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Review

Obstetric antiphospholipid syndrome

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ABSTRACT

Antiphospholipid syndrome (APS) in pregnancy has a serious impact on maternal and fetal morbidity. It causes recurrent pregnancy miscarriage and it is associated with other adverse obstetric findings like preterm delivery, intrauterine growth restriction, preeclampsia, HELLP syndrome and others. The 2006 revised criteria, which is still valid, is used for APS classification. Epidemiology of obstetric APS varies from one population group to another largely due to different inclusion criteria and lack of standardization of antibody detection methods. Treatment is still controversial. This topic should include a multidisciplinary team and should be individualized. Success here is based on strict control and monitoring throughout pregnancy and even in the preconception and postpartum periods. Further research in this field and unification of criteria are required to yield better therapeutic strategies in the future.

Contents

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1. Introduction

The relationship between pregnancy loss and antiphospholipid (aPL) antibodies has been formally recognized for over 20 years. Today, the fact that the APS or systemic autoimmune thrombotic syndrome is a treatable cause of recurrent pregnancy miscarriage (embrionary and fetal loss) is accepted [1].

APS prevalence during pregnancy varies according to the study population and criteria for measuring aPL antibodies. Antiphospholipid antibodies can be found in women with normal pregnancies, but the prevalence is low. Lupus anticoagulant (LA) has been found in 0.2% of the women with normal pregnancies and anticardiolipin antibodies (aCL) in 2% [2].

There are different pathogenic mechanisms that 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. For example, the role of β2 glycoprotein 1 (β2GP1) as a cofactor in APS pathogenesis is known, but the involvement of this protein in pregnancy loss is not clear. The role of some infections in developing obstetric APS is described.

Obstetric morbidity is one of the major manifestations of APS. However, there is a wide variety of related clinical manifestations. Treatment of obstetric APS is still controversial as there is no consensus yet. This disease is still relatively unknown. It is expected that the unification of criteria and subsequent studies will succeed in clarifying the gaps and identifying new effective alternatives for the treatment and monitoring of these patients.

2. Epidemiology

Sporadic pregnancy loss is common and not always recognized by the women involved. It is estimated that almost 50% of all conceptions fail. Of recognized pregnancies, about 10 to 12% end in spontaneous abortion and most of these cases (≥80%) are pre-embryonic or embryonic losses [1].

Between 7 and 25% of unexplained recurrent miscarriages are due to the presence of aPL antibodies. In women with pregnancy loss, the prevalence of aPL antibodies varies widely. It is calculated to be between 4.6% and 50.7% (average of 15.5%). The prevalence of LA varies between 0 and 14% (average of 8.3%). However, in women with fetal loss after week 20, the prevalence becomes 30% [2]. Differences in these findings can be explained by a diversity of study groups, different inclusion criteria and lack of standardization in the aPL antibodies detection methods.

Cervera et al. [3], from the Euro-Phospholipid Project cohort, in which the clinical characteristics of 1000 patients with APS were analyzed, showed that in 590 pregnant women the prevalence of preeclampsia, eclampsia, abruptio placentae and postpartum cardiopulmonary syndrome were 9.5%, 4.4%, 2.0% and 0.5% respectively. Likewise, in this study, which included 1580 pregnancies, the prevalence of early fetal loss (<10 weeks) and late fetal loss (≥10 weeks) was found to be 35.4% and 16.9% respectively while the number of live births was 47.67% and ratio of premature births/live births was 10.6%. It should be stressed that 74% of the women in the cohort who became pregnant succeeded in having one or more live births, probably due to a better understanding of the disease, closer monitoring and the use of antiplatelet and anticoagulant therapies.

Another study done on this cohort [4], showed that the most common fetal complications were early fetal loss (17.1% of pregnancies), late fetal loss (6.7% of pregnancies), premature birth (35% of live births) and intrauterine growth restriction (13.7% of live births).

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 with preeclampsia/eclampsia, an incidence of 10 to 12% has been reported. However, the real prevalence of HELLP in obstetric APS has been difficult to estimate [5,6]. Catastrophic APS is an aggressive form of this disease. Almost 6% of this APS variant occurs during pregnancy or puerperium [7].

