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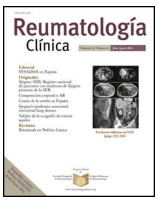

Review Article

Controversies Concerning the Antiphospholipid Syndrome in Obstetrics☆

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ABSTRACT

Antiphospholipid antibody syndrome is a non-inflammatory autoimmune disease characterized by recurrent thrombotic events and/or obstetric complications associated with the presence of circulating antiphospholipid antibodies (anticardiolipin antibodies, anti-β_2 glycoprotein-I antibodies, and/or lupus anticoagulant).

Antiphospholipid antibodies are a heterogeneous group of autoantibodies associated with recurrent miscarriage, stillbirth, fetal growth restriction and premature birth. The diversity of the features of the proposed placental antiphospholipid antibodies fingerprint suggests that several disease processes may occur in the placentae of women with antiphospholipid antibody syndrome in the form of immune responses: inflammatory events, complement activation, angiogenic imbalance and, less commonly, thrombosis and infarction. Because of the disparity between clinical and laboratory criteria, and the impact on perinatal outcome in patients starting treatment, we reviewed the aspects of antiphospholipid antibody syndrome related to obstetric complications and seronegative antiphospholipid antibody syndrome, and their treatment in obstetrics.

Controversias del síndrome de anticuerpos antifosfolipídicos en obstetricia

Palabras clave:
Síndrome de anticuerpos antifosfolipídicos
Síndrome de anticuerpos antifosfolipídicos obstétrico
Síndrome de anticuerpos antifosfolipídicos seronegativo
Anticuerpos antifosfilipídicos
Resultados perinatales adversos

RESUMEN

El síndrome de anticuerpos antifosfolipídicos es una enfermedad autoinmune no inflamatoria, caracterizada por eventos trombóticos recurrentes y/o complicaciones obstétricas, asociados a la presencia de anticuerpos antifosfolipídicos circulantes: anticuerpos anticardiolipina, anti-β_2 glucoproteína-I y/o anticoagulante lúpico.

Los anticuerpos antifosfolipídicos son un grupo heterogéneo de autoanticuerpos asociados con morbilidad obstétrica, como pérdida gestacional recurrente, muerte fetal, parto pretérmino asociado a insuficiencia placentaria como enfermedad hipertensiva del embarazo y/o restricción del crecimiento intrauterino. Los procesos fisiopatológicos relacionados con la morbilidad obstétrica no se han comprendido del todo, involucrándose múltiples eventos inmunológicos, entre ellos los inflamatorios, la activación del complemento, el desbalance de los factores angiogénicos y, en alguna proporción de los casos, se ha demostrado trombosis e infarto. Debido a la controversia en los criterios clínicos y de laboratorio, así como a la repercusión en la mejora de los resultados perinatales en pacientes que inician tratamiento, decidimos llevar a cabo esta revisión sobre los conceptos de síndrome de anticuerpos antifosfolipídico relacionado con complicaciones obstétricas y síndrome de anticuerpos antifosfolipídico seronegativo, así como su manejo en obstetricia.

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Introduction

Since the bases for proposing antiphospholipid antibody syndrome (APS) were suggested, the pathophysiology of that disease has not been completely understood, and questions have been raised as to whether the current criteria are sufficient to establish the diagnosis.[1,2]

In clinical practice, we identify pregnant patients who have thrombotic events and those who have obstetric complications related to APS, but rarely both disorders; in individuals with APS, antibody levels can vary, or even be undetectable. The classification criteria of Sapporo and Sidney consider intermediate or high antibody titers, but not low or negative values; it is essential that we do not underestimate the diagnosis of APS in patients with obstetric complications, as an intervention can improve the implicated perinatal outcomes and, thus, it is important to analyze concepts of obstetric antiphospholipid antibody syndrome (O-APS) and seronegative antiphospholipid syndrome (SN-APS).[3–5]

The objective of this study is to provide a review of the controversies that surround the diagnosis of APS and its relationship to obstetrics and adverse perinatal outcomes, as well as the current recommendations for its management. We performed an analytical search of the available literature up to December 2015 in the major electronic databases, PubMed (MEDLINE), EMBASE (Elsevier), Cochrane, EBSCO (Dynamed) and Ovid, to retrieve the best available evidence (meta-analyses, systematic reviews, randomized clinical trials and observational studies). The languages used were English and Spanish, and we utilized a combination of the following terms: "antiphospholipid syndrome", "international consensus criteria", "antiphospholipid antibodies", "obstetric APS", "low titer aPL", "antiphospholipid antibodies" and "seronegative obstetric antiphospholipid syndrome", using the Boolean operators "AND" and "OR".

