Antiphospholipid Syndrome in Pregnancy

Susana Maria Agüero

Abstract
Antiphospholipid Syndrome (APS) is associated in pregnancy with repeat abortions and fetal loss; other frequently reported complications are preeclampsia and placental insufficiency.
The pathogenesis of fetal losses in the APS is due to the thrombophilic effect caused by the presence of antibodies against phospholipids and to other mechanisms that include direct effects on the trophoblast and inflammatory phenomena. Accurate laboratory identification is a fundamental pillar in differential diagnosis of other obstetric pathologies. The combination of a very detailed and close follow up in conjunction with an established treatment will result in a successful pregnancy.

Keywords
Antiphospholipid syndrome in pregnancy, antiphospholid antibodies, pregnancy loss, thrombosis

INTRODUCTION

Antiphospholipid syndrome is defined as an autoimmune disease, which is associated with the presence of circulating antiphospholipid antibodies (APL) and a history of blood clots, as well as complications of pregnancy such as miscarriages and stillbirths.

Although the clinical phenomena that characterize this disease frequently occur; the incidence of APS is relatively low. This is why the identification of antiphospholipid antibodies by specific assays is important.

In 1952, Moore described a series of patients suffering from lupus erythematosus (SLE), who had a positive VDRL test that used an anionic phospholipid, cardiolipin, as antigen. In that same year, Conley and Hartmann refer to two SLE patients that had a coagulation inhibitor in circulation. This antibody could inhibit a coagulation test in vitro, but was not associated to hemorrhagic diathesis. In 1972, Feinstein and Rapaport named this phenomenon lupus anticoagulant (LA).

Although the relationship between SLE, thrombosis and the presence of these antibodies is known since 1963, it is not until 1980 that the disease recognized as such, with a clear association between positivity for antiphospholipid antibodies, either with anticardiolipin antibodies and/or lupus anticoagulant, and thrombotic phenomena and/or fetal losses and thrombocytopenia.

In 1990, two research groups reached the conclusion that the antibodies are not directed against phospholipids directly, but rather require the presence of a plasma/serum cofactor, which is the beta-2 glycoprotein I (ß2GPI). ß2GPI forms part of the antigen to which aPL are bound in APS.

There are other antiphospholipids directed against proteins which generally have high affinity for phospholipids and which have functions within the coagulation system.

PATHOPHYSIOLOGY

In APS, homeostatic regulation of blood coagulation is altered; however, the mechanisms of thrombosis are not yet defined. One hypothesis postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various plasma proteins, such as beta-2 glycoprotein I. Once bound, a phospholipid-protein complex is formed and a neoepitope, uncovered, which subsequently becomes the target of auto antibodies. Recent evidence suggests that oxidized beta-2 glycoprotein I is able to bind to and activate dendritic cells in a manner similar to activation triggered by Toll-like receptor 4 (TLR-4), which could amplify the production of auto antibodies.
Other proposed mechanisms for the hypercoagulable effect of aPL antibodies, which may or may not depend on beta-2 glycoprotein I, include the following:
• Production of antibodies against coagulation factors, including prothrombin, protein C, protein S, and annexins
• Activation of platelets to enhance endothelial adherence
• Activation of vascular endothelium, which, in turn, facilitates the binding of platelets and monocytes
• Reaction of antibodies to oxidized low-density lipoprotein, thus predisposing to atherosclerosis and myocardial infarction (MI)

1 Corresponding author: MD, specialist in gynecology, obstetrics and ultrasonography. Ramón Sarda Hospital, Esteban de Luca 2151, Buenos Aires, Argentina. Email: susanaaguero_34@hotmail.com

Complement activation has been increasingly recognized as possibly having a significant role in the pathogenesis of APS. Emerging evidence from murine models suggests that APL-mediated complement activation may be a primary event in pregnancy loss.
Clinically, the series of events that lead to hypercoagulability and recurrent thrombosis can affect virtually any organ system, including the following:
• Peripheral venous system (deep venous thrombosis [DVT])
• Central nervous system (cerebrovascular accident [CVA], sinus thrombosis)
• Hematologic (thrombocytopenia, hemolytic anemia)
• Obstetric (pregnancy loss, eclampsia)
• Pulmonary (pulmonary embolism [PE], pulmonary hypertension)
• Dermatologic (livedo reticularis, purpura, infarcts/ulceration)
• Cardiac (Libman-Sacks valvulopathy, miocardial infarction [MI])
• Ocular (amaurosis, retinal thrombosis)
• Adrenal (infarction/hemorrhage)
• Musculoskeletal (avascular bone necrosis)

CLASSIFICATION CRITERIA FOR APS

Clinical Criteria (Sydney 2004)

1) Vascular thrombosis.
One or more clinical episodes of vascular thrombosis without significant evidence of inflammation in the vessel wall.
2) Pregnancy morbidity.
a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
b) One or more premature births of a morphologically normal neonate before the 34th week of gestation due to: i) Eclampsia or severe preeclampsia, or ii) Recognized features of placenta insufficiency, or
c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

In clinical studies, it is recommended to classify patients into types 2a, 2b or 2c

The clinical features considered in the final classification have a specificity of 98% and a sensitivity of only 71%, implying that it allows us to rule out the disease with a 98% certainty, but only detect it in 71% of cases. The consequence is that there are approximately 30% of patients, who, although probably having APS, are left out and not treated adequately.

