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Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is one of the more common acquired causes of hypercoagulability. Its major presentations are thrombotic (arterial, venous or microvascular) and pregnancy morbidity (miscarriages, late intrauterine fetal demise, and severe pre-eclampsia). Classification criteria include three different antiphospholipid antibodies: lupus anticoagulant; anticardiolipin; and anti-beta 2 glycoprotein I. Management includes both preventive strategies (low dose aspirin, hydroxychloroquine) and long-term anticoagulation after thrombosis.

1. Introduction

Antiphospholipid syndrome (APS) is one of the more common acquired causes of hypercoagulability. Its major presentations are thrombotic (arterial, venous or microvascular) and pregnancy morbidity (miscarriages, late intrauterine fetal demise, and severe pre-eclampsia). Classification criteria include three different antiphospholipid antibodies: lupus anticoagulant; anticardiolipin; and anti-beta 2 glycoprotein I. Management includes both preventive strategies (low dose aspirin, hydroxychloroquine) and long-term anticoagulation after thrombosis.

2. Antibodies and Assays

There are three antiphospholipid antibodies listed in the classification criteria, but “non-criteria” antibodies exist as well (Tables Table 1). The most important antiphospholipid antibody is the lupus anticoagulant, as it is most strongly associated with both thrombotic[1,2] and adverse pregnancy outcomes[3]. Lupus anticoagulant assays are functional, using plasma. Ideally the plasma must be platelet poor. International Society on Thrombosis and Haemostasis (ISTH) criteria[4] for determination of a lupus anticoagulant include three steps. The first step is a sensitive screening assay. As lupus anticoagulants are heterogeneous, a battery of screening assays is preferred, usually including the dilute Russell Viper Venom time and a sensitive partial thromboplastin time (APTT). The next step is a mixing study to conclude that the prolongation of the screening time is not due to a factor deficiency. Although the mixing step is usually “one to one”, some lupus anticoagulants can correct

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with a one-to-one mix with normal plasma. Thus, a two-to-one mix can also be done. The final, or confirmatory step, is to prove that the inhibitor is phospholipid dependent.

Limitations of the lupus anticoagulant assay include the handling of “anticoagulated” patients. Heparin can be removed from the plasma before the assay. A few laboratories have validated their confirmatory values in patients treated with warfarin (as the mixing step does replace factors 2, 7, 9, 10). It is now possible to do valid lupus anticoagulant testing on direct oral anticoagulants (DOACs), using kits such as DOAC STOP[5,6].

The other antiphospholipid antibodies are ascertained based on ELISA assays. The two most commonly done are anticardiolipin and anti-beta 2 glycoprotein 1. Although these assays are available as IgG, IgM and IgA isotypes, most of the data on IgA comes from the United States where the IgA essays are done routinely.

In addition to the classic antibodies that are mentioned in the classification criteria, there are other antiphospholipid antibodies, sometimes called “non-criteria” antibodies. As anti-phosphatidylserine/prothrombin is performed by ELISA assay, it is valid in anticoagulated patients. Anti-phosphatidylserine/prothrombin is strongly associated with the presence of the lupus anticoagulant and with thrombosis[7,8]. A strong case can be made that it should be elevated to the level of a “criteria” antiphospholipid antibody.

3. Mechanism of Action: Thrombosis and/or Inflammation

Targets of Lupus Anticoagulants

Because antiphospholipid antibodies are heterogeneous, they might have multiple mechanisms of action. The lupus anticoagulant, for example, can be split into two subtypes, those which target beta 2 glycoprotein 1 and those which target prothrombin[9].

Most lupus anticoagulants increase the risk of thrombosis. However, pediatric patients with a lupus anticoagulant that targets prothrombin can develop a hypoprothrombinemia state and then present with bleeding, rather than thrombosis[10].

Some lupus anticoagulants act via annexin A5. By blocking (putting “holes”) in the annexin shield, the phospholipid bilayer is exposed and vulnerable to clot (including the placenta)[11].

Thrombocytopenia

Antiphospholipid antibodies bind to beta 2 glycoprotein I receptors on platelets, leading to activation and aggregation[12,13]. Thrombocytopenia, which is present in about a third of patients with antiphospholipid syndrome[14], is due to binding and activation of platelets[15]. Antiphospholipid syndrome is one of several examples (including thrombotic thrombocytopenic purpura, diffuse intravascular coagulation, heparin induced thrombocytopenia, and paroxysmal nocturnal hemoglobinuria) in which a pro-thrombotic state occurs in the setting of thrombocytopenia.