Background

Antiphospholipid syndrome is an autoimmune disease that is characterized by arterial or venous thromboembolisms and/or certain obstetric complications in association with antiphospholipid antibodies (APA).[6–9]

These antibodies react with phospholipid-binding plasma proteins (mainly anti-β_2 glycoprotein-I [aβ_2GP-I], prothrombin, protein C, protein S, annexin V, annexin II and low-density lipoproteins), protein/phospholipid complexes and anionic phospholipids.[3,4,10]

Expert consensus had been called on to establish the clinical and laboratory criteria to enable the classification of patients, in 1999 in Sapporo, Japan, and later, in 2006, in Sidney, Australia. The criteria for classification were updated and aβ_2GP-I isotypes IgG and/or IgM were added, and the interval between assessing the presence of antibodies was increased from 6 to 12 weeks between 1 measurement and the next.[11]

In 2013, in Rio de Janeiro, Brazil, a new consensus was established and the proposal was to separate as 2 different entities thrombotic APS and that associated with obstetric morbidity (APS-O), with suggestions for novel clinical criteria concerning the latter, such as early recurrent pregnancy loss (RPL [embryonic and preembryonic]), early fetal death, placental insufficiency, infertility and changes in laboratory criteria.[12]

There may be a substantial clinical correlation between aPL levels in patients with a related obstetric history, and still with low titers and against only one antibody, which could represent a reduced immune function when compared with patients with thrombotic aPL.[13]

The diagnostic criteria considered have implications in clinical practice, with novel antigen targets, cut-off points, laboratory techniques and the intervals for their measurement, as well as their correlation with the clinical manifestations.

Pathophysiological Mechanisms of Obstetric Complications

Fetal well-being depends critically on the role of the uteroplacental circulation, which joins the mother and the fetus. A normal pregnancy is associated with homeostatic changes, including an increase in the concentration of coagulation factors, and a decrease in natural anticoagulants and the fibrinolytic activity; these pregnancy-related physiological changes predispose the mother to thromboses and to vascular complications, which are related to an increase in the adverse perinatal outcomes in patients with APS.

The pathophysiological mechanisms related to the obstetric complications of aPL have yet to be completely clarified, and initially would involve extensive infarctions and placental microthrombi[14] and, although these phenomenon are more frequent in patients with who are positive for aPL, they are not the primary origin of the obstetric complications. Placental infarctions are caused by the incapacity of the uteroplacental blood flow, which is secondary to the occlusion of the spiral arteries by an intraluminal thrombus, which can cause ischemic injury in the intervillous space, affecting the placental villosity; however, these lesions are present in only one sixth of the cases and, thus, we must consider that there are multiple pathophysiological processes occurring in patients with APS.[15]

Considering that aPL are a heterogeneous group of antibodies, with different mechanisms of action, it is not very likely that the obstetric morbidity be caused by a single mechanism like infarction and/or thrombosis. Antiphospholipid antibodies can induce changes in spiral artery remodeling, decidual inflammation and decrease the vasculosyncytial membrane, secondary to other immunological phenomena, such as inflammation, complement activation,[15–17] overexpression of tissue factor in neutrophils and monocytes and imbalance between angiogenic factors, even in the absence of thrombosis.[13]

Inflammatory manifestations related to aPL are mainly mediated by complement and, secondarily, by the activation of the coagulation cascade,[16,18] as well as a reduction in annexin vand placental tissue damage.[15]

Other mechanisms are indirect damage to the trophoblast through apoptosis, inhibition of proliferation and syncytiotrophoblast formation, a decrease in chorionic gonadotropin hormone production, and damage to trophoblastic invasion and growth factor secretion, which result in pregnancy loss or placental dysfunction.[15,19]

The extravillous trophoblast is the target of inflammatory injury, even for placental infarctions associated with the presence of aPL secondary to the occlusion of the spiral arteries.[15]

