The management of obstetric antiphospholipid syndrome

DOROTA DARMOWAL-KOLARZ, ANITA WYLPEK, IRMINA BUDA, BOŻENA LESZCZYŃSKA-GORZELAK, JAN OLESZCZUK

Abstract

The antiphospholipid syndrome (APS) is characterized by vascular thromboses, fetal losses and thrombocytopenia in association with the production of autoantibodies against phospholipids. This review focuses on the question, how today, the application of an effective therapy can change the prognosis of pregnancy in group of women with APS. The pharmacological management of obstetric APS is still controversial and need to be individualized, for each women. The combination of aspirin and heparin is considered as the standard of care for women with antiphospholipid syndrome and recurrent early miscarriage. Steroids and immunoglobulins are not routinely used, due to their side effects and high costs. Doses and duration of therapy depend on the history of pregnancy and thrombosis. All pregnant women with APS should be considered to be at high risk and be managed in combined medical-obstetrical clinic throughout the whole pregnancy to increase the chances for delivery of live and healthy baby.

Key words: antiphospholipid syndrome, pregnancy, recurrent miscarriage

The antiphospholipid syndrome (APS) is a condition defining by thrombotic or pregnancy related clinical features in women with positive level of antiphospholipid antibodies. In these women there is wide spectrum of pregnancy loss from first trimester miscarriage, through arterial or venous thrombosis, pre-eclampsia, intrauterine growth restriction, placental insufficiency or preterm labour. The antiphospholipid syndrome is the most established acquired thrombophilia in early pregnancy loss [11]. Previous researches suggest that blood coagulation defects are responsible for 55-62% of recurrent miscarriages, whereas 90% of first time miscarriages are caused by chromosomal defects [19].

Nowadays, APS is recognized as the most significant cause of RPL – recurrent pregnancy loss. In group of women with RPL in obstetric history there is a range of APS – incident between 20% and 40%. Some authorities claim that the unifying feature of these processes is abnormal placental function due to necrosis, infarction and thrombosis. Some others associate abnormalities in the decidual spiral arteries with fetal loss in APS especially thickening, atherosclerosis and fibrinoid necrosis. These conditions may result from thrombosis during the development of the normal maternoplacental circulation. However, there is a wide variety of related clinical manifestations, obstetric morbidity is one of the major manifestations of APS.

There are three primary classes of antibodies associated with the antiphospholipid syndrome: 1) anticardiolipin antibodies (aCL), 2) the lupus anticoagulant (LA) and 3) antibodies directed against specific molecules including a molecule known as beta-2-glycoprotein 1 (anti-b2GPI). Lupus antibody is the most powerful predictor of thrombosis and recurrent miscarriages. Anti-b2-glycoprotein-1 antibodies are not associated with recurrent miscarriage in isolation, however, in combination with positive results for lupus anticoagulant (LA) and aCL, there is a high risk of obstetric complications [13].

Antiphospholipid antibodies can be detected in 1-5% of healthy women. The prevalence of positive antiphospholipid antibodies increases to 15% in women with recurrent first trimester pregnancy losses and up to 20% in women suffering a stroke at or before the age of 50 years. Around 40% of women with lupus have antiphospholipid antibodies; it is estimated that less than 40% of them will eventually develop thrombotic events. The prevalence of APS is unknown, but it has been estimated to be 0.5% in the general population [20].

A sporadic spontaneous abortion occurs in up to 15% of all recognized pregnancies, and recurrent miscarriage occurs in about 1% of women at reproductive age. They can be caused by chromosomal, anatomic, hormonal (progesterone, oestrogens, diabetes or thyroid disease), coagulation or platelet abnormalities. Taking into account all possible causes, APS could be responsible for 10-15% of recurrent miscarriages, whereas antiphospholipid antibodies could be identified in 5-20% of these women [18].
Early onset, severe preeclampsia, complicated with HELLP syndrome (hemolysis, liver enzyme elevation and thrombocytopenia), is a frequent association probably due to shared pathogenic mechanisms. In the general obstetric population, the incidence of HELLP is between 0.01 and 0.2% while in pregnancies complicated by preeclampsia/ eclampsia, an incidence of 10 to 12% has been reported. About one-third of untreated women with APS may develop pre-eclampsia during pregnancy, and more than 10% of these women will deliver small for gestational age infants [13]. Catastrophic APS is an aggressive form of this disease. Almost 6% of this APS variant occurs during pregnancy or puerperium.