Inflammatory Targets

Inflammatory manifestations of antiphospholipid antibodies include some of the non-thrombotic neurologic syndromes associated with antiphospholipid antibodies (including chorea and longitudinal myelitis)[16,17]. Cardiac valvulitis is a mixture of an inflammatory effect of antiphospholipid antibodies binding to the mitral and aortic valves as well as superimposed thrombosis with fibrin deposition[18]. Antiphospholipid syndrome nephropathy, however, may be a microvascular complication rather than inflammatory[19].

Molecular Events in APS

Antiphospholipid antibodies bind to receptors on endothelial cells leading to eNOS inhibition, impairing nitric oxide production and release[20,21]. This leads to endothelial dysfunction[22], likely through the transcription factors KLF2 and KLF4, critical regulators of eNOS and endothelial cells[23]. There can later be endothelial cell proliferation and intimal hyperplasia[24–28].

Different molecular mechanisms may underlie the two major subsets of APS, obstetric APS and thrombotic APS. Gene expression profiling of monocytes exposed to IgG from thrombotic APS found upregulation of genes associated with cell response to stress, regulation of MAPK signaling pathway and cell communication. The obstetric APS analysis found genes involved in cell adhesion, extracellular matrix and embryonic and skeletal development[29].

In thrombotic APS, neutrophils have spontaneous neutrophil extracellular trap (NET) release with products then incorporated into thrombi. Surface adenosine receptors trigger cyclicAMP in neutrophils, regulating NETosis. Selective agonism of the adenosine A2A receptor and dipyridamole (which increases extracellular adenosine) suppress antiphospholipid induced NETosis[30]. PSGL-1, a neutrophil protein that mediates adhesion to the endothelium, is a regulator of the pro-thrombotic neutrophil functions[31]. APS neutrophils also have upregulation of CD64, CEACAM1, beta-2 glycoprotein and activated MAC-1, explaining their increased adhesion[32].

In obstetric APS, complement activation products and TNFα, among others, contribute to fetal loss[33]. There is impairment of cell adhesion molecules in the trophoblast and decidua, as well as defects in endometrial differentiation. Compromise of the mitochondria in obstetric APS may increase the risk of pre-eclampsia[34].

Role of Complement

Animal models have been particularly helpful in tying together both thrombotic and obstetric APS through the single mechanism of complement activation. In a pregnancy model, obstetric APS required complement activation and was blocked by complement inhibition[35]. The benefit of prophylactic doses of heparin in the model could be explained by heparin blocking complement activation[36]. In a different animal model for thrombotic APS[37], blockade of complement prevented thrombosis from infusion of antiphospholipid antibodies.

4. Classification Criteria

There have been multiple classification criteria for antiphospholipid syndrome, with the most recent, that of Miyakis et al[38] called the Sydney classification criteria (Table 2). Although it is often stated that the classification criteria are not to be used for diagnosis, in the antiphospholipid field they are often used to confirm diagnosis. The Sydney classification criteria divide the criteria into clinical and laboratory. The first clinical criterion is thrombosis. Thrombosis subsets include: venous (usually deep vein thrombosis or pulmonary emboli); arterial (usually stroke or myocardial infarction); and microvascular (which would include catastrophic antiphospholipid syndrome). The second criterion, pregnancy morbidity, is further subdivided into late fetal loss (the most classic), recurrent early miscarriage, and severe preeclampsia or HELLP syndrome[38].

Gaps in the classification criteria include the non-thrombotic (or “non-criteria”) manifestations of antiphospholipid antibodies. These include neurologic manifestations, particularly chorea and longitudinal myelitis. Cardiac valvulitis can be both inflammatory and thrombotic (with fibrin deposition). Hematologic manifestations include thrombocytopenia. APS nephropathy is microvascular, usually manifesting as hypertension and proteinuria[19,39]. Livedo racemosa and skin ulcers are often considered as a non-criteria manifestations, as well.

The laboratory criteria include lupus anticoagulant, anticardiolipin (IgG or IgM) and anti-beta 2 glycoprotein I (IgG or IgM). The criteria require that the laboratory test be positive twice over a three-month period of time. Only 59% meeting the earlier 1999 Sapporo criteria met the 2006 Sydney criteria[40]. The Sydney criteria also required that other causes of thrombosis must be excluded in older patients and that clinical criteria must be present within five years of the positive antiphospholipid assays.

