Chapter

Obstetric Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is characterized by thrombotic events and obstetric complications in the presence of persistently positive antiphospholipid antibodies. Obstetric manifestations include, recurrent miscarriages, fetal death at or beyond the 10th week of gestation, and premature birth due to pre-eclampsia/placental insufficiency. Even now, both clinical features and laboratory parameters are controversial. Both can be used to stratify women with APS in terms of risk of adverse pregnancy outcome, and thus adjust treatment. APS pregnancies should be classified into low, medium and high-risk classes based on clinical and laboratory features. Depending on the risk class, the most appropriate therapy must be then selected. Heparin plus LDA is considered the standard of care for patients with a confirmed diagnosis of obstetric APS and generally results in over 70–80% successful pregnancies. The 20–30% pregnancies in which treatment fails are defined as "high-risk" or "refractory" pregnancies. Numerous treatments have been used in addition to standard of care, to treat these patients, but no well-designed trial has yet been conducted. New insights into the etiopathogenetic mechanisms of obstetric APS have led to the testing of new therapeutic approaches, that may soon change the way we manage this condition.

Keywords: fetal death, obstetric antiphospholipid syndrome, antiphospholipid antibodies, pregnancy, therapy

1. Introduction

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disease characterized by thrombotic events and obstetric complications in the presence of persistently positive antiphospholipid antibodies (aPLs) [1]. The condition may occur alone, that is primary APS, or in association with other autoimmune diseases, most commonly systemic lupus erythematosus (SLE), and is then referred to as secondary APS. The classification criteria (**Table 1**), developed in 1999 [2] and revised in 2006 [1] include clinical features consisting of thrombosis and/or obstetric morbidity in the presence of laboratory criteria such as lupus anticoagulant (LA), medium-high titer IgG/IgM anticardiolipin antibodies (aCL) and/or anti-β2 glycoprotein I (anti-β2GPI). They are often used, also, as diagnostic tools. Obstetric APS (OAPS) subsets are featured by recurrent early miscarriages, fetal death at or beyond 10 weeks of gestation, and early delivery due to severe preeclampsia or placental insufficiency [3, 4]. The first associations between recurrent pregnancy loss and a circulating anticoagulant later known as LA, date back to 1975 [5], but it was not until 1984 Hughes linked the presence of aCL with recurrent miscarriages

defining APS [6]. Nowadays, OAPS is considered one of the few treatable causes of recurrent loss and represents an important health burden for women of childbearing age and a challenge for the physicians [7]. Management of OAPS is challenging for the physician, as individual women with APS do not have the same obstetric risk profile. In the last decade, the importance to stratifying them based on their laboratory and clinical features has been emphasized to quantify the risk of adverse pregnancy outcome. Many efforts have also been made to adjust therapy according to risk stratification [8]. Moreover, new insights into the pathogenesis and clinical understanding of APS have led to potential new therapeutic approaches [9, 10].

This chapter aims to clarify aspects of pathogenesis, clinical features, risk stratification and therapeutic strategies in OAPS.

2. Antiphospholipid antibodies

The aPLs are a heterogeneous group of autoantibodies that bind primarily to circulating plasma proteins such as β2GPI, prothrombin, and others when bound to phospholipids themselves. The prevalence of aPL is about 1–5% in the general population and increase up to 40% in patients with pregnancy complications [11–14].

2.1 Criteria antiphospholipid antibodies

Currently, there are three types of aPLs, depending on the detection method, which are included in the laboratory classification criteria for APS (**Table 1**).

