Treating obstetric antiphospholipid syndrome

Systemic autoimmune thrombosis or antiphospholipid syndrome is a treatable cause of miscarriages and of recurrent spontaneous pre-embryonic and embryonic abortions. Three groups of management could be identified for antiphospholipid syndrome. Low doses of aspirin and low-molecular-weight heparins are recommended for treatment of this disorder. The use of glucocorticoids and intravenous immunoglobulins can be justified in special cases. Strict control and an interdisciplinary approach during treatment of these patients is mandatory. Inflammatory autoimmune mechanisms in the pathophysiology of obstetric antiphospholipid syndrome and anti-inflammatory and immunomodulatory mechanisms of drug action should be considered during individual treatment scheme selection.

KEYWORDS: antiphospholipid antibodies ■ antiphospholipid syndrome ■ aspirin ■ heparin ■ miscarriages ■ spontaneous abortions ■ thrombosis

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The connection existing between pregnancy loss and antiphospholipid antibodies (aPLs) has been formally recognized for over 20 years. Today it is accepted that systemic autoimmune thrombosis [1] or antiphospholipid syndrome (APS) is a treatable cause of thrombosis, miscarriages and recurrent spontaneous pre-embryonic and embryonic abortions [2].

The prevalence of APS during pregnancy varies according to the population being studied and the criteria used to measure the aPLs. Low levels of aPLs are found in women with normal pregnancies. Lupus anticoagulant (LA) has been found in 0.2% and anticardiolipin antibodies (aCLs) in 2% of women with normal pregnancies [3].

Between 7 and 25% of recurrent spontaneous abortions unexplained by other causes are caused by the presence of aPLs. In women who have had pregnancy loss, the prevalence of aCLs varies between 4.6 and 50.7%, with an average of 15.5%, and the prevalence of LA varies between 0 and 14%, with an average of 8.3%. However, in women who have miscarriages later than week 20, the prevalence of aPLs can be as high as 30% [3]. The difference between these percentages can be explained by the diversity of the groups being studied and the application of different inclusion criteria for patients and the lack of standardization of detection methods for aPL used in the studies.

It is not recommended to request examinations of aPL for women without a history of obstetric losses or complications and with normal pregnancies. Considering the low titers of antibodies, the risk of complications does not increase; these women require close monitoring but no treatment.

During gestation, apart from causing miscarriage, APS has been linked to every dysfunction during the three trimesters of pregnancy: intrauterine growth restriction, pre-eclampsia, preterm birth and pregnancy loss [4–6]. Other complications include oligohydramnios, fetal distress [7] and, infrequently, fetal or neonatal thrombosis [8]. Obstetric complications such as HELLP syndrome (hemolysis, elevated liver enzimes, low platelets count) could also be related to the action of the aPLs [9].

Pathophysiology

Understanding the pathophysiology of APS remains complicated because autoantibodies are not directed against phospholipids, but towards the plasma protein β2-glycoprotein I (β2GPI) [10,11]. Its relationship with pregnancy is characterized by arterial, venous thrombosis or recurrent miscarriages in an individual when laboratory tests for aPLs are positive. One of the pathological effects of aPLs is the alteration of adhesion molecules in trophoblast components. During a normal pregnancy the endometrial implantation produces events involving trophoblast and decidua. In APS, aPLs can act directly in the trophoblast, altering its differentiation and maturation, causing direct cellular damage, apoptosis, inhibition of syncytium formation, decreased chorionic gonadotropin and impaired implantation. In addition, aPLs induce a hypercoagulable state that causes placental thrombosis and ischemia.

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Growth restriction and fetal loss in patients with APS are caused by spiral artery vasculopathy leading to uteroplacental insufficiency by decreased normal maternal blood flow into the intervillous space, making the exchange of gases and nutrients difficult [12].

