UDC: 616.151.511: 616-002.77: 618.3: 616.8-009.24

# ACQUIRED THROMBOPHILIA IN THE FORM OF ANTIPHOSPHOLIPID SYNDROME



Berger Inna Viktorovna[1], Makhmudova Aziza Djumanovna[1], Madasheva Anajon Gazkhanovna[2]
1 - Republican Specialized Scientific and Practical Medical Center for Hematology of the Ministry of Health of the Republic of Uzbekistan, Tashkent;
2 - Samarkand State Medical University, Republic of Uzbekistan, Samarkand

# АНТИФОСФОЛИПИД СИНДРОМИ ШАКЛИДА ОРТТИРИЛГАН ТРОМБОФИЛИЯ

Бергер Инна Викторовна[1], Махмудова Азиза Джумановна[1], Мадашева Анажон Газхановна[2]
1 - Ўзбекистон Республикаси Соғлиқни Сақлаш Вазирлиги Республика ихтисослаштирилган гематология илмий - амалий тиббиёт Маркази, Тошкент ш.;
2 - Самарқанд давлат тиббиёт университети, Ўзбекистон Республикаси, Самарқанд ш.

# ПРИОБРЕТЕННАЯ ТРОМБОФИЛИЯ В ВИДЕ АНТИФОСФОЛИПИДНОГО СИНДРОМА

Бергер Инна Викторовна[1], Махмудова Азиза Джумановна[1], Мадашева Анажон Газхановна[2]
1 - Республиканский специализированный научно-практический медицинский Центр гематологии министерства здравоохранения Республики Узбекистан, г. Ташкент;
2 – Самаркандский государственный медицинский университет, Республика Узбекистан, г. Самарканд

e-mail: nodiraxon2001@mail.ru

***Резюме.*** *Жаҳон маълумотларига кўра, антифосфолипид синдроми аҳолида 2-4% частотада учрайди, аммо шунга қарамай, ушбу патологияни аниқлаш учун скрининг текширувлари ўтказилмайди. Тромбознинг яққол белгилари намоён бўлганидан сўнг, шунингдек бемор анамнезида бир неча бор тромбоз аниқланганидан сўнггина врач тромбоз сабабининг диагностик изланишларини бошлайди. Мақолада антифосфолипид синдромининг классик курсининг клиник ҳолатлари кўрсатилган ва антифосфолипид синдроми бўлган ҳомиладор аёлларни даволаш бўйича тавсияларга амал қилишнинг аҳамияти ва зарурлиги кўрсатилган.*

***Калит сўзлар:*** *гемостаз тизимининг патологияси, тромбофилия, антифосфолипид синдроми, скрининг, орттирилган тромбозлар, гиперкоагуляция тестлари.*

***Abstract.*** *According to world data, antiphospholipid syndrome occurs with a frequency of 2-4% in the population, however, as such, screening tests for the detection of this pathology are not carried out. And only with severe symptoms and repeated cases of thrombosis in history, the doctor begins a diagnostic search for the causes of thrombosis. The article presents clinical cases of the classical course of antiphospholipid syndrome and presents the importance and necessity of following the recommendations for the management of pregnant women with APS.*

***Keywords:*** *pathology of the hemostasis system, thrombophilia, antiphospholipid syndrome, screening, acquired thrombosis, hypercoagulation tests.*

Antiphospholipid syndrome (APS) is an acquired autoimmune hypercoagulable syndrome characterized by venous and/or arterial thrombosis and/or pregnancy complications, as well as the presence of antiphospholipid antibodies. Antiphospholipid antibodies (APA) are a diverse group of autoantibodies directed against self-proteins associated with membrane phospholipids. The AFA group includes anticardiolipin antibodies (ACA); antibodies to beta-2-glycoprotein; lupus anticoagulant (LA); antibodies to annexin V; antibodies to phosphatidylserine-prothrombin complex and others [1].

