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EDITORIAL

The Antiphospholipid Syndrome in Pregnancy: A Review Article

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ABSTRACT

The antiphospholipid syndrome is an autoimmune thrombophilic disease characterized by occurrence of vascular events (arterial, venous, or small vessel thrombosis) and/or pregnancy complications, in association with persistently positive antiphoshpolipid antibodies such as lupus anticoagulant, anticardiolipid antibodies, and/or anti-β2-glycoprotein I antibodies. The international consensus (revised Sapporo) criteria for antiphospholipid syndrome-related pregnancy morbidity include a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b) one or more premature births of a morphologically normal neonate before 34th week of gestation because of eclampsia or severe pre-eclampsia (PE); or c) three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation. The recognition of aPLAbs by endothelial cells, monocyte and platelets is one of the pathogenic mechanisms contributing to antiphospholipid syndrome. The mandatory laboratory criteria for antiphospholipid syndrome are repeated positive tests for the antiphopsholipid antibodies on 2 or more occasions al least 12 weeks apart. Lupus anticoagulant is clinically the most relevant among all tests. Recently, two coagulometric tests have been recommended by recent guidelines for lupus anticoagulant detection: activated partial thromboplastin time and/or diluited prothrombin time. Obstetric antiphospholipid syndrome is currently managed by administering low-dose aspirin and either low-dose unfractioned heparin (twice daily) or low-molecular-weight heparin (once daily).

Key words: Pregnancy; Antiphospholipid antibodies; Thrombosis

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INTRODUCTION

The antiphospholipid syndrome (APS) is an autoimmune thrombophilic disease characterized by occurrence of vascular events (arterial, venous, or small vessel thrombosis) and/or pregnancy complications, in association with persistently positive antiphoshpolipid antibodies (aPLAbs) such as lupus anticoagulant (LA or LAC), anticardiolipid antibodies (aCL), and/or anti-β2-glycoprotein I antibodies (aβ2-GPI)[1]. In the absence of other associated autoimmune disorders, such as lupus erythematosus, the disease is classified as primary APS (PAPS). In association with other disease processes, including connective tissue diseases, the APS is defined secondary (SAPS)[1]. The international consensus (revised Sapporo) criteria for APS-related pregnancy morbidity, which may occur in women with no history of vascular thrombosis and who present APS during pregnancy (purely obstetric APS), include a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b) one or more premature births of a morphologically normal neonate before 34th week of gestation because of eclampsia or severe pre-eclampsia (PE) defined according to standard definitions or recognised features of placental insufficiency; or c) three or

more unexplained consecutive spontaneous miscarriages before the 10th week of gestation (i.e. recurrent miscarriages), with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded[2-5]. The recognition of aPLAbs by endothelial cells (EC), monocyte and platelets is one of the pathogenic mechanisms contributing to APS. LA is clinically the most relevant among all aPLAbs tests. LA belongs to a group of autoantibodies direct against proteins with affinity for negatively charged phospholipid (PLs)[1,5]. The in vitro anticoagulant effect of LA is explained by the assumption that this antibody competes with clotting factors for anionic PLs acting as catalytic surface for coagulation reactions[1,5]. Since β2GP-I-dependent LAs are antibodies directed against β2GP-I, such competition can only be explained by an increased affinity of β2GP-I for PLs upon antibody binding to this protein[5]. It has been shown that β2-GPI-dependent LAs are better predictors of thrombotic comlications than LAs directed against prothrombin[1,5]. The mandatory laboratory criteria for APS are repeated positive tests for the aPLAbs on 2 or more occasions al least 12 weeks apart[1,4]. The 3 tests exploring aPLAbs are LA, aCL, and aβ2-GPI detected by standardized ELISA[1,4]. ELISA-detected positive Abs must be of IgG and/or IgM isotype present in medium or high titer (Table 1). Recently, two coagulometric tests have been recommended by recent guidelines for LA detection: activated partial thromboplastin time (aPTT) and/or diluited prothrombin time (dRVVT)[1,6]. Obstetric APS is currently managed by administering low-dose aspirin (LDA) and either low-dose unfractioned heparin molecular-weight heparin (twice daily) or low-molecular-weight heparin (LMWH, once daily)[7].