Classification & criteria of pregnancy loss in APS

In 1999, the first preliminary criteria for classification of APS were developed in Sapporo (Japan) [13]. These criteria resulted from the 8th International Symposium on Antiphospholipid Antibodies and are commonly recognized as the 'Sapporo criteria for APS.' In 2006, criteria were updated in Sydney (Australia) for the 11th International Congress of Antiphospholipid Antibodies. Currently, the Sydney criteria remain valid and include the following obstetric morbidity [14]:

- Unexplained deaths of normal fetus at or beyond week 10 of gestation;
- Unexplained consecutive spontaneous abortions before week 10 of gestation;
- Premature births (before week 34 of gestation) owing to eclampsia or severe pre-eclampsia, or placental insufficiency (**Box 1**).

The above criteria have helped to guide physicians in making decisions, but there are several aspects of obstetric APS that will have to be revised in order to improve the classification for these patients [15].

Treatment

Obstetric APS treatment methods have focused on affecting two aspects of the possible pathogenic mechanisms: one to reduce the action of the antibodies with the administration of glucocorticoids and intravenous immunoglobins and the other to prevent thrombosis with the use of antiaggregants and anticoagulants. It must also include a multidisciplinary team of specialists such as gynecologists and obstetricians, rheumatologists, medical specialists in autoimmune diseases and medical imaging specialists with experience in working with the syndrome. The success of the treatment is based not only on medication, but also on strict control and follow-up during the entire pregnancy and even during the preconception period.

Corticosteroids

In 1952, Conley and Hartmann observed that adrenocorticotropic hormone suppresses the activity of LA, therefore justifying the use of corticosteroids in APS [16].

The first treatment method used to prevent fetal death linked to aPLs was the combination of prednisone 40 mg/day in addition to low doses of asprin (LDA), a proposal made by Lubbe *et al.* [17].

However, in 1989 Lockshin *et al.* determined prednisone to be ineffective in handling recurrent fetal death linked to aPLs [18], and currently, corticosteroids are used for patients with obstetric APS only to control the symptoms of a worsening concomitant systemic lupus erythematosus or thrombocytopenia. Prednisolone was also associated with increased risk of gestational diabetes, elevations in blood pressure during pregnancy, asymptomatic infections and preterm deliveries [19]. Nevertheless, as investigations reveal the increasing evidence for underlying inflammatory mechanisms in the pathogenesis of APS, theoretically, the benefits of immunosuppression for preserving pregnancies could not be discarded and, in a recent study, Bramham *et al.* suggest that low-dose prednisolone, in addition to aspirin and heparin, may be of benefit in women with APS refractory to standard treatment [20].

Intravenous immunoglobins

The application of intravenous immunoglobins (IVIGs) has been reported by various authors. For example, Carreras *et al.* used IVIGs for a patient who had had nine previous abortions, and after the administration of these had a successful pregnancy. Since then, the use of IVIGs has been limited to APS pregnancies that have not responded to conventional treatment [21].

Nonrandomized studies have shown a 70–100% response rate to IVIGs in pregnancies in which aspirin and heparin had failed to work [22–24], and immunoglobulins are either used during the first trimester or after week 20 of gestation.

Spinnato *et al.* used IVIGs in five patients with 17 previous failed pregnancies, in combination with LDA and heparin [25]. The results were healthy neonates for all, except one preterm at 32 weeks of gestation (due to decreased fetal movements and fetal distress). Moreover, among these five patients, three showed a 50% reduction in anticardiolipin IgG; the other two presented titers in the low-positive range throughout pregnancy.

In 2000, the first multicentric, placebo-controlled randomized trial was carried out by Branch *et al.* with 16 patients in a group that

Box 1. 2006 classification criteria for antiphospholipid syndrome†.

Clinical criteria

- Vascular thrombosis.
- One or more clinical episodes of:
  - Arterial thrombosis‡
  - Venous thrombosis‡
  - Small vessel thrombosis‡

Pregnancy morbidity

- One or more unexplained deaths of a fetus at or beyond week 10 of gestation, with normal fetal morphology (demonstrated by ultrasound or direct examination of the fetus).
- One or more premature births of a morphologically normal neonate before week 34 of gestation because of eclampsia or severe pre-eclampsia, or features of placental insufficiency (abnormal or nonreassuring fetal surveillance test[s]; for example, a nonreactive nonstress test suggestive of fetal hypoxemia, abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, oligohydramnios or a postnatal birth weight less than the tenth percentile for the gestational age).
- Three or more unexplained consecutive spontaneous abortions before week 10 of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

