ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

UDC: 618.39-021.3:618.396-085.35

A NEW VIEW ON THE PATHOLOGY OF ANTIPHOSPHOLIPID SYNDROME COMBINED WITH PRE-ECLAMPSIA OF PREGNANCY

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Summary: Antiphospholipid syndrome (APS) is a multisystem disease characterized by the production in the human body of large amounts of antibodies to phospholipids, the chemical structures that make up parts of the cell. APS is one of the most urgent multidisciplinary problems of modern medicine and is considered as a unique model of autoimmune thrombotic vasculopathy. APS is the cause of recurrent miscarriage in 27-42%. More often detected in women (5:1). In recent years, in the scientific field, we are increasingly faced with the problem of combining APS with other pathologies, for example, with hypertensive conditions during pregnancy. In this article, we have provided our opinion on APS associated hypertension during pregnancy.

Relevance. Antiphospholipid syndrome is an autoimmune disease, the manifestation of which may be thrombosis and/or pathology of pregnancy due to the presence of persistent antibodies to phospholipids in the blood [1,2,13]. Antibodies to phospholipids were registered in 5% of the general population [3,4,5]. Antiphospholipid antibodies are represented by lupus anticoagulant (LAC), antibodies to cardiolipin (aCL) and antibodies to β2-glycoprotein I (β2gpi). Anti-phospholipid antibodies are a heterogeneous group of autoantibodies (hereditary and acquired) associated with an increased risk of thrombosis and obstetric complications. The presence of these antibodies can lead to an autoimmune hypercoagulable state.Antibodies bind to phospholipid-binding proteins that activate cell surface receptors, leading to changes in intracellular signaling pathways and creating a proinflammatory or hypercoagulable environment [6,8,11]. In patients with antiphospholipid syndrome, the following clinical signs were identified: thrombocytopenia, migraine or migraine-like headaches, nosebleeds, livedo reticularis, epilepsy, valvular heart disease, aseptic bone necrosis, chorea (hyperkinesis) and arterial hypertension. These manifestations do not serve as clinical criteria, but their presence in the mother, together with antibodies to phospholipids, is an important diagnostic factor for suggesting antiphospholipid syndrome in the newborn [7,9,10].

The European Group for the Study of this disease in children (Euro-Phosphpolipid Project Group) explains the variety of clinical signs by the localization of non-inflammatory thrombotic vasculopathy and highlights venous thrombosis, thrombocytopenia, livedo reticularis as the most characteristic manifestations of antiphospholipid syndrome in school-age children. Circulating antibodies to phospholipids cause a wide range of neurological symptoms, which are found in approximately 20% of patients with antiphospholipid syndrome [6]. Thus, in these patients, the risk of developing epilepsy increases by 3.2 times, and in children with multifocal convulsive syndrome, an increased titer of antibodies to phospholipids is often detected [12].The diagnosis of antiphospholipid syndrome requires the presence of at least one clinical criterion and one or more laboratory criteria that are moderately positive and have been consistently present in the patient for at least 12 weeks [5]. It is important to note that these criteria are designed to diagnose the syndrome in adults and school-age children and do not take into account the characteristics of a newborn child.

Clinical criteria (at least one must be present):

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AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