Antiphospholipid syndrome may also be present with other frequent clinical manifestations (more than 20% of cases) that are not included in the classification criteria, such as thrombocytopenia, migraine and livedo reticularis. Other less common manifestations are heart valve disease, haemolytic anaemia, coronary artery disease and the haemolysis, elevated liver enzymes and low platelet count syndrome (HELLP). It is a wide diversity in clinical presentations that may cause problems in the diagnosis and treatment of APS.

Antiphospholipid syndrome can occur as primary APS in over 50% of women or is associated with other systemic autoimmune diseases, mainly systemic lupus erythematosus [13].

Clinical features, laboratory assessment and classification criteria

The first classification criteria for the APS were formulated in 1987, then in 1998 were amended during 8 International Statement Meeting in Sapporo in Japan. Final Criteria for the Classification of the APS were addressed at a workshop in Sydney, Australia before the Eleventh International Congress on antiphospholipid antibodies in 2006 (Table 1).

APS is diagnosed if at least one of the clinical criteria and one of the laboratory criteria are present.

The pathogenesis of antiphospholipid syndrome

The pathogenesis of the disease is still relatively unknown. There are different pathogenic mechanisms that try to explain pregnancy loss associated with aPL antibodies.

Although some of them have been well described such as murine models of APS, where a direct causal association between aPL antibodies and pregnancy loss has been shown, there is still uncertainty with respect to this.

Table 1. 2006 classification criteria for APS

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<tr>
<th>Clinical criteria</th>
<th>Vascular thrombosis</th>
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<tr>
<td></td>
<td>One or more clinical episodes of</td>
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<td></td>
<td>a) Arterial thrombosis</td>
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<td>b) Venous thrombosis</td>
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<td>c) Small vessel thrombosis</td>
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<tr>
<th>Pregnancy morbidity</th>
<th>a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology (demonstrated by ultrasound or direct examination of the fetus)</th>
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<td>b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia, or features of placental insufficiency:</td>
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<td>• abnormal or non-reassuring fetal surveillance test,</td>
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<td>– a non-reactive, non-stress test, suggestive of fetal hypoxemia,</td>
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<td>– abnormal doppler flow velocimetry wave form analysis suggestive of fetal hypoxemia,</td>
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<td>– oligohydramnios &lt; 5 cm,</td>
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<td>– postnatal birth weight less than the 10th percentile for the gestational age</td>
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<td>c) Three or more unexplained consecutive spontaneous abortions before the10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded</td>
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<th>Laboratory criteria</th>
<th>a) A minimum of two positive tests for LA present in plasma at least 12 weeks apart</th>
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<td></td>
<td>b) aCL antibody (IgG and/or IgM isotype)in serum or plasma that is present in medium or high titer in 2 or more tests at least12 weeks apart</td>
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<td></td>
<td>c) Anti-β2GPI antibody (IgG and/or IgM isotype) in serum or plasma (in titer the 99th percentile) which is present on two or more occasions at least 12 weeks apart as measured by a standardized ELISA</td>
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The hallmarks of this syndrome are vascular thrombosis involving both the venous and arterial beds, as well as placental circulation. Thrombosis in the placental vasculature may lead to infarctions and placental insufficiency. This is not exclusively seen in APS, and may also occur in pre-eclampsia. On the other hand, it has been observed that in many women with obstetric APS there is no evidence of placental thrombosis, infarctions or vasculopathy; instead of that inflammatory signs are seen. This finding has contributed to the redefinition of the concept of APS as an inflammatory disorder. Studies have proved the important role played by endothelial cells, neutrophils, monocytes, platelets, cytokines and
complement in the induction of thrombosis and fetal death in APS. Maternal endothelial cell activation may play a role in a defective placentation.

