Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterised by venous or arterial thrombosis, and/or pregnancy loss or complications in the presence of persistently positive antiphospholipid antibodies (aPL). Patients can also develop other organ involvement, referred to as non-criteria manifestations including livedo reticularis, thrombocytopaenia and nephropathy. Increasingly, non-thrombotic inflammatory mechanisms are identified in APS pathogenesis along with recognition that obstetric APS may be a specific subset of APS. Treatment remains focused on lifelong anticoagulation, and prevention of further thrombosis/ obstetric complications. Identification however, of novel mechanisms are leading development of diagnostic tests and more targeted therapies to improve management of this disease.

Introduction

Clinical manifestations of venous or arterial thrombosis and/or certain forms of pregnancy loss in the presence of persistently positive antiphospholipid antibodies (aPL) are required to classify (1) antiphospholipid syndrome (APS) according to international criteria (Table 1). These criteria, primarily intended to create well defined cohorts for research studies, are routinely applied in clinical practice to aid diagnosis. Current criteria aPL tests include detection of: anti-cardiolipin antibodies (aCL) and/or anti-β2-glycoprotein I (β2GPI) antibodies by enzyme linked immunosorbent assay (ELISA); and/or positive lupus anticoagulant (LA) assay by prolongation of *in vitro* phospholipid (PL) dependent clotting assays that can be corrected by addition of excess PL.

Epidemiology

Estimates of aPL in the general population vary around 1-5% and their prevalence is increased in: the elderly; various medications; infections (including human immunodeficiency virus, varicella, hepatitis C, syphilis, malaria and leprosy);

lymphoproliferative disorders; and other autoimmune rheumatic diseases (ARD), principally systemic lupus erythematosus (SLE). The precise prevalence of APS however is unknown. The APS Alliance for Clinical Trials and International Networking (APS ACTION) systematically analysed published studies to produce estimates of aPL prevalence of: 6% in pregnancy morbidity; 10% in deep vein thrombosis (DVT); 11% in myocardial infarction; 14% in stroke; and 17% in stroke in individuals less than 50 years.

An observational European study (Euro-Phospholipid project) has defined the characteristics of 1000 patients with APS (2). Of these patients 82% were female and the majority (53.1%) had primary APS in the absence of another disease and the remainder had APS in association with another ARD, most commonly SLE. Although these cases were originally defined as secondary APS this distinction is now considered less useful and current classification criteria recommend any associated disorder be reported as ARD associated APS. Although, aPL are found in up to 40% of patients with SLE only 40% of those patients will develop APS. A more severe variant with widespread microvascular thrombosis and high morbidity/mortality, known as Catastrophic (C)APS occurs in 1% of patients with APS.

Pathogenesis

Animal models and in vitro studies provide direct evidence that aPL cause thrombotic and obstetric APS manifestations (3). One of the main distinguishing properties of pathogenic aPL is their binding to β2GPI, a protein composed of five regions called domains (D)I to V that contains an important epitope for pathogenic aPL on DI, particularly the region from arginine (Arg)39 to Arg43. Other antibodies have been identified in APS including those directed against prothrombin, protein C, protein S, Annexin V and Factor Xa. Interestingly, antibodies directed against β2GPI and prothrombin have shown to be responsible for prolongation of clotting times observed *in vitro* in LA tests. In contrast to this *in vitro* anticoagulant phenomenon, pathogenic aPL have been shown to have inflammatory, thrombotic and adverse obstetric effects in various animal models and upon various target cells including: monocytes, endothelial cells, neutrophils and trophoblast cells, leading to the recruitment of cell surface receptors, perturbation of intracellular signalling pathways and upregulation of pro-inflammatory and pro-coagulant factors. These effects are mediated through interactions with components of the coagulation and/or complement

cascade as well as cell surface interactions between aPL-β2GPI complexes cross-linking various receptors on different cell types (Figure 1).