3. Classification and criteria of pregnancy loss in APS

In 1999, the first preliminary criteria for classification of APS was developed in Sapporo (Japan) [8]. These criteria resulted from the Eighth International Symposium on Antiphospholipid Antibodies and are commonly recognized as “Sapporo criteria for APS”. In 2006, these criteria were updated in Sydney (Australia) for the Eleventh International Congress of Antiphospholipid Antibodies. Currently, these criteria remain valid and include following obstetric morbidity [9]: unexplained deaths of normal fetus at or beyond the 10th week of gestation, unexplained consecutive spontaneous abortions before the 10th week of gestation and premature births (before the 34th week of gestation) because of eclampsia or severe preeclampsia, or placental insufficiency (Table 1).

The above criteria have helped to guide physicians in making decisions, but there are several aspects of obstetrics APS that will have to be revised to improve the treatment for these patients [10].

4. Pathogenic mechanisms of pregnancy loss associated with antiphospholipid antibodies

Experiments with APS murine models have shown a direct causal relationship between aPL antibodies and pregnancy loss. Inoculation of normal rats with serum from women with high titers of aPL antibodies causes resorption of pregnancy in the early stages [11] and the active immunization with pathogenic monoclonal aCL induces clinical signs of APS in BALB/c rats [12]. This shows that the serum from women with APS is highly pathogenic for rat embryos, effects that have been shown both in pre-embryo cultures and embryonic growth during gestation. However, the serum may have multiple components and require purification to establish the true causal factors. Purification of the immunoglobulin G (IgG) in the serum of women with APS which was then injected into pregnant rats successfully demonstrated a direct effect on the yolk sac and the embryo in that it reduced growth [13].

It is well known that aPL antibodies require a cofactor like beta 2-glycoprotein 1 (β2GP1). β2GP1 is a highly glycosylated glycoprotein with five sushi domains, which interact with membrane phospholipids through their lysine-rich V domain. The binding of aPL antibodies with β2GP1 forms a divalent complex that increases its affinity for membrane phospholipids [14]. The functional role of β2GP1 has not yet been elucidated, but it is known that a deficiency of this glycoprotein does not appear to be associated with the disease. The binding of aPL antibodies-β2GP1 complex to cell membranes, including the trophoblast, causes damage and activation of cytokines such as IL-3, which is involved in the process of embryo implantation [15].

Experimental models using active immunization of normal rats with i) human β2GP1, ii) representative synthetic peptides from the β2GP1 phospholipid binding site and iii) synthetic peptides that are microbial in origin and share sequence and functional properties with the β2GP1 phospholipid binding site induced high titers of aPL antibodies, which can cause miscarriages in some strains of mice [16–18]. However, these experiments, which indicate that aPL antibodies are a cause of miscarriages, do not explain the mechanisms by which such losses occur.

Table 1
2006 classification criteria for APS [a].

Clinical criteria
Vascular thrombosis
One or more clinical episodes of
a) Arterial thrombosis[b]
b) Venous thrombosis[b]
c) Small vessel thrombosis[b]
Pregnancy morbidity
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).
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 (abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive, non-stress test, suggestive of fetal hypoxemia, abnormal doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, oligohydramnios or a postnatal birth weight less than the 10th percentile for the gestational age).
c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
a) A minimum of two positive tests for LA present in plasma at least 12 weeks apart.[c]
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 least 12 weeks apart.[d]
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.[d]

[a] APS is present if at least one of the clinical criteria and one of the laboratory criteria are met.
[b] Thrombosis must be confirmed by objective validated criteria.
[c] Detected according the guidelines of the International society on Thrombosis and Haemostasis.
[d] Measured by the standardized Enzyme-Linked Immunosorbent Assay (ELISA).

It is believed that the pathological effects of aPL antibodies are mediated by three mechanisms: thrombosis, interference with the prostacyclin/thromboxane balance, and the alteration of adhesion molecules between the components of the trophoblast [19].

The hypercoagulable state induced by aPL antibodies produces placental infarction and thrombosis, and vasculopathy of the spiral arteries. These lead to uteroplacental insufficiency which, in turn, results in intrauterine growth restriction, signs of hypoxia (abnormal fetal heart rate), oligohydramnios, fetal distress, preterm delivery or miscarriages.

Vasculopathy of the spiral arteries in the placenta decreases the normal flow of maternal blood to intravillous space which creates difficulties in the exchange of gases and nutrients with the fetus. This uteroplacental insufficiency may lead to, depending on its severity, fetal growth restriction and, in the worst cases, fetal loss.