Antiphospholipid antibodies bind to negatively charged phospholipids, protein-binding phospholipids, or both, triggering the activation of endothelial cells, monocytes, and platelets. In addition, antiphospholipid antibody complexes, mainly formed by b2 glycoprotein I and anti-b2 glycoprotein I, activate the classical and alternative complement pathways. Therefore, complement deficiency or inhibition of complement activation proved a protective effect against pregnancy loss and thrombosis in a murine model. This fact could explain the benefits of low dose heparin, owing to its capacity of complement inactivation rather than by its antithrombotic effects [18].

Activated endothelial cells express adhesion molecules and, along with monocytes, upregulate the production of tissue factor. Tissue factor is the major initiator of the coagulation cascade in vivo, playing an important role in thrombosis and inflammation. Growing evidence suggests that antiphospholipid antibodies-dependent induction of tissue-factor activity on circulating monocytes is an important mechanism of hypercoagulability in APS. Tissue factor, acting as a proinflammatory molecule, enhances neutrophil activity causing trophoblastic injury, placental dysfunction and damage in the developing placenta and embryo. In addition, antiphospholipid antibodies seem to cause direct trophoblastic dysfunction, resulting in impaired transplacental exchange between the mother and the fetus, which can lead to early miscarriage, pre-eclampsia, intrauterine fetal growth restriction or even intrauterine fetal death.

The disruption of the annexin A5 shield also plays an important role in the pathogenesis of APS.

Annexin A5 is a potent vascular and placental anticoagulant protein, which has high affinity for negatively charged phospholipids. It is highly expressed on the apical membranes of placental villous syncytiotrophoblast, at the interface between the fetus and the placenta. Its anticoagulant effect results from the capacity to crystallise over phospholipid bilayers, blocking their availability for coagulation reactions. Antiphospholipid antibodies interfere with annexin A5 function, leading to accelerated coagulation reactions, and probably contributing to pregnancy loss and to the thrombogenic effects of these antibodies [18].

Infection has been proposed as another mechanism that could lead to APS. In humans, infection with varicella has also been associated with APS. The most common infections associated with APS include parovirus B19, cytomegalovirus (CMV), varicella-zoster virus, human immunodeficiency virus (HIV), Streptococcus, Staphylococcus, gram-negative bacteria, and Mycoplasma pneumoniae [21].

The treatment of antiphospholipid syndrome

Different ways of treatment are motivated by multidirectional mechanism of antyphospholipid antibody action.

The ideal treatment of women with APS during pregnancy should improve maternal and fetal outcome by preventing pregnancy loss and eliminate the maternal thrombotic events. At the present time the treatment of choice of antiphospholipid syndrome in pregnancy is administration of low dose aspirin together with heparin. Clinicians try to establish when should this treatment start and when can it be stopped safely. It is usually initiated in early first trimester when live embryo is present in uterine during ultrasound examination.

A variety of pharmacological treatment options in obstetric APS have been used (aspirin, steroids, heparin) either as single or in combination to improve fetal-neonatal outcome. In randomized trials there was reported that use of steroids is associated with high risk for the development of gestational diabetes, hypertension or prematurity. Intravenous immunoglobulin has also been used usually with heparin and low dose aspirin, but studies of this treatment found no benefit to this expensive therapy.

The optimal treatment of pregnant women with APS is combination therapy with low molecular weight heparin (5000 units subcutaneously daily) and aspirin 75-100 mg daily.

The managment of obstetric APS is still controversial. In discussing the literature we divided patients into two categories [13].

Group 1 – aPL positive patients with no history of pregnancy loss or thrombosis. In the case of these women the appropriate strategy are strict control of their pregnancies and administration of low doses of aspirin.