- A minimum of two positive tests for lupus anticoagulant present in plasma at least 12 weeks apart§.
- Anticardiolipin antibody (IgG and/or IgM isotype) in serum or plasma that is present in medium or high titer in two or more tests at least 12 weeks apart¶.
- Anti-â2GPI antibody (IgG and/or IgM isotype) in serum or plasma (in titer the 99th percentile) that is present on two or more occasions at least 12 weeks apart, as measured by a standardized ELISA.

†*Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria are met.*
‡*Thrombosis must be confirmed by objective validated criteria.*
§*Detected according to the guidelines of the International Society on Thrombosis and Haemostasis.*
¶*Measured by the standardized ELISA.*
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received IVIGs and a placebo, and another that was assigned IVIGs in combination with aspirin and low-molecular-weight heparin (LMWH) [26]. Meta-analyses published by Clark *et al.* indicate that IVIGs significantly increase the probability of successful pregnancy in patients with immunological risk factors including positive aPL and natural killer cell activity [27]. The mechanisms of action of IVIGs are suppression of B-cell production of antibodies, action on binding complement by Fc component of IgG and regulation of activity of natural killer and suppressor T cells [28].

Aspirin

LDA has been used by different groups as a monotherapy for obstetric APS due to its antiplatelet mechanism of action by inhibition of platelet cycloxygenase, a key enzyme in thromboxane A2 generation [29]. Other mechanisms of aspirin in obstetric APS, as a reduction of inflammatory response and potent antioxidative properties, may also work [30]. Silver RK *et al.* compared the effectiveness of LDA 81 mg/day against LDA plus prednisone 20 mg/day and concluded, in a group of 39 patients, that LDA was more effective and safer than combination therapy [31]. Other authors, such as Carmona *et al.* in 2001, Lima *et al.* in 1996 and Granger and Farquharson in 1997, have described the use of LDA in the treatment of obstetric APS, showing good results with a probability increase in live births of 70–80%, despite obstetric complications [32–34].

Heparins

Since thrombosis is considered to be the main cause of APS, a logical consequence was the use of heparins in the treatment of obstetric manifestations of these diseases. In 1990, Rosove *et al.* described the use of subcutaneous heparin for 15 patients with a history of pregnancy loss (28 previous losses) and achieved a therapeutic success in 14 of these patients [35].

The current recommendations for the use of LMWH for patients with obstetric APS are based mainly on three studies. Rai *et al.*, in a group of 90 women diagnosed with obstetric APS, demonstrated that the combination of LMWH and LDA was more effective than aspirin on its own [36]. Kutteh obtained similar results [37], while Farquharson *et al.* found no significant differences between the combination of LMWH and LDA and LDA alone

[38]. Although the use of LMWHs was initially focused on the prevention of thrombosis, multiple recent studies reveal other possible uses for this drug. These uses include its ability to prevent the binding of aPLs to the trophoblast cell membrane and to reduce complement activation by aPLs [39–41]. D'Ippolito *et al.* proved that LMWHs are able to antagonize the aPL-mediated effects on human endometrial endothelial cells by disrupting the interaction of β2GPI with aPLs on the surface of these cells in a dose-dependent manner [42].

The history of obstetric APS treatment is being written each day because we still do not understand many aspects of its treatment; furthermore, there is a logical limit to clinical trials on pregnant patients due to ethical considerations.

Management of pregnancy with APS

Human chorionic gonadotropin (hCG) values in the first trimester can be followed to evaluate the viability of the pregnancy. If hCG levels are increasing normally (i.e., doubling every 2 days) in the first month of pregnancy, a successful outcome is predicted in 80–90% of cases. A poor outcome is predicted when the increases are abnormal (70–80% of cases) [43].

Blood pressure and the amount of protein in the urine must be monitored closely at each visit, especially during the second and third trimesters. Once a woman is known to have persistently positive aPLs, there is no need to repeat these tests. However, a negative result does not eliminate the risk of complications [44].