In order to differentiate between the placental pathology of APS and the lupus placental features, Magid et al. [20], analyzed 40 placentas. Study findings were characteristic of hypoxia–ischemia, decidual vasculopathy, thrombosis, chronic villitis and lower placental weight. Large areas of infarction that correlated with the presence of fetal anomalies were found in placentas with APS.

With standard pathological staining, the APS placentas cannot be differentiated from the placentas with toxemia. However, the distribution of laminin and collagen IV is higher in the APS placentas but not in patients with toxemia without APS. One possible explanation is the existence of higher regenerative activity in placental tissue in cases of APS [21].

There are different hypotheses about the mechanisms by which aPL antibodies cause a hypercoagulable state. The most accepted are:

a) Antiphospholipid antibodies can alter eicosanoid balance by reducing the endothelial cell production of prostacyclin and raising thromboxane production (potent vasoconstrictor that increases platelet aggregation) [22,23].
b) There is cross reactivity between aPL antibodies and glycosaminoglycans, a family of heparin-like substances involved in non-thrombotic properties of vascular endothelium. The inhibition of the function of glycosaminoglycans by aPL antibodies may partly explain the thrombosis occurring in patients [24].
c) Antiphospholipid antibodies can induce a procoagulant effect by inhibiting the activation of the phospholipid-dependent C–S protein pathway [25].
d) The reduction of annexin-V (placental anticoagulant protein), which is produced by the competition between it and aPL antibodies to bind to phospholipids, can lead to a placental hypercoagulable state [26].

Currently, in addition to the prothrombotic mechanisms described, there is debate about the possibility of direct harm caused by the aPL antibodies in the trophoblast that is non-prothrombotic [27]. The implantation of the embryo into the endometrium is a dynamic process in which a series of events closely involving the trophoblast and decidua develops. Any alteration in the functional state of the trophoblast may cause implantation failure.

There is evidence in experimental models of APS, suggesting that aPL antibodies may act directly on the trophoblast thus altering its differentiation and maturation and causing direct cellular damage, apoptosis, inhibition of syncytium formation, decreased human chorionic gonadotropin (hCG) and disrupting implantation [28,29].

β2GP1 is one of the major antigenic targets for aPL antibodies. Its presence on the trophoblastic membrane explains the tropism of aPL antibodies for the placenta. These findings help us understand why, after pregnant rats receive a passive innoculation of aPL antibodies, these antibodies disappear from peripheral circulation and accumulate in placental tissue [1,2]. These studies suggest that aPL antibodies can directly affect trophoblast function thus causing changes in the implantation without necessarily causing thrombotic events.

Infection has been proposed as another mechanism that could lead to APS. In experimental models in mice, immunization with *Haemophilus influenzae*, *Neisseria gonorrhoeae* or tetanus toxin leads to the development of antibodies against β2GP1 [30]. The inoculation of pregnant rats with these antibodies results in clinical findings of APS, including thrombocytopenia, prolonged activated partial thromboplastin time (aPTT) and increased miscarriages. In humans, infection with varicella has also been associated with APS [31]. The most associated infections with APS include parvovirus B19, cytomegalovirus (CMV), varicella-zoster virus, human immunodeficiency virus (HIV), *Streptococcus*, *Staphylococcus*, gram-negative bacterias, and *Mycoplasma pneumoniae* [32].

The possibility of a genetic predisposition to APS has also been proposed due to the evidence from the large family and population studies in which it was found that several family members could be positive for LA and aCL with or without clinical evidence of APS. This familial tendency could be genetically determined. Positive associations between aPL antibodies and human leukocyte antigens (HLA) DR and DQ have been described. Moreover, a polymorphism in the gene encoding the β2GP1, which determines an exchange of a valine for a leucine in the mature protein, has been studied as a possible genetic risk factor for β2GP1 antibodies and APS [33].

The role of complement has also been the subject of study. Increases in the deposits of C4d and complement factors C3b in placentas of patients with APS have been found compared with

normal controls and correlated with histopathological findings such as deciduitis, decidual necrosis, villous infarction, decidual vasculopathy, retroplacental hematomas [34]. Using murine models of induced APS, it has been reported that complement activation is essential for pregnancy loss and intrauterine growth restriction [35].