Laboratory Criteria

1- Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart.
2- Anticardiolipin antibody (ACL) of IgG or IgM isotype in serum or plasma, present in medium or high titers (i.e. higher than 40 GPL units or MPL units, or higher than the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA).
3- Anti-ß2GPI antibody of IgG or IgM isotype, present in serum or plasma (in titer higher than the 99th percentile), present in two or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA).

Laboratory tests for APL concentrate are indicated in those patients with unexplained thrombotic events, mainly in unusual sites (mesenteric, cerebral) and occurring at an early age (under 50 years). In SLE, as part of the antibody profile (approximately 50% of patients with SLE are aPL positive) and in women with a history of abortions and pregnancy complications, such as: intrauterine growth restriction, preeclampsia and HELLP syndrome. Tests are also recommended in patients presenting a prolonged PTT without apparent cause, only as laboratory finding. Generalized testing is not recommended in asymptomatic persons or categories other than those mentioned, avoiding thus the risk of false positive; a relatively common situation due to the low specificity of the tests used.
Antiphospholipid antibody syndrome is present if at least one of the clinical criteria and one of the laboratory criteria are met.

Other features, associated with APS, but not included in the revised criteria are: heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological manifestations, IgA ACL, IgA anti-ß2GPI, antiphosphatidylserine antibodies, antiphosphatidylethanolamine antibodies, antibodies against prothrombin only and antibodies to the phosphatidylserine/prothrombin complex.

OBSTETRIC MANIFESTATIONS

About a quarter of women suffering recurrent abortions are positive for one or more APL. In these women the risk of fetal loss is higher after 10 weeks, unlike in the general population, in whom it typically occurs during the first 9 weeks of gestation.

In APL-positive pregnant women, complications leading to intrauterine growth retardation (IUGR), preterm birth and pre-eclampsia can be present. Pre-eclampsia, if combined with hemolysis, increased hepatic enzymes and decreased platelet count, can lead to HELLP syndrome, which also occurs in patients with APL.

Regarding the role of these antibodies in infertility cases, the issue is still controversial. Since APL may affect growth of the placenta and embryo implantation, it could, at least in theory, cause infertility.

Mechanisms of obstetric morbidity

PLACENTAL THROMBOSIS
Placental thrombosis is considered the main pathogenic mechanism of pregnancy loss, especially in the first and second trimesters. It is often possible to detect thrombotic histological features in biopsy material, but this phenomenon

is not exclusive to APS. For Rand, APL interferes with the activity of annexin V, a natural anticoagulant protein. This protein binds to anionic phospholipids with high affinity, mainly to cells of the syncytiotrophoblast and to endothelial cells, forming a protective layer that β2GPI and anti-β2GPI disrupt, allowing the formation of coagulation complexes carried to a fibrin deposit on trophoblast cells.

The mechanism of placental morbidity is not only limited to organ thrombosis, but also includes defects in the implantation and local inflammatory phenomena. Other mechanisms have been described, apart from thrombosis, in an effort to explain maternal-fetal morbidity, based on various histological findings.

IMPLANTATION DEFECTS

Several in vitro studies show that APL have direct effect on the trophoblast without any relation to thrombosis. These antibodies could induce: direct cell damage, apoptosis, inhibition of the formation and proliferation of syncytial trophoblast and decreased production of HCG (chorionic gonadotropin). All this would lead to defective placentation and would explain, to some extent, non-thrombotic early loss.

LOCAL INFLAMMATION

During pregnancy there are important physiological changes in the maternal immune response, to protect the fetus from potential maternal immune system attack. Important evidence exists that the complement system could mediate fetal damage produced by APL. The APL join to the placenta, where they produce activation of the classical complement pathway.

This leads to the production of potent anaphylatoxins, mediators of cellular activation, like C5a.

This attracts and activates monocytes, neutrophils and platelets, with the production of cytokines, chemokines, C3 and properdin. Properdin, together with the presence of necrotic tissue, accelerates decidual activation via the alternative complement pathway and production of more C5a. Depending on the damage level, either growth restriction or stillbirth will occur.