A "two-hit" hypothesis has been proposed, whereby the first hit is an aPL induced pro-thrombotic/inflammatory state and the second is exposure to an acute precipitating event such as surgery, immobilisation, exogenous oestrogen or pregnancy. Interestingly, pregnancy does not serve purely as a precipitating pro-thrombotic state, since comparison of products of conception from aPL-positive and negative patients with recurrent early miscarriage demonstrates a specific defect in decidual endovascular trophoblast invasion in obstetric (O)APS and that placental infarction is not unique to APS. Increasingly, experimental evidence implicates non-thrombotic mechanisms in the pathogenesis of OAPS by aPL mediated complement activation, inflammation as well as impairment of placental development and function (Figure 1). In addition, clinical data from the European registry on Obstetric APS (EUROAPS) on 247 patients with OAPS demonstrated that progression to thrombosis and SLE are scarce compared with patients with thrombotic APS (4), thus lending credence to the hypothesis that OAPS is a specific subset with APS.

Clinical features

Although vascular thrombosis and certain adverse pregnancy outcomes remain are the main clinical features of APS other non-classification criteria clinical features are increasingly recognised (Table 2) and indicate the variety of non-thrombotic effects of aPL. For instance, in the Euro-Phospholipid project the most common presenting non-criteria features were thrombocytopenia (21.9%), livedo reticularis (20.4%), superficial thrombophlebitis (9.1%), and haemolytic anaemia (6.6%).

Vascular thrombosis

Thrombotic events are the hallmark of APS, most commonly venous events in the lower limbs. The presence of aPL increases the risk of venous thrombosis in patients with SLE two-fold for aCL and six-fold for LA, compared to normal populations. In patients without an underlying ARD, venous thrombotic risk is increased 1.5-fold for aCL and up to 10-fold for LA, whilst arterial thrombosis is increased three (aCL) and four (LA) - fold. The risk of recurrent thrombosis or thromboembolism may be further enhanced in patients with triple

positivity to LA, aCL and anti- β2GPI antibodies. Vascular events in the Euro-Phospholipid project included DVT (32%), stroke (13.1%), pulmonary embolism – PE - (9.0%), transient ischaemic attack (7.0%) and amaurosis fugax (2.8%). Given that aPL positivity is found in 17% of strokes in patients less than 50 years of age (compared with 0.7% of controls), the British Society of Haematology guidelines on investigation and management of APS recommends that anyone presenting with an ischaemic stroke under the age of 50 be screened for aPL (5).

Obstetric manifestations

The current classification of obstetric APS is shown in Table 1. Recurrent miscarriages are a hallmark of APS. In the Euro-Phospholipid project the most common fetal complications were early fetal loss (35.4%), late fetal loss (16.9%), and premature birth (10.6% of live births). The most common obstetric complications in the mother were preeclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae (2.0%). Similarly, recurrent miscarriage and late fetal loss were the commonest complications in the EUROAPS registry. Whilst, laboratory data from the Euro-phospholipid and EUROAPS series confirm associations between all criteria aPL and pregnancy complications, the strongest association was found with LA and triple positivity.

Non-Criteria Manifestations

Although many of the multisystem manifestations of APS (Table 2) are thrombotic in nature, it is increasingly recognised that aPL have other immune mediated effects that give rise to manifestations that fall outside of current APS classification criteria. These non-criteria manifestations involve multiple organ systems. Patients may present with valvular heart disease, and develop a sterile endocarditis (Libman-Sacks endocarditis) that give rise to embolic complications. Livedo reticularis is the most common dermatological manifestation of APS and when associated with aPL and stroke is known as Sneddon syndrome; less commonly skin ulceration may occur. Other non-ischaemic neurologic complications include chorea, psychiatric disorders, Guillain-Barre syndrome, transverse myelopathy, dementia and seizures. Thrombocytopaenia is a common finding on laboratory investigations, as is a prolonged aactivated Partial Thromboplastin Time (aPTT), yet bruising is rarely seen. An APS nephropathy has been described in which aPL cause renal endothelial intimal hyperplasia

independently of thrombosis due to activation of the mammalian target of rapamycin (mTOR) pathway.