NATURAL HISTORY AND PATHOGENESIS OF APS PREGNANCY

Women who carriers aPLAbs (LA, aCL, aβ2-GPI) are at higher risk of obstetric complications and general thrombotic risk including venous thromboembolism (VTE) and cerebrovascular thrombosis (Figure 1 from Giannakopoulos et al with permission)[2,8].

The pregnancy morbidity include fetal loss (early is defined as before 10 weeks gestation, late as miscarriage at or beyond 10 weeks according APS classification criteria), recurrent spontaneous abortions, abruptio placentae, intrauterin growth restriction (IUGR), PE, eclampsia, small gestational age (SGA), premature delivery[2,8,9,7,10]. The vascular morbidity during pregnancy is clinically characterized by the occurrence of venous, arterial or microvascular thrombosis in any tissue or organ. The episodes of venous and arterial thrombosis include proximal unprovoked deep vein thrombosis, distal unprovoked vein thrombosis (DVT), superficial vein thrombosis (SVT), transient ischaemic attach (TIA) or stroke, respectively[2].

The obstetric and/or vascular morbidity is associated with disturbance of hemostasis leading abnormal placental development and thrombosis[9,11]. Transvaginal ultrasonography has shown that the arterial signals in the yolk sac circulation disappear, and the umbilicoplacental circulation increases between the beginning of the eighth and the 10th weeks of gestation, indicating that the placenta replaces the yolk sac as an essential source of blood supply to the embryo at the time. During these 2 crucial weeks, in such an early placental circulation, hypercoagulability in the mother may induce pregnancy termination[12]. aPLAbs are heterogeneous autoantibodies that recognize PL-binding proteins such as β2-GPI and prothrombin, protein C (PC), protein S (PS), annexin V, complement factor H, high- and low- molecular-weight kininogen, prekallikrein, Factor IX, tissue factor pathway inhibitor (TFPI), Factor VII/VIIa, platelet factor 4 (PF4)[1,13,14]. Animal studies have shown that the most prominent antigen target in APS is β2-GPI[15]. The potential binding site for autoantibodies against β2-GPI is located in domain I. This epitope includes Arg39 and Arg43 (Figure 2 from Giannakopoulos et al with permission)[15].

The pathogenetic mechanism underlying pregnancy complications in women with APS differ from that in thrombotic APS, where thrombosis is neither a universal nor a specific feature. There is an association between LA positivity and adverse pregnancy outcomes[7]. LA is a heterogeneous group of antibodies, and its activity can be β2-GPI dependent or independent; β2-GPI dependent LA is strongly correlated with thrombosis[7]. LA may be associated with extensive placental necrosis, infarction and thrombosis in women with recurrent

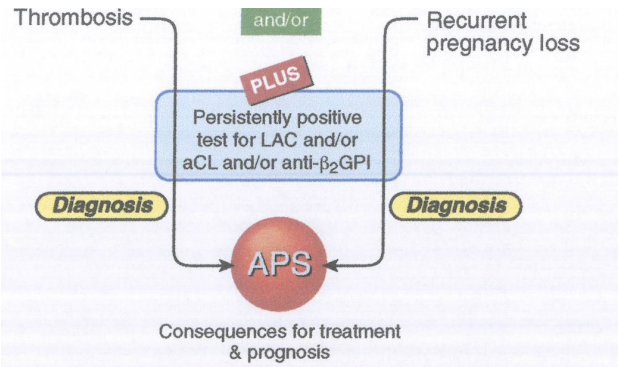

Figure 1 The updated classification criteria for APS.