In the clinic, a clinical treatment decision often must be based on a single set of laboratory tests, as waiting to repeat the tests in three months would leave a patient potentially insufficiently treated. In addition, the criteria do not account for the fact that, in particular in systemic lupus erythematosus, there is fluctuation over time in antiphospholipid antibodies[41]. Finally, there is confusion, as the cut-offs for anticardiolipin and anti-beta 2 glycoprotein in the classification criteria (cut-off of 20) are different from a term for high risk patients, “triple positivity” that chose 40 as the “high risk” cut-off[42]. In SLE, patients with a geometric mean titer of IgG anticardiolipin greater than 20 did have a significantly elevated rated of thrombosis (rate ratio 1.8, $p = 0.0052$)[43].

The classification criteria do include the IgM isotype. In SLE, however, IgM anticardiolipin is not associated with lifetime risk of thrombosis[43].

The classification criteria do not include the IgA isotype. Multiple studies have shown that the IgA isotype is associated with thrombosis[44–46], and is one of the most common isotypes in SLE[43].

5. Epidemiology

Prevalence of Antiphospholipid Antibodies

Antiphospholipid antibodies, especially at lower titers, are common in the general population. In young healthy subjects, 1% to 5% may have lupus anticoagulant or anticardiolipin[47]. In older subjects, anticardiolipin and anti-beta 2 glycoprotein I were found in 12%[48].

Infection Induced Antiphospholipid Antibodies

Viral infections can induce antiphospholipid antibodies, particularly human immunodeficiency virus (HIV), hepatitis B and hepatitis C[49]. Bacterial infections, including leprosy and syphilis, can induce antiphospholipid antibodies as well[49]. These infection-induced antiphospholipid antibodies are generally not associated with thrombotic antiphospholipid syndrome. Malignancies can also lead to antiphospholipid antibodies[50,51].

Prevalence of Antiphospholipid Antibodies in Systemic Lupus Erythematosus

In antiphospholipid syndrome, about half of the patients have systemic lupus erythematosus or another autoimmune disease. This has been termed “secondary” antiphospholipid syndrome. In systemic lupus erythematosus, about 30–40% of patients will have antiphospholipid antibodies if they are looked for serially and longitudinally[43]. In the Hopkins Lupus Cohort, in 2,534 patients, 26% have had lupus anticoagulant, 47% anticardiolipin and 28% anti-beta 2 glycoprotein I[52]. In SLE, the lupus anticoagulant is more common in men (40% vs 24.5%)[53] and in Caucasians than in African-Americans (28% vs 23%)[52]. In an SLE patient with the lupus anticoagulant at baseline, the risk of venous thromboembolism in the next 20 years is 42%[54].

Antiphospholipid Syndrome Incidence and Prevalence

General population studies of incidence/prevalence of antiphospholipid syndrome are rare. One estimate of 280,000 antiphospholipid syndrome events per annum in the U.S. was based on assumptions of 6% pregnancy morbidity, 13.5% stroke, 11% myocardial infarction and 9.5% deep venous thrombosis being due to antiphospholipid syndrome[55]. In a second study in Minnesota, the 2006 Sydney criteria or a diagnosis of APS by physician consensus were used. Laboratory results came from a centralized laboratory. Incidence rates (adjusted to the 2010 Caucasian population), and prevalence estimates from the incidence rates were then estimated. The annual incidence was 21 per 100,000 population and prevalence 50 per 100,000 population. Eighteen percent had SLE[56].

6. Thrombotic Antiphospholipid Syndrome

Antiphospholipid antibodies are more strongly associated with stroke in patients under the age of 50[57–59]. In myocardial infarction the titers of antiphospholipid antibodies were elevated in those less than 50 years of age[60]. Up to 20% of cases of deep vein thrombosis are associated with antiphospholipid antibodies[61].

7. Obstetric Antiphospholipid Syndrome

There are three kinds of pregnancy morbidity listed in the classification criteria of antiphospholipid syndrome. The first, recurrent early miscarriage, is nonspecific. In the general obstetric population, 10–15% of pregnancies end in early loss. One to two percent of women will have recurrent early miscarriage. Most women with recurrent early miscarriage will not have a known cause. In 25% to 60% of recurrent early miscarriage one partner will have an abnormal karyotype[62]. Most may have a successful pregnancy without any specific treatment[63].

