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Antiphospholipid Autoantibodies in Women with Recurrent Gestational Failures – Controversies in Management

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1. Introduction

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia in pregnant women. This syndrome is characterized by vascular thrombosis and/or pregnancy morbidity in association with the presence of circulating antiphospholipid antibodies (aPL). The APS may occur alone (primary APS), or in association with an underlying autoimmune connective tissue disorder (secondary APS).(1)(2) The APS diagnosis requires at least one of the clinical criteria and one of the laboratory criteria described in Table 1.

APS has been largely related to recurrent miscarriages (RM) and several pregnancy complications as pre-eclampsia, but their association with implantation failure (IF) after *in vitro* fertilization (IVF) is still a matter of debate. IF, defined as a failure in conceive after IVF treatment, is considered a cause of recurrent gestational failure (RGF), a current concept that includes both RM and IF. There is no consensus about the number of IVF failures cycles or the number of embryos transferred needed for the diagnostics of IF, but the majority of the clinicians consider 3 fresh IVF attempts' failures for the diagnosis.(3)

Assisted Reproduction Techniques (ART) development has tremendously increased the pregnancy rates (around 50%) by improvements in culture conditions, embryo selection and technical advances, but implantation is consider to be an important limiting factor in this field. Numerous anatomical, endocrine, immunological, thrombophilic and genetic alterations have been described as risk factors in IF. (4)

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Clinical criteria	
Vascular thrombosis	≥1 clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue being confirmed by appropriate imaging studies or histopathology without evidence of inflammation in the vessel.
Pregnancy morbidity	≥1 unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented.
	≥1 premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia and severe preeclampsia, or to recognized features of placental insufficiency.
	≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, and paternal and maternal chromosomal causes excluded.
Laboratory criteria	
Lupus anticoagulant	Present in plasma, on ≥2 occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)
Anticardiolipin antibody of IgG and/or IgM isotype	Present in serum or plasma at medium or high titre (>40 GPL or MPL, or >99th percentile), on >2 occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA)
Anti-β2GPI antibody of IgG and/or IgM isotype	Present in serum or plasma (titre >99th percentile), ≥2 occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

Table 1. Clinical and Laboratory criteria for the diagnosis of the APS. Adapted from Miyakis, S. *et al.* (2006). Abbreviations: β2GPI, β2 glycoprotein I; ELISA, enzyme-linked immunosorbent assay; GPL, IgG phospholipid units; GPM, IgM phospholipid units.

2. Implantation process

Embryo implantation and successful establishment of pregnancy require delicate interactions between the blastocyst and the maternal uterine cells. From the embryo phase, the trophectoderm and the throphoblast establish contact with the specialized maternal tissue, the uterine endometrium. Classically, implantation process has been divided into three phases: apposition, adhesion and invasion of a developmentally competent embryo in the receptive endometrium. Implantation begins with attachment of the blastocyst trophoblast (derived from the trophectoderm) at the embryonic pole through the outer epithelial uterine lining (day 6 from the fertilization). The site of implantation is marked on the surface by a coagulation plug left where the blastocyst has entered the uterine wall (day 12 from the fertilization). This phenomenon triggers changes in both the trophoblast and the

connective tissue (stroma) beneath the uterine epithelium. Some trophoblast cells fuse to make a syncytium called the syncytiotrophoblast that releases proteolytic enzymes that allow passage of the blastocyst into the endometrial wall first, then into the stroma (carrying the whole conceptus with it).

During this migration, the trophoblast cells destroy the wall of the maternal uterine spiral arteries, converting them from muscular vessels into flaccid sinusoidal sacs. This vascular transformation is important to ensure an adequate blood supply to the feto-placental unit and the beginning of the histiotrophic nutrition. (5)

A change in endometrial gene expression is necessary to allow the embryo implantation. In fact, already in the late luteal phase, physiological changes occur in the endometrium to allow blastocyst implantation. Uterine cells changes their phenotype during the menstrual cycle and these critical events during this so called "window of implantation or receptivity" results in the presence of the embryo, in a decidual reaction, leading to programs of gene expression particular to pregnancy. Failure to properly begin these critical events results in early implantation failure.

