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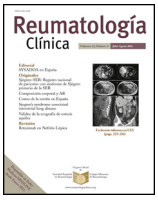

Review Article

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