Clinical criteria
• *Vascular thrombosis*
One or more clinical episodes of arterial, venous or small vessels thrombosis in any organ or tissue
Thrombosis must be confirmed by appropriate imaging studies or histopathology
Thrombosis on histopathology specimen must be present without inflammation of vessel wall
• *Obstetric morbidity*
One or more unexplained fetal death of a morphologically normal fetus at or beyond 10th week of gestation
One or more premature birth of a morphologically normal neonate before 34th week of gestation due to placental insufficiency and/or eclampsia or severe pre-eclampsia
Three or more consecutive early miscarriages before 10th week of gestations; with maternal and paternal factors such as anatomical, hormonal and chromosomal abnormalities should be ruled out
Laboratory criteria
Medium to high levels of aPLs antibodies detected on two or more occasions, at least 12 weeks apart
• Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Hemostasis
• Anti-cardiolipin antibodies (IgG and/or IgM) at medium-high levels (>40 units or above the 99th percentile)
• Anti-B2-glycoprotein I antibodies IgG and/or IgM at medium-high levels (>40 units or above the 99th percentile)
aPLs: antiphospholipid antibodies, IgG: immunoglobulin G, IgM: immunoglobulin M.

Table 1.
Clinical and laboratory criteria of definite antiphospholipid syndrome. APS is diagnosed when at least one of the following clinical criteria and one of the following laboratory criteria are met.

2.1.1 Lupus anticoagulant

LA are heterogenous antibodies detected with a functional test that measures the ability of aPL to prolong phospholipid-dependent clotting reactions. Anti-β2GPI [15] and anti-prothombin (aPT) antibodies [16] have been identified as the main mediators of this reaction. LA detection is very challenging, as it has many pitfalls leading to either false positive or false negative results. The International Society for Thrombosis and Hemostasis (ISTH) guidelines released in 2009, updated in 2018 provided a step toward standardization of LA [17, 18]. Following those guidelines LA detection is based on the simultaneously use of two assays with different principles following a multi-step procedure, with screening, mixing and confirmation steps. The most commonly used are activated partial thromboplastin time followed by the diluted Russell's viper venom test. The presence of LA should always be confirmed by performing the assays in the presence of excess of phospholipids, with a correction of the prolongation of the times as a result.

2.1.2 Anticardiolipin antibodies

aCL are heterogeneous antibodies that in immunoassay's bind to a complex of phospholipids and plasma proteins, mainly β2GPI. In this assay there can be measured two types of aCL, "β2GPI-indipendent" that bind to phospholipids alone and are typically free of clinical significance and "β2GPI-dipendent" which are related to clinical manifestations of APS [19–21].

2.1.3 Anti-β2 glycoprotein antibodies

Anti-β2GPI antibodies are specific to the β2GPI, a cofactor with affinity for anionic phospholipids which inhibits in vitro the activation of prothrombin and the ADP-dependent platelet aggregation [22].

Both aCL and anti-β2GPI antibodies of IgM and IgG isotypes are detected by immunological assays following the ISTH subcommittee recommendation [23]. IgG and IgM isotype, at medium-high titer have greater clinical significance [24].

2.2 Non-criteria antiphospholipid antibodies

A series of autoantibodies non included in laboratory classification criteria the so called "non-criteria" aPLs have been reported in the last years related to APS manifestations. Those directed against two major phospholipids-binding protein representing the true antigenic targets for aPL (i.e. prothrombin and β2GPI) have demonstrated the highest significant association with thrombotic and obstetric features of APS [25–27].

2.2.1 Anti-prothrombin antibodies

APT antibodies are detected by ELISA using a purified prothrombin as antigen coated onto irradiated plates [28] or phosphatidylserine/prothrombin complex [29]. Although a correlation between the two assays have been reported, these antibodies differed either in affinity or in epitopes that they recognized [30]. The ones directed against anti-phosphatidylserine/prothrombin complex (aPS/PT) seems having a closer association with APS and LA activity than with antibodies to prothrombin alone [31, 32]. aPS/PT have been reported to be significantly associated with both thrombotic and obstetric manifestations of APS [33–35]. Moreover, since they have

been shown to be closely related to LA, have been proposed as a surrogate test for and as an additional serologic marker of APS, to be performed with other aPL tests to improve diagnosis [36, 37].

2.2.2 Anti-domain I antibodies

A subgroup of anti-β2GPI, those directed to domain I of the molecule [15], have been reported to be strongly associated with thrombosis and LA in APS patients while those directed to domain IV/V are less frequent [25, 26]. Recently has been suggested that the ratio between anti-β2GPI-DI and anti-β2GPI-DIV/V IgG can provide a better profile of anti-β2GPI antibodies linked to APS and antibodies occurring in other pathologic condition [38].

