Antiphospholipid syndrome

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The antiphospholipid syndrome causes venous, arterial, and small-vessel thrombosis; pregnancy loss; and preterm delivery for patients with severe pre-eclampsia or placental insufficiency. Other clinical manifestations are cardiac valvular disease, renal thrombotic microangiopathy, thrombocytopenia, haemolytic anaemia, and cognitive impairment. Antiphospholipid antibodies promote activation of endothelial cells, monocytes, and platelets; and overproduction of tissue factor and thromboxane A2. Complement activation might have a central pathogenetic role. Of the different antiphospholipid antibodies, lupus anticoagulant is the strongest predictor of features related to antiphospholipid syndrome. Therapy of thrombosis is based on long-term oral anticoagulation and patients with arterial events should be treated aggressively. Primary thromboprophylaxis is recommended in patients with systemic lupus erythematosus and probably in purely obstetric antiphospholipid syndrome. Obstetric care is based on combined medical-obstetric high-risk management and treatment with aspirin and heparin. Hydroxychloroquine is a potential additional treatment for this syndrome. Possible future therapies for non-pregnant patients with antiphospholipid syndrome are statins, rituximab, and new anticoagulant drugs.

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Pathogenesis

The term antiphospholipid syndrome was coined in the early 1980s to describe a unique form of autoantibody-induced thrombophilia, whose hallmarks are recurrent thrombosis and pregnancy complications.[1] The clinical spectrum of this syndrome has widened,[2,3] with important advances in the knowledge of its pathogenesis and clinical management made during the past several years.

Research shows the central role of endothelial cells, monocytes, platelets, and complement in induction of thrombosis and fetal death in antiphospholipid syndrome. Endothelial cells and monocytes can be activated by antiphospholipid antibodies with anti-β2-glycoprotein-1 activity. In turn, endothelial cells 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.[4] Activated platelets increase expression of glycoprotein 2b-3a and synthesis of thromboxane A2. Nuclear factor κB (NFκB) and p38 mitogen-activated protein kinase (p38 MAPK) are important mediators of these three processes.[4–7] Despite the historical view that inflammation was unimportant in the pathogenesis of antiphospholipid syndrome, results from studies in mice show a pivotal role for complement activation in thrombosis and fetal loss induced by antiphospholipid antibodies.[8,9] Moreover, C4d and C3b fragments are deposited in the placentas of patients with antiphospholipid syndrome.[10]

Pierangeli and colleagues[11] have proposed that, after activation of endothelial cells, monocytes, and platelets by antiphospholipid antibodies, a procoagulant state is induced, which is mainly mediated by the increased synthesis of tissue factor and thromboxane A2. Activation of the complement cascade might close the loop[7] and provoke thrombosis, often in the presence of a second hit[12] (figure 1). Traditional cardiovascular risk factors such as tobacco, inflammation, or oestrogens might have an important role at this point, and such risk factors are present in more than 50% of patients with antiphospholipid syndrome. Findings from an epidemiological study showed that the risk of myocardial infarction or stroke in young women with lupus anticoagulant is increased in those who smoke or take oral oestrogenic therapy.[13]

Furthermore, interaction of antiphospholipid antibodies with proteins implicated in clotting regulation, such as prothrombin, factor X, protein C, and plasmin, might hinder inactivation of procoagulant factors and impede fibrinolysis.[4,12] Interference with annexin A5, a natural anticoagulant, might favour placental thrombosis and fetal loss.[4] Abnormalities in placentation have also been described in pregnancy loss related to antiphospholipid antibodies.[14] β2-glycoprotein 1 directly binds to cultured cytotrophoblast cells and is subsequently recognised by antibodies to β2-glycoprotein 1.[15] Antiphospholipid antibody binding reduces the secretion of human chorionic gonadotropin (hCG). Moreover, antiphospholipid antibodies might trigger an

Search strategy and selection criteria

In this Seminar we aimed to offer an up-to-date view of the main pathophysiological, clinical, diagnostic and therapeutic advances in the discipline of the antiphospholipid syndrome. The literature search was done from January, 2005, to January, 2010. The PubMed database was used with the medical subject heading terms "antiphospholipid syndrome" OR "antibodies, antiphospholipid " OR "lupus coagulation inhibitor". Embase search included the terms "antiphospholipid syndrome", "lupus anticoagulant", and "cardiolipin antibody". The Cochrane database of systematic reviews was searched, with the key word "antiphospholipid". We obtained additional articles from reference sections of the selected manuscripts as well as from personal databases of the authors. We paid special attention to systematic reviews, randomised clinical trials, consensus documents and review articles focused on the pathogenesis of antiphospholipid syndrome. Older articles were also included to draw attention to pathogenetic, clinical, and epidemiological issues.