Mechanisms of pregnancy loss in APS are heterogeneous, complex and not yet fully explained. Future studies should seek out other mechanisms, for example, the role of complement system components such as C5a, other antigenic targets (β2GP1 peptides) and genetic predisposition, which will help us better understand the pathological processes of this syndrome [36,37]. Currently, the fact that aPL antibodies are associated with fetal growth restriction and fetal distress, both of which trigger prematurity and fetal death, is accepted. These complications are caused by uteroplacental insufficiency subsequent to multiple infarction and vascular thrombosis of spiral arteries. The main targets are platelets, endothelial cells, anticoagulant proteins and fibrinolytic pathways [38]. We summarize pathogenic mechanisms of pregnancy loss associated with aPL antibodies in Fig. 1.

5. Clinical findings

The clinical manifestations of APS are numerous and have a very broad spectrum thus affecting everything from the pregnancy alone to association with other autoimmune phenomena. The ones that are most commonly found are [3], in order of frequency: deep vein thrombosis (31.7%), thrombocytopenia (21.9%), livedoreticularis (20.4%), cerebrovascular accident (13.1%), superficial thrombophlebitis (9.1%), pulmonary embolism (9.0%) and fetal loss (9.0%). Transient ischemic attack (7.0%), hemolytic anemia (6.6%), skin ulcers (3.9%), epilepsy (3.4%), myocardial infarction (2.6%), amaurosis fugax (2.8%) and digital necrosis (1.9%) are found more rarely. The prevalence of obstetric findings of APS has been reviewed previously. Several of the systemic findings of the syndrome can be explained by vascular disease and occlusion of small vessels due to platelet aggregation.

In pregnancy, aPL antibodies have been implicated as the cause of intrauterine growth restriction, preeclampsia, preterm delivery and fetal death as well as pregnancy loss in any period and placental alteration in the third period. Each of these events may or may not include thrombocytopenia. Usually there is a small placenta with histopathological evidence of vascular abnormalities.

Recently, APS has been reported to be a cause of preclinical pregnancy loss and, therefore, associated with infertility. Although the classic works of Lyden et al., which showed the effect of aPL antibodies in trophoblast development, support the concept of a partnership between aPL antibodies and infertility, not all studies have confirmed this association [39].

Many of the pregnancy losses caused by APS occur after the first trimester of pregnancy; therefore, it is possible to identify fetal cardiac activity in 86% of the spontaneous abortions in women with APS,