1) vascular thrombosis (one or more clinical episodes of arterial, venous or small vascular thrombosis in any tissue or organ, confirmed by imaging or histological examination;
2) one or more unexplained deaths of a morphologically normal fetus at or after 10 weeks of gestation, one or more premature births of a morphologically normal newborn at or before 34 weeks of gestation due to eclampsia or recognized signs of placental insufficiency;
3) three or more unexplained consecutive spontaneous abortions before the 10th week of pregnancy with anatomical or hormonal abnormalities in the mother and excluded chromosomal causes in the mother and father [5].
Laboratory criteria (at least one must be present):
1) lupus anticoagulant is detected in blood plasma 2 times or more with an interval of at least 12 weeks;
2) antibodies to anticardiolipin (IgG or IgM isotype) in serum or plasma contain an average or high titer in 2 or more cases with an interval of at least 12 weeks;
3) antibodies to β2-glycoprotein-1 (IgG or IgM isotype) in serum or plasma are determined in medium or high titer in 2 or more cases with an interval of at least 12 weeks [5].
There are several clinical variants of antiphospholipid syndrome:
1. Primary - develops in individuals without autoimmune diseases.
2. Secondary - develops in patients with rheumatic and autoimmune diseases, with malignant neoplasms, with the use of a number of drugs (hormonal, contraceptive, psychotropic substances, high doses of interferon-alpha), infectious diseases (herpesvirus infection, mycoplasmosis).
3. Catastrophic - multisystemic, predominantly organ thrombosis at the level of the microvasculature with a high titer of antibodies to phospholipids, disseminated intravascular activation with thrombosis in vessels with a small diameter, multiple organ damage to the body.
4. Neonatal - develops in newborns with the transfer of thrombotic factors by the transplacental route from mothers with antibodies to phospholipids. Serological variants of antiphospholipid syndrome are seropositive and seronegative [12]. Acquired abnormalities of the maternal coagulation system, such as antiphospholipid syndrome, may predispose to neonatal arterial ischemic stroke [13].
Neonatal seizures are the most common symptom of this disease: in 90% of cases they occur in the first 3 days of life, they are focal in 50% of cases, in less than 10% of cases the seizures are non-motor. Then we are talking mainly about episodes of apnea and / or cyanosis; convulsions may manifest as jaw movements, gaze fixation, eye aversion, nystagmus, or simple hiccups.Rarely observed on clinical examination, lateralization of signs with asymmetry of spontaneous movements or the Moro reflex. Hemiplegia in the neonatal period is extremely rare and manifests itself much later. Such a shift in time is explained by the functional and structural features of the ipsilateral corticospinal bundle of the developing brain [13].
So far, only a few cases of neonatal antiphospholipid syndrome have been reported, most of which resulted from the transplacental passage of maternal antibodies to phospholipids [10]. At the same time, it is noted that testing of newborns for the presence of antibodies should be considered only in the case of clinical events that testify in favor of the antiphospholipid syndrome in the mother [13]. Antiphospholipid syndrome is the most common among all acquired thrombophilic conditions in pregnant women [10]. Approximately 10-15% of women with recurrent miscarriage are diagnosed with this disease [6]. At the same time, many women with antibodies to phospholipids have a normal pregnancy, some have only severe thrombocytopenia in the II and III trimesters of pregnancy [7,8], some pregnant

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AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

women have latent antiphospholipid syndrome [5]. The relationship between the presence of antibodies to phospholipids and placental-mediated pregnancy complications is being actively studied.

Pregnant women with antiphospholipid syndrome have an increased risk of developing placental insufficiency [1]. Placental infarction may play a role in the child's subsequent neurological disability. Pathological examination of the placenta after childbirth complicated by preeclampsia or intrauterine growth retardation of the fetus revealed ischemic thrombotic lesions due to the formation of blood clots in the blood vessels of the placenta on the maternal side. In the placentas of women with antiphospholipid syndrome, thrombotic phenomena were detected, trophoblast invasion and transformation of the spiral arteries decreased due to the binding of β2-glycoprotein to the trophoblast. The absence of extravillary invasion of the trophoblast into the placental bed can lead to a decrease in uteroplacental blood flow and, consequently, to chronic intrauterine fetal hypoxia.It was found that newborns with intrauterine hypoxia, who were later diagnosed with cerebral palsy, had a higher incidence of macroscopically identified placental infarcts, cysts, thinning and reduction of the placenta, which indicates a violation of the normal functioning of the placenta [9].

Despite treatment, according to cardiotocography, in many pregnant women with antiphospholipid syndrome after 34 weeks of pregnancy, this or that degree of chronic fetal hypoxia is detected. Doppler ultrasound of the fetal-placental blood flow has a great prognostic value in assessing the condition of the fetus [1]. With proper management, the use of modern therapeutic and diagnostic technologies in 2/3 of pregnant women with antiphospholipid syndrome, children are born full-term and do not have gross disorders [6]. The effect of antibodies to phospholipids circulating in a pregnant woman on the fetal brain has not been studied enough, despite the large amount of data on the pathogenesis and manifestations of this disease in adult patients. The problem requires further analysis and search for methods for effective diagnosis and prevention of neurological complications of antiphospholipid syndrome in newborns.