Late losses (fetal death) occur in 1–2% in the general obstetric population[64]. The frequency of early miscarriage (<10 weeks gestation) or late fetal death in untreated obstetric APS is unknown. The frequency of live birth is 70–80% in trials of treated obstetric APS (although the trials mostly included recurrent early miscarriage and would not meet the stringency of current APS criteria)[65,66].

Severe preeclampsia can happen idiopathically and particularly in SLE is problematic, as active lupus and renal disease can also contribute to severe preeclampsia[67].

8. Catastrophic Antiphospholipid Syndrome

The third type of thrombosis in the classification criteria is microvascular, which describes catastrophic antiphospholipid syndrome. This is a devastating, but very rare, form of APS occurring in only about 1% of total APS patients. A recent review of the International CAPS registry found a mortality of 37%. Forty-eight percent of catastrophic antiphospholipid syndrome patients will have primary antiphospholipid syndrome, 40% SLE, and 12% other predisposing causes[68].

Characteristics of Catastrophic Antiphospholipid Syndrome

Thrombotic APS usually presents with deep venous thrombosis, pulmonary emboli, stroke, or fetal loss. Catastrophic antiphospholipid syndrome, however, presents with renal involvement in 73%, pulmonary 60% (such as acute respiratory distress syndrome), cerebral 56% (including encephalopathy), cardiac 50% and skin 47% (such as cutaneous necrosis)[69].

Triggers of Catastrophic Antiphospholipid Syndrome

Triggers of catastrophic antiphospholipid syndrome include withdrawal or non-adherence with anticoagulation, malignancies, drugs, surgery, trauma, infection, SLE flare, or pregnancy/post-partum state[70]. Often, however, no predisposing factor is found. Infection was more often a trigger in younger patients and malignancy in older patients[69].

Criteria for catastrophic antiphospholipid syndrome have been developed and require involvement of three or more organs (or systems or tissues), manifestations that have developed within one week, histopathology of small vessel occlusion, and confirmation of antiphospholipid antibodies[71].

Catastrophic antiphospholipid syndrome can occur both in a patient who already has antiphospholipid syndrome and in a de novo way. Interestingly, although it can recur, recurrences are very rare[72].

9. Natural History of Antiphospholipid Antibodies in SLE

Antiphospholipid antibodies tend to fluctuate in SLE. This is true for both lupus anticoagulant and anticardiolipin[41,43]. This is not surprising, as many auto-antibodies, including anti-dsDNA, also fluctuate in SLE. Antibodies that tend not to fluctuate in SLE are those that are made primarily by plasma cells, such as anti-Smith, anti RNP, anti-Ro and anti-La.

The fact that antiphospholipid antibodies tend to fluctuate in SLE has not been addressed in the classification criteria. It makes it particularly problematic to make a classification or diagnosis of APS in SLE and to make treatment decisions. Examples of fluctuations in antiphospholipid bodies in SLE patients are shown in Figure 1.

10. Risk Stratification for Thrombosis in APS, including in SLE

Multifactorial pathogenesis – “multiple hits” – is accepted in APS. Clinical situations that increase risk include hypertension, surgery, pregnancy and post-partum period. The Global Antiphospholipid Syndrome Score (GAPSS) added points for hyperlipidemia and for arterial hypertension for this reason[73]. Drugs that increase hypercoagulability, such as estrogen and thalidomide, can act as “second hits”, as well.

Laboratory risk stratification includes lupus anticoagulant, IgG over IgM isotype, higher IgG titers, and persistence of antiphospholipid antibodies for 6 months or longer[74,75]. One risk score, the Antiphospholipid Score, or aPLS, added a weighted system of points for multiple different lupus anticoagulant, anticardiolipin, anti-beta 2 glycoprotein I and anti-phosphatidylserine/prothrombin assays[76].

A different laboratory risk stratification called “triple positivity”, is defined as the presence of lupus anticoagulant, high titer (>40) anticardiolipin, and high titer (>40) anti-beta 2 glycoprotein I. “Triple positivity” has been defined as all present at one visit[42]. “Triple positivity” required that the anticardiolipin and anti-beta 2 glycoprotein I be the same isotype[77–79].

“Triple positivity”, however, was not validated in the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study of pregnancy morbidity due to antiphospholipid antibodies. Only the lupus anticoagulant explained the risk of adverse pregnancy outcomes in PROMISSE[80]. Similarly, in SLE, it is the lupus anticoagulant that explains risk (the IgM isotype, for example, is not associated with thrombosis)[43].