Diagnosis of APS is quite complex and complex. The most common diagnostic method in APS is the study of the parameters of the hemostasis system, which has the following main functions - maintaining the liquid state of blood in the vessels, stopping bleeding in case of injury, and lysis of formed clots [9]. Often, a standard coagulogram includes one or two indicators - clotting time and prothrombin index (PTI), routinely performed in primary care laboratories, where for the first time markers can be detected that indicate the presence of antiphospholipid syndrome in a patient. In specialized clinical laboratories of blood coagulation of the hematology center, the

number of studied parameters reaches more than a dozen. It should be noted that due to the rapid development of companies producing laboratory equipment and the constant improvement of diagnostic parameters, the value of some manual tests is changing, and some coagulogram indicators are becoming less significant for diagnosis. For example, the previously widely used plasma recalcification test, plasma heparin tolerance, fibrinogen B, and thrombotest are not very informative and are not currently recommended for use in a diagnostic algorithm, since they are not specific and indicate only generalized changes [2].

The problem of diagnosing and correcting coagulation disorders is very relevant in the practice of doctors of all directions, including hematologists, surgeons, gynecologists, and rheumatologists [2]. It is known that pregnancy and the postpartum period are characterized by a tendency to develop hypercoagulability. According to Momot A.P. et al. during physiological pregnancy, the level of fibrinogen can vary from 4.5 to 9.1 g/l, the concentration of D-dimer from 135 to 771 ng/ml, depending on the duration of pregnancy [3,4]. However, the presence of an existing pathology of the hemostasis system, congenital or acquired, during pregnancy can manifest itself in the form of venous thromboembolism, lead to non-developing pregnancy and / or recurrent miscarriages and maternal mortality. Primary and secondary APS are found with almost the same frequency. According to the literature, the frequency of detection of various antibodies to cardiolipin (ACA) and LA in the blood of healthy people varies from 0 to 14% (average 1–5%; in high concentrations - less than 0.2%) and increases in elderly people. age, especially with chronic diseases [3, 9, 11, 13]. Like other autoimmune diseases, APS is more common in women than men (5:1 ratio) and usually develops in middle age (20-40 years). In secondary APS, the ratio of women to men is 7.5:1, and in primary - 3.5:1. [10, 13]. Venous thromboembolism can occur at any age, but it is more common in people over 45 years of age, it can occur at any stage of pregnancy, but the time of greatest risk is the postpartum period, when, according to statistics, venous thromboembolism can occur up to 15 cases per 1000 women in labor [6,12]. Clinical manifestations during pregnancy with venous thrombosis or in the postpartum period include pain in the legs, edema (usually one-sided - on the side of the lesion), may be accompanied by pain in the lower abdominal region, shortness of breath, chest pain, hemoptysis [15].

Patients eligible for APS study are young patients (less than 50 years of age) with unexplained and unprovoked venous thromboembolism and/or arterial thrombosis, thrombosis of unusual location, cases of late pregnancy loss, or any thrombosis or pregnancy complications in patients with autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, autoimmune thrombocytopenia, autoimmune hemolytic anemia) [11,14].

APS can be reliably diagnosed if patients have a history of clinically confirmed venous or arterial thrombosis of various localization, pregnancy complications in the form of recurrent miscarriage up to the 10th week. If a patient has two or more times laboratory-confirmed positive test (with an interval between studies of at least 12 weeks) for lupus anticoagulant (LA), antibodies to cardiolipin (ACA), antibodies to β2 glycoprotein, this indicates a tendency to form thrombosis [5, 7.8].