Uncontrolled complement activation[20] plays a critical role in the pathogenesis of placental damage induced by aPL; hypocomplementemia is found in up to half of the patients with APS and pregnancy, and is related to adverse perinatal outcomes such as prematurity, low birth weight, death, preterm delivery and preeclampsia (PE).[16,17,21] Fetal loss can be explained by histopathological inflammatory signs secondary to the overexpression of tissue factor in neutrophils and monocytes, or to an imbalance in the angiogenic factors, there being evidence of biochemical markers.[17]

Obstetric antiphospholipid antibody syndrome

Antiphospholipid syndrome is considered a thromboembolic disease; however, in the group with associated obstetric complications, only a small percentage will have thrombotic events

Table 1
International Consensus (Sapporo Revisited) for the Diagnosis of Antiphospholipid Antibody Syndrome Associated With Obstetric Morbidity.

Clinical criteria	Laboratory criteria
One or more unexplainable deaths of a morphologically normal fetus or after 10 gw	LA in plasma on 2 or more occasions at intervals of 12 weeks
One or more preterm births in a morphologically normal newborn prior to 34 gw due to eclampsia or severe PE or other manifestations of placental insufficiency	Intermediate or high titers of aCL IgG and/or IgM in plasma/serum (>40 GPL, or >99p) on 2 or more occasions at intervals of 12 weeks
Three or more spontaneous inexplicable miscarriages prior to 10 gw, with exclusion of an anatomic or hormonal maternal cause and maternal and fetal chromosomal causes	aβ_2GP-I IgG and/or IgM in plasma/serum (>99p) on 2 occasions at an interval of 12 weeks

aCL, anticardiolipin antibodies; gw, gestational week; LA, lupus anticoagulant; 99p, percentile; PE, preeclampsia.
O-APS is diagnosed with at least 1 clinical criteria and 1 laboratory criteria.

(either systemic or uteroplacental). In a prospective, multicenter study of 1000 patients, Cervera et al. studied patients with APS for 5 years, and found that the group with a related obstetric disease had no thrombosis or other manifestations of APS, and less than 5% progressed to a demonstrated thrombosis or systemic lupus erythematosus,[22] a fact that suggests that the concept of O-APS involves pathophysiological mechanisms other than the aPL, in comparison with thrombotic APS, in which thrombosis and progression to systemic lupus erythematosus are less frequent than in classical APS.

The concept of O-APS as being different from the thrombotic disorder involves both nonconventional clinical and laboratory criteria (Tables 1 and 2), as prospective and retrospective have shown that this group of patients has a higher risk of placental dysfunction (PE, intrauterine growth restriction [IUGR]) and prematurity, as well as a long-term increase in the risk of thrombotic events.[23]

In 2012, Mekinian et al. compared perinatal outcomes in patients with a confirmed diagnosis of APS, using the Sapporo criteria, and patients with an obstetric background and low aPL titers, and found that the perinatal outcomes were similar in the two groups and, even more notable, they observed a significant reduction in adverse perinatal outcomes in both groups with the implementation of standard management (low-molecular weight heparin and acetyl salicylic acid [LMWH + ASA]); however, the limitation to this study was the fact that it was retrospective.[13] Nevertheless, these findings support the premise that patients with a diagnosis of O-APS could benefit with a standard treatment and, thus, have live newborns, with few maternal complications.[15,24–26]

At the 9th meeting of the European Forum on Antiphospholipid Antibodies, it was proposed that O-APS should be distinguished from the thrombotic syndrome as a distinct entity since, in the absence of thrombosis, there is histological and biochemical evidence of the action of aPL, aside from the improvement in the perinatal outcomes with conventional treatment. At that forum, the classical notions were joined by additional clinical criteria, such as 2 consecutive pregnancy losses or 3 non-consecutive losses, late PE, *abruptio placentae*, late preterm birth and 2 or more unexplained unsuccessful in vitro fertilizations.[18]

The O-APS concept also covers biochemical aspects, proposing novel situations such as the presence of nonstandardized antibodies like antiannexin v, antiphosphatidylserine, and even low titers of anticardiolipin antibodies (aCL), detected at some time, during the pregnancy, since it has been demonstrated that with therapeutic management the perinatal outcomes are better.[17]

Up to 50% of the patients with related obstetric morbidity have low titers of aCL and/or aβ_2GP-I, with perinatal outcomes similar to those of individuals with high or intermediate titers, if they do not receive treatment.[13,27]

Like triple positivity of aPL, which is related to a higher rate of loss during pregnancy, just one positivity (lupus anticoagulant [LA] or aβ_2GP-I, more than LA) has been reported more frequently in O-APS.