Immunothrombosis

In SLE the lupus anticoagulant is the most important autoantibody[43,81]. By itself, the lupus anticoagulant explains most of the thrombosis risk that can be attributed to antiphospholipid

antibodies. Although in the non-SLE population the approach called “triple positivity” has been taken to assign risk[77–79], triple positivity (positive for lupus anticoagulant, anticardiolipin and anti-beta 2 glycoprotein I) is not validated in SLE. In SLE the situation is more complicated because of the role of immunothrombosis[82].

Immunothrombosis refers to the multiple interactions of complement, platelets and coagulation. Plasmin cleave C5 to C5a. C5a increases tissue factor and catalyzes Factor X. C3a and C5b lead to platelet activation, increase tissue factor, activate endothelial cells, increase von Willebrand factor and expose P selectin. C5b-9 increases exposure of prothrombinase assembly sites on platelets[82,83].

Platelets are also involved in the thrombosis risk in SLE. This was shown initially by the Manzi group that found that a complement split product, C4d, bound to platelets, was associated with thrombosis, both arterial and venous, in SLE patients. They found that it was also associated with stroke and with stroke severity in the general population[84,85].

Complementopathies

The field of “complementopathies” includes diseases, such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, that lead to thrombosis and involve complement activation. Thrombosis in complementopathies can be blocked by a complement inhibitor such as anti-C5a[83]. In SLE, it has been possible to show the role of immunothrombosis in two ways, both by a reduction in C3 being associated with thrombosis and by complement split products bound to platelets[86].

Hopkins SLE Thrombosis Risk Equation

A simple three variable model, the Hopkins SLE thrombosis risk equation, that includes low C3, C4d bound to platelets, and lupus anticoagulant, is highly associated with thrombosis occurring within the last five years[86]. The greater the number of risk factors, the greater the association with thrombosis. The Hopkins SLE thrombosis risk equation performed better than “triple positivity” in receiver operating characteristics analysis[86].

11. Complement Mutations in Catastrophic Antiphospholipid Syndrome

A modified Ham assay (complement-dependent cell killing) and corresponding C5b-9 deposition were found in 86% of patients with catastrophic antiphospholipid syndrome, 36% of APS, but only 7% of SLE. Anti-beta 2 glycoprotein I antibodies induced C5b-9 deposition (which was blocked by anti-C5 but not by factor D inhibitor), indicative of classical (but not alternate) complement participation. Complement mutations have now been shown to be a risk factor, if not the major risk factor, for catastrophic antiphospholipid syndrome. Sixty percent of catastrophic antiphospholipid syndrome had germline variants in complement regulatory genes[87].

12. Treatment

Preventive Treatment

In SLE patients with the lupus anticoagulant at baseline, there is a 42% risk of venous thrombosis in the next 20 years[54]. There are multiple potential candidates for prophylactic treatment. The most obvious one is low dose aspirin. Low dose aspirin was studied in a nested case control study within the Physicians Health Study and was not found to be preventive of deep venous thrombosis / pulmonary embolus in male physicians[88]. It was also examined in a randomized clinical trial. The clinical trial was likely underpowered, but did not show a protective role of low dose aspirin[89]. A more recent analysis of five cohort studies did find a protective effect of aspirin against arterial but not venous thrombosis[90].

Hydroxychloroquine has been widely studied in SLE patients and in multiple studies has been shown to reduce the risk of thrombosis[91,92]. It has a good safety profile, but because of the rare risk of retinopathy it is necessary to do retina safety screening at baseline, five years, and then yearly[93]. The benefit of hydroxychloroquine is likely due to multiple actions, including an anti-platelet role, but it may also reduce antiphospholipid antibody titers[91,94]. The combination of low dose aspirin and hydroxychloroquine reduced thrombosis risk in SLE patients, but the study did not include primary APS[95].

Potential Prophylactic Treatments

Vitamin D is a potential prophylactic drug against thrombosis. It reduces activation of tissue factor by antiphospholipid antibodies[96]. It has been shown in oncology to reduce the risk of thrombosis in patients with prostate cancer[97]. Subjects with low vitamin D have a higher risk of thrombosis both in SLE and in antiphospholipid syndrome[96,98].