Even positive results of detection of antiphospholipid antibodies require the exclusion of other causes of thrombosis, especially in the case of the presence of such risk factors as smoking, hyperlipidemia, atherosclerosis, varicose veins, oral contraceptives. Some medications and infectious diseases can lead to the appearance of ACA, which, however, is transient and is not associated with an increased risk of thrombosis. For this reason, it is necessary to conduct at least 2 analyzes at intervals of twelve weeks [7]. From laboratory data, patients with APS may experience: accelerated ESR, moderate thrombocytopenia, hypergammaglobulinemia; if APS is accompanied by damage to the renal vessels - an increase in the content of creatinine, urea; with liver damage - an increase in alkaline phosphatase, hyperbilirubinemia, an increase in the content of aminotransferases. In an immunological study, antibodies to cardiolipin are determined, and antibodies of the IgG class have the greatest diagnostic value, especially if they are detected in high concentrations. In some patients with undoubted classical manifestations of APS, antibodies to cardiolipin may not be detected, but lupus anticoagulant is detected [13].

The researchers of our Republic have not yet studied the prevalence of antiphospholipid syndrome in the Uzbek population. Patients with APS often receive treatment from different specialists, and therefore it is not possible to make a single register of patients. There are currently no recommendations for an ideal strategy for the diagnosis and treatment of APS. In the Russian Federation, according to the clinical protocols of the Scientific Center for Obstetrics, Gynecology and Perinatology named after academician V.I. Kulakov, I.M. Sechenov First Moscow State Medical University and the Association of Phlebologists of Russia (2014), patients with APS and pregnancy are usually recommended to use heparin and/or low-dose aspirin to prevent miscarriage [7]. However, in one third of pregnant women with APS, the protocols mentioned above, as well as additional therapies, including intravenous immunoglobulins, low doses of prednisolone, or apheresis procedures such as plasmapheresis and

immunoadsorption were found to be of little or no effect [7].

The purpose of our work with the description of cases with APS was to familiarize practitioners with the clinical manifestations of antiphospholipid syndrome and the need for its early diagnosis and treatment. Patient S.Kh. 36 years old, she applied to the RSNPMC of Hematology with a referral from a gynecologist at a medical facility for a consultation. From the patient's anamnesis: the first 3 pregnancies ended in spontaneous miscarriages up to the 10th week, at the time of treatment she had a 4th pregnancy, a period of 12 weeks. During treatment, there were complaints of pain and swelling of the right leg. She was referred for a consultation with a vascular surgeon who diagnosed deep vein thrombosis of the left lower extremity. A council of doctors from gynecologists and hematologists assessed the risk of developing venous thromboembolism. Examination for a general detailed blood test revealed no pathological changes. In the study of the hemostasis system in the patient, a shortening of the activated partial thromboplastin time was determined - 24 seconds (at a rate of 26 to 38 seconds) and the fibrinogen level reached 6 g/l. Lupus anticoagulant in the examined woman was 1.8 (normal ratio ≤1.2), antiphospholipid antibodies were detected. Taking into account three pregnancy losses up to 10-11 weeks, episodes of thrombosis and the presence of antiphospholipid antibodies, a clinical diagnosis of APS was made. It was decided to start therapy with low molecular weight heparin at a prophylactic dose from week 13, and folic acid preparations (800 mcg/day) were also added. Within a month, the clinic of deep vein thrombosis resolved, after 3 months of therapy, drug injections were discontinued. The birth period at 39-40 weeks passed without complications. In the postpartum period, low molecular weight heparin (enoxaparin sodium) was administered for 1 week.

The next case is about the late diagnosis of APS. Patient R.T., 36 years old, was consulted by a hematologist in the therapeutic department of the Tashkent Medical Academy, where he was diagnosed with cardiomyopathy; chronic hepatitis, postthrombophlebtic syndrome of the lower extremities. Upon admission, he complained of dry cough, shortness of breath with little physical exertion, palpitations, and swelling in the legs. State at admission - moderate severity. There were swelling of the legs, more than the right, the skin of the legs is hyperemic with a bluish tint. In the lungs - vesicular breathing. The borders of the heart are expanded: the right one is 3 cm from the right edge of the sternum, the left one is 2 cm. The heart sounds are rhythmic, the heart rate is 96, the accent of the II tone over the pulmonary artery is heard, the systolic murmur is at the apex, the blood pressure is 110/70 mm Hg. Art. The liver is painful on palpation, dense, enlarged, protrudes from under the edge of the costal arch by 4 cm.