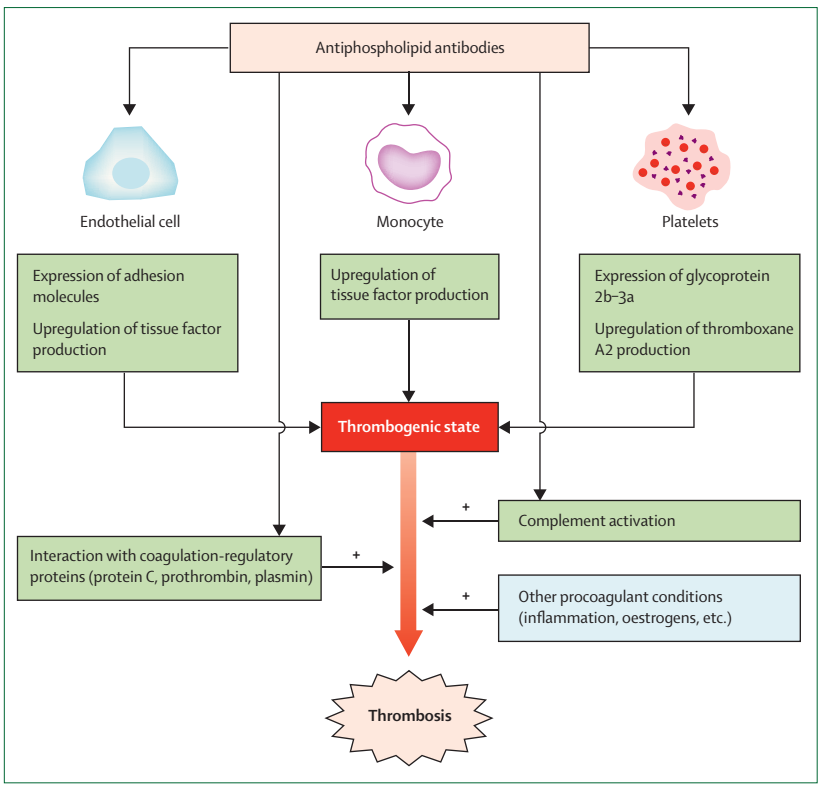

Figure 1: **Pathogenesis of thrombosis in antiphospholipid syndrome**

inflammatory response mediated by the TLR4/MyD88 pathway resulting in trophoblast damage.[16]

Epidemiology

The likelihood that an antiphospholipid antibody contributes to the pathogenesis of thrombosis or pregnancy complications, or both, varies between clinical settings. About 40% of patients with systemic lupus erythematosus have antiphospholipid antibodies,[17] but less than 40% of them will eventually have thrombotic events.[18,19] However, thrombotic antiphospholipid syndrome is regarded as a major adverse prognostic factor in patients with lupus.[18] In the general population, antiphospholipid antibodies can be detected in about one in five patients who have had a stroke at less than 50 years of age.[20] The clinical presentation modifies the pretest probability, with higher likelihood of positivity for antiphospholipid antibodies in young patients presenting with other features of antiphospholipid syndrome, such as miscarriage. However, patients older than 70 years with several vascular risk factors have a much lower probability of having antiphospholipid antibodies in the presence of a cerebrovascular accident than do younger patients.[20] 24% of 4494 patients with venous thromboembolism in whom a thrombophilia test was done had antiphospholipid antibodies,[21] although this frequency might depend on the type of testing done and the definition of a positive test. This frequency was close to that of factor V Leiden, and was not substantially modified by age of patients or by presence of recurrent events.

Recurrent miscarriage occurs in about 1% of the general population attempting to have children.[22] About 10–15% of women with recurrent miscarriage are diagnosed with antiphospholipid syndrome.[23,24] Fetal death in the second or third trimesters of pregnancy occurs in up to 5% of unselected pregnancies,[25] dependent on the span of gestational age studied, but is less likely as pregnancy advances.[26] Although fetal death is linked to antiphospholipid syndrome,[27] the overall contribution of this syndrome is uncertain, partly because of the effect of other possible contributing factors such as underlying hypertension or pre-existing comorbidities such as systemic lupus erythematosus or renal disease. Pending results from a population-based study of fetal deaths at more than 20 weeks' gestation (the Stillbirth Collaborative Research Network sponsored by National Institutes of Health) should prove relevant to better understanding of the frequency of antiphospholipid syndrome as a cause of fetal death. About 5–10% of all pregnancies are complicated by pre-eclampsia or placental insufficiency (as manifested by fetal growth restriction), or both, and severe manifestations of these disorders account for about 75% of indicated preterm deliveries.[28] Pregnant women with a previous diagnosis of antiphospholipid syndrome are at increased risk for developing pre-eclampsia or placental insufficiency, but the association between antiphospholipid antibodies and these disorders in the absence of antiphospholipid syndrome is uncertain.[29] Results of case-control studies show that antiphospholipid antibodies are detected in 11–29% of women with pre-eclampsia, compared with 7% or less in controls. Findings from one study showed that 25% of women delivering growth restricted fetuses had antiphospholipid antibodies, but results from others do not show an association.[29] Results from prospective cohort studies indicate that of pregnant women with high concentrations of antiphospholipid antibodies, 10–50% develop pre-eclampsia, and more than 10% of these women deliver infants who are small for gestational age.[29]

Clinical manifestations

Panel 1 shows the main clinical manifestations of antiphospholipid syndrome. Thromboses are one of the hallmarks of this syndrome, and venous thrombosis, or embolism, is the most frequent manifestation.[2] However, by contrast with thromboses associated with congenital thrombophilias, those associated with antiphospholipid syndrome might also occur in any vascular bed.[2] In the arterial bed, the CNS is most generally affected,[2] usually in the form of stroke or transient ischaemic attacks. Antiphospholipid antibodies have also been associated with venous sinus thrombosis, myelopathy, chorea,