3. Disorders of implantation

Adequate implantation is a limiting factor in human reproduction. The study of the possible causes responsible of this failure is technically difficult in the daily clinical routine. As previously described, implantation is the result of the remarkable synchronization between the development of the embryo and the differentiation of the endometrium.

Uterine pathologies like adhesions, septa, intrauterine polyps, hydrosalpinx, endometriosis and other disorders might impair implantation. Several studies suggest that reparatory surgery improves the conception rate. However, there is still an ongoing debate on the benefits of surgery in infertile patients. (6-10)

During the last few years several authors have reported different gene networks important for the endometrium receptivity that controls the expression of key transcription factors (e.g. HOXA10, STAT3, p53) (11-15), growth factors and cytokines [e.g. HB-EGF, leukaemia-inhibiting factor (LIF), prokineticin 1] (16-18)(and cell adhesion molecules and their ligands (e.g. avb3 integrin, trophinin, L-selectin ligand) (19-21), all of which are essential for coordinated cross-talk with the implanting embryo. (22) Altmae *et al.* demonstrated that women with IF show a somewhat different endometrial gene profile during the window of implantation, (23) which is thought to contribute to the lower implantation rates seen in these patients. In particular, investigations focusing on endometrium of IF patients showed changes in known implantation markers, such as integrins, as well as leukaemia inhibitory factor (LIF) and interleukin-1 (IL-1). (24)

Natural killer (NK) cells have been recently identified among the relevant immunological factors for reproductive success (25). Of note, uterine natural killer (NK) cells ($CD56^{bright}CD16^{-}$) represent the dominant type of immune cells in the decidua (around 70% of feto-maternal interface lymphocytes), and it has been suggested that they contribute to the normal trophoblast invasion control and angiogenesis process. An increased number and cytotoxic activity of blood NK cells ($CD56^{dim}CD16^{+}$) and their presence in the endometrium of pregnant women has been related to pregnancy loss. Circulating NK cell

expansion has been also associated to the presence of antiphospholipid antibodies in women with RM and has been ascribed to antiphospholipid-mediated specific reactions [26].

4. Thrombophilias and IF

Acquired and inherited thrombophilias are associated with adverse pregnancy outcome. Thrombophilias has been largely related to RM and several pregnancy complications as pre-eclampsia, late foetal dead, foetal grow restriction and placenta abruption.

With respect to recurrent IF, although the medical literature is not as substantive as that of the recurrent pregnancy loss field, the data again suggest that thrombophilia is associated with repeated IF. Several authors have reported a significantly higher prevalence of thrombophilias in women with four or more failed IVF cycles when compared with spontaneous conceptions.[27-30] Due to the limitations on the knowledge of the implantation process, the mechanisms underlying these associations still remain unclear. Thrombophilias would affect on the ability of the endometrium to develop adequately, communicate effectively with the embryo, or potentially disrupt the early interactions with the maternal circulation.

The inherited thrombophilic conditions can be classified into five broad groups. Each inherited thrombophilia has variable frequency depending on race and ethnicity. In Caucasians, the most common are showed in Table 2. [31,32]

Trombophilia	Incident VTE (%)	Recurrent VTE (%)	Normal population
Factor V Leiden	20	40–50	3–7
Prothrombin G20210A mutation	3–8	15–20	1–3
Antithrombin deficiency	1–2	2–5	0.02–0.04
Protein C deficiency	2–5	5–10	0.2–0.5
Protein S deficiency	1–3	5–10	0.1–1

Table 2. Prevalence of genetic defects among Caucasians

APS has been largely related to recurrent miscarriages (RM) and several pregnancy complications such as pre-eclampsia, prematurity, abruption placentae and the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets count), and others. It is considered the most frequently acquired risk factor for thrombophilia and the main risk of pregnancy loss. However, their association with IF after IVF is still a matter of debate. [33,34] *In vitro* and *in vivo* mice models have demonstrated that antiphospholipid antibodies (aPL) are able to increase thrombus formation in venous and arteries. [35,36]

Antiphospholipid syndrome antibodies (aPL), anticardiolipin (aCL), anti-β2 glycoprotein I (β2GPI) and lupus anticoagulant (LA), are believed to have a pathogenic role. Several authors have reported changes in endothelial adhesion molecules expression as well as in nitric oxide and tissue factor expression in the presence of aPL. These changes could induce coagulation cascade activation but the cells and the exact mechanism involved in clot formation still remains to be elucidated.

