Rev Clin Esp. 2016;**216(3)**:135–145

Revista Clínica Española

www.elsevier.es/rce

REVIEW

Obstetric antiphospholipid syndrome☆

E. Esteve-Valverde[a,c], **R. Ferrer-Oliveras**[b], **J. Alijotas-Reig**[c,*]

[a] *Servicio de Medicina Interna, Althaia, Xarxa Assistencial de Manresa, Barcelona, Spain*
[b] *Servicio de Obstetricia y Ginecología, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[c] *Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna, Hospital Universitari Vall d'Hebrón, Universitat Autònoma, Barcelona, Spain*

Received 13 July 2015; accepted 9 September 2015

KEYWORDS
Recurrent miscarriages;
Antiphospholipid antibodies;
Pregnancy;
Fetal loss;
Preeclampsia;
Obstetric antiphospholipid syndrome

Abstract Obstetric antiphospholipid syndrome is an acquired autoimmune disorder that is associated with various obstetric complications and, in the absence of prior history of thrombosis, with the presence of antiphospholipid antibodies directed against other phospholipids, proteins called cofactors or PL-cofactor complexes. Although the obstetric complications have been related to the procoagulant properties of antiphospholipid antibodies, pathological studies of human placenta have shown the proinflammatory capacity of antiphospholipid antibodies via the complement system and proinflammatory cytokines. There is no general agreement on which antiphospholipid antibodies profile (laboratory) confers the greatest obstetric risk, but the best candidates are categories I and IIa. Combined treatment with low doses of aspirin and heparin achieves good obstetric and maternal outcomes. In this study, we also review the therapeutic possibilities in refractory cases, although the likelihood of progressing to other autoimmune diseases is low. We briefly comment on incomplete obstetric antiphospholipid syndrome, also known as antiphospholipid antibody-mediated pregnancy morbidity syndrome.

PALABRAS CLAVE
Abortos recurrentes;
Anticuerpos antifosfolipídicos;
Embarazo;
Pérdidas fetales;
Preeclampsia;

Síndrome antifosfolipídico obstétrico

Resumen El síndrome antifosfolipídico obstétrico es una alteración autoinmune adquirida que asocia diversas complicaciones obstétricas, en ausencia de historia trombótica previa, junto con la existencia de anticuerpos antifosfolipídicos dirigidos contra fosfolípidos, proteínas denominadas cofactores o contra complejos fosfolípidos-cofactor. Aunque las complicaciones obstétricas se han relacionado con sus propiedades procoagulantes, estudios anatomopatológicos en placentas humanas han demostrado su capacidad proinflamatoria vía sistema del

☆ Please cite this article as: Esteve-Valverde E, Ferrer-Oliveras R, Alijotas-Reig J. Síndrome antifosfolipídico obstétrico. Rev Clin Esp. 2016;216:135–145.

* Corresponding author.
E-mail addresses: jalijotas@vhebron.net, 16297jar@comb.cat (J. Alijotas-Reig).

Síndrome antifosfolipídico obstétrico

complemento-citocinas proinflamatorias. No hay acuerdo general sobre cuál es el perfil de anticuerpos antifosfolipídicos (categoría de laboratorio) que confiere más riesgo obstétrico, aunque las denominadas categorías I y IIa son las mejores candidatas. El tratamiento combinado con dosis bajas de aspirina y heparina consigue buenos resultados obstétricos y maternos. Se revisan también las posibilidades terapéuticas en los casos refractarios. La evolución a otras enfermedades autoinmunes es baja. Se comenta brevemente el denominado síndrome antifosfolipídico obstétrico incompleto, también conocido como síndrome de morbilidad obstétrica asociada a anticuerpos antifosfolipídicos.