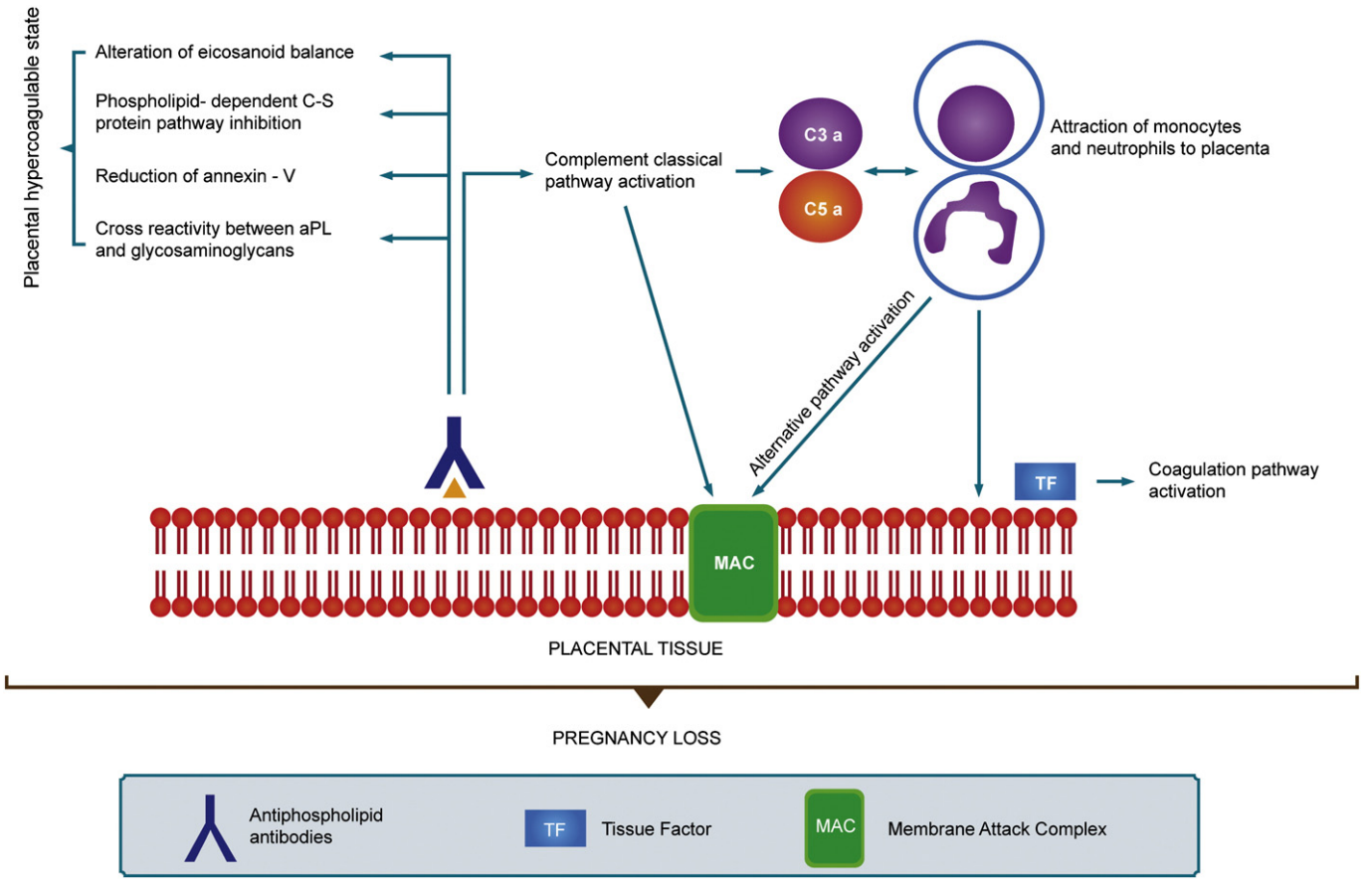

Fig. 1. Pathogenic mechanisms of pregnancy loss associated with aPL antibodies. aPL antibodies can produce i) eicosanoid disbalance (increasing platelet aggregation), ii) phospholipid-dependent C–S protein pathway inhibition, iii) cross reactivity with glycosaminoglycans, and iv) reduction of annexin-V. These findings lead to a placental hypercoagulable state. Likewise, aPL antibodies can activate the complement through the classical pathway, generating C3a and C5a which attract monocytes and neutrophils to placenta. These inflammatory cells promote complement alternative pathway. Membrane attack complex (MAC) results in expression of Tissue Factor (TF), which leads to coagulation pathway activation. These mechanisms lead to placental tissue damage, thrombosis and, consequently, pregnancy loss.

but fetocardia can only be identified in 43% of the spontaneous abortions in women without APS.

Placental detachment diagnosed by ultrasound and associated with the presence of aPL antibodies could be a sign of obstetric APS. (Galarza-Maldonado C unpublished observation).

6. Laboratory findings

The presence of aPL antibodies can be detected by coagulometric (LA) or solid phase immune tests (aCL). Reaginic techniques are no longer used because of their low sensitivity. It should be noted that aPL antibodies are only detected in many patients through one of these techniques. This is due to the heterogeneity of these antibodies, which are directed against different phospholipid epitopes.

6.1. Lupus anticoagulant (LA)

LA gets its name from the fact that it was initially identified in patients with systemic lupus erythematosus. It is a heterogeneous population of immunoglobulins, mainly IgG, IgM and IgA isotypes, with anticoagulant activity directed mainly towards β2GP1 and prothrombin. The determination of LA is functional and based on its interference effect when prolonging phospholipid-dependent coagulation tests, especially activated partial thromboplastin time (aPTT), the kaolin clotting time (KCT), the tissue thromboplastin time (PTT), diluted prothrombin time (dPT) and dilute Russell's viper venom time (dRVVT). The determination of LA has higher specificity but lower sensitivity than the determination of aCL has for diagnosing APS although most patients are positive for both. The presence of LA is considered the most important risk factor for thrombotic events, especially arterial ones, in patients with APS [40].

