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Adverse Pregnancy Outcome in Antiphospholipid Antibodies Syndrome: Pathogenic Mechanisms and Clinical Management

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1. Introduction

The term antiphospholipid antibodies syndrome (APS) defines an autoantibody induced thrombophilia, associated to recurrent thrombosis and pregnancy complications (Hughes, 1993). Diagnosis of APS requires both serological positivity for antiphospholipid antibodies (aPL), a heterogeneous family of autoantibodies directed against protein phospholipid complexes, and the onset of the diagnostic clinical manifestations (see more below). Indeed, it has been widely shown that aPL are not sufficient *per se* to determine clinical manifestations of APS and that the likelihood that aPL may contribute to the pathogenesis of thrombosis or pregnancy complications, or both, varies between clinical settings (Meroni et al., 2004).

To better define this complex syndrome, it must clarify that APS is commonly distinguished between "primary APS", not associated to other autoimmune diseases, and "secondary APS", when aPL serological positivity and clinical features of APS occur in the context of a known autoimmune disease. The majority of patients with secondary APS are affected from Systemic Lupus Erythematosus (SLE) and develop aPL serological positivity. About 40% of patients with SLE have aPL positivity (Mok et al., 2005) but less than 40% of them will eventually have thrombotic events (Ruiz-Irastorza et al., 2004; Tektonidou et al., 2009). Actually, it is still unknown if APS and SLE are two manifestations of the same disease or if underlying SLE could favour the development of APS (Miyakis et al., 2006). Accordingly, distinction between primary or secondary APS it is not so easy and have to be made carefully (Miyakis et al., 2006).

2. Clinical manifestations of APS

2.1 Systemic features

Venous thrombosis, or embolism, are the most frequent manifestations of APS and might occur in any vascular vessel while, in congenital thrombophilias, mostly involve venous bed (Cervera, 2002). Among the arterial vessels, the central nervous system is the district most

often affected, usually in the form of stroke or transient ischaemic attack (Cervera et al., 2002). aPL have also been associated with venous sinus thrombosis, myelopathy, chorea, migraine, and epilepsy (Sanna et al., 2003). Furthermore, in patients with SLE an association between serum anticardiolipin antibodies and cognitive impairment has been found (Hanly et al., 1999; Menon et al., 1999) as well as a mild cognitive dysfunction in more than 40% of patients with APS (Tektonidou et al., 2006).

Cardiovascular features of APS include valvular disease, coronary artery disease, intracardiac thrombus formation, pulmonary hypertension and dilated cardiomyopathy (Koniari et al., 2010). Cardiac valvular pathology commonly affects the mitral valve, followed by the aortic and tricuspid ones, determining irregular thickening of the valve leaflets due to deposition of immune complexes that may lead to vegetations and valve dysfunction. These lesions are almost frequent and may be a significant risk factor for stroke (Khamashta et al., 1990; Koniari et al., 2010).

Renal manifestations of APS generally took place as hypertension with proteinuria and renal insufficiency (Amigo et al., 1992; Tektonidou et al., 2004) with the most frequent renal histopathological features associated being thrombotic microangiopathy or, less often, fibrous intimal hyperplasia, focal cortical atrophy and arterial occlusions (Tektonidou et al., 2004).

Other clinical features associated to APS are haematological alterations, like thrombocytopenia and haemolytic anaemia, skin ulcers, avascular bone necrosis and also the endocrinologic manifestation of adrenal insufficiency (Cervera et al., 2002). Livedo reticularis, found in about a quarter of patients with APS, represents a physical sign that often suggests to the clinician the right diagnosis and, among patients with APS, it also identifies those at a higher risk for arterial thrombosis (Ruiz-Irastorza et al., 2010; Francès et al., 2005).

2.2 Adverse pregnancy outcomes associated to APS

Beyond thromboses, obstetric complications are the other main features of APS. Such association is confirmed by several epidemiological studies and experimental models showing that passive transfer of aPL IgG induces foetal loss and growth retardation in pregnant naive mice, giving the proof that aPL are involved in determining the clinical manifestations of the syndrome (Meroni et al., 2010).