Catastrophic antiphospholipid syndrome (CAPS)

CAPS is a rare form of APS with high mortality presenting as a microangiopathic storm in the presence of aPL with no other likely diagnosis. Classification criteria have been developed and require presence of aPL, rapid onset of microthrombii in three or more organs within a week, biopsy confirmation of microthrombii and exclusion of other causes. In 65% of cases there is a precipitating cause such as infection, a surgical procedure or cessation of anticoagulation. It typically presents with multi-organ failure of kidneys, lungs, bowel, heart and brain. Mortality is high (44%) without treatment.

Seronegative APS

The occurrence of typical thrombotic or obstetric manifestations satisfying APS classification criteria in patients who are persistently negative for criteria aPL and lack any other identifiable cause has led to the concept of seronegative APS. This concept has not been as readily accepted as in other ARD, such as seronegative rheumatoid arthritis, but may be explained by a problem with sensitivity of current criteria tests rather than inaccurate diagnosis and has led to a search for other non-criteria aPL. A recent cohort study of 40 patients with seronegative APS, found 10% of patients to be positive for one or more non-criteria aPL, including anti-DI IgG and IgA aCL.

Diagnosis

The diagnosis of APs should be considered in the presence of otherwise unexplained: one or more thrombotic events; one or more specific adverse pregnancy events; thrombocytopenia or prolongation of clotting assay. Antibody testing for aPL should then be performed in these patients. Diagnosis is usually made according to classification criteria (Table 1) and based on the presence of one or both major clinical (thrombotic or obstetric) manifestations and persistent positivity of criteria aPL. It is important to recognise however, that these classification criteria are primarily a research tool that are currently undergoing revision and may alter in future iterations. Therefore, although they are routinely used to diagnose APS, consideration of this diagnosis may be made in certain patients who do not fulfil these

criteria, such as individuals with otherwise unexplained thrombocytopenia, heart valve disease, renal thrombotic microangiopathy, or those with aPL-related clinical events and borderline positive aPL testing. In these circumstances however, consultation with a clinician with expertise in the diagnosis of APS is advised.

Investigations

Laboratory tests

Current criteria aPL tests consist of two direct ELISAs that detect antibodies against CL or β2GPI and the LA assay. Interpretation of the LA test is often challenging and a true positive result requires positivity in two clotting assays one of which must be the Factor Xa dependent dilute Russell Venom Viper Time (dRVVT) and one other, commonly the aPTT. The diagnosis of APS requires persistently positive (on at least two occasions, 12 or more weeks apart) IgG/M aCL and/or IgG/M anti-β2GPI and/or LA tests. There are no data to validate this time interval but it is designed to avoid inclusion of transiently positive (non-pathogenic) aPL that may arise due to infections and are not typically associated with the clinical features of APS.

Further investigations are required to exclude other associated conditions or causes of thrombotic/obstetric manifestations (Table 3). Standard blood tests are useful to examine for complications, coexistent ARD and alternative causes of positive aPL including infections, medications, malignancy as well as other coagulopathies. Thrombocytopaenia is a frequent finding in APS. Raised inflammatory markers, such as ESR may indicate co-existing inflammatory disease. Renal function is required, with a protein to creatinine ratio to exclude renal involvement. Immunology tests include ANA, ENA, C3/C4 and anti-dsDNA antibodies are important to examine for associated ARD, particularly SLE. A thrombophilia screen may be appropriate to exclude other coagulopathies if the findings will alter management as well as evaluation of other risk factors for thrombosis and/or pregnancy morbidity.

Imaging

If respiratory symptoms are the predominant feature, then a chest x-ray is required, followed by a ventilation-perfusion scan or a CT pulmonary angiogram to exclude a

pulmonary embolus. If neurological deficits are apparent then imaging of the brain is required to examine for cerebrovascular disease. Doppler ultrasound is required to confirm suspected DVTs.