In all, 15% of the patients with a history of rRPL, embryonic and preembryonic, have persistent aPL positivity, and, if they do not receive treatment, up to 90% will have another pregnancy loss[24]; the combination of low-dose LMWH + ASA promotes embryo implantation during the early stages of pregnancy and additionally protects against thrombosis of the uteroplacental vasculature after a successful placentation, with a low rate of complications.[24–26,28]

Seronegative Antiphospholipid Antibody Syndrome

There is a group of patients that has a clinical history, including the obstetric background, strongly related to repetitive adverse perinatal outcomes (RPL, history of disease related to placental insufficiency), persistently negative in laboratory tests, that could be classified as SN-APS. This concept was introduced for the first time in 2003 by Hughes and Khamashta, who described patients with clinical manifestations highly indicative of APS, in individuals who rapidly developed the classical accelerated and progressive multiorgan damage of patients with catastrophic APS, but with persistently negative aPL tests.[5]

In this group of patients it is important to consider the following clinical and biochemical aspects:

- Antiphospholipid antibodies may be consumed over time, meaning that at the time of measuring them, we obtain a positive laboratory test that later becomes negative.[28]

Table 2
Nonconventional and Classical Criteria for the Diagnosis of Antiphospholipid Antibody Syndrome Associated With Obstetric Morbidity.

Clinical criteria	Laboratory criteria
Two or more unexplainable consecutive miscarriages	Low positivity for aCL or aβ_2GP-I between 95p and 99p
Three or more unexplainable nonconsecutive miscarriages	Intermittent presence of aPL in patients with classical clinical manifestations of obstetric APS
Late PE	
Abruptio placentae, late preterm birth	
Two or more unexplained failed IVF-ET	

aβ_2GP-I, anti-β_2 glycoprotein-I; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; IVF-ET, in vitro fertilization-embryo transfer; 95p, percentile; PE, preeclampsia.
A diagnosis of nonconventional or classical criteria for antiphospholipid antibody syndrome is considered if the patient has a combination of nonconventional clinical manifestations with laboratory criteria in accordance with the international consensus, or international clinical criteria with nonconventional laboratory criteria.

- The aPL titers can decrease notably during treatment with corticosteroids and nonsteroidal anti-inflammatory drugs used frequently during pregnancy (ASA, inducers of lung maturity): in these cases, a future titration should be requested (for 3–6 months later).[29]
- If the patient has a thrombotic event during pregnancy, aPL can be consumed and are reduced. Thus, their determination can never be considered definitive. The cases in which this situation has occurred are referred to as transient SN-APS, since the follow-up of serial measurements of aPL reveals a positive seroconversion after the resolution of the thrombotic event.[30,31]
- We should consider whether the patient has nephrotic syndrome, as there would be a reduction in aPL levels, attributed to urinary excretion of IgG, decreased synthesis and/or increased catabolism.[31,32]
- Analyze whether the laboratory techniques employed in detection comply with internationally standardized guidelines.[3–5]
- Lupus anticoagulant quantification can be undetected if the antibody is weak because the sample is not completely free of platelets, producing an erroneous result. Therefore, LA determination should be performed with ultracentrifugation and plasma filtration.[28]
- A small proportion of patients who are negative for aCL or aβ_2GP-I IgG and IgM, may be positive for the IgA isotope of these antibodies, which is not generally investigated by conventional laboratories.[32] In a retrospective study involving 170 patients with kidney disease, who had been classified as SN-APS, who were tested for IgA aβ_2GP-I. This isotype was positive in 66% of the patients and 91% had persistently positive titers.[33,34]

However, the most convincing explanation for the existence of a group of seronegative patients could be that the series of tests is insufficient, either because of the limitations of standard techniques or because of the existence of different antigenic targets.