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Panel 1: Clinical manifestations of antiphospholipid syndrome

Frequent (>20% of cases)
- Venous thromboembolism
- Thrombocytopenia
- Miscarriage or fetal loss
- Stroke or transient ischaemic attack
- Migraine
- Livedo reticularis

Less common (10–20% of cases)
- Heart valve disease
- Pre-eclampsia or eclampsia
- Premature birth
- Haemolytic anaemia
- Coronary artery disease

Unusual (<10% of cases)
- Epilepsy
- Vascular dementia
- Chorea
- Retinal artery or vein thrombosis
- Amaurosis fugax
- Pulmonary hypertension
- Leg ulcers
- Digital gangrene
- Osteonecrosis
- Antiphospholipid syndrome nephropathy
- Mesenteric ischaemia

Rare (<1% of cases)
- Adrenal haemorrhage
- Transverse myelitis
- Budd-Chiari syndrome

migraine, and epilepsy.[30] The presence of anticardiolipin antibodies has been linked with cognitive impairment in patients with systemic lupus erythematosus.[31,32] Similarly, mild cognitive dysfunction has been recorded in more than 40% of patients with antiphospholipid syndrome, with a strong association with cerebral white matter lesions.[33] Multiple sclerosis-like CNS lesions and compatible clinical presentations have been noted in a subset of patients with antiphospholipid syndrome.[34]

Antiphospholipid antibodies are associated with cardiac valvular disease, with the mitral valve most frequently affected, followed by the aortic valve.[35] Regurgitation is more common than is stenosis and many patients remain asymptomatic for years.[35] Acute coronary syndromes are much less prevalent than cerebrovascular disease.[2]

Renal involvement in antiphospholipid syndrome was first described in 1992.[36] Thrombotic microangiopathy is the most characteristic finding in this syndrome nephropathy; however, fibrous intimal hyperplasia, focal cortical atrophy, and arterial occlusions have also been described.[37] Hypertension with proteinuria (often subnephrotic) and renal insufficiency are typical presentations of antiphospholipid syndrome nephropathy.[36,37] Renal artery stenosis can also present as refractory hypertension.[38]

Other clinical features associated with antiphospholipid antibodies are, in order of frequency, thrombocytopenia, haemolytic anaemia, skin ulcers, avascular bone necrosis, and adrenal insufficiency.[2] Livedo reticularis (figure 2) is present in about a quarter of patients with antiphospholipid syndrome, constituting a physical sign that should make the clinician suspect the diagnosis of this syndrome in the appropriate clinical context. Moreover, livedo reticularis can be a marker of patients at a high risk for arterial thrombosis.[39]

The most severe and fortunately infrequent form of antiphospholipid syndrome is catastrophic antiphospholipid syndrome. This form is characterised by widespread small-vessel thrombosis with multiorgan failure and more than 50% mortality.[40]

Obstetric complications are the other hallmark of antiphospholipid syndrome. The most common obstetric manifestation of this syndrome is recurrent miscarriage, which is usually defined as three or more consecutive miscarriages before the mid-second trimester, with most losses occurring before the 10th week of gestation. Other obstetric features of antiphospholipid syndrome are one or more fetal deaths occurring at or beyond the 10th week of gestation, severe pre-eclampsia, or placental insufficiency prompting delivery at more than 34 weeks' gestation.[2,41,42] In a population-based analysis of 141 286 deliveries in Florida, USA, positivity for antiphospholipid antibodies increased the risk for both pre-eclampsia and placental insufficiency (adjusted odds ratio 2·93 (95% CI 1·51–5·61) and 4·58 (95% CI 2·00–10·51), respectively.[43] In a retrospective study, women with obstetric antiphospholipid syndrome were at high risk of subsequent thrombotic complications.[44]

Classification criteria and risk stratification

In 1998, the preliminary classification criteria for antiphospholipid syndrome were proposed at Sapporo,

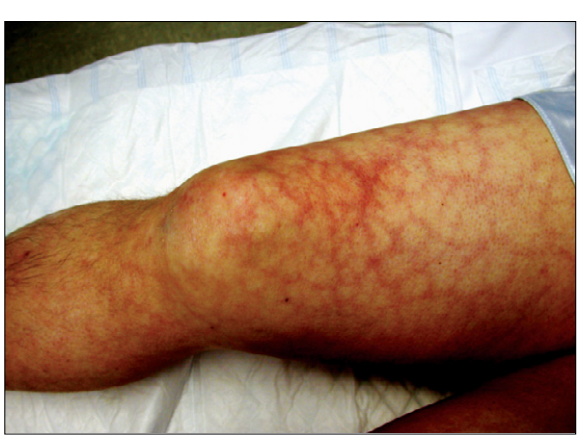

Figure 2: Livedo reticularis in a woman with antiphospholipid syndrome

Panel 2: **Revised classification criteria for antiphospholipid syndrome[46]**

Clinical 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 fetus at or beyond the 10th week of gestation, with healthy fetal 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 pre-eclampsia defined according to standard definitions or recognised 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.