Table 1 Research criteria for defining the antiphospholipid syndrome. Adapted from Miyakis et al (2006). With permisssion, John Wiley & Sons, Inc. 2006 International Society on Thrombosis Haemostansis.

Clinical criteria
1. Vascular thrombosis
One or more clinical episodes of arterial, venous or small vessel thrombosis
2. Pregnancy morbidity
(a) One or more unexplained deaths of a morphologically normal fetus at or beyond 10th week of gestation
(b) One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency
(c)Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
Laboratory criteria
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart
2. Anticardiolipin (aCL) antibody of immunoglobulin (Ig)G and /or IgM isotype in serum or plasma, present in mdium or high titre (i.e. >40GPL units or MPL units, or > the 99th centile), on two or more occasions, al least 12 weeks apart
3. Anti-β2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th centile), present on two or more occasions at least 2 weeks apart
Antiphospholipid antibody syndrome (APS) is present if at lesat one of the clinical criteria and one of the laboratory criteria are met

GPL units, IgG antiphospholipid units; MPL units, IgM antiphosphoilpid units.

pregnancy loss. These abnormalities may result from thrombosis during the development of the normal materno-placental circulation, perhaps via interference with trophoblastic annexin V[3]. It has been reported that pregnant women with aPLAbs show decreased levels of annexin V on the placental villi[9]. The human placental syncytiothrophoblast is a rich source of annexin V, a protein that displays a strong in vitro anticoagulant activity due to its high affinity binding to negatively charged phospholipids and to its capacity to displace coagulation factors from phospholipid membranes, creating a protective shield against procoagulant reactions[9]. The anatomic location of annexin V on the apical surface of placental villi facing the maternal slow-moving blood in the intervillous circulation might, therefore, play an antithrombotic role by inhibiting intervillous thrombosis and maintaining blood fluidity, so that nutrition exchange functions in the placenta result unimpaired[9].

During differentiation syncytium, trophoblasts express cell membrane anionic phospholipid that can bind β2-GPI. aPLAbs which are β2-GPI-dependent may recognise their own antigen on trophoblast and decidual cells as a "planted antigen" and it has been suggested that the binding to this antigen affects several trophoblast cell functions, leading to defective placentation[3]. In addition, the β2-GPI/anti-β2-GPI complex formation may activate complement and thereby induce local inflammatory damage[3]. Complement activation by aPLAbs appears to play a major role in the pathogenesis of recurrent pregnancy loss, and there is evidence that complement activation may also have a role in the pathogenesis of thrombosis in APS[3].

Ruffatti *et al*[16] reported that there is a strong association with recurrent late fetal loss (>10 weeks gestation) in women who are positive on all 3 assays (LA, a-β2-GPI, aCL), compared with women who are either dual or single assay positive. In particular, a-β2-GPI with LA activity may mediate a more prominent effect in late gestation miscarriage via distinct mechanism, perhaps by inducing intrauterine placental thrombosis, in view of the strong association