To improve risk prediction of recurrent thrombosis and pregnancy loss the Global Anti-Phospholipid Syndrome Score (GAPSS) was developed, considering the aPL profile, conventional cardiovascular risk factors, and autoimmune antibody profile. Validated in APS and in SLE patients, a high GAPSS score predicted thrombosis better than aPLs alone [39, 40]. Recently, the GAPSS score has been shown to be a useful tool for predicting a higher likelihood of favorable pregnancy outcome in pregnant women treated with conventional therapy [41].

3. Pathogenesis of obstetric antiphospholipid syndrome

The exact etiopathogenetic mechanism liable for obstetric morbidity in APS is not yet known. The aPLs are not only a diagnostic marker but have a key role in determining thrombosis and obstetric complications [42]. In the early stages, during pregnancy, the cytotrophoblastic cells differentiates into two cell types. The villous trophoblast will fuse to form the syncytiotrophoblast, a barrier of protection between the mother and the fetus. While, the extravillous trophoblast will progressively invade and colonize the maternal endometrium [43]. aPLs target the placenta, especially the cytotrophoblastic cells. Trophoblast, synthetize β2GPI, a 70 kDa cationic protein that is normally in a "closed conformation", when free in the plasma of patients. It is composed of five homologous domains of approximately 60 amino acids each. Domains I and V are the two domains positively charged [44]. During normal pregnancy and syncytiotrophoblast formation, anionic phospholipids are externalized at trophoblastic cell surface, leading to the binding of β2GP1 via domain V. This binding offers a potential site of actions for aPL by changing the conformation of the protein from a circular to an open form and exposing domains I–IV to the surface [45, 46]. aPL have been incriminated in alteration of trophoblastic cells via different mechanisms. Pathogenesis of aPL in pregnancy include thrombotic mechanisms, inflammation, apoptosis and immunomodulatory molecules impairments in trophoblast [47].

3.1 Thrombotic mechanisms

The placental infarctions due to aPLs-mediated thrombosis of spiral arteries have been thought to be the main cause of fetal demise [48]. However, thrombosis of placental surface is not a universal feature. Recently, placental infarction has been demonstrated [49], only in one third of the placenta of aPLs-positive women and moreover, similar lesions were also reported in those of aPLs-negative women who had had a miscarriage [50, 51]. According to a review of 34 studies comparing the prevalence of placental features between aPL-positive women and aPLs-negative ones, five lesions, have been identified, as fingerprint of human placental aPLs including: placental

infarction, impaired spiral artery remodeling, decidual inflammation, an increase of syncytial knots and a decrease of vasculo-syncytial membranes [52]. These different features of aPLs placenta fingerprints give rise to thought that pregnancy complications by aPLs are due to different pathologic events mainly non-thrombotic related.

3.2 Non-thrombotic mechanisms

The non-thrombotic mechanism which leads to defective placentation are thought to be the main cause of obstetric manifestations. Especially, aPLs have direct effect on trophoblast viability and syncytialization as well as on trophoblast invasion and alter the production of syncyotrophoblast hormones. Moreover, signs of inflammation within the decidua, such as fibrin deposits, were more represented than thrombosis in histological analysis of placenta from women with APS, suggesting another mechanism in pregnancies affected by aPL [52, 53].

3.2.1 Defective placentation

aPLs affect trophoblast viability by both decreasing their proliferation and promoting their death [49] and by altering their expression of the apoptotic regulators BcL-2 and Bax [54]. Furthermore, aPLs decrease the expression of caspases 3 and 7, suggesting that they are involved in death mechanism of the trophoblast [55]. Moreover, as demonstrated by different studies [49, 56], aPLs are involved in the inhibition of syncytialization, an essential process for the replenishment of the syncytiotrophoblast. It has been speculated that the mechanism by which aPLs inhibit syncytializationis due to the decrease of caspase expression, the activation of which is required for cytotrophoblast fusion [52]. Thus, proliferation of cytotrophoblast is reduced, while death increases. This results in a fewer cytotrofoblasts available to replenish the syncytiotrophoblasts. On the other hand, increased death of the syncytiotrofoblasts, leads to increased production of trophoblast debris and increased denudation of syncytiotrophoblasts and fibrinoid deposition. This process leads to a decrease in de syncytialisation and thus impaired placentation [49].