Other tests

An ECG may display left ventricular hypertrophy in acute or chronic PE. Echocardiography may be required to detect heart valve lesions.

Histology

Histopathological confirmation is rarely required in primary APS but may be helpful if there is diagnostic uncertainty with manifestations. A typical finding in APS is thrombosis without evidence of inflammation in the vessel wall. Renal biopsies in renal APS carry a high mortality and are rarely indicated unless there is uncertainty as to aetiology of renal impairment, such as in SLE/APS. In patients with primary APS, vasculo-occlussive lesions in small renal vessels may cause fibrous intimal hyperplasia and thrombotic microangiopathy.

Non-criteria tests

Problems with performance of criteria assays has led researchers to try and identify other aPL that are not recognised in standard criteria tests, by the development of alternative "non-criteria" assays. Particular attention has focussed on assays to detect antibodies against other PLs (such as phosphatidylethanolamine and phosphatidylserine (PS)); other proteins of the coagulation cascade (such as prothrombin (PT) and PS-PT complexes); to specific domains (particularly DI) of β2GPI; and a functional assay measuring annexin A5 resistance. In addition, there is increasing interest in detection of IgA aCL and anti-β2GPI. None of these assays however are available or indeed validated for routine clinical use (Table 3).

Management

The management of APS is outlined in Table 4.

Asymptomatic patients

The risk of thrombosis in asymptomatic aPL carriers depends upon the type, titre and number of different aPL positive. A prospective study following aPL positive patients with no

previous thrombosis found that the risk of thrombosis if only one aPL antibody is present is the same for the general population (0.65% per year). The risk increases to 5.3% per year if the patient is triple antibody positive. Although there is no evidence to support routine thromboprophylaxis in asymptomatic aPL carriers, other modifiable vascular risk risk factors should be actively managed, smoking cessation encouraged and oestrogen containing therapies avoided. In transient situations of increased thrombotic risk such as hospitalisation or prolonged immobility short term heparin prophylaxis is advisable. Evidence is limited in women with asymptomatic aPL and no previous pregnancy morbidity and various consensus groups recommend careful monitoring and administration of low-dose aspirin in pregnancy. In women with coexistent SLE the administration of low aspirin has the additional benefit to reduce the risk of pre-eclampsia in pregnancy.

Vascular thrombosis

Anticoagulation treatment is required lifelong for any patient with persistently positive aPL and a history of unprovoked thromboembolism. Anticoagulation is initiated with heparin and continued with warfarin. The intensity of anticoagulation has been much debated and the current standard of care for long term management of venous thrombosis in APS to maintain an INR between 2-3 is based on two randomised controlled trials that found no benefit of high intensity (INR >3) compared with low intensity (INR 2-3) warfarin in preventing recurrent thrombosis. Given that the recurrence rate and number of arterial events was low in these studies, the optimal management of arterial thrombosis in APS remains a matter of debate with some experts recommending a combination of warfarin (INR of 2-3) with low dose aspirin, whilst others advocate warfarin with higher INR of 3-4. It is important to note however, that as the anticoagulant target dose is increased so too is the risk of haemorrhage.

The use of direct oral anticoagulants (DOAC) are established as alternatives to VKAs for a wide range of indications outside of APS and rivaroxaban (a FXa inhibitor) has been shown to be a safe alternative to warfarin in secondary prevention of venous thrombotic APS in the Rivaroxaban in APS (RAPS) study. There is no current evidence however, to support use of DOACs in arterial thrombosis in APS.

For recurrent thrombosis on warfarin options include: increasing target INR to 3-4 if recurrence occurred at INR 2-3; addition of low dose aspirin (or clopidogrel); or switching to low molecular weight heparin (LMWH). Other potential adjunctive agents include: hydroxychloroquine, with proven anti-inflammatory and anti-thrombotic properties in SLE; statins, which have anti-inflammatory properties in small APS cohorts and reduce venous thromboembolism in large population cohorts; and sirolimus, an mTOR inhibitor that has been shown to reduce renal vasculopathy post-renal transplantation for APS nephropathy. Multiple case reports and series have shown benefit of Rituximab in refractory APS and in an open-label phase IIa descriptive pilot (RITAPS) study RTX was effective at controlling some non-criteria manifestations. Potential alternative and future therapies are outlined in Table 5.