6.2. Anticardiolipin antibodies (aCL)

Anticardiolipin antibodies belong, like the LA, to different isotypes of IgG, IgM and IgA. Cardiolipin (diphosphatidylglycerol) is an antigenic complex consisting of mainly phospholipids found in the mitochondrial membrane. Its determination is made by ELISA that allows identification of the isotype and quantification of the titles. For aCL to bind to its antigen, the presence of a plasma cofactor, the β2GP1, is necessary. Consequently, there are β2GP1-dependent aCL, which are associated with thrombotic processes, and β2GP1-non-dependent aCL, which are mainly identified over the course of various infections and have no relationship with the clinical manifestations of the syndrome (IgG isotype of the aCL best correlates with thrombotic events) [41].

6.3. Anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies

Anti-β2GP1 are low affinity antibodies that recognize this protein in the presence of anionic phospholipids or of an oxidized surface such as the plastic ELISA plates that have been subjected to irradiation. Several studies have established that of the different isotypes of anti-β2GP1 antibodies, IgG is the one that best correlates with the presence of LA and the major APS events. Its detection can be useful in the cases of patients with clinical manifestations of APS in which the determinations of aCL and LA have been repeatedly negative. The anti-β2GP1 are more specific and have greater positive, predictive value than do aCL for APS. However, the anti-β2GP1 are not considered a thrombotic risk factor apart from aCL.

6.4. Antiprothrombin antibodies

Another group of autoantibodies with LA activity are antiprothrombin antibodies that are found in one third of the patients with APS. ELISA plates that have been irradiated previously, which increases their affinity, are used to detect them. Their presence has been associated with thrombotic events in different studies, but due to the fact that prothrombotic mechanisms are multifactorial and are not fully explained, research on the clinical utility of these antibodies is still developing. Currently, their determination is not recommended in clinical practice.

6.5. Other autoantibodies

Other autoantibodies against negatively charged phospholipids such as phosphatidylserine, phosphatidylinositol and phosphatidic acid or neutral ones, for example, phosphatidylethanolamine have been detected. However, their usefulness in clinical practice seems to be limited to those patients who have clinical manifestations of APS but who were serologically negative on several occasions. In patients with APS, other autoantibodies such as anti-annexin V antibodies, anti-C protein antibodies, anti-S protein antibodies, anti-thrombomodulin antibodies, anti-oxidized LDL antibodies(which may be related to the formation of atherosclerotic plaques) antiplatelet antibodies, anti-erythrocyte antibodies, anti-endothelial cell antibodies, antinuclear antibodies (ANA) and anti-mitochondrial antibodies have also been found [42].

Although there are new and more specific tests, the aCL and the LA are still ideal for diagnosing APS. More recent evidences, such as anti-β2GP1 antibodies and the APhL ELISA Kit (Louisville APL Diagnostics) use different antibodies and may provide a more specific diagnosis (and perhaps, a more reliable one) of APS while retaining a sensitivity that goes from good to excellent [43].

7. Treatment

Treatment of obstetrical APS should include a multidisciplinary team of specialists such as Rheumatologists, Gynecologists and Internists who have experience in this field. The treatment's success is based on not only the drug intervention, but also strict control and monitoring throughout the entire pregnancy and even in the preconceptional period and puerperium.

The pharmacological management of obstetric APS is still controversial and, therefore, needs to be individualized for each patient because multiple studies have not yet provided solid evidence that would allow us to establish rigorous treatment protocols. Similarly, the existence of clinical subgroups of obstetric APS makes the use of strict drug therapies difficult.

However, for practical purposes we may divide the obstetric APS patients into 3 different groups that we describe below (Table 2).

7.1. Group 1 (aPL positive patients with no history of pregnancy loss or thrombosis and with or without concomitant autoimmune disease)

This group consists of patients in whom, for whatever reason, the presence of aPL antibodies were detected in the serum. These patients have a legitimate concern because of the presence of antibodies and how these might affect a future pregnancy. In the case of these women, strict control of their pregnancies or the administration of low doses of aspirin may be the appropriate strategy.

7.2. Group 2 (patients with a history of two or more miscarriages and the presence of positive aPL)

Regarding this group of patients, in which obstetric APS has been previously diagnosed, it is very important to talk to them in detail about the risk to their pregnancies that the presence of these antibodies implies and the different therapies that could be used for treatment. The active participation of the patient in deciding the strategy in her particular case is essential. The patient should know

Table 2
Treatment groups in Obstetric APS.