β2GPI-dependent aPL is considered the antibody subpopulation responsible for the thrombotic manifestations of APS. The expression of β2GPI on trophoblast cell membranes explains the placental tropism of anti-β2GPI antibodies and the possible role of these antibodies in pregnancy loss. Placental thrombosis, acute inflammation and complement activation have been described as possible responsible of foetal loss in APS patients.

In vitro studies showed that aPL might induce a procoagulant status at the placental level through several mechanisms including the ability of the aPL antibodies (specifically, anti-β2GPI antibodies) to disrupt the anticoagulant annexin A5 shield on trophoblast but histopathological studies have not demonstrated thrombosis findings in most APS women placentas. (37)

An adequate balance between pro-inflammatory and anti-inflammatory arms of the immune response is necessary for a successful pregnancy outcome (38). Complement activation could be involved in APS foetal loss pathogenesis because of the demonstration that the protective effect of heparin in the mouse model is linked to the anticomplement, rather than to the anticoagulant, activity. (39)

We still do not know the precise mechanisms responsible of the high diversity of clinical manifestations in APS patients. Several authors have reported studies *in vitro* and *in vivo* trying to explain pregnancy loss and vascular implications of the syndrome, but in IF cases the potential pathogenic mechanisms are less known. β2GPI-dependent antibodies bind to human trophoblast and could affect several cell functions needed for the correct embryo implantation like proliferation and syncytium formation. These antibodies could decrease production of human chorionic gonadotrophin and others important factors for the invasion of the trophoblast. (40) In addition, expression of important factors for the implantation in the endometrium has been found in reduced quantities in women with aPL. Also, it has been shown that β2GPI-dependent aPL are able to react with human stromal decidual cells *in vitro*, inducing a proinflammatory phenotype. (41,42)

A wide range of different antigenic specificities has been described in APS (Table 3), and could be determined when the clinical suspicion of obstetrical APS is strong and the classical anticardiolipin antibodies (aCL), anti- β2GPI and LA are all negative.

5. Prevalence of antiphospholipid antibodies in recurrent gestational failure

We consecutively studied 157 women that fulfilled diagnosis of RPL, of age range from 28 to 41 (mean age, 36.86±3.93), from whom 60 presented with RM with a mean of 3.28±1.14 prior miscarriages; and 97 presented with IF, with a mean of 4.75±2.17 prior failed IVF. In the group of RM, 13.62% showed positive antiphospholipid antibodies (mostly low titre anti-β2GPI or/and aCL); only a 4.60% showed moderate to high titres of antiphospholipid antibodies and therefore fulfilled criteria of APS. In the group of IF, 18.80% of patients showed positive antiphospholipid antibodies (all of them low titre anti-β2GPI or/and aCL). A 97% of patients with antiphospholipid antibodies in our series had also expanded circulating NK cells (above 12%). The allele frequency prevalence of the mutations in the genes of factor V Leiden, the prothrombin G20210A, and the methylenetetrahydrofolate reductase (MTHFR C677T) in the general population in the European population represent approximately a 2.5%, 2.2%, and 35.3%, respectively. (43) We systematically studied all three mutations in our cohort of patients with RPL. We observed that in the group of RM, the

Reagin
Anionic phospholipids
Cardiolipin
Phosphatidylserine
Phosphatidic acid
Phosfatidilinositol
Neutral phospholipids
Phosfatidilcoline
Dipolar phospholipids
Phosphatidyletanolamine
Phospholipid-linking proteins
β-2-glicoprotein I
Prothrombin
Annexin V
Protein C
Protein S
High and low molecular weight kininogens
Other

Table 3. Different specificities of antiphospholipid antibodies

10.8% was homozygous for MTHFR mutation and the 64.9% were carriers. In the group of IF, the 8.3% was homozygous for MTHFR mutation and the 55.6% were carriers. The frequencies of carriers of mutations of factor V Leiden were 3.12% in RM and 6.25% in IF, respectively; the frequencies of carriers of mutations of prothrombin were 3.12% in RM and 0% in IF, respectively. No homozygous for both factors were observed in our series of patients.