The most common adverse pregnancy outcome associated to APS is recurrent miscarriage, defined as three or more unexplained consecutive miscarriages before the 10th week of gestation. Other obstetric features of APS are unexplained foetal deaths, occurring at or beyond the 10th week of gestation, and premature births of a morphologically healthy newborn baby before the 34th week of gestation because of eclampsia or severe pre-eclampsia (Miyakis et al., 2006).

Recurrent miscarriage occurs in about 1% of the general population attempting to have children (Stirrat, 1990) and about 10-15% of women with recurrent miscarriage are diagnosed with APS (Rai et al., 1995; Yetman & Kutteh, 1996). Foetal death in the second or third trimesters of pregnancy occurs in up to 5% of unselected pregnancies (Silver , 2007) but it is less likely as pregnancy advances (Smith et al., 2004). Although foetal death occurs significantly most often in APS (Oshiro et al., 1996), the overall contribution to the pathogenesis of this syndrome is unknown, because of the effect of other possible contributing factors such as underlying hypertension or pre-existing comorbidities, like SLE or renal diseases.

Pregnant women with diagnosis of APS are at increased risk for developing preeclampsia or placental insufficiency, but it is still unknown the precise relationship between aPL and the occurrence of such clinical manifestations (Clark et al., 2007). Furthermore, aPL seem to be detectable in 11 – 29% of women with preeclampsia, compared with 7% or less in controls and in 25% of women delivering growth restricted foetuses (Clark et al., 2007). Finally, results from prospective cohort studies indicate that of pregnant women with high concentrations of aPL, 10 – 50% develop preeclampsia, and more than 10% of these women deliver infants who are small for gestational age (Clark et al., 2007).

3. Diagnostic criteria

According to the last International consensus statement for APS diagnostic criteria, in order to make diagnosis of the syndrome the combination of at least one clinical and one laboratory criterion is required (Miyakis et al., 2006) (Table 1).

Clinical criteria	Laboratory criteria
Vascular thrombosis • One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. • Thrombosis should be supported by objective validated criteria—ie, unequivocal findings of appropriate imaging studies or histopathology. For histopathological support, thrombosis should be present without substantial evidence of inflammation in the vessel wall. **Pregnancy morbidity, defined by one of the following criteria:** • One or more unexplained deaths of a morphologically healthy foetus at or beyond the 10th week of gestation, with healthy foetal morphology documented by ultrasound or by direct examination of the fetus. • One or more premature births of a morphologically healthy newborn baby before the 34th week of gestation because of: eclampsia or severe preeclampsia defined according to standard definitions or recognized features of placental failure. • Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of patients according to one of the three criteria.	• Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on lupus anticoagulant/ phospholipid- dependent antibodies). • Anticardiolipin antibody of IgG or IgM isotype, or both, in serum or plasma, present in medium or high titres (ie, >40 GPL or MPL, or greater than the 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. • Anti-β2-gycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titres greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Table 1. Revised diagnostic criteria of APS (Miyakis et al., 2006).

4. Pathogenetic mechanisms mediated by aPL

4.1 Vascular thrombosis

The molecular mechanisms underlying thrombosis and foetal death in APS have long been investigated. The main target antigens reported in patients with APS include beta-2-glycoprotein-1 (β2GPI), prothrombin and annexin V (Galli et al., 2003). Other putative antigens are thrombin, protein C, protein S, thrombomodulin, tissue plasminogen activator, kininogens (high or low molecular), prekallikrein, factor VII/VIIa, factor XI, factor XII, complement component C4, heparan sulfate proteoglycan, heparin, oxidised low-density lipoproteins (Galli et al., 2003; Rand et al., 2010). The main autoantigens are attracted to negatively charged phospholipids exposed on the outer side of cell membranes in great amounts only under special circumstances such as damage or apoptosis (e.g. endothelial cell) or after activation (e.g. platelets) (Galli et al., 2003).