Group 2 – aPL positive patients with a history of one or more miscarriages. The treatment that can be proposed to these patients are aspirin (75-100 mg) before conception and then throughout pregnancy and the first 4 postpartum weeks and the administration of low molecular weight heparin (LMWH) 5000 units daily which is the most widely accepted plan for this group of patients. If this plan fails, the next plan should be followed which would entail adding LMWH to the treatment for the next
pregnancy. We need to take into consideration the fact that the babies from these pregnancies are strongly desired and after the treatment options are explained, many patients prefer to start with the second plan due to the possibility that the first one could fail.

The therapeutical benefits of heparin interfere in the aPL binding to trophoblast cells and is also able to restore normal trophoblast invasiveness and differentiation. Some studies have demonstrated that heparin and aspirin regulate trophoblast cell apoptosis and protein expression. The success of implantation results from a balance between the secretion of matrix metalloproteinases (a group of type IV collagenases- MMPs) by trophoblast and the inhibition by their tissue inhibitors – TIMPs. Some trials noticed the increase in the production of MMPs and their activity in trophoblast cells after treatment with LMWH. Moreover, the heparin is able to promote trophoblast invasiveness through the regulation of its degradative capacity by acting on MMPs at three levels: transcription, conversion of proenzyme into their active form, and synthesis of the specific inhibitors of TIMPs.

It is believed that aspirin improves vasodilation, prostacyclin production and reduces levels of thromboxane A2. Aspirin is commonly used to treat women with thrombophilia who have had recurrent miscarriages, who are also deemed idiopathic and as prophylaxis pre-eclampsia.

It is useful to know that the rationale for aspirin use is related to the stimulation of IL-3 production. In fact, IL-3 is a growth factor for the trophoblast. IL-3 serum levels are reduced in APS women during pregnancy and, in the experimental model, the addition of exogenous IL-3 was able to completely eliminate aPL-related obstetrical complications.

The treatment’s success is not only based on the drug intervention, but also strict control and monitoring throughout the entire pregnancy and even in the preconceptional period and puerperium. Women receiving heparin should have regular platelet counts performed in order to detect the rare occurrence of heparin induced thrombocytopenia. Fetal welfare is monitored with ultrasound assessments of growth and Doppler studies of the uterine and umbilical circulations. Abnormal Doppler studies are predictive of pregnancies at increased risk for the development of pre-eclampsia and intrauterine growth restrictions. This will help the physicians to make the decisions if complications should arise and if early delivery be necessary. Monthly monitoring of fetal growth and amniotic fluid volume is recommended. Doppler studies of umbilical artery flow should be done during the 20th and 24th week of pregnancy to detect those pregnancies with an increased risk of developing preeclampsia or uteroplacental insufficiency. As of the 30th week, ultrasound studies can be done more frequently, depending on the progress of the pregnancy and the medical team approach. Best care needs also frequent rheumatological consultation every 2-4 weeks during pregnancy.

Treatment of obstetrical APS should include a multidisciplinary team of specialists such as gynecologists, rheumatologists, and internists who have the experience in this field.

Antiprothrombin antibodies detected by ELISA are a heterogeneous population including antibodies against prothrombin alone (aPT-A) and antibodies to the phosphatidylserine-prothrombin complex (aPS/PT). The sensitivity and the specificity of aPS/PT are higher than those for aPT-A, 95% of patients with aPS/PT are also LA positive. That data suggests that aPS/PT can also serve as a confirmatory assay for LA.

Another issue is how to classify cases with aPL and non-criteria clinical manifestations of APS, and cases that fulfill clinical criteria, but test positive only for non-criteria aPL. Based on new clinical, laboratory and experimental insights it is provided definitions on features of APS that were not included in the updated criteria [22].

Features associated with APS but not included in the revised criteria (Table 1-5).

Over the years, our understanding of APS has deeply changed.

Currently, there are controversial points in some areas, especially diagnostic tests and treatment options for obstetric APS.

All women with APS should be considered to be at high risk, and be given individualized care based on their clinical and immunological status. The likelihood of a good pregnancy outcome in women with APS is around 75-80% under correct management.