Background

Obstetric antiphospholipid syndrome (OAPS) is a variant of the classical antiphospholipid syndrome (APS). APS is characterized by the presence of arterial and/or venous thrombosis and/or obstetric morbidity, along with the recurring presence of antiphospholipid antibodies (aPLs), according to 2006 Sydney classification criteria.[1] The clinical manifestations of APS have classically been related to the ability of aPLs to trigger the coagulation pathway, which is considered the most common form of acquired thrombophilia in our community. However, aPLs can induce a primary inflammatory response that is occasionally accompanied by a second prothrombotic response. This appears to be especially the case for OAPS.

According to the current definitions, OAPS includes recurrent spontaneous miscarriages before the 10th week of pregnancy that are not explained by other causes, as well as fetal losses, prematurity, fetal growth delay and early onset preeclampsia.[1] We consider OAPS to comprise those cases that meet the obstetric APS criteria and that have not previously presented thrombotic episodes according to the Sydney criteria.[1]

Some patients have obstetric problems, such as recurrent implantation failure, up to 2 consecutive miscarriages, late or puerperal preeclampsia, premature rupture of the membranes and retroplacental hematoma and yet do not meet the clinical or laboratory criteria for OAPS.[1] This situation is known as incomplete OAPS or, following the nomenclature of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS Project), obstetric morbidity related to antiphospholipid antibodies (OMAPS).[2] The paramount importance of recognizing OAPS lies in the fact that this is one of the few treatable causes of obstetric complications. The proper management of OAPS can also prevent the maternal thromboembolic complications associated with aPL during pregnancy and postpartum. Nevertheless, due to the fact that the prevalence of aPL in the healthy population reaches 5%,[3] its routine measurement in previously healthy pregnant patients is not recommended.[4] In this clinical review, we aim to address all of these issues.

Brief historical background

Although there have been references to similar clinical–biological conditions since the 1950s[5] (and especially in the 1970s[6]), the ''modern'' APS appeared in the 1980s (1983–1986), described by the medical team at the Rayne Institute St Thomas' Hospital of London, led by professor Graham RV Hughes.[7,8] Laurell and Nilson[5] had previously reported the correlation between a syphilis false positive on one hand and the coagulation disorder and recurrent miscarriage on the other. Reaginic tests (e.g., rapid plasma regain and the venereal disease research laboratory test) for lues, which are known to be in reality a type of aPL.[9,10] From this, we base the concept of patients with a false positive syphilis serology.[11]

In 1980, Firkin et al.[12] suggested the relationship between recurrent miscarriage and lupus anticoagulant (LA). In 1981, Carreras et al.[13] described the presence of an antibody that interferes with the formation of prostacyclins and related it to arterial thrombosis and intrauterine fetal death. In 1983, Lubbe et al.[14] established for the first time the use of low-dose corticosteroids as treatment for patients with APS, with the aim of preventing fetal death by inhibiting the effects of these antibodies. Later, Harris et al.[15] standardized the technique for measuring anticardiolipin antibodies (aCL), thereby better delimiting its role in APS. In 1987, a group of experts met in Sapporo (Japan) to define the first ever classification criteria for APS.[16] At the beginning of the 1990s, the associations between aPL and gestational morbidity were described and strengthened.[17] In 1990, it was shown that β2-glycoprotein I is the main aPL cofactor.[18] The classification criteria and treatment strategies have since been revised.

Epidemiology

The prevalence of APS in the general population is unknown, although it has been estimated at 0.5–1%.[19] APLs can be detected in 1–5% of healthy women of reproductive age.[20] Approximately 40% of women with systemic lupus erythematosus have aPL, and it is estimated that less than 40% of women ultimately present thrombotic events.[21] Between 10% and 25% of recurrent miscarriages are due to aPL. The prevalence of aPL in women with obstetric morbidity varies widely from 5% to 50%. The prevalence of LA varies between 0% and 14%, but for women with fetal losses after week 20, the rate increases up to 30%.[22] The differences in these results can be explained by the diversity of the study groups, the different inclusion criteria and the lack of standardization of many of the aPL detection methods.[23]