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Management in pregnant patients with antiphospholipid syndrome

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SUMMARY

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by thrombotic episodes (either arterial or venous) and/or obstetric failures with permanent positive antiphospholipid antibodies (aPLa). Pharmacological management in obstetric APS is still controversial and requires individual approach in each case. The combination of low doses of aspirin and low-molecular-weight heparin is believed to be the standard of care in pregnant women with APS and recurring miscarriages. Dosage and therapy duration depend on the obstetric history and thrombotic events in the past. Steroids and immunoglobulins are not used for APS treatment on the routine basis due to adverse events or high treatment cost.

Lately, it has been proposed to administer hydroxychloroquines for obstetric APS, particularly in cases where the standard therapy has failed. However, this requires further prospective investigations so as to verify the initial observations. Pregnancy in patients with antiphospholipid syndrome must be considered a high-risk pregnancy. Maternal and fetal surveillance by a multidisciplinary team is recommended to increase chances for term pregnancy and delivery of a healthy child.

Key words: pregnancy; antiphospholipid syndrome; diagnostic work-up; treatment

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INTRODUCTION

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by thrombotic episodes (either arterial or venous) and/or obstetric failures with permanent positive antiphospholipid antibodies (aPLs) [1,2]. APS can be divided into primary APS (PAPS) or secondary APS (SAPS) when it accompanies other diseases, particularly systemic lupus erythematosus (SLE) [1,2].

A very special abrupt form APS is called catastrophic antiphospholipid syndrome (CAPS). It is characterized by acute multiple organ failure that involves the respiratory system, circulation, kidneys and adrenal glands. This is caused by thrombosis developing in numerous small vessels in various organs (disseminated thrombotic microangiopathy). The symptoms of CAPS develop suddenly, and include fever, dyspnea, edema and consciousness disorders. This state entails a high risk of death [3–5]. The diagnosis of catastrophic antiphospholipid syndrome involves identification of pathology in at least 3 organs/systems or tissues. The symptoms must develop simultaneously or at least within one week. In addition, histopathology should provide evidence for thrombotic microangiopathy in at least one organ/tissue, and laboratory tests for antiphospholipid antibodies must be positive [3–5].

Catastrophic APS requires aggressive treatment that includes: antibiotics for infection or pregnancy termination, heparins, corticosteroids, intravenous immunoglobulin infusions and/or therapeutic plasma exchange [3–5]. Laboratory tests show prevailing intravascular coagulation, thrombocytopenia and hemolytic anemia. CAPS may be the first symptom of APS or develop in the course of APS. Pregnancy, trauma, oral contraception or withdrawal of anticoagulants are known to be possible triggering factors [3–5].

The diagnosis of APS may be challenging due to the multifaceted etiology of thrombosis and the lack of optimal standardization of tests

to detect antiphospholipid antibodies. Also, treatment may be difficult as anticoagulants are not fully effective, which makes the development of new therapeutic options hard given the unclear etiology of the disease.

The aim of this article is to present the latest reports on the management in pregnant patients with APS.

DIAGNOSIS OF ANTIPHOSPHOLIPID SYNDROME

The current diagnostic criteria, also called the Sidney criteria, are included in the Sapporo classification, which was created in 1999 and revised in 2006. In accordance with these criteria, APS is diagnosed when at least one of the clinical criteria and at least one of the laboratory criteria listed below are met [6–9].

Clinical criteria

- Thrombosis defined as at least one episode of arterial, venous or capillary thrombosis in any tissue or organ confirmed by imaging or histopathology (thrombosis should be present without vascular inflammation). Superficial thrombosis does not meet the APS criteria [6–9].
- Obstetric failures defined as ≥1 unexplained deaths of a morphologically normal fetus (as documented by ultrasound or by direct macroscopic inspection) ≥ the 10^{th} week of gestation, or one or more births before the 34^{th} week of gestation because of pre-eclampsia, eclampsia or placental insufficiency, or 3 or more spontaneous abortions before the 10th week of gestation that cannot be explained by parental chromosomal causes or maternal anatomic or hormonal abnormalities [6–9].

Laboratory criteria

Detection of antiphospholipid antibodies at least twice within utmost 12 weeks and not later than 5 years after the onset of clinical signs. This concerns the detection of one of the following:

- Anticardiolipin antibody (aCL) of IgG and/or IgM class in medium or high titers (i.e. > 40 GPL or MPL, or > the 99^{th} percentile);
- Anti-2 bglycoprotein-I antibody (anti-b2-GPI) of IgG and/or IgM class in serum or plasma titers over the 99th percentile;
- Lupus anticoagulant detected according to the guidelines of the International Society on Thrombosis and Hemostasis [6–9].