Statins have been studied in patients with the antiphospholipid antibodies and shown to reduce some inflammatory mediators and tissue factor[99]. In addition, statins have been shown to have an antithrombotic benefit in large trials of statins in the general population[100].

Thrombosis Treatment

Degree of Anticoagulation—Once a patient has had a thrombotic event, regardless of whether venous or arterial, the preferred therapy is warfarin. Initially there was some controversy about the degree of anticoagulation necessary[101], but two subsequent randomized clinical trials by Fenazzi et al[102] and Crowther et al[103] found that an INR target between two and three was adequate.

Choice of Anticoagulant—Heparin, given acutely at the time of the thrombotic event, can have two benefits: first, blocking complement activation (even if just a prophylactic dose) and second, as an anticoagulant[36]. However, heparin is rarely continued long-term due to concerns about osteopenia[104].

With the advent of direct oral anticoagulants (DOACs), there was great interest in using DOACs instead of warfarin. However, two clinical trials have shown that APS patients should not be given DOACs as a first choice therapy. One randomized clinical trial, Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS), enrolled patients who were “triple

positive" for antiphospholipid antibodies. These patients had an increased risk of arterial thrombosis if randomized to the trial DOAC (rivaroxaban)[105]. The second trial, Astro-APS, enrolled based on a clinical diagnosis of APS. It was interrupted due to safety concerns (arterial thrombosis) and then not completed. The study design of Astro-APS was randomization to apixaban versus warfarin. Those APS patients on apixaban had an increased risk of arterial events, even when the apixaban dose was doubled[106].

Duration of Treatment—Given the high risk of recurrence in APS, anticoagulation is recommended long-term. The risk of recurrence when stopped has been particularly high in SLE (24%)[107,108].

Treatment of Thrombocytopenia

Thrombocytopenia is usually mild in APS. When severe, it is treated with corticosteroids, intravenous immunoglobulin (cautiously, as this can cause hypercoagulability), and rituximab[109]. Thrombopoietin mimetic agents may increase the risk of thrombosis[110].

Treatment of Catastrophic Antiphospholipid Syndrome

The treatment of catastrophic antiphospholipid syndrome has classically been the "triple therapy" of intravenous heparin, intravenous methylprednisolone pulse and plasmapheresis (or intravenous immunoglobulin)[71]. There has been some improvement in the very high mortality from 50% to 37%[69]. However, a large percentage of catastrophic antiphospholipid syndrome patients do not respond to triple therapy. Rituximab has had some benefit in case series[111,112] and benefit for some non-criteria manifestations (such as skin ulcers and cognitive dysfunctions)[109]. Eculizumab, the anti-C5 monoclonal antibody approved for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria, has been successful in case reports[113–115].

Treatment in Pregnancy

If a woman has had a past normal pregnancy, no pregnancies, or has had only one early miscarriage, and has antiphospholipid antibodies, it is appropriate to prescribe a baby aspirin. The role of baby aspirin includes reduction in the risk of preeclampsia[116]. If the woman with antiphospholipid antibodies has had one late fetal demise, multiple early losses, or a history of severe preeclampsia or HELLP, then prophylactic heparin as well as low dose aspirin is recommended based on clinical trials[117] and a meta-analysis[118]. The pathogenesis of pregnancy complications occurs very early during the pregnancy and during the time of implantation. This has led to the practice of starting the prophylactic heparin as soon as pregnancy is confirmed. It is important to dose LMW heparin twice daily to obtain "24 hour" coverage for the placenta. If the woman has had a past thrombotic event, then the recommendation is full dose heparin and low dose aspirin (the latter theoretically increases the risk of bleeding but reduces the risk of pre-eclampsia)[119]. An ongoing trial will evaluate the benefit of an anti-TNF biologic that does not cross the placenta in women with a past history of pregnancy losses in spite of heparin and aspirin (ClinicalTrials.gov number NCT03152058).

13. Conclusion

Antiphospholipid syndrome is defined as thrombotic, obstetric, or microvascular (catastrophic antiphospholipid syndrome). There is likely a fourth subset of inflammatory APS that includes non-thrombotic manifestations in the neurologic (chorea, longitudinal myelitis), hematologic (thrombocytopenia), and cardiac (valvulitis) systems. Antiphospholipid syndrome is one of the most important acquired causes of hypercoagulability.