Features		
Group 1 aPL positive No history of pregnancy loss No history of thrombosis Yes/no concomitant autoimmune disease	Group 2 aPL positive History of two or more miscarriages	Group 3 Obstetric APS secondary to SLE or other autoimmune diseases with or without history of thrombosis
Treatment		
Group 1 Education Low doses of aspirin may be prescribed Strict control	Group 2 Education Plan A. • Aspirin 81–100 mg before conception and then throughout pregnancy Plan B. • Aspirin 81–100 mg before conception and then aspirin 81–100 mg + LMWH throughout pregnancy	Group 3 Education Individual management strategy (e.g. glucocorticoids for SLE flares) Daily administration of LMWH plus low-dose aspirin Warfarin discontinued before 6th week of pregnancy

the risks and benefits of treatment and the importance of adherence to it.

The guidelines that can be proposed to these patients are: i) aspirin (81–100 mg) before conception and then throughout pregnancy and the first 4 postpartum weeks [44] and ii) the administration of low molecular weight heparin (LMWH) plus low-dose aspirin which is the most widely accepted plan for this group of patients [45–47]. With respect to the first plan, explain to the patient that the chance of success is high, the side effects are minimal and the cost, low. If plan A 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.

7.3 Group 3 (patients with obstetric APS secondary to systemic lupus erythematosus or other autoimmune diseases with or without history of thrombosis)

The third group includes patients with APS associated with systemic lupus erythematosus (SLE) or other autoimmune diseases and/or prior history of thrombosis. In this group, individual management strategy is essential. In patients who are using warfarin for previous thrombosis, the administration should be discontinued before the 6th week of pregnancy. The risk of teratogenicity due to warfarin is highest between weeks 6 and 12 of pregnancy [48]. Fluorinated glucocorticoids (beta and dexamethasone) are used only if there is a risk of premature delivery and non-fluorinated ones (prednisone and prednisolone) are used for non-obstetric reasons, for example, lupus flares or thrombocytopenia [49]. The plan for the prevention of pregnancy loss in this group of patients is low-dose aspirin combined with daily administration of LMWH. Unfractionated heparin can also be used. This has to be injected twice daily and a dose should be given that is sufficient to increase the ratio of the patient's baseline PTT between 1.5 and 2.0 times.

Doses of LMWH are described below [50]:

a) Unfractionated heparin
   - Mini-dose: 5000 units subcutaneously every 12 h.
   - Moderate-dose: subcutaneously every 12 h adjusted to target an anti-factor Xa level of 0.1–0.3 units/ml.
   - Adjusted-dose: subcutaneously every 12 h to target a mid-interval APTT (or, if LA is present, an anti-factor Xa level) into the therapeutic range.

b) LMWH
   - Prophylactic-dose: dalteparin, 2500 or 5000 UI/24 h; or enoxaparin 40 mg/24 h; or nadroparin 2850 UI/24 h; or any once-daily LMWH adjusted to target a peak anti-factor Xa level of 0.2–0.6 units/ml.
   - Adjusted-dose: weight-adjusted, full treatment doses of dalteparin, 200 UI/kg subcutaneously in 1 or 2 injections; OR enoxaparin 1 mg/kg subcutaneously every 12 h or 1.5 mg/kg subcutaneously every 24 h; or nadroparin, 171 UI/kg subcutaneously in 1 or 2 injections.

Mini- or moderate-dose unfractionated heparin or prophylactic-dose LMWH can be used in patients that meet the criteria for obstetric APS or patients with previous thrombotic events in presence of aPL antibodies without long-term use of oral anticoagulation. Adjusted-dose unfractionated heparin or prophylactic- or adjusted-dose LMWH can be used in patients with previous thrombotic event and with long-term oral anticoagulation.

In all patients, ultrasound is important for fetal growth monitoring and the state of the uteroplacental circulation. This will help the physicians to make 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 [51]. As of the 30th week, ultrasound studies can be done more frequently, depending on the progress of the pregnancy and the medical team approach.

Despite treatment, pregnancy loss may occur in 20–30% of cases [52]. The use of glucocorticoids should be avoided in these cases [53]. The ideal treatment for obstetric APS that does not respond to heparin plus aspirin is still unknown. Intravenous immunoglobulin is reserved for these cases and is used in combination with anticoagulant doses of heparin with two subcutaneous injections per day and low-dose aspirin. Warfarin was used in some centers during weeks 14 and 34 for patients with a history of stroke or significant arterial thrombosis [54].