Pregnancy

In patients with previous OAPS only (hence lacking thrombosis) low-dose aspirin and LMWH are advised throughout pregnancy. The level of evidence for this therapeutic regime varies for different aPL related obstetric manifestations with some studies supporting aspirin alone. Overall however, systematic reviews and consensus documents support combination with LMWH and aspirin. Where aspirin and heparin are not enough to result in a successful term pregnancy, there are few evidence based options. In patients with SLE/APS consideration should be given to concomitant treatment with medications to control disease activity that are compatible with pregnancy such as steroids and hydroxychloroquine.

In patients with thrombotic APS warfarin is not recommended throughout pregnancy because of its teratogenic effects on the foetus and should be switched to therapeutic heparin at confirmation of pregnancy. Pre-pregnancy counselling is advisable to warn patients of pregnancy risks and these therapeutic requirements.

Catastrophic APS

Management of this rare condition is based on collective experience from the international CAPS registry that suggests anticoagulation, high dose intravenous glucocorticoids, intravenous immunoglobulin, plasma exchange and cyclophosphamide, particularly in ARD

associated APS. Rituximab may be considered if patients are not responsive to standard therapy and a complement inhibitor eculizumab has shown benefit in case reports.

Prognosis

The 10 year follow-up data from the Euro-phospholipid project of patients having standard treatment for APS revealed a re-thrombosis rate of 15.3%. Although the most common presenting thrombotic event was a DVT, arterial thrombotic events increased in incidence during the course of the disease. The commonest obstetric complication was early pregnancy loss in 16.5%. Despite 72.9% of pregnancies succeeding in having one or more live births, there remained a high degree of fetal morbidity (48.2% being premature). A total of 9.3% of patients died during the 10-year period, with severe thrombotic events accounting for the majority of deaths (myocardial infarction, strokes and PE accounts for 36.5%, haemorrhages 10.7%).

Self-assessment Questions

1) A 33 year old woman with SLE presents to the acute medical services with a severe headache which has been progressively deteriorating over the last 2 days. She takes hydroxychloroquine 200 mg BD.

Her initial observations show a blood pressure of 110/70 and heart rate 80. Shortly after this she becomes drowsy and is unable to hold a conversation. There is no obvious focal neurological deficit.

Blood tests show:

ESR 20mm/hr (0-20)

WBC 12 x10^9/L (4-11)

Neutrophils 9 x 10^9/L (2-7.5)

aPTT 42 seconds (23-31 seconds)

Liver function tests normal

C3 0.93 g/L (0.9-1.8)

CRP 2 mg/L (0-5)

What is the most appropriate investigation to elicit the diagnosis?

   a) CT angiography of the brain
   b) Blood and urine culture
   c) Lumbar Puncture
   d) CT brain with venogram
   e) CT brain

Answer is d)- due to the prolonged aPTT, the patient likely has secondary antiphospholipid syndrome, and has developed a venous sinus thrombosis.

2) A 31 year old woman with SLE on hydroxychloroquine attends clinic 7 weeks pregnant. She has had one previous pregnancy 3 years ago however this ended with a miscarriage at 12 weeks, and she is not sure of the cause. She is known to have a persistently positive lupus anticoagulant on previous serological testing.

What are the current guidelines for the management of this patient?

a) Unfractionated heparin

b) Combined low dose aspirin and low molecular weight heparin

c) Low dose aspirin

d) Low molecular weight heparin

e) Hydroxychloroquine and aspirin

The answer is b) the patient fulfils APS classification criteria, and will require both aspirin and LMWH

3) Which of the following is not a criteria aPL test?

a) IgM anti-β2GPI antibodies

b) IgG anticardiolipin antibodies

c) IgG Anti-β2GPI antibodies

d) IgA anticardiolipin antibodies

e) dRVVT for lupus anticoagulant

The answer is d) IgA anticardiolipin antibodies test is not a criteria aPL test currently.