Endothelial cells, activated by aPL with anti-β2GPI activity, express adhesion molecules such as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and both endothelial cells and monocytes upregulate the production of tissue factor (TF) (Pierangeli et al., 2008). All at once, activated platelets increase expression of glycoprotein IIb-IIIa and synthesis of thromboxane A2, determining a procoagulant state (Figure 1). (Pierangeli et al., 2006; Pierangeli et al., 2008; Lopez-Pedrera et al., 2008; Montiel-Manzano et al., 2007; Vega-Ostertag et al., 2005). Additional mechanisms promoting clot formation could be represented by interaction of aPL with proteins implicated in clotting regulation; such as annexin A5, prothrombin, factor X, protein C and plasmin (de Groot & Derksen, 2005; Pierangeli et al., 2008; Rand et al., 2010).

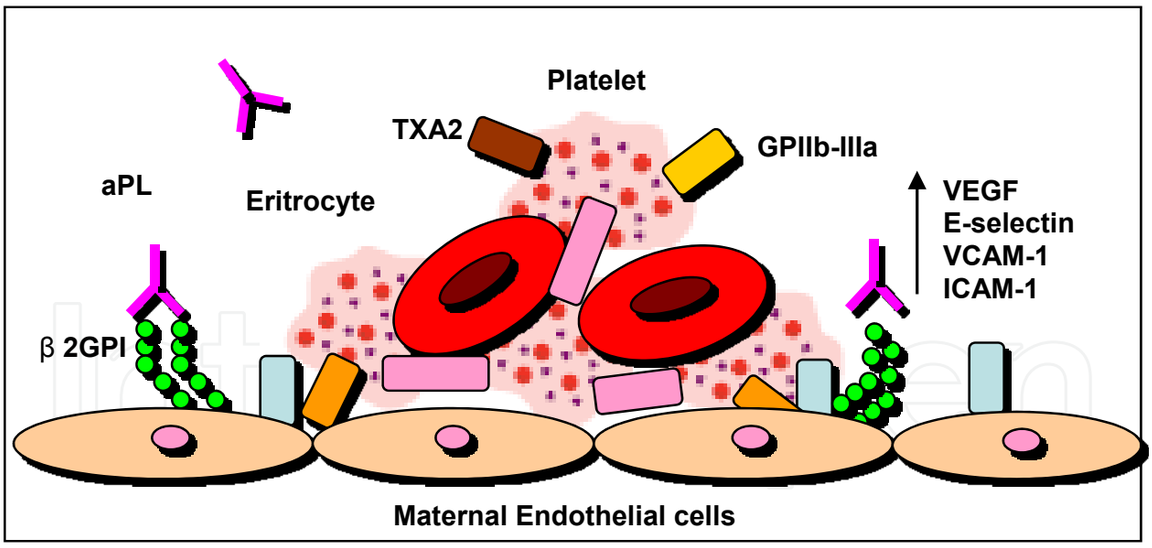


Fig. 1. aPL-mediated mechanism of trombosis.
aPL are able to activate endothelial cells and platelets leading to a procoagulant state (first hit). The occurrence of a second hit, like inflammation, can lead to clot formation.

Recent results from studies in mice highlight the role of inflammation in the pathogenesis of APS, showing a central role for complement activation in thrombosis and foetal loss induced by aPL (Pierangeli et al., 2005; Girardi et al., 2004). Because many individuals with high aPL

antibody titers remain asymptomatic, a second hit hypothesis have been proposed. It is likely that in the aPL-induced vascular procoagulant state, activation of the complement cascade might close the loop and provoke thrombosis, often in the presence of a second hit, like tobacco, inflammation, or oestrogens (Meroni et al., 2004; de Groot & Derksen, 2005; Ruiz-Irastorza et al., 2010).