Laboratory 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 standardised 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 standardised ELISA, according to recommended procedures.

Japan.[45] Classification for this syndrome needed at least one clinical manifestation together with positive tests for circulating antiphospholipid antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values, detected at least twice in 6 weeks.

In 2006, classification criteria were updated (panel 2).[46] Essentially, the clinical criteria remained unchanged; however, two important modifications were made: the time elapsed between two positive determinations was extended to 12 weeks to assure the detection of persistent antibodies only; and anti-β2-glycoprotein 1, both IgG and IgM, were added to the laboratory criteria. Medium titres of anticardiolipin, or anti-β2-glycoprotein 1, were defined as more than 40 GPL or MPL or higher than the 99th percentile. Notably, IgA isotypes, antiprothrombin antibodies, and antibodies directed against phosphatidylserine-prothrombin complex remained excluded from the criteria.

These modifications have been criticised,[47] and the debate about the clinical implications of different antiphospholipid antibodies is still open. Lupus anticoagulant is consistently the most powerful predictor of thrombosis.[19,48,49] In a Dutch case-control study in women younger than 50 years, lupus anticoagulant increased the odds of stroke more than 40-fold and of myocardial infarction more than five-fold.[13] Similarly, lupus anticoagulant has been strongly associated with recurrent miscarriage before the 24th week of gestation.[50]

Furthermore, lupus patients negative for lupus anticoagulant with persistently positive anticardiolipin (defined as at least two of three positive tests) had thrombosis more frequently than did patients negative for both lupus anticoagulant and anticardiolipin, although intermittent anticardiolipin positivity did not increase the frequency of thrombosis.[19,49] Both IgG and IgM anticardiolipins are associated with an increased risk of miscarriage, albeit to a lesser degree than lupus anticoagulant.[50]

Anti-β2-glycoprotein-1 antibodies were not associated with either thrombosis or recurrent early miscarriage in any of three systematic reviews.[48,50,51] In the Dutch case-control study, anti-β2-glycoprotein 1 only doubled the risk of stroke but not of myocardial infarction.[13] However, work by Galli and colleagues[52] lends support to the association between anti-β2-glycoprotein 1 and thrombosis in patients with a concomitant lupus anticoagulant. Others have noted that the presence of more than one class of antiphospholipid antibodies increased thrombotic risk.[53] Pengo and colleagues'[54] findings have shown that patients with triple positivity for lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein 1 are at the highest risk for venous and arterial thrombosis and for obstetric complications.[54,55] Moreover, results from a follow-up study showed a 30% rate of thrombotic recurrence in this subgroup of triple positivity even while on anticoagulant therapy.[56] Patients with triple positivity tend to have higher values of anti-β2-glycoprotein 1 compared with patients with less than three positive antibodies[54] and are more likely to have stable concentrations of antiphospholipid antibodies over time.[57]

Specific ELISA for antibodies directed against the domain 1 of β2-glycoprotein is one of the new expected tests that will need assessment.[57] These antibodies, with lupus anticoagulant activity, are strongly associated with

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thrombosis.[58] Moreover, results from a multicentre study including patients with repeatedly positive anti-β2-glycoprotein-1 antibodies showed an increased risk for obstetric complications and thrombosis in patients with IgG antibodies with specificity against domain 1 of β2-glycoprotein.[59] Furthermore, resistance to the anticoagulant effects of annexin A5 seems to be associated with the occurrence of both pregnancy losses and thrombosis.[60]

Management of thrombosis

Prevention of thrombosis is a major goal of therapy in patients with antiphospholipid antibodies. There are two different clinical settings: patients with antiphospholipid syndrome who have already had a thrombotic event (secondary thromboprophylaxis); and antiphospholipid antibody carriers without previous thrombosis, which can be either purely asymptomatic individuals, patients with systemic lupus erythematosus, or women with obstetric antiphospholipid syndrome (primary thromboprophylaxis).

With regard to secondary thromboprophylaxis, the main treatment for antiphospholipid syndrome patients with thrombosis is antithrombotic treatment, rather than immunosuppression (figure 3).[61] The two key issues are whether patients with antiphospholipid syndrome should receive the same treatment as the general population with similar manifestations, and whether arterial and venous events should be treated differently. The answers are not straightforward, and two systematic reviews give contradictory views of this issue.[62,63]

Lim and colleagues[62] recommended indefinite oral anticoagulation to a target international normalised ratio (INR) of 2·0–3·0 for patients with venous and arterial non-cerebral events, and either low-dose aspirin or oral anticoagulation to a target INR of 1·4–2·8 for those with stroke. Since these recommendations were based on the results of randomised clinical trials, only three studies met the eligibility criteria. Two, comparing high (target INR 3·0–4·0) with standard (target INR 2·0–3·0) intensity of anticoagulation, recruited a high proportion of definite antiphospholipid syndrome patients with venous events;[64,65] those with recent stroke[64] and those with recurrent events on anticoagulant treatment were excluded.[64,65] Anticoagulation in patients in the high-intensity groups was often lower than the prespecified therapeutic range;[64,65] and most recurrent thrombotic events in both treatment groups took place while the INR was lower than 3·0.[64]