The generally accepted approach in the treatment of APS during pregnancy is the administration of low molecular weight heparins and a low dose of acetylsalicylic acid [7, 8]. According to a meta-analysis by M. Empson et al. [9], this therapy reduces the incidence of pregnancy loss by 50% in women with recurrent miscarriage and APA circulation.

The safety of using LMWH during pregnancy has been proven [10], however, the analysis of this clinical case raises a number of questions regarding the use of such groups of drugs as acetylsalicylic acid (ASA), prednisolone, and IVIG, as well as the use of plasmapheresis in a pregnant woman with APS.

With regard to the use of ASA, the main issue under discussion at the moment is the timing of the start of prescribing this drug during pregnancy. According to the instructions for the use of ASA, its administration in the I and III trimesters is contraindicated due to an increased risk of fetal developmental defects, possible premature closure of the ductus arteriosus in the fetus, and the risk of increased bleeding in the mother and fetus when administered in the III trimester. This instruction serves as the only legal justification for the application of ASA in our country. However, in 2017, the use of low doses of ASA (up to 100 mg per day) in early pregnancy was also reflected in foreign recommendations. For example, in the recommendations of the European League against Rheumatism for the management of patients with systemic lupus erythematosus (SLE) and / or APS at the stage of family planning, the use of assisted reproductive technologies, pregnancy management and menopause.In accordance with these recommendations, patients with positive APA /

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

APS during induction of ovulation and in vitro fertilization procedures should receive anticoagulant therapy at a dose that would be prescribed during pregnancy and / or a low dose of aspirin; moreover, APA-positive women who did not take low doses of ASA during the ovarian stimulation period should start taking low doses of ASA on the day of embryo transfer, usually in combination with LMWH (therapy should be continued during pregnancy) [1].

The authors of the European Society of Human Reproduction and Embryology guidelines for the management of women with recurrent pregnancy loss (2017) suggest that women with APS who have had three or more previous pregnancy losses begin low-dose aspirin (75 to 100 mg daily) before conception, and from the date of a positive pregnancy test, add a prophylactic dose of heparin (unfractionated or low molecular weight) [2]. In light of these new data, there is promise in the rationale for low-dose aspirin use in early pregnancy in women with APS and multiple pregnancy losses.

Currently, the use of glucocorticosteroids, in particular prednisolone, has not been justified in randomized controlled trials in groups of women with recurrent miscarriage and AFA. When comparing prednisolone and aspirin therapy with placebo or isolated aspirin, there were no significant differences in the reduction in pregnancy loss [10]. In addition, a number of adverse effects associated with prednisolone have been reported: there was a significant increase in the incidence of preterm birth, preeclampsia, hypertensive disorders, and the risk of gestational diabetes [10].

Controversial is the use of IVIG during pregnancy. The pathogenetic rationale for the use of IVIG is based on its ability to reduce the production of antibodies by blocking their synthesis by β-cells and to inhibit the action of autoantibodies themselves [4]. The anti-idiotypic antibodies contained in IVIG preparations bind and neutralize pathogenic antibodies and prevent their interaction with the antigen [14].The immunological tolerance required to maintain pregnancy is provided by IVIG administration by reducing the proliferation of T cells and NK cells [15]. At the Research Institute of AgiR them. BEFORE. Ott conducted a study on the effectiveness of supplementing the standard therapy of APS in pregnant women with the introduction of IVIG in comparison with the appointment of a combination of LMWH and a low dose of aspirin. As a result, in the IVIG group, it was possible to achieve a significant reduction in the incidence of placental insufficiency, intrauterine growth retardation, and preeclampsia [16].

Conclusion. The lethal level of maternal mortality increases when these two pathologies are combined than when they occur separately, which aggravates the pathological processes in the mother's body.

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