The pharmacological treatment of obstetric APS remains controversial and, therefore, patients must receive personalized treatment since the numerous studies have not yet provided conclusive evidence to enable us to establish rigorous treatment methods. Similarly, the existence of clinical subgroups of obstetric APS makes it difficult to apply strict pharmacological schemes.

However, for practical purposes, the patients with obstetric APS could be divided into different groups [45,46]:

- Patients with positive APS, without a history of pregnancy loss or thrombosis, with or without concomitant autoimmune disease;
- Patients with a history of two or more pregnancy losses and the presence of positive APS symptoms;
- Patients with multiple pregnancy losses associated with APS, with or without systemic lupus erythematosus or previous thrombosis, or both.

Group 1

This group includes patients who had aPLs detected in their serum. These patients are justifiably concerned by the existence of the antibodies and how these may affect a future pregnancy, even though they do not meet the criteria for APS. For these women, the most appropriate strategy is a tight control of their pregnancy, without any kind of pharmacological treatment. However, in some cases (high titers of antibodies, family history of autoimmune diseases, migraines, marked livedo reticularis, among others), the use of 81 mg of aspirin as primary antithrombotic prevention may be acceptable [47]. The association between the presence of aPLs and risk of lower live-birth rate, severe pre-eclampsia or low neonatal birth weight in this group of women must be considered when making a decision about primary prevention [48,49].

Group 2

It is essential to have a broad-ranging discussion with patients who present with positive aPLs about the risk that the presence of these antibodies implies for their pregnancy, and the different treatment methods that could be used. The patient must actively participate in deciding on the right strategy for their particular case and must understand the risks and benefits of treatment, as well as the importance of being persistent with the treatment.

These are the suggested guidelines for these patients:

- For patients who are not pregnant at the time of their first visit and who are planning on a pregnancy in the short term: preconception LDA and then, when the pregnancy is confirmed, LMWH is recommended;
- For patients who are already pregnant and are referred by gynecologists as being diagnosed with obstetric APS: aspirin (81–100 mg) and LMWH, on a daily basis, during the entire pregnancy and the first 4–6 weeks of the postpartum period are recommended.

Group 3

The third group includes patients with secondary APS and/or a prior history of thrombosis. In this group, a personalized treatment strategy is essential. For patients who are using dicumarol for prior thrombosis, administration must be interrupted before week 6 of pregnancy. The teratogenic risk owing to the use of dicumarol is greatest between weeks 6–12 of pregnancy

[50]. The fluorinated glucocorticoids (beta and dexamethasone) are only used when there is risk of premature birth, and nonfluorinated glucocorticoids (prednisone and prednisolone) for nonobstetric reasons, such as the activation of the lupic process or thrombocytopenia [51]. Prevention of pregnancy loss for these patients can be achieved through LDA combined with the daily administration of LMWH. For all patients, a follow-up ultrasound is important to monitor fetal growth and the state of uterine placental circulation. This will help in decision-making should complications arise and the delivery needs to be induced. A monthly follow-up is recommended to check on intrauterine growth and the volume of amniotic fluid. Uterine artery Doppler analyses are required between weeks 20–24 of pregnancy in order to detect pregnancies with an increased risk of developing pre-eclampsia or uterine placental insufficiency [52]. From week 30, ultrasounds should be taken more frequently, depending on the development of the pregnancy and the criteria of the medical team.

Despite the treatment, pregnancy loss can occur in 20–30% of cases [53]. The use of glucocorticoids is questionable in these cases. Nevertheless, as mentioned above, Bramham *et al.* presented encouraging results of pregnancy outcomes in 18 women with aPLs and refractory pregnancy loss(es) despite the use of aspirin and heparin, with additional low-dose prednisolone administered in the first trimester [20].

The ideal treatment for patients with obstetric APS who do not respond to heparin with aspirin remains unknown. IVIGs are reserved for these cases and used in combination with heparin as well as LDA [54].