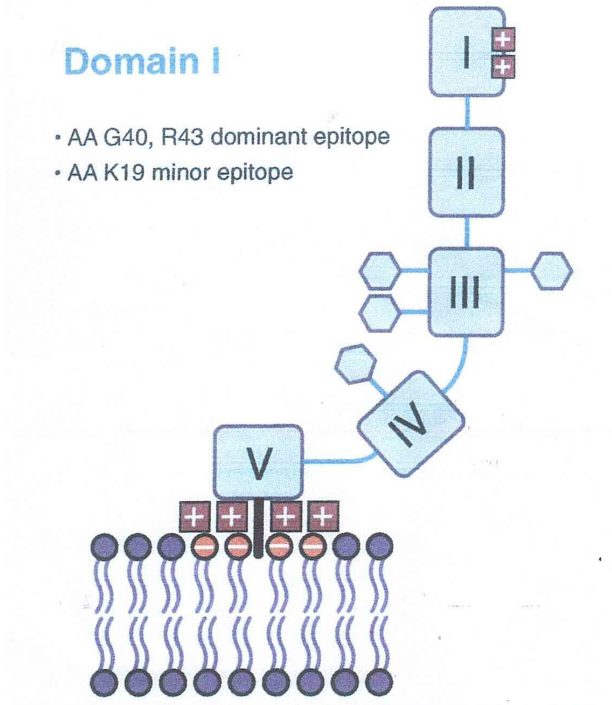

Figure 2 The β2GPI B-cell epitope in patients with APS is on domain I of the molecule. AA indicates amino acids; G40, glycine at position 40; R43, arginine at position 43; K19, lysine at position 19; I-V, domains I through to V.

of this class of antibodies with thrombosis (predominantly the IgG isotype, particularly IgG2 subclasses)[16]. *In vivo* observations raises the possibility that non-β2-GPI antibodies may be particularly relevant in early miscarriages, perhaps via the induction of an inflammatory mechanism[16].

The mechanism by which aPLAbs lead to thromboembolic events is unknown[15]. The most popular theory to explain why APS patients have an increased thrombotic risk is that these autoantibodies can cause activation of different cell types involved in regulation of the hemostatic balance, such as EC, monocytes, platelets, neuthrophils, fibroblasts and trophoblasts[15,17-19]. Activation of these cells results in a shift toward a prothrombotic state.

One mechanism by which aPLAbs/antiβ2-GPI may promote activation of EC is that these autoantibodies are thought to interfere with "anticoagulant" surface-mediated processes. One anticoagulant pathway involves PC, activated by thrombin on endothelial thrombomodulin, and PS. Activated PC in association with PS cleaves factor Va and factor VIIIa on the PL surface and thereby inactivates the intrinsic tenase and prothrombinase reactions. Occupancy of the surface by immune complexes could impede these interactions and thereby promote coagulative activation[1,5]. Indeed, LAs can induce "activated protein C resistance". A second anticoagulant mechanism involves TFPI. This protein binds to negatively charged PL and to factor Xa on PL. This protein complex then links to the TF-factor VIIa complex, and shuts off further TF-mediated clotting. Occupancy of the PL surface by immune complexes may impede this interaction, leading to prolonged thrombin generation[1,5]. Recent studies have demonstrated that the aPLAbs/antiβ2-GPI cross-link a receptorial multiprotein signaling complex consisting of annexin A2, TLR4, calreticulin, and nucleolin that is present on the EC surface and mediates the EC activation[20]. EC activation leads to increased expression of adhesion molecules (E-selectin, ICAM-1, VCAM-1), inflammatory cytokines and chemokines as well as procoagulant activity and the release of microparticles expressing anionic phospholipid that is a site for assembly of coagulation complex and TF[19-21].

Toll like receptor 2 (TLR2) and TLR1 or TLR6, and CD14 contribute to monocyte activation of aPLAb. In particular, TLR2, TLR1, and TLR6 are involved in aPLAb recognition by human monocytes. The CD14-dependent internalization of TLR2 by aPLAb in monocytes triggers NF-kB activation inducing TF expression and upregulating TF activity[1,15,18,22]. In addition, aPLAbs induce TLR8 expression and signaling in monocytes leading to the secretion of inflammtory cytokines[22]. Proteomic analysis has identified the vimentin (VIM) as a key antigen in the APS. VIM is an intermediate filament cytoskeletal protein, which is expressed by neuthrophils, T cells, monocytes and EC. Anti-VIM/CL antibodies were found in 92% of patients with APS[1,19]. The β2-GPI antibody/β2-GPI complex binding apolipoprotein E2 receptor and GPIb is responsible for platelet activation/adhesion[14]. Other target proteins are plasminogen activator inhibitor type-1 (PAI-1) linked to APS thrombogenesis. Immunoglobulin G isotype activates p38 mitogen-activated protein kinase (MAPK) causing the upregulation of TF activity and inducing the expression of vascular endothelial gowth factor (VEGF)[1,19].