6. Clues in management of thrombophilia in recurrent pregnancy loss

In addition to the risk of embryo and foetal losses, there is a low but actual risk of maternal morbidity due to coagulation disorders. The risk of pulmonary embolism and/or deep vein thrombosis increases during pregnancy and puerperium, and is further enhanced by the presence of acquired or inherited thrombophilias. [1] This thromboembolic complications remain as a main cause of maternal death during pregnancy, and its incidence is increasing. For the presence of antiphospholipid antibodies, the risk of pregnancy-related severe maternal thrombosis has been estimated by an odds ratio of 15.8 (95%CI 10.9–22.8). [44]

Based on meta-analyses of randomized controlled studies, observational studies and clinical reports, the American College of Physicians has made the following recommendations: [45,46]

1. For women with aPL and recurrent pregnancy loss, and no history of venous or arterial thrombosis, a prophylactic dose of unfractionated heparin combined with low-dose aspirin antepartum is recommended (Grade 1B). This combination has been shown to be effective in reducing miscarriage rates in women with aPL and prior recurrent foetal loss. This treatment regimen is significantly more effective that others, such as corticosteroids either alone or with aspirin, and IV gammaglobulin. Two recent pilot

studies suggest that the combination of low molecular weight heparin (LMWH) and aspirin might be equivalent to unfractionated heparin and aspirin in preventing recurrent pregnancy loss.[47,48] Our protocol is based in the modified protocol proposed by Ray with combined low-dose aspirin and low-molecular weight heparin.[49]

2. For women at high risk for pre-eclampsia, low-dose aspirin throughout pregnancy is recommended (Grade 1B). Treatment seems to be more effective if started early in pregnancy and at appropriate dose (75–100 mg once daily). An effect of anticoagulant therapy on the risk of preeclampsia is biologically plausible. However, the results of previous small sized studies are still controversial, and the presence of thrombophilia has not been considered in randomized trials on prevention.[1]
3. For women with thrombophilia and previous late foetal loss, placental abruption and/or foetal growth retardation, the available data do not suffice to form the basis of a recommendable prophylactic protocol.

From a clinical perspective, there is still controversial the decision of the adequate thromboprophylaxis protocol for preventing IF and RM in several thrombophilic alterations, such as factor V Leiden and/or prothrombin mutations' carriers in otherwise asymptomatic women. In particular, MTHFR mutation has been shown to lack clinical significance alone. However, an argument to justify prophylaxis could be made that the recurrence risk of women with prior foetal loss, abruption, severe IUGR, or severe preeclampsia is high enough (5–30%). Although there are no randomized clinical trials to support such an approach, observational studies of low-dose aspirin, and LMWH have reported improvement in birth weight compared with untreated pregnancies. Such patients should be offered postpartum anticoagulation prophylaxis if they have an affected first-degree relative or thrombotic risk (e.g., caesarean delivery)[50] Finally, although low corticosteroid doses (<20 mg/day) are occasionally used, particularly in women unresponsive to the standard combination therapy (low-dose aspirin and heparin), there is no evidence to support the routine use of corticosteroids.[2]

7. Conclusions

Multiple acquired and genetic thrombophilic conditions may interact or act in addition as causes of recurrent pregnancy loss. Antiphospholipid antibodies are a heterogeneous group of autoantibodies with varying affinity for different phospholipids and protein-phospholipid complexes with direct pathogenic role resulting in lower blood flow and/or thrombosis at the maternal-foetal interface and final embryo/foetus loss, among other potential maternal complications. Our results in a cohort of patients with recurrent pregnancy loss suggest that aPL may have a similar role in IF patients as in RM patients. Quantification of these thrombosis risk factors in women with RPL will contribute to a better understanding of the interaction of genetic and acquired risk factors, and to better adjust in a more personalized approach the best management for a successful gestation.

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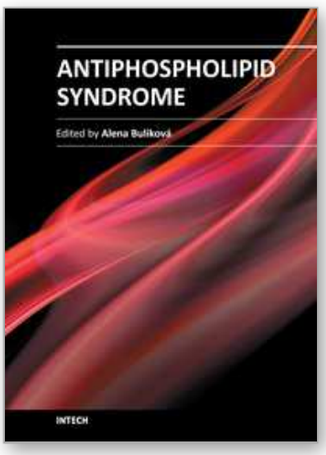

Antiphospholipid Syndrome
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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. Form that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities . This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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