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Abbreviations

aPLS	Antiphospholipid Score
APS	Antiphospholipid syndrome
APTT	Partial thromboplastin time
CAPS	Catastrophic Antiphospholipid Syndrome
DOAC	Direct oral anticoagulant
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
GAPSS	Global Antiphospholipid Syndrome Score
HELLP	Hemolysis, Elevated Liver enzymes, Low Platelets
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ISTH	International Society on Thrombosis and Haemostasis
LMW	Low molecular weight
NET	Neutrophil extracellular trap
PROMISSE	Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus
RVVT	Russell Viper Venom Time
SLE	Systemic Lupus Erythematosus
TNF	Tumor necrosis factor

TRAPS Trial on Rivaroxaban in AntiPhospholipid Syndrome

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Patient 1 – Positive 17% of the time

	Ref Range & Units	2mo ago (6/17/19)	5mo ago (3/11/19)	1yr ago (1/20/18)	2yr ago (4/24/17)	2yr ago (1/23/17)	2yr ago (10/13/16)
DRVVT	27.0 - 45.0 Seconds	71.9 ^	54.3 ^	78.2 ^ R	69.1 ^	48.4 ^	77.6 ^
1:1 Mix Study RVVT	27.0 - 45.0 Seconds	42.4	38.8		42.3	42.7	45.5 ^
4:1 Mix Study RVVT	27.0 - 45.0 Seconds	47.0 ^	41.6		47.8 ^	44.4	54.3 ^
RVVT : Confirm Ratio	1.0 - 1.4 Ratio	1.5 ^	1.1	1.3	1.3	1.4	1.2

Patient 2 – Positive 33% of the time

	Ref Range & Units	2mo ago (6/6/19)	7mo ago (12/20/18)	1yr ago (6/21/18)	1yr ago (12/21/17)	2yr ago (6/22/17)	2yr ago (12/15/16)
DRVVT	27.0 - 45.0 Seconds	60.1 ^	66.5 ^	54.3 ^	56.0 ^	77.2 ^	62.0 ^
1:1 Mix Study RVVT	27.0 - 45.0 Seconds	41.1	45.0	41.2	40.3	47.3 ^	42.7
4:1 Mix Study RVVT	27.0 - 45.0 Seconds	45.2 ^	52.9 ^	44.4	44.4	56.6 ^	47.5 ^
RVVT : Confirm Ratio	1.0 - 1.4 Ratio	1.3	1.5 ^	1.3	1.2	1.6 ^	1.2

Patient 3 – Positive 50% of the time

	Ref Range & Units	4d ago (8/12/19)	4mo ago (4/18/19)	8mo ago (12/10/18)	12mo ago (8/20/18)	1yr ago (3/26/18)	1yr ago (10/16/17)
DRVVT	27.0 - 45.0 Seconds	56.5 ^	67.6 ^	68.2 ^	51.7 ^	70.7 ^	74.8 ^
1:1 Mix Study RVVT	27.0 - 45.0 Seconds	39.6	39.7	45.2 ^	37.0	39.9	52.2 ^
4:1 Mix Study RVVT	27.0 - 45.0 Seconds	44.7	46.3 ^	53.3 ^	40.0	47.5 ^	62.9 ^
RVVT : Confirm Ratio	1.0 - 1.4 Ratio	1.4	1.5 ^	1.5 ^	1.3	1.4	1.8 ^

Figure 1 -
Fluctuations in Antiphospholipid Antibodies

Table 1 –

Antiphospholipid Antibodies

Criteria Antiphospholipid Antibodies	Non-Criteria Antiphospholipid Antibodies
Lupus anticoagulant Anticardiolipin Anti-beta 2 glycoprotein I	Anti-phosphatidylserine/prothrombin (aPS/PT) Domain-specific anti-beta 2 glycoprotein I Annexin A5 IgA isotopes

Table 2:

Sydney Classification Criteria for Antiphospholipid Syndrome

Clinical Criterion

Clinical criteria must be present within 5 years of the positive aPL assays

- Vascular thrombosis
  - Arterial
  - Venous
  - Small vessel
  - Other causes of thrombosis must be excluded in older patients
- Pregnancy morbidity
  - One or more fetal losses after 10th wk
  - One or more premature births (<34 wk)
    - Pre-eclampsia
    - Placental insufficiency
  - Three or more consecutive spontaneous abortions

Laboratory Criterion

- Laboratory
  - Lupus anticoagulant or anticardiolipin IgG, IgM medium-high
  - Anti-beta 2 glycoprotein I IgG and IgM
  - Positive over 3 months