The only selected study focusing on patients with stroke, the Antiphospholipid Antibodies and Stroke Study (APASS),[66] was actually a subgroup analysis of a previous trial.[67] A nested design was used, thus one measure of antiphospholipid antibodies was done in samples stored at the time of enrolment.[66] Most patients positive for antiphospholipid antibodies had low concentrations of anticardiolipin (IgA anticardiolipin included) and did not have double positivity for both anticardiolipin and lupus anticoagulant. No patients included in APASS met accepted classification criteria for antiphospholipid syndrome since repeat testing was not done.[45,46] Therefore, patients with this syndrome and stroke are not well represented in Lim and colleagues' systematic review.[62]

With a different approach, the systematic review by Ruiz-Irastorza and colleagues[63] included observational studies that raised the number of reports to 16 and of patients to 1740.[63] Several subgroups could be identified according to the risk of recurrent thrombosis. Patients not fulfilling laboratory criteria for definite antiphospholipid syndrome were at a risk of recurrences similar to that for the general population, irrespective of whether presenting with venous or arterial events. Patients with definite antiphospholipid syndrome presenting with a first venous event were well protected from recurrences with oral anticoagulation to a target INR of 2·0–3·0. However, patients with definite syndrome having arterial or recurrent events, or both, were at an increased risk for recurrences, even when treated with oral anticoagulation to a target INR of 2·0–3·0. Overall, recurrences were very infrequent in patients effectively receiving oral anticoagulation to an INR of 3·0–4·0. 18 patients died as a result of recurrent thromboses, mostly arterial, versus only one dying of bleeding. The investigators could not address the effect of concomitant cardiovascular risk factors on the outcome of the study.

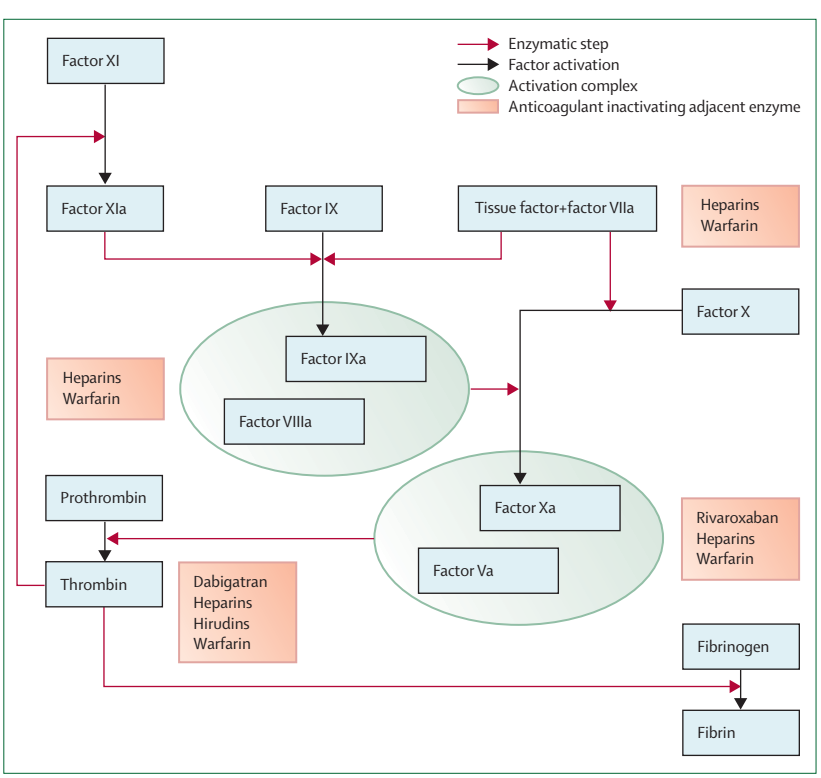

Figure 3: **Coagulation cascade and sites of action of antithrombotic drugs**

	Secondary prophylaxis
Patients with definite antiphospholipid syndrome and first venous event*	Indefinite anticoagulation to a target INR 2·0–3·0
Patients with definite antiphospholipid syndrome and arterial event*	Indefinite anticoagulation to a target INR 3·0–4·0 or combined antithrombotic treatment
Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2·0–3·0	Indefinite anticoagulation to a target INR 3·0–4·0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin
Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for deep vein thrombosis treatment
Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for arterial thrombosis

INR=international normalised ratio. *Less aggressive or long-lasting antithrombotic treatments might be appropriate in low-risk patients.