Obstetric morbidity is not limited to recurrent pregnancy loss. It extends to other clinical findings such as intrauterine growth restriction, pre-eclampsia, HELLP syndrome, preterm delivery placental detachment and intrauterine fetal death.

Adequate pregnancy management of women with APS rests on three pillars: a co-ordinated medical-obstetrical care, an agreed and well-defined management protocol and a good neonatal unit. Doppler studies are essential in the follow-up protocol of pregnant women with antiphospholipid antibodies.
The management of obstetric antiphospholipid syndrome

Table 2. Definition of aPL-associated cardiac valve disease [22]

aPL-associated cardiac valve disease is:

Coexistence of aPL (Laboratory Criteria for APS) along with

• Echocardiographic detection of lesions and/or
• Regurgitation and/or stenosis of mitral and/or aortic valve or any combination of the above.

Valve examination can be performed with TTE and/or with TEE

Defining valve lesions include:

– Valve thickness > 3 mm,
– Localized thickening involving the leaflet’s proximal or middle portion,
– Irregular nodules on the atrial face of the edge of the mitral valve, and/or the vascular face of the aortic valve.

The presence and severity of regurgitation and/or stenosis should be documented with Doppler echocardiography.

Interpretation should be carried out by two expert echocardiographers.

Both functional capacity and objective assessment of heart status should be reported according to the revised NYHA Criteria for Diagnosis of Heart Disease.

Confirmation of valve disease may also be provided by histopathological findings of Libman-Sacks endocarditis in patients with concomitant SLE.

In all the above cases, the presence or history of rheumatic fever and infective endocarditis must be excluded.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.

Researchers should also state if the patient meets the American College of Rheumatology (ACR) revised criteria for SLE.

Table 3. Definition of aPL-associated livedo reticularis (LR) [22]

aPL-associated LR is the coexistence of aPL (Laboratory Criteria for APS) and LR.

Livedo reticularis is the persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled, pattern of the skin of trunk, arms or legs. It may consist of regular unbroken circles (regular LR) or irregular-broken circles (livedo racemosa). The width of the branching pattern can be ≥ 10 mm (large LR) or < 10 mm (fine LR). Four variants may be recognized: fine livedo racemosa, large livedo racemosa, fine regular LR, and large regular LR.

Pathologic changes confirmative, but not required, for LR classification and diagnosis include partial or complete occlusion of the lumen of small- to medium-sized arteries and/or arterioles at the dermis-subcutis border with no evidence of perivascular inflammatory infiltrate and negative direct immunofluorescence examination.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.

Table 4. Definition of aPL-associated nephropathy (APLN) [22]

aPL-associated nephropathy is the coexistence of aPL (Laboratory Criteria for APS) along with the histopathologic detection of:

Thrombotic microangiopathy involving both arterioles and glomerular capillaries and/or

One or more of:

• Fibrous intimal hyperplasia involving organized thrombi with or without recanalization
• Fibrous and/or fibrocellular occlusions of arteries and arterioles
• Focal cortical atrophy
• Tubular thyroidization (large zones of atrophic tubules containing eosinophilic casts)
• Vasculitis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, and other reasons for chronic renal ischemia are exclusions.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.

If SLE is also present, the above lesions should be distinguished from those associated with lupus nephropathy.

Table 5. Definition of aPL-associated thrombocytopenia [22]

aPL-associated thrombocytopenia is the coexistence of aPL (Laboratory Criteria for APS) along with the following:

Thrombocytopenia (< 100 × 10^9 l^-1), confirmed at least twice 12 weeks apart.

Exclusion of patients with thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, pseudo-thrombocytopenia, and heparin-induced thrombocytopenia

Thrombocytopenia is further characterized as moderate (platelet count 50 – 100 × 10^9 l^-1) or severe (< 50 × 10^9 l^-1).

Subclassification of patients according to the presence or absence of SLE is advantageous.

Patients who fulfill Clinical Criteria for APS are excluded from the definition above.
Antiphospholipid syndrome (APS) remains a challenge for clinicians in a wide range of specialities and is a serious perinatologic problem.

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References

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