3.2.2 Trophoblast invasion

Trophoblast invasion, into maternal spiral arteries, is an essential physiologic change that allows the anchoring of placenta to the decidua as well as the transplacental passage of nutrients and wastes between the mother and the fetus. Several studies in vitro [49] have shown that aPLs reduce the ability of extra-villous cytotrophoblast to invade the maternal decidua, so affecting both the anchorage of placenta and the spiral arteries transformation, the latter leading to a reduced blood flow to the placenta. The aPLs are thought to impaire trophoblast invasion by altering the expression of adhesion molecules such as placental growth factor (PIGF), vascular endothelial growth factor (VEGF) and soluble FmS-like kinase I (sFlt-I) as well as cytokines such as interleukin 1β [49, 52, 57]. Altered trophoblast invasion of leads to impaired transplacental passage resulting in pre-eclampsia and intrauterine growth restriction (IUGR). In fact, increased sFlt-I levels in the first trimester have been shown to correlate with later onset pre-eclampsia, suggesting them as predictors of preeclampsia [58].

3.2.3 Inflammation, complement activation, and disruption of annexin shield

A well-known fingerprint of APS placenta histology is inflammation. In addition to increased release of cytokines such as IL-1β as described above, aPLs effect complement activation. Girardi et al. [59] had shown that aPLs increased complement

deposition on the trophoblast surface in vitro. While, murine models of APS demonstrate a crucial role of the complement system in determining pregnancy morbidity [59–61], on the other hand, the placenta of women with APS showed deposition of C4d and C3b [62]. Moreover, data from the PROMISSE study in pregnant SLE and/or APS or aPL positive patients, showed that detection of increased Bb and sC5b-9 levels early in pregnancy was predictive of adverse pregnancy outcome, confirming complement activation as a contributor to pregnancy failure [63]. Complement activation stimulates neutrophils to release tumor necrosis factor-alfa (TNF-α); pregnant mice lacking TNF-α are protected from pregnancy loss induced by injections of aPLs [64].

Last, but not least, aPLs disrupt the binding of annexin V, an anticoagulant protein that crystallizes over phospholipid bilayers blocking their availability for coagulation reactions. This disruption additionally contributes to both thrombosis and miscarriages in the APS [65, 66].

Overall, the pathogenetic mechanisms by which aPLs cause obstetric complications are complex and include both inflammatory and non-inflammatory mechanisms, which are not mutually exclusive and may coincide in time. This could reflect the different characteristics of fetal complications. Adequate invasion of the trophoblast into the maternal decidua remains crucial for a normal-evolving pregnancy. Inadequate invasion of the maternal spiral arteries by the extravillous cytotrophoblast and severe inflammation of the placenta, together with reduced hormone secretion leading to early miscarriages are thought to be the major pathogenic mechanisms of early pregnancy loss in APS patients. While, a lack of transformation of the maternal spiral arteries together with activation of the complement and of the coagulation cascade are responsible for late pregnancy loss and preeclampsia.

4. Clinical manifestations of obstetric APS

Obstetric morbidity of APS is characterized by various pregnancy complications such as recurrent miscarriage, fetal death, and premature birth. These manifestations can occur in the same patient during her childbearing years.

Recurrent early miscarriage (REM) is the most frequent obstetric feature of APS. In the European Registry on Obstetric Antiphospholipid Syndrome REM was observed in almost 54% of women with obstetric APS [67]. On the other hand, aPLs are found in up to 20% of women who experience an early abortion [11]. REM can be caused by various maternal and paternal factors such as anatomical abnormalities, endocrine diseases such as diabetes and thyroiditis, autoimmune diseases, parental chromosomal abnormalities and infectious agents. Therefore, these causes must be systematically excluded specifically in cases where REM is the only clinical manifestation.