Antiphospholipid antibodies are directed against phospholipids, but also against protein/phospholipid complexes and cofactors. In recent years there have been new lines of research, focused on finding other antigenic targets, as well as on improving present techniques and proposing novel methodologies, that detect not only antibodies against phospholipids, but against protein/phospholipid complexes and cofactors.[20]

In a series of cases, Conti et al. studied 24 patients with a diagnosis of SN-APS, using a thin-layer chromatography immunostaining technique, which is able to detect the reactivity of phospholipid molecules other than those identified by enzyme-linked immunosorbent assay (ELISA), and found that 54.2% were positive to aCL, 45.8% to anti-vimentin/cardiolipin, 12.5% to antiprothrombin and 4.2% to antiannexin V[10]; this proposes other lines of research related to the search for nonclassical antibodies, like those directed against proteins of the coagulation cascade, domains other than β_2GP-I, platelets, glycoproteins, mitochondrial antigens and other surface molecules.[10,20]

Antiphospholipid antibodies can also be directed against other phospholipids, like lysophosphatidic acid and phosphatidylethanolamine or proteins like vimentin and protein C components. On occasion, these patients are positive to zwitterionic phospholipid antibodies (such as phosphatidylethanolamine), to several protein/phospholipid complexes, or to phospholipids other than those studied conventionally.[23]

Clinical research of other aPL targets, the implementation and development of other novel laboratory techniques could improve our capacity to detect APS. Nevertheless, the availability of laboratory tests for antibodies of this type is limited in routine practice, and is done only for investigative purposes.[28,34] There is debate as to whether to demand costly additional tests in the attempt to identify those novel aPL, or to establish the diagnosis of SN-APS and introduce a treatment, given the potential risk of thrombosis and adverse perinatal outcomes,[35,36] on the part of those who would possibly benefit from the treatment. However, to date, there is no quality evidence that can demonstrate the key.

Rodríguez-García et al. compared 87 patients with APS and 67 with SN-APS, and found no significant differences with respect to thrombotic events and obstetric morbidity, early spontaneous miscarriage (67.1 vs 52.1%), death (62.5% vs 59.4%), prematurity (28.1% vs 21.7%) or PE (28.1% vs 23.1%); however, the retrospective design is a limitation to this study.[37]

The existence of SN-APS continues to be controversial. Nonetheless, it is important that this entity be considered, since the prognosis of the pregnancy may benefit from a proper management. However, there is still not enough evidence to establish a standard for attending to these patients, which should be personalized and multidisplinary.[36,38] Nevertheless, the diagnosis of SN-APS could increase the rate of false positives, leading to the implementation of unnecessary pharmacological management, which would imply elevated economical and emotional resources.

Management of Patients With Antiphospholipid Syndrome in Obstetrics

We used the grade, recommendation, assessment, development and evaluation (GRADE) system to describe the available evidence on patients with APS (Table 3).

Owing to the close relationship, when there are serious medical problems for the mother and child, management should begin prior to conception. In patients with a related obstetric history, the complete panel of aPL should be requested (level of evidence 1b).[39]

If the patient has confirmed or a suspicion of APS, O-APS or SN-APS, the approach is multidisciplinary, involving specialties like rheumatology, hematology, fetal medicine, neonatology and psychology.

In those cases in which the patient is receiving prenatal care and is taking a vitamin K antagonist, this anticoagulant could be changed for therapeutic doses of LMWH in combination with ASA, especially during the first trimester, because of the relationship to serious structural defects, especially during organogenesis.

Current recommendations consider that patients with a diagnosis of APS, whether primipara or with previous term pregnancies without related complications, close monitoring of the dyad with surveillance of fetal growth, maternal blood pressure, weight gain of mother and infant, and management of low-dose ASA, as prophylaxis for placental dysfunction (PE and/or IUGR); however, this decision will be made according to the common sense of the attending physician (level of evidence 2B).[38]

In a meta-analysis, Mak et al. included 5 clinical trials that involved 334 patients who were positive for aPL, with RPL, and found that the patients who received LMWH + ASA in comparison with those who received only ASA had a significantly higher rate of live newborns (relative risk [RR] 1.3, 95% confidence interval [CI] 1.04–1.6), demonstrating that the combination of LMWH + ASA is superior, with a number needed to treat of 5.6 with a reduction of 72% in PE in that group of patients and, thus, in preterm births associated with RPL.[40]