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Classification Criteria

Clinical Criteria:
- Vascular thrombosis
  - Arterial, venous or small vessel thrombosis in any tissue or organ (excluding superficial thrombosis), confirmed by appropriate imaging or histopathology
- Pregnancy morbidity- at least one of the following
  - One or more unexplained deaths of a morphologically normal foetus at or beyond 10th week of gestation
  - One or more premature births or a morphologically normal neonate before 34th week of gestation due to eclampsia or severe pre-eclampsia or placental insufficiency
  - Three or more unexplained consecutive spontaneous abortions before 10th week of gestation, with hormonal, chromosomal or maternal anatomic causes excluded

Laboratory Criteria: Any must be present on 2 or more occasions at least 12 weeks apart:
- Lupus anticoagulant present in plasma, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
- Anticardiolipin antibody of IgG and/or IgM isotype present in medium to high titre (i.e. more than 40 GPL or MPL units) as measured by standard ELISA
- Anti-β2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma, present in medium/high titre (e.g. > 99th centile)

Table 1: Classification Criteria for APS.

Presence of one feature from both clinical and laboratory criteria is required to fit the classification. The classification criteria are primarily a research tool, and do not include all clinical features or manifestations.

Clinical Manifestations in the APS criteria	
Vascular	Venous/arterial thromboembolic disease
Neurological	Stroke, TIA
Obstetric	Recurrent miscarriage, intrauterine fetal death, stillbirth, early severe pre-eclampsia, placental insufficiency,
Non-Criteria Clinical Manifestations of APS	
Cardiovascular	Valvular heart disease, Libman-Sachs endocarditis with embolism
Obstetric	HELLP syndrome, intrauterine growth restriction
Neurological	Chorea, dementia, psychiatric disorders, transverse myelopathy, seizures, Guillain-Barre syndrome, Sneddon syndrome
Haematological	Autoimmune thrombocytopaenia, autoimmune haemolytic anaemia, prolonged aPTT
Dermatological	Livedo reticularis, skin ulceration
Renal	Microthrombotic nephropathy, renal artery stenosis, hypertension

Table 2: Criteria and non-criteria clinical manifestations of APS.