In contrast, fetal death and premature birth due to pre-eclampsia and/or placental insufficiency are considered more specific clinical manifestations of APS [3]. Fetal death, in particular the late fetal loss, i.e. beyond 20 weeks of gestation is strongly associated with aPLs [68, 69]. In a population-based study by The Stillbirth Collaborative Research Network in the United States [69], elevated aCL and anti-β2GPI levels were associated with a 3- to 5-fold increased likelihood of stillbirth. Pre-eclampsia, eclampsia, and placental abruption are maternal complications of APS. Preeclampsia occurs in approximately 10–17% of pregnancies with APS, compared to 3–5% of pregnancies without the condition [3, 70]. Preeclampsia in patients with APS is often severe and occurs early in pregnancy [70]. These data were recently confirmed in a case-control study, which found that more than 10% of women who gave birth before 34 weeks' gestation due to pre-eclampsia or

placental insufficiency were positive for aPLs [71]. In a study of 1000 consecutive APS pregnancies, the presence of early pre-eclampsia and early IUGR was found in 181 (18.1%) and 161 (16.1%), respectively, despite treatment [67].

Even when treated with heparin plus low-dose aspirin (LDA), 9–10% of pregnant women with APS develop pre-eclampsia. This highlights the fact that counseling these pregnancies and identifying risk factors are very important to personalize therapy, as will be discussed later.

5. Risk stratification in obstetric antiphospholipid syndrome

The outcome of pregnancy in women with APS depends on their clinical history and aPLs profile. Therefore, women with APS or high levels of aPLs should be counseled before pregnancy to perform risk stratification.

Several risk factors are predictors of poor pregnancy outcome. The presence of triple aPL positivity [72, 73], which refers to IgG/IgM aCL plus IgG/IgM anti-β2GPI plus LA, correlates strongly with vascular thrombosis and pregnancy morbidity. Moreover, the presence of persistent positive LA [74, 75] has been reported as the strongest predictor for either pregnancy loss or recurrent thrombosis. These high-risk aPL profiles (**Table 2**) are associated with an increased risk of pregnancy morbidity such as intrauterine growth restriction and premature birth as well as pre-eclampsia despite appropriate anticoagulant treatment [73, 76–78]. Regarding clinical features, women with aPLs and a history of thrombosis, severe pregnancy complications such as pre-eclampsia, eclampsia, or HELLP syndrome, a concomitant SLE diagnosis, or low complement levels are associated with a higher risk of pregnancy morbidity [78, 79]. On the other hand, there are consistent data showing that a history of pregnancy morbidity alone and a single aPLs positivity for aCL or anti-β2GPI are associated with a higher live birth rate [73].

According to the risk stratification, women with obstetric APS can be divided into three groups (**Figure 1**), namely A-low risk pregnancy, those with obstetric morbidity alone and single or double positivity for aPL, B-medium risk pregnancy, those with prior thrombosis and single or double positivity for aPL, and C-high risk pregnancy, those with prior thrombosis and/or severe pregnancy complications and LA/triple positivity for aPL. This subdivision could guide the therapeutic approach in these patients.

Pregnant women with APS must also be closely monitored during pregnancy to promptly identify signs of placental insufficiency. It has been shown that upgrading therapy at the first signs of placental insufficiency results in a higher birth rate [80].

High-risk aPLs profiles
• Persistent LA positivity (measured according to ISTH guidelines in two or more occasions at least 12 weeks apart)
• Double aPL positivity (any combination of lupus anticoagulant, aCL antibodies or anti-β2 glycoprotein I antibodies)
• Triple aPL positivity (LA + aCL IgG/IgM + anti-β2GPI IgG/IgM
Low-risk aPLs profiles
• Isolated, positive aCL or anti-β2GPI IgG/IgM at low-medium titres, particularly if transiently positive

aPLs: antiphospholipid antibodies, LA: lupus anticoagulant, aCL: anti-cardiolipin antibodies, anti-β2GPI: anti-β2glycoprotein I, IgG: immunoglobulin G, IgM: immunoglobulin M.

