100% of cases, the pregnancy ended in childbirth. Premature birth occurred in 3 (8.1%) women, urgent delivery - in 34 (91.9%). In patients of the main group, who had a history of two or more gestational losses, in subgroup I1, pregnancy ended in childbirth in 88.9% of cases, in subgroup I2 — in 77.8%. In subgroup I1, one (11.1%) case of spontaneous miscarriage was recorded, in subgroup I2 there were two (22.2%) such cases. In 33.3% of cases, delivery was performed by caesarean section.

In the comparison group, pregnancy ended in childbirth in 47.4% of cases only in women with a history of one gestational loss. Pregnancy ended in childbirth in 4 (40%) cases in women of subgroup II-1 with a history of two or more gestational losses. In 7 (77.8%) cases in pregnant women of subgroup II1, delivery was performed by caesarean section. Among the indications for operative delivery by caesarean section, severe preeclampsia, bleeding, hypoxia, and fetal growth retardation prevailed. In total, in the comparison group, pregnancy ended in childbirth in 8 (42.1%) cases, of which premature births were registered in 4 (21.05%) cases, reproductive losses amounted to 3 (15.8%) cases.

Among the most common causes of the "first" spontaneous miscarriage are hormonal dysfunction, genetic mutations, and infections. Perhaps the primary cause was also APS, which, as the number of reproductive losses increased, as well as the addition 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.

Based on the data, it follows that the isolated presence of AFA 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 8 patients, in the comparison group - in 9 people.

Conclusions. Antiphospholipid syndrome often developed in patients with a complicated obstetric and gynecological history. In patients with persistent TORCH infection, chronic endometritis and salpingo-oophoritis were significantly more common. The APA titer, regardless of the presence or absence of TORCH infection, decreased after plasmapheresis, while such a positive trend was observed only in patients with a history of gestational loss less than four.

The level of APA in relation to the initial values decreased by 60-95%, which indicates the optimal choice of characteristics of plasmapheresis therapy and its duration.

When performing a correlation analysis, the strongest direct dependence was revealed in women with a large number of reproductive losses in history to IgG β2GP1, which was moderate only in case of TORCH infection. Least of all, such a correlation was typical for lupus anticoagulant (from moderate to moderate). The level of IgG to cardiolipin correlated with the number of reproductive losses only in the absence of TORCH infection. It is likely that at least two factors affect the decrease in the effectiveness of plasmapheresis therapy with an increase in the number of gestational losses and gestational age: firstly, a significant number of abortions leads to the inclusion of other, non-hemostasiological and immunological, mechanisms of miscarriage; secondly, as the time interval from the moment of plasmapheresis is increased, its elimination effect is gradually leveled and the concentration of antibodies increases again.

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