Abbreviations; TIA (transient ischaemic attack); HELLP (haemolysis elevated liver enzymes, low platelets); aPTT (activated partial thromboplastin time).
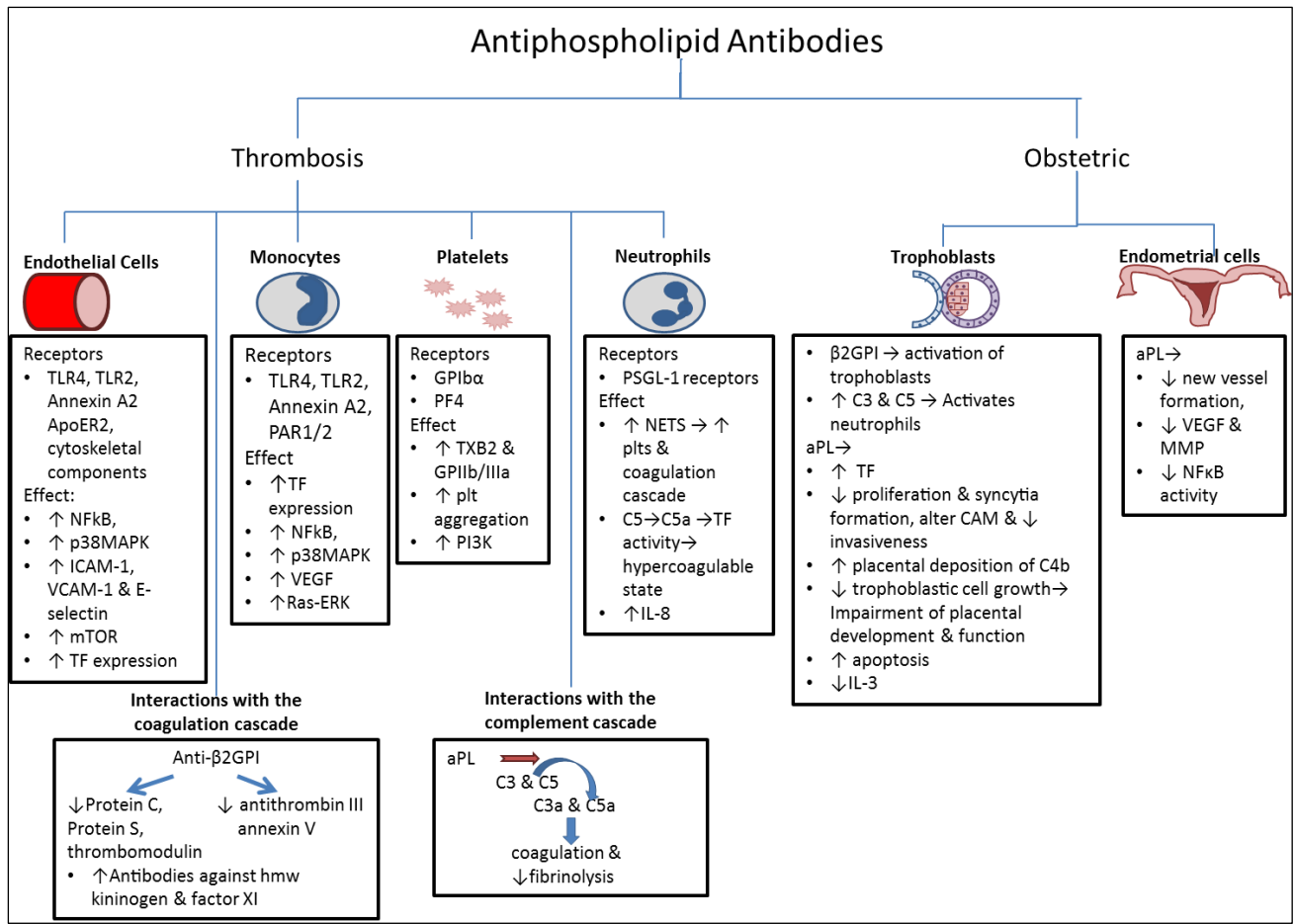
Figure 1: Pathogenesis of thrombotic and obstetric APS.

Abbreviations; TLR (toll like receptor), ApoER (Apolipoprotein E receptor), NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), p38MAPK (p38 mitogen-activated protein kinases), ICAM-1 (Intercellular Adhesion Molecule 1), VCAM (vascular cell adhesion molecule), mTOR (mammalian target of rapamycin), TF (tissue factor), PAR (protease activated receptor), VEGF (vascular endothelial growth factor), Ras-ERK (extracellular signal-regulated kinase), hmw (high molecular weight), aPL (antiphospholipid antibodies), PSGL-1 (P-selectin glycoprotein ligand 1), NETS (neutrophil extracellular traps), IL (interleukin), β2GPI (β2glycoprotein-I), MMP (matrix metalloproteinase)

Investigations in APS

Laboratory tests
- Standard tests
  - FBC
  - Renal & Liver function
  - ESR
  - CRP
  - Coagulation
  - Fasting lipids
  - Glucose &Hba1c
- Urinalysis
  - Urine protein:creatinine ratio
- Immunology
  - IgG/M Anticardiolipin antibodies
  - IgG/M Anti-β2GPI antibodies
  - Lupus anticoagulant
  - ANA, ENA, C3/C4, dsDNA
- ± Thrombophilia screen

Imaging/other tests
- ECG
- CXR
- ± Doppler US (exclude DVT)
- ± CTPA (exclude PE)
- ± Brain MRI (exclude stroke)
- ± Echocardiography (exclude heart

Potential Future Tests (not currently clinically validated)
- Anti PS/PT complex
- IgA anticardiolipin
- IgA anti-β2GPI
- Anti-D1

Table 3: Summary of investigations for suspected APS.