Lupus anticoagulants are IgG and IgM antibodies able to bind phospholipids *in vitro*, which causes prolongation of APTT and to a lower extent also prothrombin time. This typically manifests with thrombophilia and rarely with greater tendency to bleeding [10]. Patients with high clinical suspicions of APS with strongly positive results in the initial examinations (positive LA or high aCL titer >40, or anti-2 glycoprotein-I antibody) that were not confirmed after 12 weeks must undergo repeated tests after several weeks, the results of which will be deemed decisive. If the initial test yields weak positive results for aCL or anti-2 glycoprotein-I antibody, and the confirmative test is negative, the third examination should be conducted only after clinical signs develop. Until then, the test is considered negative [11,12].

In the case of high clinical suspicions of APS and negative tests for aPL, assays of additional antiphospholipid antibodies very rarely give positive results [11,12]. Routine assays of antiphospholipid antibodies that are not included in guidelines (antibodies against prothrombin, phosphatidylserine, phosphatidylinositol) are not recommended due to the lack of standardization as well as poorly explored sensitivity, specificity and prognostic value [11,12]. It is also important to note that cases of suspected APS with thrombosis but with negative anticardiolipin antibody, anti-2 glycoprotein-I antibody or LA are extremely rare [11,12].

The diagnostic process for congenital and acquired thrombophilias (factor V Leiden mutation, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency) should be conducted in patients with venous thrombosis. If the initial test for antiphospholipid antibodies is negative, further tests for thrombophilia should be ordered. If, however, the test is positive, the presence of additional risk factors of thrombophilia should make these patients included into a high-risk group of thrombotic events (APS + thrombophilia) [13].

It must be remembered that transient elevation in the level of anticardiolipin antibodies (IgG and/or IgM) as well as a positive test for lupus anticoagulant may be observed in both healthy individuals and in association with certain viral (AIDS, varicella, mumps, rubella, mononucleosis, B19 parvovirus infection, hepatitis B and C), bacterial (syphilis, Lyme disease, leptospirosis, tuberculosis, pneumococcal pneumonia, infection with *E. coli*, *Mycoplasma pneumoniae*, *Salmonella* sp. and *Staphylococcus*

aureus) and parasitic infections (toxoplasmosis, malaria, chlamydia) or with certain drugs (e.g. hydralazine, procainamide, quinidine or chlorpromazine) [14,15].

PATHOGENESIS OF ANTIPHOSPHOLIPID SYNDROME

APS was initially identified as autoantibody-mediated thrombophilia. In obstetric APS, thrombosis affects venous and arterial vascular bed as well as placental circulation. Placental thrombosis may lead to placental infarcts and insufficiency. Similar phenomena are also observed in pregnancies with pre-eclampsia [10,16–18]. Moreover, clots, infarcts or vascular changes in the placenta do not develop in all pregnant women with APS, by contrast with inflammatory changes. These findings were the basis to treat APS as an inflammatory disease [10,16,17].

In-vitro and *in-vivo* studies confirmed the significance of endothelial cells, neutrophils, monocytes, thrombocytes, cytokines and complement system in induction of thrombotic processes and intrauterine fetal death in APS [16,17]. By binding with negatively charged phospholipids and/or phospholipid-binding proteins, antiphospholipid antibodies become the triggering mechanism that activates endothelial cells, monocytes and thrombocytes [16,17]. In addition, antiphospholipid antibody complexes, comprising mainly ß2-glycoprotein I and anti-ß2-glycoprotein I antibodies, trigger the conventional and alternative complement activation pathway [10,16]. Studies on mice have revealed that complement insufficiency or inhibition, observed during pregnancy, may be a defense mechanism against pregnancy loss and thrombosis [19]. This would mean that benefits resulting from the use of low-dose heparin are linked with its ability to inactivate the complement system rather than with its anti-thrombotic properties [20].

Activated endothelial cells with monocytes increase tissue factor production. It is the main initiator of the coagulation cascade (*in vivo*), and plays a significant part in coagulation and inflammatory processes [10,16,17]. The aPL-induced enhanced activity of tissue factor in circulating monocytes is believed to be an important mechanism of hypercoagulability in APS [16]. The complement may also contribute to thrombosis by increasing tissue factor expression in various types of cells [10,16]. Through action as a proinflammatory substance, tissue factor promotes neutrophil activation leading to trophoblast damage and placental dysfunction [21,22]. It also seems that aPL directly cause trophoblast malfunction resulting in maternal–fetal exchange disorders, early miscarriages, pre-eclampsia, intrauterine growth restriction or even stillbirth [16–18].