4.2 Placental thrombosis

Based on the knowledge of the process of intravascular aPL-mediate clot formation (Figure 1), initially intraplacental thrombosis was considered the main pathogenic mechanism mediating foetal loss in APS. This hypothesis of placental damage was supported by the finding of thrombosis and infarction in placentas from women with APS and by the demonstration of aPL capability to induce a procoagulant state *in vitro* through several mechanisms including the ability of the aPL antibodies (specifically, anti-β2GPI antibodies) to disrupt the anticoagulant annexin A5 shield on trophoblast and endothelial cell monolayers (Peaceman & Rehnberg, 1993; Nayar & Lage, 1996; Rand et al., 2010). Supporting the *in vitro* findings, a significantly lower distribution of annexin A5 covering the intervillous surfaces was found in the placentas of aPL-positive women in comparison with normal controls (Rand et al., 1994). Nevertheless, thrombotic events cannot account for all of the histopathologic findings in placentae from women with APS and other mechanisms of reproductive impairment are likely to be involved (Out et al., 1991; Park, 2006).

4.3 Defective placentation

4.3.1 Trophoblast invasiveness impairment

New aPL-mediated pathogenic mechanisms have been proposed during the last ten years: anti-β2GPI antibodies seem to bind directly the maternal decidua and the invading trophoblast, determining defective placentation.

On the foetal side, β2GPI has been shown to be expressed on trophoblast cell membranes, explaining the placental tropism of anti-β2GPI antibodies. Being a cationic plasma protein, β2GPI has been suggested to bind to exposed phosphatidylserine on the external cell membranes of trophoblasts undergoing syncitium formation (Meroni et al., 2010).

β2GPI-dependent antibodies can adhere to human trophoblast cells *in vitro* (Di Simone et al., 2000), consistently with the hypothesis that the visibility of anionic PLs on the external cell surface during intertrophoblastic fusion might offer a useful substrate for the cation PL-binding site (Katsuragawa et al., 1997; Rote et al., 1998). The binding to anionic structures induces the expression of new cryptic epitopes and/or increases the antigenic density, two events that are apparently pivotal for the antibody binding (Wang S.X. et al., 2000). *In vitro* studies with both murine and human monoclonal antibodies as well as with polyclonal IgG antibodies from APS patients have clearly demonstrated a binding to trophoblast monolayers (Lyden et al., 1992; Di Simone et al., 2000). Interestingly, once bound antibodies obtained from patients with APS can affect the trophoblast functions *in vitro*, inducing cell injury and apoptosis, inhibition of proliferation and syncitia formation, decreased production of human chorionic gonadotrophin, defective secretion of growth factors and impaired invasiveness (Figure 2) (Di Simone et al., 2000). β2GPI-dependent aPL seem, therefore, to represent the main pathogenic autoantibodies in obstetrical APS. Accordingly, it has been hypothesized that most of these potentially pathogenic autoantibodies should be absorbed at the placental level, where β2GPI is expressed, and should not be transferred to the fetus.