Among all aPLAbs, LA is the unique risk factor independent for vascular thrombotic disease, including proximal unprovoked deep vein thrombosis, distal unprovoked deep vein thrombosis, and SVT. Surprisingly, no single aPLAb is an independent risk factor for cerebrovascular events[2]. LA is considered to be the most powerful predictor of thrombosis[8]. Strong risk factors for thrombosis are generally associated with spontaneous, rather than provoked, thrombotic events, which fits with the Rosendaal thrombosis potential model[8].

NON-CRITERIA OBSTETRIC APS: CLINICAL MANIFESTATIONS AND LABORATORY

Several obstetric manifestations additional to those in the international consensus criteria have been proposed as 'obstetric morbidity associated with APS (OMAPS)'[3]. These include two unexplained miscarriages, three non-consecutive miscarriages, late pre-eclampsia, placental abruption, late premature birth, or two or more unexplained in vitro fertilisation failures (Table 2 from Arachillage et al with permission). The preliminary first report from the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) suggested that there were no statistically significant differences in pregnancy outcome between women with obstetric APS, as defined by the International consensus criteria, or OMAPS[2]. There are women who are strongly suspected of having obstetric APS, showing the classical clinical features but persistently negative for currently recommended laboratory tests for aPLAbs. It has been proposed that autoantibodies directed against negatively charged phospholipids other than cardiolipin; other proteins of coagulation cascade; specific domains of β2-GPI, or those interfere with the anticoagulant activity of annexin A5; may be relevant to APS and defined as non-criteria aPL. Some authors have described this phenomenon as 'seronegative APS'. These patients were often positive for antibodies to zwitterionic phospholipid (e.g. phoshpatidylethanolamine); various phospholipid-binding plasma proteins/phospholipid-protein complexes; and anionic phospholipids other than cardiolipin[3]. It has been reported that women with non-criteria clinical and/or laboratory obstetric APS may benefit from standard treatment for obstetric APS with LMWH plus LDA with good pregnancy outcomes[3]. However, prospective multicentre studies are required to investigate the diagnostic validity, management implications and long-term outcomes of non-criteria clinical and/or laboratory manifestations of obstetric APS. In meantime, decisions about the use of antithrombotic therapy during pregnancy in women with non-criteria clinical and/or laboratory manifestations of obstetric APS, should be based on an individual risk/benefit assessment. Management should ideally be within a high risk antenatal clinic setting and treatment decisions discussed with the patient and documented[3]. Interestingly, Comellas–Kirkerup and collaborators[23] report that thrombocytopenia and autoimmune hemolytic anemia ("hematologic APS") may antedate thrombosis or pregnancy morbidity. Even more, some authors have proposed that these hematologic manifestations might represent a prethrombotic state preceding the onset of APS.

DIAGNOSTIC CRITERIA FOR APS

The presence of aPLAb alone does not constitute APS. Definitive APS is defined by the simultaneous presence of clinical and laboratory criteria as agreed upon International criteria for APS (Sapporo criteria) in 1998 and revised in 2006[1,4]. The clinical criteria are one or more objectively confirmed episodes of pregnancy morbidity and/or vascular thrombosis at any site defined as more than one unexplained death of a morphologically normal foetus, more than one premature birth of a morphologically normal neonate, or more than 3 unexplained consecutive spontaneous abortions before the 10th week of gestation[1,4]. The laboratory criteria are the presence of aPL. i.e. LA; and/or moderate or high positive IgG or IgM aCL (i.e. >40 GPL or MPL or >99th centile); and/or aβ2-GPI (IgG and/or IgM) antibodies >99th centile. Persistently positive aPL is defined on two or more consecutive occasions at least 12 weeks apart (Table 3 from Arachchillage et al with permission)[1,4,6].