Studies in mice have shown tumor necrosis factor alpha (TNF α) to be a potential target in the treatment of obstetric APS [55].

8. Controversies

In January 2010 the task force for obstetric APS was established for report to the 13th International Congress on antiphospholipid antibodies. The group identified 5 areas in obstetric APS that were controversial or uncertain: early, recurrent spontaneous abortion, stillbirth, birth <34th week for severe preeclampsia or placental insufficiency, postpartum and implications, and long-term care [8].

As regards recurrent, early spontaneous abortions, the discussion is open because we still do not understand their relationship to current laboratory criteria and other antibodies. Future recommendations are made for several critical factors: specific diagnostic markers, their methodology and reference laboratory; a requirement to repeat the test and assign cutoffs; a choice of signs and symptoms for diagnosis of both APS and recurrent, early spontaneous abortion with their definitions and inclusion/exclusion criteria. Regarding the treatment, they concluded that any study with respect to this needs to be large,

multicenter, randomized and must have clear definitions as a first step to building a consensus.

In terms of fetal death, it is proposed that a study population of women with miscarriages between weeks 10 and 19 would be more accessible to treatment, given the emotional nature of the loss ≥ week 20 and taking into account the fact that there is very little information on this group of pregnant women.

With regard to preeclampsia before the 34th week, the working group found that the relationship between aPL antibodies and severe preeclampsia before week 34 is poorly defined and most studies are flawed because they do not include repetition of diagnostic tests. Studies are needed to improve the designs.

With respect to postpartum care, thromboprophylaxis duration was discussed. There is no consensus on this issue and the evidence as well as the use of devices for sequential compression or compression stockings is limited. The field is open to investigation.

The recommendation to not use low-dose aspirin with warfarin for long-term treatment as well as to follow a healthy lifestyle does not seem controversial although the effectiveness is unknown. Avoiding the use of prothrombotic agents such as oral anticoagulants is also accepted. However, some members felt that the benefit of using these agents in patients with full anticoagulation outweighs the prothrombotic risk.

9. Conclusions

APS is a disease with a wide epidemiological, pathogenic and clinical spectrum. Therefore, treatment is not easy. Currently, there are controversial points in some areas, especially diagnostic tests and treatment options for obstetric APS.

Three groups of treatment have been identified. However, each patient should be given individualized care based on their clinical and immunological status.

Further research on pathogenic mechanisms, new autoantibodies and therapeutical options will give us a better understanding of obstetric APS and will enable us to develop effective treatments for these patients.

Take-home messages

- Obstetric APS has multiple pathogenic pathways some of which are not fully elucidated.
- 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 and probably placental detachment.
- Treatment is still controversial. Further research and criteria unification are necessary for consensus in obstetric APS.

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Histone epigenetic alterations in systemic lupus erythematosus could be reversed by specific modifying agents

It is well established that the pathogenesis of systemic lupus erythematosus (SLE) is complex and multifactorial, with both genetic polymorphisms and environmental factors concurring to the disease development and progression. Recently, alterations in epigenetic mechanisms involved in the regulation of gene expression have been reported in SLE and could be a promising target for therapeutic interventions. Epigenetics determines heritable changes in cell phenotype that are not caused by mutations in DNA sequence. The main epigenetic modifications are DNA methylation and histone acetylation, both of which are altered in SLE. They are crucial in determining differentiation of many cell types, including both B and T cell lineages. The epigenetic face of SLE has been discovered by studying monozygotic twins discordant for the disease, and recent studies on human and murine lupus provided evidence that histone deacetylase (HDAC) proteins are upregulated in SLE. Aberrant histone deacetylation can alter cell phenotype differentiation by causing either polygenic or single-gene silencing.
In the present review, Reilly *et al.* (**Mol Med 2011;17:417-25**) focused on histone acetylation status in SLE and on therapeutic challenges targeting histone epigenetic alterations. In particular, class- specific HDAC inhibitors act as potent anti-inflammatory and immunomodulatory agents and are effective in reversing site-specific histone hypoacetylation status in both in vitro and in vivo experiments on animal models, with a significant improvement of disease phenotype. However, further studies and clinical trials are mandatory to establish their efficacy and safety in humans.