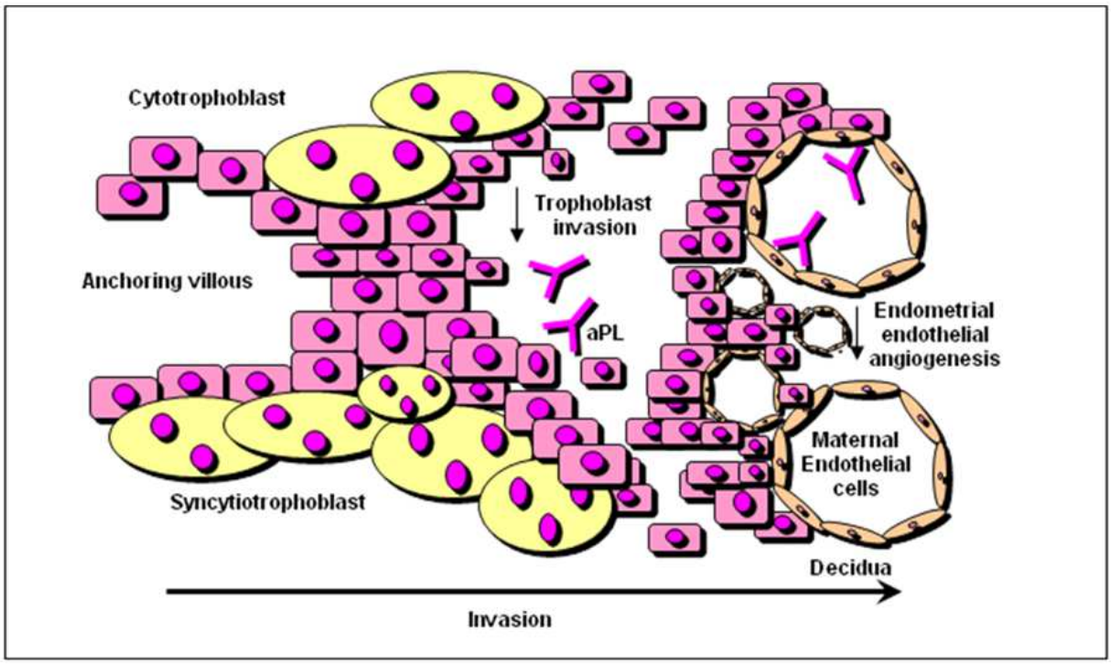


Fig. 2. aPL-mediated inhibition of trophoblast invasiveness and endometrial angiogenesis. Placental development has been proposed to be impaired by aPL direct binding to trophoblast cells, reducing its invasiveness and inhibiting cell proliferation, syncitia formation, secretion of human chorionic gonadotrophin and growth factors. Furthermore, aPL have also been suggested to inhibit maternal decidual angiogenesis, providing an additional mechanism able to explain placental failure associated to APS.

Recent findings have underlined a further mechanism by which aPL binding to human trophoblast could affect its functions: the aPL-mediated reduction of placental Heparin-Binding Epidermal Growth Factor–like growth factor (HB-EGF) expression. HB-EGF is a member of the EGF family (Raab & Klagsbrun, 1997; Iwamoto & Mekada, 2000). It has been shown to induce an invasive trophoblast phenotype in human and mouse blastocysts (Martin et al., 1998; Wang J., 2000) and to initiate molecular and cellular changes characteristic of decidualization in mice (Paria et al., 2001). HB-EGF is expressed in the human placenta during the first trimester, primarily within the villous trophoblast, but also in the extravillous cytotrophoblast, predominantly at the sites of cytotrophoblast extravillous invasion (Leach et al., 1999). Women with preeclampsia and infants small for gestational age display decreased placental expression of HB-EGF (Leach et al., 2002), strongly suggesting an association between HB-EGF down-regulation, poor trophoblast invasion, and failed physiologic transformation of the spiral arteries occurring in these disorders.

Interestingly, also in placental tissue obtained from women with APS, reduced expression of HB-EGF has been found (Di Simone et al., 2010a). Furthermore, polyclonal and monoclonal aPL have been shown to bind trophoblast monolayers *in vitro* significantly reducing the synthesis and the secretion of HB-EGF (Di Simone et al., 2010a). The ability of exogenous recombinant HB-EGF to reduce the aPL mediated effects on trophoblast cells supports the hypothesis of a key pathogenic role of this molecule in mediating APS-related adverse pregnancy outcomes. The experimental conditions did not involve complement activation,

indicating that aPL may also affect placental tissue through direct, complement-independent effects, as previously suggested (Pierangeli et al., 2008).

4.3.2 Endometrial angiogenesis inhibition

On the maternal side, endometrial endothelial angiogenesis inhibition has been suggested to be an additional aPL-mediated mechanism of placental damage (Figure 2). aPL seem to selectively bind *in vitro* to endothelial cells isolated from human endometrium (HEEC) and to inhibit endothelial cell differentiation into capillary-like tubular structures, by reducing MMP-2 activity and VEGF secretion, via a suppression of NFKB DNA binding activity. Such an aPL-mediated inhibition of angiogenesis has also been confirmed *in vivo* in murine models showing a reduced angiogenesis in subcutaneous implanted angioreactors in aPL-inoculated mice (Di Simone et al., 2010b). Since it is well known that endometrial angiogenesis and decidualization, as well as trophoblast invasion, are fundamental prerequisites for successful implantation and the beginning of pregnancy, aPL-inhibition of such a central process in human placental development provides an important additional mechanism able to explain the association between APS and pregnancy complications associated to placental failure, like miscarriage, foetal growth restriction and preeclampsia.