Table 2.
Definition of high-risk and low-risk antiphospholipid antibodies profile.

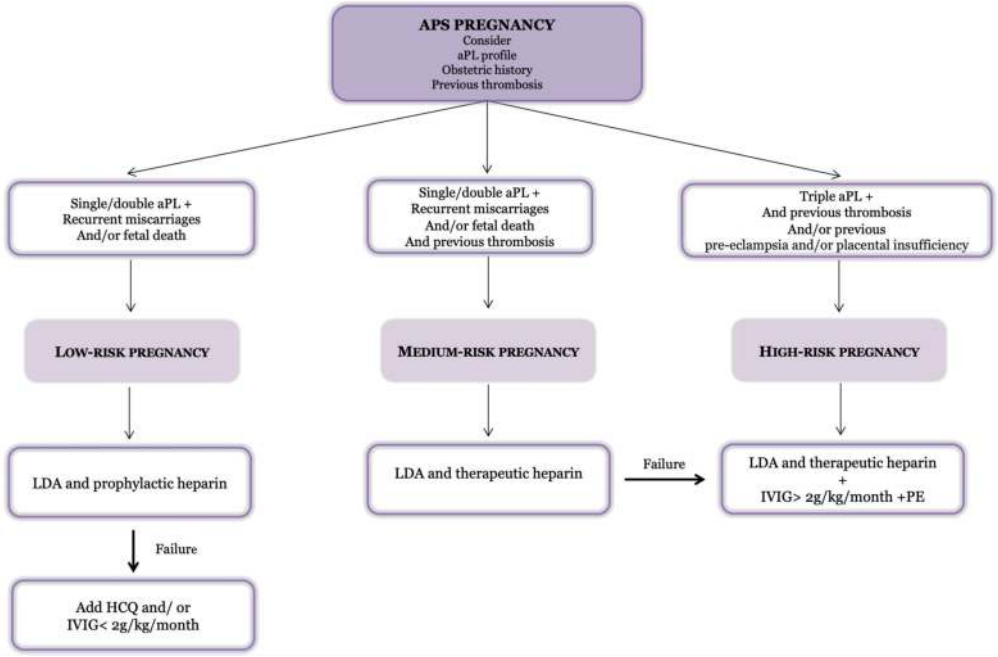

Figure 1.
Risk stratification and management of antiphospholipid pregnancies. aPL: antiphospholipid antibodies, LDA: low dose aspirin; IVIG: intravenous immunoglobulin; PE: plasma-exchange; HCQ: hydroxychloroquine.

Abnormal uterine artery flow on Doppler ultrasound is an indirect indicator of the development of placental insufficiency and/or pre-eclampsia [81]. Therefore, the European Alliance of Associations for Rheumatology, (EULAR) guidelines recommend the use of uterine artery Doppler ultrasonography for the management of SLE/APS patients [82]. In addition, a drop in platelet count in the first trimester has recently been found to be associated with the development of pre-eclampsia in APS pregnancy compared to non-APS pregnancies. APS women who later developed pre-eclampsia and/or placental insufficiency had a decrease in initial platelet count of more the 20% (personal observation, not published).

6. Management of the obstetric antiphospholipid syndrome

The current standard of care (**Table 3** and **Figure 1**) for the management of APS pregnancies [83], although controversial and supported by only a limited number of well-designed studies, is the prophylactic administration of heparin plus LDA for individuals with pregnancy morbidity alone. Mothers with a history of thrombosis alone or in association with pregnancy morbidity are usually treated with therapeutic heparin in combination with LDA to prevent both thrombosis and pregnancy morbidity. The data supporting these recommendations come almost exclusively from clinical trials evaluating the prevention of recurrent early miscarriages rather than late pregnancy complications. A total of 140 women with APS-related recurrent early miscarriages, were enrolled in two randomized control trials comparing treatment with LDA alone or in combination with heparin [84, 85]. The combination of LDA with heparin showed a significantly higher live birth rate than LDA alone. These data were however not confirmed in two subsequent studies [86, 87]. Nevertheless, a subsequent follow-up meta-analysis [88] and a recent Cochrane review [89] concluded that combining heparin with LDA during pregnancy may increase the live birth rate in women with APS compared with LDA alone. Since low