Tight control

Treatment protocol must include:

- A series of tests to confirm the diagnosis and to exclude other diseases, such as: aCLs, LA, anti-β2GPI, antinuclear antibodies, anti-DNA, anti-Ro, anti-La, C3, C4;
- Monthly visits to the gynecologist and rheumatologist or a specialist in autoimmune diseases up to week 28–30 of pregnancy. Subsequently, visits shall be conducted every 2 weeks;
- Monthly obstetric ultrasonography with a special focus on intrauterine growth, volume of amniotic fluid, placental growth, development of abruption of the placental lining or placental hematomas. This follow-up is important since the results allow us to decide on the dose of LMWH to apply;
- Uterine artery Doppler analyses are required between week 20–24 of pregnancy in order to detect pregnancies with an increased risk of developing pre-eclampsia or uterine placental insufficiency.

In the postpartum stage, the administration of LMWH during a period of 4–6 weeks for patients without any history of prior thrombosis is recommended.

Future treatments

Studies identified by Alijotas-Reig *et al.* doubt the central place of the classic thrombotic hypothesis in the pathogenesis of the obstetric APS, demonstrating the absence of decidual thrombosis or placenthal vasculopathy, while inflammation signs are present [55]. Increasing numbers of investigations suggest the central role of the complement system in the pathogenesis of these syndromes, especially obstetric APS [56–59]. Based on these insights on the pathophysiology of APS and a better understanding of the involved receptors and intracellular pathways, the role of inflammatory mediators and the immunomodulatory properties of drugs are increasingly being investigated [60].

The safety of the antimalarial drug hydroxychloroquine during pregnancy and lactation has been documented in several studies [61–64]. The latest studies on its mechanism of action show the ability of hydroxychloroquine to dissociate aPL immune complexes [65], reduce binding of aPLs to syncytiotrophoblasts and restore annexin A5 expression [66,67].

Several studies show the possible benefits of statins in the treatment of APS due to inhibition of the inflammatory and thrombotic action of aPLs [68–71]. Nevertheless, there are no conclusive data about their safety during pregnancy [72].

Some investigators highlight the primary importance of TNF-α in inflammatory and thrombotic complications of obstetric APS [73], and propose it as a critical cause and target for therapy in aPL-induced pregnancy loss [74].

B-cell depletion therapy agents could be promising for the treatment of obstetric APS. Rituximab, a chimeric anti-CD20 monoclonal antibody, and belimumab, a specific inhibitor of B-lymphocyte stimulator, have been proven to reduce anticardiolipin IgG antibodies and normalize low complement levels [75,76]. Although there is little evidence of their practice

in pregnancy, their use is increasing in certain autoimmune diseases, such as rheumatoid arthritis, autoimmune hemolytic anemia and idiopathic thrombocytopenia purpura [77,78]. However, studies on the use of rituximab in the first trimester of pregnancy found that normal levels of CD19 and CD34 result in healthy neonates, which can be explained by low placental transfer of this biologic agent in the first trimester of pregnancy [77]. These results contrast with other studies in which a B-cell depletion occurs in the second and third trimesters of pregnancy [79,80]. The US FDA categorized rituximab as category C (insufficient evidence). Therefore, further studies are required to evaluate the safety of rituximab during pregnancy.

Conclusion & future perspective

Three groups of management can be used for obstetric APS. However, each patient should be given individualized care based on their clinical and immunological status. Further research on pathogenic mechanisms, new autoantibodies and therapeutic options will provide a better understanding of obstetric APS and will enable the development of effective treatments for these patients. It is probable that the inflammatory hypothesis in the pathogenesis of obstetric APS will become more important and treatment will focus on drugs with action on complement and other inflammatory cytokines.

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Executive summary

- Antiphospholipid syndrome is a treatable cause of miscarriages and of recurrent spontaneous pre-embryonic and embryonic abortions.
- Three groups of management can be used for antiphospholipid syndrome.
- Low doses of aspirin and low-molecular-weight heparins are recommended for treatment of this disorder.
- Tight control and an interdisciplinary approach during treatment of these patients is mandatory.
- Inflammatory autoimmune mechanisms in the pathophysiology of obstetric antiphospholipid syndrome should be considered during individual treatment scheme selection.

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