4.4 Inflammation

It is widely accepted that a physiological pregnancy development requires a fine regulation of the maternal immune response during embryo implantation. Acute inflammatory events are recognized causes of a negative pregnancy outcome, and proinflammatory mediators, such as complement, tumor necrosis factor (TNF), and CC chemokines, have been shown to play a role in animal models of aPL-induced foetal loss (Chaouat, 2007). Intraperitoneal injections of large amounts of human IgG with aPL activity to pregnant naive mice after embryo implantation induce considerable placental inflammatory damage that results in foetal loss and growth retardation. An inflammation-mediated aPL damage has also been demonstrated by immunohistochemical and histological examination of murine deciduas, showing deposition of human IgG and mouse complement, neutrophil infiltration and local TNF secretion, in association with a transient but significant increase in blood TNF levels (Holers et al., 2002; Girardi et al., 2003; Berman et al., 2005). Furthermore, it has been demonstrated that in response to aPL-generated C5a, neutrophils express TF potentiating inflammation in the deciduas and leading to miscarriages in mice (Figure 3). Importantly, TF in myeloid cells, but not trophoblasts, seem to be associated with foetal injury, suggesting that the site for pathologic TF expression is neutrophils (Redecha et al., 2007). The pathogenic mechanism of complement-mediated foetal loss induced by aPL is also supported by the protection that deficiency in complement components confers on the animals, or that follows from *in vivo* inhibition of complement (Thurman et al., 2005; Girardi et al., 2006).

In another experimental model of foetal loss, mice deficient in chemokine-binding protein D6, a placental receptor that recognizes the majority of inflammatory CC chemokines and targets them for degradation, were more susceptible to foetal loss when passively infused with a small amount of human aPL IgG than wild-type mice or mice infused with normal IgG (Martinez de la Torre et al., 2007). Altogether, these findings suggest that a local acute inflammatory response might have a role in experimental aPL-mediated foetal loss.

Although C4d and C3b fragments have been shown to be deposited in the placentas of patients with APS, analysis of abortive material or full-term placentae from women with APS has not provided conclusive information about the pathogenic contributions of acute local inflammatory events and complement deposition (Park, 2006; Shamonki et al., 2007). In order to confirm this hypothesis more studies on human placentas are required.