Clinical/laboratory features	Treatment
High-risk aPLs profile but no history of thrombosis or pregnancy complications, with or without SLE.	Close monitoring of mother and fetus; LDA (75–100 mg daily) during pregnancy should be considered.
Obstetric APS only (no prior thrombotic events), with or without SLE:	
a. History of ≥3 recurrent spontaneous miscarriages <10th week of gestation or history of fetal loss (≥10th week of gestation),	LDA and heparin at prophylactic dosage.
b. History of delivery <34 weeks of gestation due to eclampsia or severe pre-eclampsia or due to recognized features of placental insufficiency,	LDA or LDA and heparin at prophylactic dosage considering the individual's risk profile.
c. Clinical 'non-criteria' obstetric APS such as the presence of two recurrent spontaneous miscarriages <10th week of gestation, or delivery ≥34 weeks of gestation due to severe pre-eclampsia or eclampsia.	LDA alone or in combination with heparin might be considered based on the individual's risk profile.
Thrombotic APS.	LDA and therapeutic dose of heparin.
Patients with obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage.	Increasing heparin dose to therapeutic dose; consider addition of HCQ or low-dose prednisolone in the first trimester and IVIG in highly selected cases.

APS: antiphospholipid syndrome, aPLs: antiphospholipid antibodies, LDA: low dose aspirin, HCQ: hydroxychloroquine, IVIG: intravenous immunoglobulin, SLE: systemic lupus erythematosus.

Table 3.
Current recommendation [83] for the management of pregnant women with antiphospholipid antibodies or APS.

molecular weight heparin (LMWH) is easier to administer and have less adverse events it is the drug of choice in most cases. Furthermore, the dose of LMWH should be personalized. Case-control studies comparing a fixed dose of LMWH with a weight-adjusted dose of LMWH have shown a higher live birth rate with the latter [80, 90]. Several studies, recently summarized [91] suggest that women with either clinical and/or laboratory non-criteria manifestations of obstetric APS may benefit from standard obstetric APS treatment with LMWH plus LDA, with good pregnancy outcomes.

6.1 Management of refractory/high-risk pregnancies

Even if current recommendations are carefully followed [83], 20–30% of pregnancies fail [92], and these are the so-called refractory pregnancies and/or high-risk pregnancies. High-risk pregnancies are pregnancies of APS patients with one or more laboratory or clinical risk factors who may or may not have experienced adverse pregnancy outcomes despite treatment with heparin/LDA [8]. Experts in the field believe that women should receive additional treatments when the risk of having pregnancy complications is elevated based on their antibody profile and certain clinical characteristics [93] as this will improve these women's live birth rate and/or reduce their pregnancy complications. Various therapeutic options, such as low-dose prednisolone, intravenous immunoglobulins, hydroxychloroquine, plasmapheresis alone or in combination have been used in an attempt to achieve a better pregnancy outcome [94–104]. Usually, these treatments were administered in conjunction with conventional heparin/LDA therapy. An Experts' Consensus [8] following a systematic review of the literature recently suggested that hydroxychloroquine and low-dose steroids, alone or in combination, may be an option for

pregnant APS women whose previous pregnancies were not successful despite receiving conventional therapy. Intravenous immunoglobulins (IVIG) and plasma exchange (PE), alone or in combination, could be considered in refractory high-risk APS pregnancies. Furthermore, a recent systematic literature review [9] analyzed 313 refractory/high-risk pregnancies from 14 studies comprising 134 (42.8%) pregnancies refractory to conventional treatment, and 179 (57.2%) high-risk/refractory pregnancies. The findings from this review suggest introducing low-dose IVIG (< 2 g/kg/month) or HCQ 400 mg/day before pregnancy in women with APS refractory to conventional therapy, and high-dose IVIG (2 g/kg/month) in combination with PE or alone in those with high risk/refractory APS with both approaches leading to improved pregnancy outcome. It should be noted that, drug related side-effects were observed in 3/313 (0.9%) of pregnancies, and none of which required hospitalization.