When a patient has a diagnosis of APS, with a history of RPL, even without a history of thrombosis, LMWH is recommended at a prophylactic or intermediate dose, together with ASA (level of evidence 1B),[39] and if the history includes thrombosis, therapeutic doses of LMWH should be considered (level of evidence 1B).[38]

In patients with documented APS, the use of fractionated heparin + ASA vs ASA and a history of RPL has demonstrated a decrease in pregnancy loss with a RR 0.44 and 95% CI 0.33–0.66 (level of evidence 1B); however, there was no significant difference in

Table 3
Grades of Recommendation and Level of Evidence (GRADE).

Grade of recommendation	Risk/benefit	Methodological quality of the evidence	Implications
1A/strong recommendation, quality of the evidence high	The benefits clearly surpass the risks	RCT without important limits, high quality observational	Recommendation to apply the recommendation is clear
1B/strong recommendation, quality of evidence moderate	Clear benefits that surpass the risks	RCT with important limitations (inconsistent results, methodological flaws or inaccuracies)	Recommendation that can be applied in the majority of the patients
1C/strong recommendation, quality of the evidence low or very low	The benefits surpass the risks	Observational studies or case series	The recommendations can change when there is evidence of greater quality
2A/weak recommendation, quality of the evidence high	The benefits are nearly on the par with the risks	RCT with important limitations or overwhelming evidence from observational studies	Weak recommendation, the best intervention can vary depending on the circumstances of the patients or social values
2B/weak recommendation, quality of the evidence moderate		RCT with important limitations (inconsistent results, methodological flaws or inaccuracies)	Weak recommendation, the best intervention can vary depending on the circumstances of the patients or social values
2C/weak recommendation, quality of the evidence low or very low	There is nothing certain regarding the benefits, risks	Observational studies or case series	Very weak recommendation, there are other alternatives that are just as reasonable

GRADE, grade, recommendation, assessment, development and evaluation; RCT, randomized clinical trials.

the development of complications related to placental dysfunction (IUGR: RR 1.71, 95% CI 0.48–6.17; PE: RR 0.43, 95% CI 0.09–2.08) (level of evidence 1C) in randomized clinical trials, although they had a low methodological quality, with inaccuracies and biases.

With respect to the management in the puerperium of patients with a diagnosis of APS, who did not receive thromboprophylaxis and had no risk factors for thrombosis, it is recommended that only LMWH be used 7 days postpartum; in those who have risk factors for thrombosis or were being treated with LMWH during the pregnancy, the treatment could be extended for 6 more weeks (level of evidence 2C).[38]

However, the controversy revolves around the management of the group of patients with O-APS more than around the diagnosis, as the mainstay of treatment in this group of patients is LMWH + ASA (which helps to limit vascular, thrombotic and inflammatory events, as well as complement activation and the coagulation cascade), which potentially improves the prognosis for the dyad, reducing adverse perinatal outcomes; then again, at the present time, there is no evidence demonstrating that the usual management has a significant beneficial effect. There are no well-designed, randomized clinical trials and, thus, the recommendation for treatment should be based on expert opinion, and be discussed with the patient (level of evidence 2B).[38]

In women with a history of RPL, who do not meet the clinical and/or diagnostic criteria for APS, there is still not enough evidence to maintain that there is an improvement in perinatal outcomes with the utilization of low-dose LMWH + ASA. Moreover, it could even increase the risk of bleeding during the resolution of the pregnancy (level of evidence 2B).[40,41]

In the pathophysiology of PE, endothelial and platelet dysfunction is the main hypothesis for the utilization of antiplatelet agents that prevent or delay platelet dysfunction (low-dose ASA), which is associated with a decrease in the relative risk of PE. A Cochrane systematic review evaluated 43 clinical trials with 32,590 patients with risk factors for platelet dysfunction. The finding was a significant reduction in the risk of PE (RR 0.83, 95% CI 0.77–0.89), with a number needed to treat (NNT) of 28 high-risk patients (level of evidence 1B). Some have recommended anticoagulant therapy with LMWH or fractionated heparin in patients with a very high risk of PE. This is biologically valid, not only because of the decrease in thrombus formation, but also due to the antiapoptotic effects of LMWH in the trophoblast, which is a potential trigger of PE.