Complete blood count without pathology, platelets - 187 x 10 * 9 / l. In OAM: protein - 0.33 g/l, er. - 3-5, leukocytes - 8-10. In the biochemical analysis of blood, an increase in bilirubin to 48 μmol / l was noted, and the blood coagulation index - INR (international normalized ratio) was in the normal range - 1.2. Prothrombin index - 0.8, blood fibrinogen - 3.1 g/l, D-dimer -0.3 mg/l. Blood for C reactive protein, rheumatic factor, antistrepolizin 0, ELISA HBSAg - negative results.

X-ray of the lungs: the lung pattern is enhanced, the roots are expanded; the arch of the left pulmonary artery bulges, the heart is moderately dilated in all departments. On the electrocardiogram: a sharp deviation of the EOS to the right, atrioventricular blockade of the 1st degree, complete blockade of the right leg of the His bundle, signs of right ventricular hypertrophy, pronounced changes in the myocardium of the septum, apex, lower and lateral wall of the left ventricle. Ultrasound of the abdominal organs: liver - enlarged, CVR - 17.8 cm; the parenchyma of the kidneys is compacted, signs of chronic pyelonephritis; spleen, pancreas, gallbladder - without features. From the anamnesis it was found out that from childhood he was professionally engaged in wrestling (Kurash). At the age of 26, he noticed for the first time that the right shin was enlarged, slightly painful, and after some time the skin over the place of edema acquired a bluish tint. He did not go to the doctors, as he associated his condition with heavy loads during training. A year later, the left shin also swelled and bursting pains were periodically felt, already in both legs. After some time, strong, already unbearable pains appeared in the right leg, it increased in size, and the patient turned to the Republican Specialized Scientific and Practical Medical Center for Surgery named after V. Vakhidov, where he was diagnosed with right-sided ileofemoral phlebothrombosis. The patient was prescribed warfarin in low doses, but after 2 weeks, after the general condition improved, he stopped taking this drug. A year later, the patient enters the therapeutic department with a worsening condition, accompanied by shortness of breath with little physical exertion, with a diagnosis of thromboembolism (PE) of small branches of the pulmonary artery, acute respiratory failure of I-II stage; postphlebitic syndrome of the lower extremities with trophic lesions on the right, chronic lymphatic congestion. The hematologist was called for a consultation to correct the treatment with heparin preparations and normalize the coagulogram. Thus, we can conclude that the patient has the entire symptom complex characteristic of autoimmune APS with venous thrombosis of small vessels of all internal organs (lungs, heart, liver, kidneys) and lower extremities. To confirm the diagnosis, a blood test

was carried out for antibodies to phospholipids and an increase in their blood levels by more than 6 times from the normative values was found. The patient was prescribed therapy in the form of cardio- and hepatoprotectors, potassium-sparing diuretics and indirect anticoagulants under the control of INR. Discussion. According to modern concepts, the diagnosis of APS requires the presence of one of the characteristic clinical signs in the anamnesis (thrombosis or miscarriage) and one of the laboratory criteria that are detected during two consecutive patient visits. These cases are presented by us, since doctors of many specialties (surgeons, therapists, rheumatologists, cardiologists, etc.) are not quite familiar with the diagnosis of APS and the diagnoses are treated after the fact, omitting the etiopathology. For example, myocardial infarction, stroke, thrombosis of the lower extremities, etc. consider atherosclerosis of the vessels to be an etiology. And an excessive examination for non-informative indicators leads to an incorrect interpretation of blood parameters and, as a result, to polypharmacy, when they try to prescribe therapy to correct each slightly changed indicator.

In the first clinical case, there are all the components for establishing the diagnosis of APS, in the future, the patient will need to take anticoagulants for life, and in the event of pregnancy, she will be observed by a gynecologist and hematologist while receiving therapy with low molecular weight heparins.