Abbreviations; FBC (full blood count), ESR (erythrocyte sedimentation rate), CRP (C reactive protein), β2GPI (β2 Glycoprotein I), ANA (Antinuclear antibody), ENA (extractable nuclear antigen), C3 (complement C3), dsDNA (double-stranded DNA), ECG (electrocardiogram), CXR (Chest radiograph), US (ultrasound), DVT (deep vein thrombosis), CTPA (computerised tomography pulmonary angiogram), PE (pulmonary embolism), PS/PT (phosphatidylserine/prothrombin), D1 (domain 1)

Management of APS positive patients	Treatment regimen
Previous VTE not on anticoagulation	Warfarin (Target INR 2-3), or DOAC
Previous VTE on anticoagulation	Warfarin (Target INR 3-4)
Previous arterial TE not on anticoagulation*	Warfarin (Target INR 2-3) + ld aspirin OR Warfarin (Target INR 3-4)
Recurrent arterial TE on anticoagulation	Warfarin (Target INR 3-4)
Recurrent thrombosis	Ld aspirin or clopidogrel + warfarin
Management of pregnancy in aPL positive women	**Recommendations**
No previous thrombosis + aPL	Careful monitoring + ld aspirin
SLE/APS	Ld aspirin + LMWH (+ Hydroxychloroquine)
Previous thrombosis	Ld asprin + LMWH (therapeutic dose)
Recurrent early miscarriage	Ld aspirin + LMWH (prophylaxis dose)
Late fetal loss/ severe pre-eclampsia/ previous IUGR	Ld aspirin + LMWH

Table 4: Management of APS.

Abbreviations; VTE (venous thromboembolism), INR (international normalised ratio); DOAC (direct oral anticoagulants); ld (low dose); LMWH (low molecular weight heparin); IUGR (intrauterine growth retardation); *conflicting expert opinion.

Potential adjunctive therapies	
Statins	Some benefit in recurrent TE despite anticoagulation Potential adjunctive therapy
Eculizumab	C5 inhibitor. Case reports of its use in preventing APS-associated thrombotic microangiopathy post renal transplantation, as well as recurrent CAPS.
Sirolimus	Blocks B and T cell activation by inhibiting mTOR. No recurrent of APS nephropathy in renal transplants receiving sirolimus, and decreased vascular proliferation
Autologous stem cell transplant	Promising early studies in SLE and APS, but high rates of adverse events.
Novel Therapies in development	
NF-ƙB and p38 MAPK inhibitors	Effective in reducing the *in vitro* pro-inflammatory/pro-thrombotic effect of APS and reduced TF expression
Recombinant DI	Inhibit development of anti-β2GPI antibodies and inhibits aPL mediated pro-thrombotic effects in animal models
A1-A1	Dimeric inhibitor selectively targets β2GPI in β2GPI/antibody complexes, interfering with the *in vitro* interaction with anionic phospholipids and ApoER2.

Table 5: Alternative and future potential therapies and diagnostic assays in APS.

Abbreviations; aPL (antiphospholipid antibodies), TE (thromboembolism), SLE (systemic lupus erythematosus), APS (antiphospholipid syndrome), VTE (venous thromboembolism), CAPS (catastrophic antiphospholipid syndrome), β2GPI (β2-glycoprotein I), TF (tissue factor), D1 (domain 1), VTE (venous thromboembolism), aCL (anticardiolipin).

Key Points

- APS is an appreciable cause of unprovoked thrombosis and acquired pregnancy morbidity

- Obstetric and thrombotic APS have distinct phenotypes & mechanisms

- Triple aPL positivity confers the highest risk of clinical events

- Non-thrombotic manifestations are increasingly recognised

- Current treatment remains focused on anticoagulation

- Emerging evidence supports use of DOACs in venous thrombosis & other non-anticoagulant therapies in refractory APS