Numerous studies also suggest that malfunction of annexin V is significant in the pathogenesis of APS [23–25]. Annexin V can be found in various tissues of the human body. It belongs to the family of calcium-binding cytoplasmic proteins, and its biological role associated with apoptosis is quite well-explored. Each protein of this family is capable of binding negatively charged phospholipids and each has a permanent element in the form of a sequence of 70 amino acids. The major role of annexin is maintaining the integrity of various biological structures, particularly the cell membrane. Moreover, annexins take part in signal transduction, cell proliferation and cell transport regulation [23–25].

Annexin V is a potent anticoagulant; it is phospholipase A2 and protein kinase C inhibitor. It has been found in endothelial cells, vascular smooth muscle cells, platelets, lymphocytes, macrophages and on erythrocytes. The anticoagulant role of annexin V is linked with its ability to form a sort of a protective shield on the surface of activated platelets that show phospholipid expression. This shield separates phospholipids from pro-coagulation factors [23–25]. Strong annexin V expression is also observed on membranes of placental villous syncytiotrophoblast at the maternal–fetal interface. That is why aPL-mediated disorders of anticoagulant action of annexin V are considered to be a possible cause of enhanced coagulation processes, clot formation and, in consequence, pregnancy loss [26]. The presence of antibodies against annexin V observed in APS patients induces thrombotic processes [27]. Annexin plays a significant role in fibrinolysis. It is a component of complexes that are located on the cell surface and act as co-receptors for plasminogen and tissue plasminogen activator. This way plasmin is produced, and subsequently fibrin is degraded [28].

TREATMENT OF ANTIPHOSPHOLIPID SYNDROME

The presence of antiphospholipid antibodies is associated with increased risk of an adverse pregnancy outcome at all its stages. Early dia-

gnosis of APS helps prevent thrombotic complications and reduces the risk of pregnancy loss. Patients with the history of obstetric failures (stillbirth, IUGR, severe pre-eclampsia, eclampsia, HELLP, particularly before week 34 of pregnancy) and with additional clinical signs suggesting APS should be tested for antiphospholipid antibodies [29–31]. It must be remembered that these tests should not be suggested to patients too hastily, e.g. after one miscarriage. However, tests for antiphospholipid antibodies should be performed in patients with autoimmune diseases, particularly SLE, who wish to become pregnant [29–31].

Pregnancy complicated with APS requires strict surveillance over the mother and fetus. Treatment of pregnant patients with APS should be conducted by a multidisciplinary team of physicians who must develop a common and carefully defined treatment protocol. In current treatment of obstetric APS, low doses of aspirin and low-molecular-weight heparins are the standard of care [32–34]. Aspirin should be administered immediately after pregnancy has been confirmed, whereas low-molecular-weight heparin should be started once intrauterine pregnancy has been confirmed. Doses must be modified in excessively overweight or obese patients [32–34].

According to the recommendations of Lockwood et al. (UptoDate 2017) and the American College of Obstetricians and Gynecologists ACOG (2012), patients with APS and venous or arterial thrombosis but without the history of obstetric failures should be administered low-molecular-weight heparin in a therapeutic dose during pregnancy (enoxaparin 1 mg/kg every 12 h, dalteparin 200 U/kg once daily, dalteparin 100 U/kg every 12 h) and warfarin for four to six weeks after childbirth (therapeutic INR level: 2.00–3.00) with an initial overlapping 2-day low-molecular-weight or unfractionated heparin therapy until INR=2.0 or higher [35–38]. Patients with APS, venous or arterial thrombosis and history of obstetric failures should, in addition to therapeutic doses of low-molecular-weight heparin, be administered low doses of aspirin (50–100 mg daily) and, after childbirth, warfarin [35–38].

Patients with APS that meets the laboratory criteria and with obstetric failures (≥ 1 pregnancy loss ≥ 10 weeks of gestation or 3 consecutive unexplained miscarriages < 10 weeks of gestation) but without venous or arterial thrombosis are recommended low-molecular-weight heparin in prophylactic doses (enoxaparin 40 mg daily, dalteparin 5,000 U subcutaneously once daily) and low aspirin doses (50–100 mg daily). This treatment is continued after childbirth [35–38].

Patients with APS that meets the laboratory criteria and with significant obstetric history (?1 premature labor of a morphologically normal fetus before week 34 of gestation due to pre-eclampsia, eclampsia or other pathologies resulting from placental insufficiency) but without arterial or venous thrombosis are recommended low aspirin doses (50–100 mg) from the end of the third trimester until delivery. This treatment is not continued after childbirth [35–38].