When arterial or venous thrombosis of the extremities or visceral organs occurs for the first time, it is necessary to examine the blood for the presence of antibodies to phospholipids in order to prescribe permanent anticoagulant therapy and prevent the development of further thrombosis. If APS is suspected, platelet count, aPTT, prothrombin time, lupus anticoagulant, D-dimer, and fibrinogen should be included in the examination list. But, it should be borne in mind that the level of fibrinogen and D-dimer during pregnancy can be increased and are not absolute signs for prescribing anticoagulants [2].

**Literature:**


1. Okorokov, A.N. Diagnosis of diseases of internal organs: Vol.2. Diagnosis of rheumatic and systemic connective tissue diseases. Diagnostics of endocrine diseases / A.N. Okorokov - M .: Medicine, 2001 .-- 576 p.
2. Makhmudova A.D., Tursunova N.A., Berger I.V. Thrombosis in hematological practice. // Monograph. P. 120.Uzbekistan 2020
2. Momot A.P. Features of the behavior of the hemostasis system during pregnancy. Russian Forum on Thrombosis and Hemostasis "Clinical and Legal Aspects of the Problems of Thrombosis and Bleeding" Part 1. 22.02.2020 / https: //www.hemostas.ru
3. Momot A.P., et al. Assessment of the hemostasis system during physiological pregnancy. Examination algorithms in risk groups J. Thrombosis, hemostasis, rheology №4 2019 p.80-130
5. Nasonov EL. Antiphospholipid syndrome. Moscow: Litterra; 2004.424 s.
6. Papayan K.A., Kapustin S.I., Fedotova E.P. Clinical observation of antiphospholipid antibody syndrome and thrombophilia in a patient with lupus nephritis Nephrology. 2012. Volume 16. No. 3 (issue 2) p.90-94.
7. Prevention of venous thromboembolic complications in obstetrics and gynecology Clinical guidelines (Protocol) 2014. p. 1-34.
8. Reshetnyak TM. Antiphospholipid syndrome: diagnosis and clinical manifestations (lecture). Scientific and practical rheumatology. 2014; 52 (1): 56–71.
9. Asherson R. A. et al. The antiphospholipid syndrome: history, definition, classification, and differential diagnosis. Thromb Haemost. 2006; 4: 295-306.
10. Asherson RA, Cervera R, Piette J-Ch, Shoenfeld Y, editors. The antiphospholipid syndrome II: Autoimmune thrombosis. New York: Elsevier; 2002.3-445.
11. Cervera R, Piette JC, Font J, et al; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002; 46 (4): 1019-27.
12. Erkan D, Pierangeli SS, editors. Antiphospholipid syndrome: insights and highlights from the 13th International Congress on Antiphospholipid Antibodies. New York:Springer Science + Business Media; 2012.
13. Lim W. Antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program. 2013; 2013: 675-80. Review.
14. Rand JH, Wolgast LR. Dos and don'ts in diagnosing antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program. 2012; 2012: 455-9.
15. Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management Green-top Guideline No. 37b April 2015 RCOG 1-32.


## *ПРИОБРЕТЕННАЯ ТРОМБОФИЛИЯ В ВИДЕ АНТИФОСФОЛИПИДНОГО СИНДРОМА*


*Бергер И.В., Махмудова А.Дж., Мадашева А.Г.*



***Резюме.*** *По мировым данным антифосфолипидный синдром встречается с частотой 2-4% в популяции, однако как таковых скрининговых тестов на выявление этой патологии не проводится. И лишь при выраженной симптоматики и неоднократных случаев тромбоза в анамнезе врач начинает диагностический поиск причин тромбоза. В статье представлены клинические случаи классического течения антифосфолипидного синдрома и представлена важность и необходимость соблюдения рекомендаций по ведению беременных женщин с АФС.*



***Ключевые слова:*** *патология системы гемостаза, тромбофилия, антифосфолипидный синдром, скрининг, приобретенные тромбозы, гиперкоагуляционные тесты.*