Table 1: **Recommendations for secondary prophylaxis in patients with antiphospholipid antibodies and thrombosis**

	Primary thromboprophylaxis
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
All patients with antiphospholipid antibodies	Strict control of vascular risk factors
High-risk situations (surgery, post partum, long-lasting immobilisation)	Adequate thrombophylaxis

Table 2: **Primary thromboprophylaxis in patients with antiphospholipid antibodies**

With the present state of knowledge, which is largely based on retrospective studies with inherent weaknesses, we recommend indefinite anticoagulation at an INR of 2·0–3·0 for patients with antiphospholipid syndrome presenting with first venous events.[62,63] However, debate persists about treatment for patients with arterial thromboses.[61–63,68] We believe that antiphospholipid patients with arterial disease or recurrent events, or both, need a more aggressive treatment, which might include warfarin with a target INR of more than 3·0 or combined antithrombotic therapy. However, new recommendations, taking into account both the clinical and immunological profile of patients with antiphospholipid syndrome, are likely to be agreed after the recent International Congress on Antiphospholipid Antibodies, held in Texas, USA, in April, 2010. Patients with single positivity for antiphospholipid antibodies (anticardiolipin or anti-β2-glycoprotein 1) and non-life threatening thrombosis will probably be recommended to receive less intense or extended antithrombotic regimens, especially in the setting of reversible triggers. Concomitant vascular risk factors, which increase the likelihood of thrombosis in patients with antiphospholipid antibodies,[13,69–71] have to be addressed and treated. Patients with thrombosis and antiphospholipid antibodies not meeting laboratory criteria for antiphospholipid syndrome should be managed in the same way as the general population.[63] Table 1 shows a summary of recommendations for secondary prophylaxis.

With regard to primary thromboprophylaxis, retrospective studies suggest that patients with lupus and antiphospholipid antibodies will develop thrombosis at a yearly rate of about 3–4%.[72,73] Between 3% and 7% of women with purely obstetric antiphospholipid syndrome might also have subsequent thromboses per year,[44,73] although other series have recorded yearly incidences of less than 1%.[74] However, the actual risk in healthy asymptomatic carriers of antiphospholipid antibodies is probably low.[75]

Results from a randomised trial showed no difference between asymptomatic antiphospholipid antibody carriers given low-dose aspirin and those given placebo.[76] However, the rate of thrombosis in patients given placebo was zero, and the study was underpowered to detect a beneficial effect of aspirin. Such a low risk of events could be attributable to short follow-up, good control of vascular risk factors, and patients' immunological profile, which included IgA anticardiolipin. The number of patients with lupus anticoagulant or with obstetric antiphospholipid syndrome was not clear. By contrast, results from observational studies have consistently shown a protective effect of aspirin in asymptomatic antiphospholipid antibody carriers with systemic lupus erythematosus[13,71,77–79] and in women with obstetric antiphospholipid syndrome.[44]

In view of its low potential for toxic effects, many experts understandably recommend low-dose aspirin (combined with hydroxychloroquine) to be considered as primary thromboprophylaxis in patients with systemic lupus erythematosus having lupus anticoagulant or persistently positive anticardiolipin, or both. Women with obstetric antiphospholipid syndrome are also candidates for long-term treatment with aspirin, dependent on the characteristics of their profile of antiphospholipid antibodies. Data from higher-quality studies would be useful. Therapy for healthy carriers of antiphospholipid antibodies should be individualised,

and treatment of patients with persistent positivity of several antiphospholipid antibodies, including lupus anticoagulant, should be considered. Other vascular risk factors should be aggressively sought and managed in all patients with antiphospholipid antibodies (table 2).

On the basis of experience of the CAPS registry, less severe cases of CAPS can be managed with anticoagulation and high-dose steroids. For life-threatening manifestations, either intravenous immunoglobulins or plasma exchange should be added.[80] With this regimen, more than 65% of patients with severe disease survive.[80]

Pregnancy management

With proper management, more than 70% of pregnant women with antiphospholipid syndrome will deliver a viable live infant.[81] Ideally, preconception counselling gives the physician the opportunity to understand the specific context of each patient with the syndrome and to outline the risks of pregnancy and treatment. Pregnancy should be discouraged in all women with important pulmonary hypertension because of the high risk of maternal death,[82] and should be postponed in the setting of uncontrolled hypertension or recent thrombotic events, especially stroke.[82]

A complete profile of antiphospholipid antibodies, including repeated anticardiolipin and lupus anticoagulant, should be available before planning of pregnancy. However, these tests do not need to be repeated during pregnancy, since subsequent negative results (after diagnostic, repeatedly positive tests) do not eliminate the risk of complications.[82] We recommend frequent prenatal visits, at least every 2–4 weeks before mid-gestation and every 1–2 weeks thereafter. The objectives of prenatal care in the second and third trimesters are close observation for maternal hypertension, proteinuria and other features of pre-eclampsia, frequent patient assessment, obstetric ultrasound to assess fetal growth and amniotic fluid volume, and appropriate fetal surveillance testing. Surveillance testing should begin at 32 weeks' gestation, or earlier if the clinical situation for placental insufficiency is suspected, and should continue at least every week until delivery. Uterine and umbilical artery Doppler assessments are widely used in Europe to assess the risk for pre-eclampsia, placental insufficiency, and fetal growth restriction after the 20th week of gestation, and normal examinations have high negative predictive values.[83] Regular and coordinated medical consultation every 2–4 weeks, especially in women with systemic lupus erythematosus, is recommended.