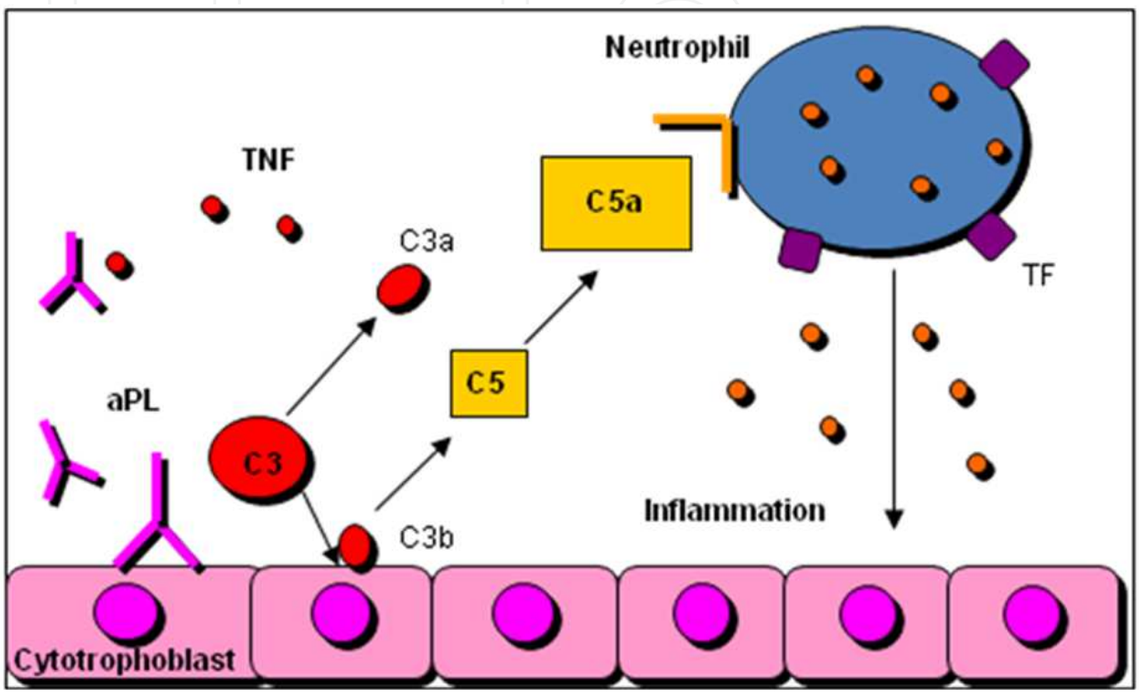


Fig. 3. aPL-mediated activation of complement system and foetal loss.
Endothelial cells, activated by aPL, express adhesion molecules and activated platelets increase expression of glycoprotein IIb-IIIa and synthesis of thromboxane A2, determining a procoagulant state (first hit). The occurrence of a second hit, like inflammation, can lead to clot formation.

5. Pregnancy management

Women with APS should be carefully managed by the physician during pregnancy. A clinical manifestations of APS associated to a high risk for maternal health in pregnancy is severe pulmonary hypertension, representing a contraindication to pregnancy. Furthermore, women with APS should be suggested to delay pregnancy when uncontrolled increase of blood pressure or recent thrombotic events have occurred (Ruiz-Irastorza et al., 2008, 2010).
More than 70% of pregnant women with APS properly managed will have a good pregnancy outcome (Bramhan et al., 2010). However, a complete profile of aPL should be performed before planning of pregnancy. These tests do not need to be repeated during pregnancy, since subsequent negative results after diagnosis do not eliminate the risk of complications (Ruiz-Irastorzaet al., 2008, 2010). Frequent prenatal visits and obstetric ultrasound, every 2-4 weeks, should be done in order to early detect pregnancy

complications like maternal hypertension, proteinuria and other features of preeclampsia, placental insufficiency, foetal loss, foetal growth restriction and the need for iatrogenic preterm birth (Branch & Khamashta, 2003). Surveillance testing should begin at 32 weeks' gestation, or earlier if placental insufficiency is suspected, and should continue at least every week until delivery. Uterine and umbilical artery Doppler assessments are used for the high risk for preeclampsia, placental insufficiency, and foetal growth restriction after the 24th week of gestation in this category of patients and normal examinations have high negative predictive values (Le Thi Huong et al., 2006).

Nowadays, despite the controversies raised by clinical trials (Kutteh, 1996; Rai et al., 1997; Farquharson et al., 2002; Laskin et al., 2009; Noble et al., 2005; Stephenson et al., 2004), the gold standard treatment of patients with APS and history of recurrent early miscarriage is a combination of either low-dose heparin or low-molecular weight heparin and low-dose aspirin (Empson et al., 2005, Bates et al., 2008). Best pregnancy outcomes are achieved with heparin started in the early first trimester when a live embryo is detectable by ultrasound. For pregnant women with APS who have had a previous thrombotic event, low-dose aspirin and therapeutic dose heparin or low-molecular weight heparin anticoagulation are recommended (Bates et al., 2008).

Results from randomised trials do not define optimum treatment for women with foetal death (>10 weeks'gestation) or previous early delivery (<34 weeks'gestation) due to severe preeclampsia or placental insufficiency. Most experts recommend low-dose aspirin and either prophylactic or intermediate-dose heparin (Branch & Khamashta, 2003; Empson et al., 2005; Bates et al., 2008).