C5a attracts and activates neutrophils expressing tissue factors. This contributes to oxidative burst and damage to the trophoblast.

Neonatal APS

This is an extremely rare entity, which produces neonatal thrombosis, possibly due to transplacental passage of antibodies from mother to neonate. Only 16 clinical cases have been described and the main clinical manifestation was stroke. The incidence is very low compared to the number of pregnant antiphospholipid-positive mothers

TREATMENT

Treatment in pregnant women positive to APL focuses on preventing placental thrombosis (heparin and aspirin), increasing placental blood flow and decreasing the thromboxane/prostacyclin ratio (aspirin), and in certain cases suppressing the immune system with corticosteroids and intravenous immunoglobulin (IVIG). The first therapies used were corticosteroids plus low-dose aspirin.

In obstetric patients, aspirin use has resulted in the successful prevention of preeclampsia, preterm birth, intrauterine growth retardation and perinatal death.

Heparin is the drug of choice for preventing thromboembolic complications in patients with known risks (for example cardiac valve replacement). Aside from inhibiting coagulation, it has anti-inflammatory effects, preventing the adhesion of leukocytes to endothelial cells and inhibiting the complement cascade at multiple levels.

Cases of women with previous thrombosis are different from those presenting only fetal loss. The first ones are normally given oral anticoagulants, and should stop this medication during conception due to its characteristics of being teratogenic between weeks 6 and 14 of gestation. Treatment should be resumed only after completing the period of fetal organogenesis. Patients with APL should continue anticoagulation for at least six weeks after delivery, due to the risk of thromboembolism. In women where therapy with heparin and aspirin has failed, the use of intravenous immunoglobulin has occasionally been successful.

As established during the 5th International Conference on Sex Hormones, Pregnancy and Rheumatic Diseases (April 2007, Florence, Italy), most specialists recommend the use of aspirin in APL-positive women during in vitro fertilization (IVF), while the use of heparin is reserved for those with previous thrombotic manifestations.

CONCLUSIONS

The antiphospholipid syndrome is an auto immune entity with defined clinical characteristics and associated with measurable antibodies.

Recurrent pregnancy loss represents a common and frequent problem of difficult resolution in the obstetric practice.

Even today, almost half of the cases have not been clarified; while in the remaining 50%, causes can be attributed to genetic alterations, diabetes and other endocrinopathies, maternal-fetal infections, anatomic alterations of the genital tract or immunopathies among them those related with antiphospholipid antibodies.

Probably better knowledge of the biological phenomena and a more rational use of the therapeutic agents will allow achieving more favorable results in this obstetric area.

REFERENCES

1. Alarcón Segovia D, Delezé M, Oría CV, Sánchez Guerrero J, Gómez Pacheco L, Cabiedes J, et al. Antiphospholipid antibodies and antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of Consecutive Patients. Medicine 1989; 68: 353-365.

2. Belilos E. Antiphospholipid Syndrome. http://emedicine.medscape.com/article/333221-overview

3. Bermas BL, Doruk E, Shur PH. Clinical manifestations of the antiphospholipid syndrome. http://www.uptodate.com/contents/clinical-manifestations-of-the-antiphospholipid-syndrome Revised on Feb. 22, 2011

4. Brown HL. Antiphospholipid antibodies and recurrent pregnancy loss. Clin Obstet Gynecol 1991: 34; 17-26.

5. Camps MT, Gutiérrez A, Guil M, Sedeño J, García R, Belmonte A, De Ramón E. Anticuerpos anticardiolipina en mujeres con abortos de repetición. Estudio de casos y controles. An Med Intern 1992: 9;585-90.

6. Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. BMJ. 2010; 14;340:c2541. doi: 10.1136/bmj.c2541

7. Der Parsehian S. Síndrome Antifosfolípido en Obstetricia y Ginecología. Rev Hosp Mat Inf Ramón Sardá 1999; 18; 14-9.

8. Donadini MP, Crowther M. Antiphospholipid syndrome: A challenging hypercoagulable state with systemic manifestations. Hematol Oncol Clin North Am 2010;24:669-76.

9. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10:1222-6.

10. Love PE, Santoro SA. Antiphospholipid antibodies, anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Ann Intern Med 1990; 112:682-98.

11. Raimondi R, Der Parsehianb S. Sindrome Antifosfolípido en el embarazo: Características Clínicas, Diagnóstico, Patogénesis y Tratamiento. Rev Hosp Mat Inf Ramón Sardá 2010;29: 147-154

12. Rand JH, Wu XX, Quinn AS, Ashton AW, Pojen CP, Hathcock JJ, et al. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. Blood 2010; 115: 2292-9.