The goals of treatment in pregnant women with antiphospholipid syndrome are to improve maternal and fetal-neonatal outcomes by keeping to a minimum the risks of the recognised complications of the disorder, including maternal thrombosis, fetal loss, pre-eclampsia, placental insufficiency, and fetal growth restriction, and the need for iatrogenic preterm birth.[41] Heparin and low-dose aspirin are the treatments of choice for antiphospholipid syndrome in pregnancy. Heparin is usually started in the early first trimester after presence of a live embryo is shown by ultrasonography. Most investigators recommend preconceptional aspirin because of its possible beneficial effect on early stages of implantation.[84] Early enthusiasm for glucocorticoids to treat pregnant women with antiphospholipid syndrome waned in the early 1990s when two small randomised trials recorded no benefit.[85,86] Moreover, results from randomised trials showed no benefit from use of intravenous immunoglobulins either when added to heparin or used alone.[87–89] A subsequent Cochrane analysis concluded that intravenous immunoglobulins were associated with an increased risk of pregnancy loss or premature birth, compared with heparin and low-dose aspirin.[90]

Pregnant patients with antiphospholipid syndrome without having had a previous thrombotic event might be classified into one of two groups for the benefit of treatment: (1) patients with recurrent early (pre-embryonic or embryonic) miscarriage and no other features of antiphospholipid syndrome, or (2) those with one or more previous fetal deaths (at more than 10 weeks' gestation) or previous early delivery (at less than 34 weeks' gestation) because of severe pre-eclampsia or placental insufficiency. A third group of patients consists of those with a history of thrombosis, irrespective of pregnancy history. Table 3 summarises recommended treatments for the three groups.

Three randomised trials[92–94] and one trial with consecutive treatment assignment[95] have addressed pregnancy in patients with antiphospholipid syndrome who have predominantly recurrent early miscarriage. In two trials,[92,95] the proportion of successful pregnancies substantially improved with the addition of unfractionated heparin to low-dose aspirin. Two other randomised trials,[93,94] both using low-molecular-weight heparin, proved negative. Of note is that the heterogeneity in the results is attributable to outcomes in women receiving aspirin only. Additionally, two studies recorded no differences in pregnancy outcomes when comparing unfractionated heparin with low-molecular-weight heparin, both combined with aspirin.[96,97] Finally, several observational studies have reported pregnancy success rates of 79–100% with low-dose aspirin alone.[84,85,98–102] Moreover, data from meta-analysis[103] have shown a significant reduction of pregnancy complications in women at high risk for pre-eclampsia who were given antiplatelet agents (mostly aspirin). In all clinical trials, maternal and fetal-neonatal outcomes in pregnancies progressing beyond 20 weeks' gestation were benign, with the frequencies of fetal death, pre-eclampsia, severe placental insufficiency, and iatrogenic preterm birth close to those of the general obstetric population.

Despite the obvious controversies raised by these trials, a 2005 Cochrane systematic review concluded that

	Regimen
Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage	Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)
Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency	Low-dose aspirin plus: • Unfractionated heparin (7500–10 000 IU subcutaneoulsy every 12 h in the first trimester; 10 000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1·5 times the control mean) • LMWH (usual prophylactic doses)
Antiphospholipid syndrome with thrombosis	Low-dose aspirin plus: • Unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the mid-interval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range) • LMWH (usual therapeutic dose—eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1·5 mg/kg/day subcutanously, or dalteparin 200 U/kg/day subcutaneously)†

aPTT= activated partial thromboplastin time. LMWH=low-molecular-weight heparin. *Women without a lupus anticoagulant in whom the aPTT is normal can be monitored with the aPTT. Women with lupus anticoagulant should be monitored with antifactor Xa activity. †Need for dose adjustments over the course of pregnancy remains controversial.[91] Some experts argue that in the absence of better evidence, it is prudent to monitor anti-factor Xa LMWH concentrations 4–6 h after injection with dose adjustment to maintain a therapeutic antifactor Xa concentration (0·6 to 1·0 U/mL if a twice-daily regimen is used; slightly higher if a once-daily regimen is chosen).

Table 3: **Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy**

women with recurrent miscarriage and antiphospholipid syndrome should be given a combination of heparin 5000 IU subcutaneously twice daily and low-dose aspirin.[90] Expert guidelines recommend the combination of aspirin with either low-dose heparin or low-molecular-weight heparin.[91] However, we believe that the option of monotherapy with aspirin cannot be ruled out in this subgroup of women.

Results from randomised trials do not define optimum treatment for women with fetal death (>10 weeks' gestation) or previous early delivery (<34 weeks' gestation) due to severe pre-eclampsia or placental insufficiency. Most experts recommend low-dose aspirin and either prophylactic or intermediate-dose heparin (table 3).[41,90,91] The preponderance of data show that good pregnancy outcomes are achieved with heparin started in the early first trimester when a live embryo is detectable by ultrasound.

For pregnant women with antiphospholipid syndrome who have had a previous thrombotic event, low-dose aspirin and therapeutic dose heparin or low-molecular-weight heparin anticoagulation are recommended (table 3).[91] Vitamin K antagonists are teratogenic and should be avoided between 6 and 12 weeks' of gestation. Because of the risk of fetal bleeding thereafter,[91,104] warfarin after 12 weeks' gestation should be given only in exceptional circumstances.