Use of glucocorticoids to treat pregnant women with APS have been shown to be less effective than heparin plus aspirin (Silver et al., 1993; Cowchock et al., 1992) as well as administration of intravenous immunoglobulins, either when added to heparin or used alone, do not ameliorate pregnancy outcome. However, intravenous immunoglobulins treatment should be considered whether classic treatment with aspirin plus heparin is not effective (Triolo et al., 2003; Branch et al., 2000; Vaquero et al., 2001), although it has been associated to an increased risk of pregnancy loss or premature birth, compared with heparin and low-dose aspirin (Empson et al., 2005).

Vitamin K antagonists (warfarin) are the gold standard treatment of APS clinically manifested with thromboses but, because of teratogenic risk, should be avoided between 6 and 12 weeks' of gestation. To avoid risk of foetal bleeding, warfarin after 12 weeks' gestation should be given only in exceptional circumstances (Bates et al., 2008; Østensen et al., 2004). Furthermore, women with APS should be treated with antithrombotic drug also during the post-partum period (Bates et al., 2008). Women with history of thrombosis need long-term anticoagulation, and it would be better to switch the treatment to warfarin, as soon as possible after delivery. In patients with no previous thrombosis, prophylactic dose heparin or low-molecular-weight heparin therapy for 6 weeks after delivery are recommended (Bates et al., 2008). Finally, both heparin and warfarin are safe for breastfeeding mothers (Østensen et al., 2004).

6. Conclusions

Although modern management and treatment of APS in pregnancy significantly ameliorate pregnancy outcome, more efforts are needed in order to unravel aPL-mediated pathogenic mechanisms still not understood and to open new perspective of therapies of this complex and multifactorial syndrome.

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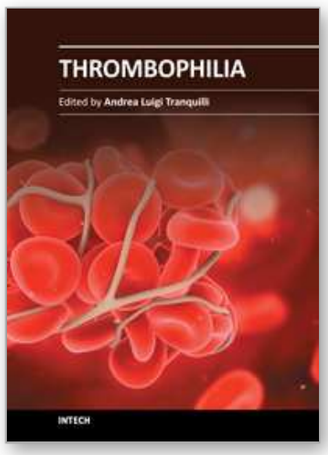
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Thrombophilia

Edited by Prof. Prof. Andrea Tranquilli

ISBN 978-953-307-872-4
Hard cover, 226 pages
Publisher InTech
Published online 09, November, 2011
Published in print edition November, 2011

Thrombophilia(s) is a condition of increased tendency to form blood clots. This condition may be inherited or acquired, and this is why the term is often used in plural. People who have thrombophilia are at greater risk of having thromboembolic complications, such as deep venous thrombosis, pulmonary embolism or cardiovascular complications, like stroke or myocardial infarction, nevertheless those complications are rare and it is possible that those individuals will never encounter clotting problems in their whole life. The enhanced blood coagulability is exacerbated under conditions of prolonged immobility, surgical interventions and most of all during pregnancy and puerperium, and the use of estrogen contraception. This is the reason why many obstetricians-gynecologysts became involved in this field aside the hematologists: women are more frequently at risk. The availability of new lab tests for hereditary thrombophilia(s) has opened a new era with reflections on epidemiology, primary healthcare, prevention and prophylaxis, so that thrombophilia is one of the hottest topics in contemporary medicine.

How to reference

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Nicoletta Di Simone and Chiara Tersigni (2011). Adverse Pregnancy Outcome in Antiphospholipid Antibodies Syndrome: Pathogenic Mechanisms and Clinical Management, Thrombophilia, Prof. Prof. Andrea Tranquilli (Ed.), ISBN: 978-953-307-872-4, InTech, Available from: http://www.intechopen.com/books/thrombophilia/adverse-pregnancy-outcome-in-antiphospholipid-antibodies-syndrome-pathogenic-mechanisms-and-clinical

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