Although statins appear to be a potential therapy in the treatment of APS refractory pregnancies, as suggested by murine studies [105] and a small case-control study of the use of pravastatin for placental dysfunction/pre-eclampsia in patients with APS [106], they have not yet been routinely used to date. Pravastatin was administered to 11 women with obstetric APS and preeclampsia/IUGR at the time of diagnosis of the complication (range 22–30 weeks) in addition to standard of care; they were compared with 10 control patients with preeclampsia/IUGR who did not receive pravastatin. The pravastatin group achieved a 100% rate of live births (34–36 week of gestation) and rapid improvement in uterine artery hemodynamics was observed, while the control group had a 50% rate of live births, all of which were delivered preterm (26–32 week of gestation). An ongoing multicenter study, the StAmP trial, is testing pravastatin for the prophylaxis of preeclampsia (double-blind, randomized and placebo-controlled) in the general population [107]. However, several concerns remain about their use, as they are classified as FDA category X. However, no congenital abnormalities have been reported in the pilot studies to date.

7. Future perspectives

Much has been done over the past three decades to understand the pathogenesis of aPL-mediated obstetric injury and to diagnose and treat obstetric APS. However, much remains to be done to provide the best diagnostic and therapeutic approach to our patients.

Future research should be conducted to evaluate the intracellular signaling pathways that are affected by aPLs and lead to trophoblastic dysfunction. Identification of these mechanisms could lead to identification of potential therapeutic targets in the future.

The redefinition of the classification criteria is currently under evaluation and should provide a valuable tool for future clinical trials of APS. It is important to include in these studies the concept of risk stratification according to aPLs profile and clinical features. The possible inclusion of new autoantibodies such as anti-domain I and aPS/PT in the new classification criteria could be helpful in improving the diagnosis of obstetric APS, especially in cases where conventional antibodies are not detectable.

Clinical trials of new therapeutic approaches for refractory obstetric APS syndrome are currently underway. Two randomized clinical trials (NCT04275778 and NCT04624269) and two prospective studies [108, 109] are evaluating the effect of HCQ in addition to standard treatment to prevent pregnancy morbidity in APS patients. According to a recent prospective case series, the use of TNF-alpha

inhibitors in addition to standard treatment seems to be a promising treatment for refractory obstetric APS [10]. If these findings are confirmed by the ongoing IMPACT Study: IMProve Pregnancy in APS with certolizumab (NCT03152058), the TNF-alfa inhibitors may constitute a valid second-line treatment for refractory and/or high-risk APS pregnancies in the near future.

8. Conclusions

Nowadays, we have gained new insights into the pathogenesis and management of obstetric APS. Contrary to what was first thought, aPLs determine pregnancy morbidity with both inflammatory and non-inflammatory mechanisms. These findings have led to a better understanding of the different features of obstetric APS. While, inadequate invasion of maternal spiral arteries by the extravillous cytotrophoblast leads to early miscarriage, a lack of transformation of these arteries along with activation of the complement and the coagulation cascade is responsible for late pregnancy loss and preeclampsia. APS pregnancies should be classified into low, medium and high-risk classes based on clinical and laboratory features. Depending on the risk class, the most appropriate therapy must then be selected. Although studies have shown that intervention at the first signs of placental insufficiency can improve the pregnancy outcome, it is advisable to initiate the most appropriate therapy based on the risk class immediately at the beginning of pregnancy. It should be remembered that invasion of the trophoblast into the maternal spiral arteries occurs in the very early stages of placentation and adequate anchorage of the placenta is essential for the development of the pregnancy. Therefore, we need to start most appropriate therapy as soon as possible to facilitate a favorable pregnancy outcome.

Conflict of interest

The authors declare no conflict of interest.

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