Antithrombotic coverage of the post-partum period is recommended in all women with antiphospholipid syndrome, with or without previous thrombosis.[91] Generally, women with previous thrombosis will need long-term anticoagulation, and we prefer switching the treatment to warfarin, as soon as the patient is clinically stable after delivery. In patients with no previous thrombosis, the recommendation is prophylactic dose heparin or low-molecular-weight heparin therapy for 4–6 weeks after delivery,[91] although warfarin is an option. Both heparin and warfarin are safe for breastfeeding mothers.[104]

Future therapies

Several potential new therapeutic approaches for antiphospholipid syndrome are emerging (panel 3). Antiplatelet drugs other than aspirin have been used only rarely in patients with this disorder.[105] However, combination treatment with aspirin plus dipyridamole and aspirin plus clopidogrel have shown higher efficacy than has aspirin alone in patients with stroke[106] or atrial fibrillation,[107] respectively. Such combinations might be considered in selected patients with antiphospholipid syndrome in whom warfarin is not effective or safe. Likewise, studies of new oral antifactor Xa and anti-factor IIa drugs have not been done in patients with antiphospholipid syndrome.[108] Rivaroxaban and dabigatran have been licensed for primary thrombo-prophylaxis after orthopaedic surgery in many settings. The results of the RE-LY trial, done in 18 113 patients with atrial fibrillation at high risk for arterial thromboembolism, showed that dabigatran, at a dose of 110 mg twice daily is as effective but safer than warfarin, whereas doses of

Panel 3: **Potential future therapies for antiphospholipid syndrome**

- Combination antiaggregant therapy (low-dose aspirin plus clopidogrel or dipyridamole)
- Oral antifactor Xa drugs (rivaroxaban, apixaban)
- Direct thrombin inhibitors (dabigatran)
- Statins (fluvastatin, rosuvastatin)
- Hydroxychloroquine
- B-cell depletion (rituximab)

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150 mg twice daily are more effective and equally safe.[109] Data of the RE-COVER study,[110] comparing dabigatran 150 mg twice daily with warfarin in the treatment of acute venous thromboembolism after heparin treatment, showed an equivalence of both therapies in relation to efficacy and toxic effects.[110] One of the major advantages of dabigatran and rivaroxaban is that regular blood tests are not needed to monitor the anticoagulant effect. However, both are limited by the inability to reverse their anticoagulant effect.

B-cell depletion therapy with the chimeric monoclonal antibody rituximab has been tested in patients with severe forms of antiphospholipid syndrome. Experience is limited to case reports; however, a high response rate—more than 90%—has been recorded.[111]

Of non-antithrombotic drugs, statins and hydroxychloroquine deserve particular attention. Statins inhibit NFκB and, in addition to their known cholesterol-lowering effects, could have antithrombotic properties in patients with antiphospholipid syndrome.[112] Fluvastatin inhibits tissue factor production induced by antiphospholipid antibodies both in mice models[113] and in cultured human endothelial cells.[114] Statins also prevent the increased adhesiveness of endothelial cells induced by anti-β2-glycoprotein 1.[115] In a pilot trial with fluvastatin in nine patients with antiphospholipid syndrome, fluvastatin at 40 mg per day decreased the concentrations of inflammatory and thrombogenic mediators after 30 days of treatment.[116] For patients without antiphospholipid syndrome, intensive lipid-lowering treatment with statins is recommended in patients with stroke or transient ischaemic attack.[117] Moreover, data from the JUPITER trial showed a decreased risk of venous thromboembolism in healthy people with normal cholesterol concentrations given rosuvastatin.[118] Thus, statins will probably be widely prescribed to patients with antiphospholipid syndrome, including those with normal cholesterol values, once clinical studies are available for this group of patients. Clinicians should be aware, though, that statins are qualified as category X by US Food and Drug Administration and are therefore contraindicated in pregnancy.

Hydroxychloroquine is a cornerstone drug for systemic lupus erythematosus because of its beneficial effects on lupus activity and damage, resulting in an improvement of survival.[119] A reduction of thrombosis and cardiovascular deaths has been recorded in lupus patients taking antimalarial drugs.[119] Observational studies have suggested an antithrombotic effect of hydroxychloroquine in patients with antiphospholipid antibodies, most of whom have systemic lupus erythematosus.[19,71,120] Furthermore, results from basic studies have shown a dose-dependent reduction by hydroxychloroquine of platelet activation and clotting induced by antiphospholipid antibodies.[121,122] Hydroxychloroquine directly inhibits the binding of antiphospholipid antibody-β2-glycoprotein-1 complexes to phospholipid surfaces.[123] An additional and previously unrecognised role of hydroxychloroquine in prevention of pregnancy loss is suggested by the description of its protective effect of the annexin A5 shield formed over phospholipid bilayers from damage induced by antiphospholipid antibodies.[124]

In view of the excellent safety profile, including the absence of any adverse effects on the fetus-neonate,[119] and the absence of associated bleeding, hydroxychloroquine should be considered for an adjuvant antithrombotic role in patients with systemic lupus erythematosus who are positive for antiphospholipid antibodies. Patients with primary antiphospholipid syndrome and recurrent thrombosis despite adequate anticoagulation, who have difficulty maintaining adequate anticoagulation intensity, or have a high-risk profile for major haemorrhage, might also benefit from hydroxychloroquine treatment.

Contributors

All authors contributed equally to writing the manuscript.

Conflicts of interest

We declare that we have no conflicts of interests.

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