# Antiphospholipid syndrome

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**Abstract**

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by thrombosis (venous and/or arterial or microvascular) and/or pregnancy loss or complications in association with persistently positive antiphospholipid antibodies (aPL). Numerous other systemic manifestations are designated in the international consensus criteria (Sydney) for diagnosis of APS as features associated with APS or non-criteria features. In recent years, research into aPL has increased our understanding of the pathogenic process and encouraged improved detection of aPL. There is growing evidence that complement activation plays a key role in the pathogenesis of APS. This review outlines the key features of APS, including the diagnostic laboratory tests and their interpretation, and offers advice regarding the management of patients with APS both in the medical and obstetric settings.

**Keywords** Anticardiolipin antibodies; anticoagulation; antiphospholipid syndrome; complement; β2-glycoprotein-I antibodies; lupus anticoagulant; obstetric morbidity; thrombosis

## What's new?

- APS ACTION is the AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) (http://www.apsaction.org/)
- Growing evidence suggests that low-positivity aPL are implicated in recurrent miscarriages and late placenta vascular-mediated obstetric morbidity
- Complement activation may play a role in both obstetric and thrombotic manifestations of APS and the terminal complement component inhibitor, eculizumab, may be useful in patients with CAPS
- There is evidence that IgG antibodies to the epitope, arginine 39-arginine 43 of the domain I (DI) portion of anti-β2-GPI (anti-DI antibodies) are strongly associated with thrombotic risk in patients with APS
- Various new assays are in development, particularly for anti-DI and an annexin A5 resistance test.
- The RAPS trial (Rivaroxaban in AntiPhospholipid Syndrome) is assessing the use of rivaroxaban, a new-generation oral anticoagulant, in thrombotic APS (http://www.controlled-trials.com/ISRCTN68222801)

Antiphospholipid syndrome (APS) is characterized by thrombosis (venous and/or arterial or microvascular) and/or pregnancy loss or morbidity in association with persistent positivity of a heterogeneous group of autoantibodies known as antiphospholipid antibodies (aPL). The international consensus criteria (Sydney) for APS were designed for scientific clinical studies, but these clinical and laboratory diagnostic criteria can be applied to diagnosis of APS in routine clinical practice. The primary targets of aPL are phospholipid-binding proteins, although antibodies directed against phospholipids and other proteins also occur. One or more of the non-criteria features of APS, such as heart valve disease, livedo reticularis (LR), thrombocytopenia, and nephropathy, may present in association with thrombosis and/or pregnancy morbidity or as isolated features. In the laboratory, the usual diagnostic tests for aPL are:

- lupus anticoagulants (LA), which cause prolongation of *in vitro* phospholipid-dependent clotting assays (e.g. activated partial thromboplastin time, dilute Russell's viper venom time [DRVVT]), which are corrected by the addition of excess phospholipid (e.g. from platelets)
- anticardiolipin antibodies (aCL) of immunoglobulin (Ig) G and IgM classes, which are determined by enzyme-linked immunosorbent assay (ELISA) and should be moderate or high positivity (i.e. exceeding 40 IgG phospholipid units (GPL) or IgM phospholipid units (MPL), or exceeding the 99th percentile, which is the cut-off beneath which aCL values lie in normal individuals for 99% of the time)
- anti-β2-glycoprotein-I (β2-GPI) antibodies of IgG and IgM class detected by ELISA that should be moderate or high positivity (>the 99th percentile).

Persistently positive aPL is defined as the presence of one or more of the antibodies defined above on two or more occasions at least 12 weeks apart.[1]

## Introduction

The prevalence of aPL in the form of LA, aCL and anti-β2-GPI, based on single-point prevalence in epidemiological studies, is approximately 1–3.5% of healthy individuals.[2] The prevalence increases in the elderly and in those with chronic disease.[3] Clinical associations of aPL are listed in Table 1. APS has been described as secondary if there is an associated autoimmune disorder, but the international consensus classification advises against using the term 'secondary' on the basis that the relationship between APS and systemic lupus erythematosus (SLE) may not be simply causal.[1] Several studies have shown that the prevalence of aPL in SLE patients is variable (15–86%). The frequency of antibody positivity is likely to be around 30%, with the wide variation found in the literature explained by study variations, ethnicity and

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## Clinical associations of antiphospholipid antibodies

Conditions associated with production of aPL

- Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Behçet's disease, temporal arteritis, Sjögren's syndrome
- Infections — HIV, varicella, hepatitis C, syphilis, malaria, leprosy
- Drugs — phenothiazines, procainamide, phenytoin, quinidine, hydralazine
- Lymphoproliferative disease (lymphoma, paraproteinaemia)

Clinical manifestations in patients with aPL

- Cardiovascular — venous/arterial thromboembolic disease, valvular heart disease, sterile endocarditis with embolism
- Obstetric — recurrent miscarriage, intrauterine fetal death (IUFD), stillbirth, early severe pre-eclampsia, HELLP* syndrome, placental insufficiency, prematurity, intrauterine growth restriction (IUGR)
- Neurological — cerebral ischaemic events, chorea, dementia, psychiatric disorders, transverse myelopathy, seizures, Guillain—Barré syndrome, Sneddon's syndrome
- Haematological — autoimmune thrombocytopenia, autoimmune haemolytic anaemia
- Dermatological — livedo reticularis

aPL, antiphospholipid antibodies; *HELLP, haemolysis, elevated liver enzymes and low platelets.