Patients who only meet the laboratory criteria for aPL and not the clinical criteria, should receive low aspirin doses (50–100 mg) during pregnancy with the therapy discontinued after childbirth [35,37,38]. As of today, there are no recommendations for maternal–fetal surveillance in APS patients. Pregnancy in these cases should be considered a high-risk pregnancy. Numerous authors advocate more frequent check-up visits and regular monitoring of arterial pressure, platelet count, transaminase activity, serum creatinine concentration and proteinuria. It is also indicated to screen for anti-Ro/SSA and anti-La/SSB antibodies as they do affect neonatal health [1,2,12]. Patients with obstetric APS should have ultrasound scans conducted every 3–4 weeks, starting from week 24 of gestation, involving assessment of fetal growth, amount of amniotic fluid and Doppler examinations [1,2,12]. Heparin should be discontinued 24 h before delivery in order to reduce the risk of obstetric hemorrhage and make anesthesia administration possible. According to Lokwood et al., termination of pregnancy (labor induction or cesarean section) must be planned for week 39 of gestation in order to discontinue anticoagulant therapy in a controlled way [35]. Patients with the history of thrombotic events should not stay without antithrombotic treatment for more than 48 hours. Aspirin administration should discontinue after week 36 of pregnancy, optimally 7–10 days before delivery, as there are reports of a slight increase in the risk of perioperative bleeding [35–39]. Patients with the history of severe complications from venous thrombosis, such as stroke or myocardial infarction, are an exception [35–39]. If the standard APS therapy fails, second-line treatment can be implemented. It consists in: intravenous immunoglobulins, therapeutic plasma exchange, corticosteroids and hydroxychloroquine [40–45]. However, the

efficacy of the second-line treatment is not well-documented.

The outcomes of steroid therapy in pregnant patients with APS are inconclusive. However, steroid use has been linked with a higher risk of obstetric complications, such as infections, premature amniotic fluid leak, premature labor, intrauterine growth restriction, pre-eclampsia or gestational diabetes [40,41]. Nevertheless, corticosteroid therapy may be necessary for thrombocytopenia in the course of APS. Severe or prednisone-resistant thrombocytopenia should be treated with azathioprine, danazol, i.v. immunoglobulins or rituximab. Mild thrombocytopenia in patients with active thrombosis is not a contraindication to antithrombotic treatment [40,41]. Attempts at intravenous immunoglobulin administration (e.g. at a dose of 0.4 g/kg daily for 5 days each month) did take place in rare cases of patients with multiple pregnancy losses and concomitant HELLP syndrome or in catastrophic APS (CAPS) [42,43]. Also, there are limited data on the application of therapeutic plasma exchange. The essence of therapeutic plasma exchange (TPE), also called plasma exchange (PE), is to separate plasma with pathogenic factors from blood components. Further investigations should be conducted to learn about the efficacy of this method when used alone or in combination with intravenous immunoglobulin infusion [44,45].

Chloroquine and its derivatives are used as anti-parasitic (mainly anti-malarial) agents. However, the interest in their application in autoimmune diseases and as agents supporting cancer therapy, has been growing [41,42]. Hydroxychloroquine (HCQ) differs from chloroquine in the presence of a hydroxyl group at the end of the lateral chain. The drug is produced as hydroxychloroquine sulfate. The mechanism of action is probably associated with the ability to stabilize lysosomal enzymes, suppress antigen presentation mechanisms, inhibit T cell stimulation and block proinflammatory cytokine cascade [46,47].

The mechanisms of action of HCQ utilized in APS treatment include platelet aggregation inhibition, suppression of arachidonic acid release and reduction of the number of aPL immune complexes that attach to phospholipids. Moreover, hydroxychloroquine prevents aPL-induced damage of the protective layer formed by annexin V and reduces the impact of anti-ß2-GPI antibodies on the capacity of the trophoblast to fuse and differentiate [48]. A number of authors have recently been speculating about the possibility of using hydroxychloroquine for obstetric APS treatment, particularly in patients that do not respond to standard therapies. Intrauterine concentrations of hydroxychloroquine to which the fetus is exposed are comparable to maternal blood levels [49]. Clinical trials conducted thus far have suggested greater probability for normal pregnancy in patients treated with HCQ or HCQ combined with conventional therapy [50–53]. The available studies on fetal adverse events of hydroxychloroquine have shown that this drug is not associated with an increased risk of congenital defects, spontaneous abortions, intrauterine fetal death, premature labor and lower number of live births in SLE patients [54]. Due to lower ability to bind with fetal tissues and lower ocular toxicity in pregnancy, hydroxychloroquine is a recommended product [54]. However, it must be underlined that even though this therapy is promising, it is still experimental, requiring further investigations and used in cases resistant to standard treatment.

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