In a randomized clinical trial, Mello et al. included 80 patients without documented thrombophilia, with an increased risk of PE based on their medical records and underlying angiotensin-converting enzyme polymorphisms or its deletion. Using LMWH (dalteparin 5000 IU/day), they found that patients with this treatment had a lower incidence of adverse perinatal outcomes, with a decrease of 74.1% in PE (RR 0.26, 95% CI 0.08–0.86) and of 77.5% in IUGR (RR 0.14, 95% CI 0.03–0.56); however, it is limited because it only deals with patients who have this polymorphism (homozygotes for angiotensin-converting enzyme polymorphisms).[42] A later pilot study with 110 patients in whom it was not possible to identify thrombophilia, and with a history of severe PE, IUGR, *abruptio placentae* or fetal death, were randomized to receive prophylactic dalteparin doses or no dalteparin. The authors reported that the group that was treated with LMWH had lower rates of PE, IUGR and *abruptio placentae* (adjusted odds ratio 0.15, 95% CI 0.03–0.70)[43]; however, this study was not double-blinded and was terminated before completing the sample size because of an exaggerated effect of the benefit. This could be attributed to the use of LMWH and, thus, is considered only a preliminary study, with no validity for use in routine practice. The results of these studies must be interpreted with caution, as it is not clear whether the positive effects of LMWH for the prevention of PE can be generalized.

In patients with a history of death, PE or IUGR, in whom APS has not been documented, low-dose ASA should be used, although there is no evidence of the benefit of utilizing prophylactic or therapeutic doses of unfractionated heparin or prophylactic doses of LMWH (level of evidence 1B).[38,39]

In patients diagnosed with SN-APS, the management should be the same as in those with diagnosed APS; however, there are no randomized studies with a suitable design to demonstrate the benefits (level of evidence 2C).[26,38]

It is important, both in patients with definite APS and with O-APS and SN-APS, to maintain close monitoring, during the pregnancy, of maternal blood pressure, weight gain of both mother and infant, and periodical laboratory studies including platelets, complement and antibody titers (aCL, LA and aβ_2GP-I). Likewise, fetal surveillance will require structural studies in both the first and second trimesters; the focus during the third trimester will be on fetal growth, in the search for evidence of early and late placental insufficiency; uterine artery Doppler has a major role, as it is correlated with the prediction of placental dysfunction (PE and/or IUGR).

Conclusions

Antiphospholipid syndrome in women of reproductive age can initially become apparent with fertility problems, in early stages of pregnancy (embryonic and preembryonic), as well as in relation to placental insufficiency and even fetal death, increasing the maternal and fetal rates of morbidity and mortality.

Obstetric complications are due to multiple immunological processes related to the heterogeneity of aPL and their diverse mechanisms of action (inflammatory phenomena, complement activation, the coagulation cascade, in some cases, infarction and thrombosis), not exclusively with a primary thrombotic event, which is the reason for proposing to differentiate this group of patients from thrombotic APS.

Obstetric manifestations related to APS are clinically relevant and warrant research areas especially concerning the therapeutic approach since, apparently, they are associated with a higher risk of disease related to placental insufficiency (PE, IUGR) and neonatal death; however, the clinical application of these observations has yet to be determined, since the evidence we have is still insufficient. The emergence of this group also obliges us to undertake a rational analysis of the clinical and technical conditions of taking samples for antibodies, as well as the possibility of the presence of other nonstandardized antibodies since, aside from the risk of morbidity related to pregnancy, both O-APS and SN-APS have the potential risk of generating thrombotic events and will require treatment during the pregnancy, the puerperium and, probably, over a long period of time.

Approaching the patient during pregnancy should be multidisciplinary, preferentially prior to conception, and should be done with close surveillance of the dyad from the moment of gestation, in order to reduce the associated maternofetal morbidity and mortality, as well as sequelae that could subsequently develop.

The management of APS is often uncertain and, in the absence of scientific clairvoyance, clinical common sense and experience are necessary for improving the perinatal outcomes; the behavior and nature of APS during pregnancy is a matter of debate, and should be confirmed by well-designed experimental studies that involve a large number of patients, to enhance the quality of care.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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