**Table 1**

extent of autoimmune disease activity. Up to an estimated 40% of patients with SLE and aPL will eventually develop clinical features consistent with APS, whereas under 5% of patients with APS will develop SLE. Well-designed multi-centre prospective studies involving large numbers of patients with APS are lacking. APS ACTION (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking; http://www.apsaction.org/) has set up a large-scale, international multi-centre clinical registry specifically designed for patients with persistently positive aPL. The primary objective of this registry is to define the natural course of at least 2000 patients over 10 years.[4]

## Pathogenesis

Animal studies suggest that aPL is directly prothrombotic, and a number of mechanisms for aPL-mediated thrombosis and pregnancy loss or complications have been proposed.[5,6] Evidence also suggests that altered regulation of complement may play a key role in the development of pregnancy loss or complications and thrombosis in APS.

Proposed mechanisms of aPL-mediated thrombosis and pregnancy complications are listed in Table 2. The clinical significance of any one or more of these hypotheses remains unclear and reflects the likely multifactorial complex nature of this condition, as is generally the case in acute thrombosis. Despite the persistent presence of aPL in the systemic circulation, thrombotic events occur only occasionally, suggesting that presence of aPL alone may not be sufficient to cause thrombosis and/or pregnancy failures. The development of aPL is probably only one step towards the development of APS, and it is likely that other factors play a role. Such 'second hits' or 'triggers' may tip the thrombotic/haemostatic balance in favour of a prothrombotic state, and include infection, endothelial injury, and other non-immunological procoagulant factors.[6] The patient's genetic make-up, in relation to candidate genes for inflammatory mediators, may also be a critical variable for the development of clinical APS manifestations. Data from several studies and systematic reviews suggest that positive LA are a stronger risk factor for the development of thrombosis than are aCL or anti-β2-GPI. In addition, a first thromboembolic event is considered rare in aPL carriers but the risk in those who are 'triple positive' for all of LA, aCL and anti-β2-GPI appears to be considerable (cumulative incidence after 10 years 37%).[6]

Among anti-β2-GPI antibodies it is those that bind specifically to a limited epitope on domain 1 of the protein (Arg39-Arg43) that appear to be most strongly associated with thrombosis.[7] Both retrospective and prospective studies suggest that weakly positive aPL (95th—99th percentile of GPL or MPL of either aCL or anti-β2-GPI or both) are implicated in recurrent miscarriage.[8] A retrospective cohort study has demonstrated that over 50% of women with clinical features of obstetric APS, but no thrombosis, had low-positivity aCL and/or anti-β2-GPI in the absence of LA.[9] Furthermore, clinical studies have demonstrated that persistent weakly positive aCL in untreated pregnancies of women with recurrent miscarriage and aPL were associated with a >90% fetal loss rate, and with significantly improved pregnancy outcome following treatment with low-dose aspirin or heparin/low molecular weight heparin (LMWH) and aspirin.[10]

## Clinical features

### Thrombosis

The association between aPL and thrombotic events is well established. Venous thromboembolism (VTE) is a common disorder, occurring in 1 per 1000 people per year[11] with APS accounting for approximately 10% of these acute VTE cases. The deep veins of the lower limbs is the most common site of venous thrombosis in APS and nearly half of patients presenting with deep venous thrombosis (DVT) also have pulmonary embolism. The most frequent site of arterial occlusion is in the cerebral vasculature, which may be thrombotic or embolic, resulting in transient cerebral ischaemic attacks (TIAs) and/or stroke. It has been observed that 13% and 7% of patients with ischaemic stroke and TIAs, respectively, are aPL positive, and that more than 20% of strokes in patients younger than 45 years of age are probably associated with APS. However, data relating to a possible association between aPL and stroke recurrence in older patients are conflicting. The British Committee for Standards in Haematology (BCSH) guidelines recommends that young adults (<50 years) with ischaemic stroke should be screened for aPL (level 2C).[3] Any site of the vascular system can be affected. Concomitant presence of other risk factors for thrombosis (e.g. pregnancy and surgery) increases the risk of thrombosis in APS patients, as do co-existent heritable thrombophilias such as factor V Leiden.

## Neurological manifestations

Ischaemic stroke due to arterial thrombosis is the most common neurological manifestation (>50% of CNS complications) in APS.