LABORATORY DIAGNOSIS OF aPLAB

According to the last revison of the "Sapporo" criteria and the recommendations published in 2009 by the Subcommittee for the detection of LA[24,25], laboratory diagnosis for APS is based on the detection of aPLAbs on 2 or more occasions at least 12 weeks apart. The 3 tests exploring aPLAbs are LA detected by coagulation assays, aCL and aβ2-GPI antibody detected by standardized ELISA.

APS requires the presence of at least one of the three aPLAbs (i.e. LA, IgG and/or IgM aCL and IgG and/or IgM aβ2-GPI antibodies)[3]. The revised criteria provided details about the titres: >40 GPL or MPL or > the 99th percentile for aCL and > the 99th percentile for aβ2-GPI[4,26]. Interestingly, LA is the strongest risk factor for thrombosis and recurrent fetal loss whereas aCL antibodies show some significant associations only at high titres. The G rather than the M isotype is significantly associated with the clinical events for both aCL and aβ2-GPI antibodies[26-28]. It has been reported that "triple LA

Table 2 Non-criteria clinical and laboratory manifestations of obstetric antiphospholipid syndrome.

Clinical criteria	Laboratory criteria
1. Two unexplained miscarrieges	1. Low positive aCL or aβ2GPI present between the 95th and 99th centiles
2. Three non-consecutive micarriages	2. Presence of intermittent aPL in women with classical clinical manifestation of obstetric APS
3. Late pre-eclampsia	
4. Placental abruption, late premature birth	
5. Two or more unexplained in vitro fertilisation failures	
A diagnosis of non-criteria obstetric APS is considered to be present if the patient has: a) a combination of non-criteria clinical manifestations with international consensus laboratory criteria; or b) international consensus clinical criteria with a non-criteria laboratory manifestation.	

aCL: anticardiolipin antibodies; aβ2GPI: antiβ2glycoprotein-I antibodies; aPL: antiphospholipid antibodies; OAPS: obstetric antiphospholipid syndrome.

Table 3 The international consensus (revised Sapporo) criteria for diagnosis of obstetric antiphospholipid syndrome.

Clinical criteria	Laboratory criteria
1. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation	1. LA present in plasma, on two or more occasions al least 12 weeks apart
2. One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of: - (i) eclampsia or severe pre-eclampsia or - (ii) recognised features of placental insufficiency	2. aCL of immunoglobulin (Ig)G and /or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40GPL units or MPL units, or >the 99th centile), on two or more occasions, al least 12 weeks apart
3. Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal cause excluded.	3. aβ2GPI of IgG and/or IgM isotype in serum or plasma (in titre >99th centile), present on two or more occasions al least 12 weeks apart
OAPS is diagnosed if at least one of the clinical criteria and one of the laboratory criteria are met	

OAPS: obstetric antiphospholipid syndrome; LA: lupus anticoagulant; aCL: anticiagulants antibodies; aβ2GPI: antiβ2glycoprotein-I antibodies.

positivity", defined by the presence of LA and high titres of aCL and aβ2-GPI antibodies, correlated with both thrombosis and pregnancy morbidity more strongly that single or double positivities[1,26].

OVERVIEW OF THE ASSAYS

The Lupus Anticoagulant/Phospholipid-Dependent Antibodies Subcommittee of the Scientific and Standardization Committee of the ISTH has recommended criteria for the diagnosis of LA[27]. The recommendation is to perform two different tests, such as the activated partial thromboplastin time (aPTT) and the diluite Russel's viper venom time (dRVVT)[27]. The LA is an assay that detects imunoglobulins that associate with thrombosis. The LA assay system chosen has to comply with the 3-step strategy defined in the International Society of Thrombosis and Haemostasis criteria[29]: (1) screening test: demonstration of the prolungation of a phospholipid-dependent clotting time beyond the upper limit of the reference interval; (2) mixing test: confirmation of the presence of a an inhibitor and the exclusion of a coagulation factor deficiency; and (3) confirmation that the inhibitor is phospholipid-dependent and no directed against a specific coagulation factor. The mixing test involve combining the patient's plasma with normal plasma (1:1) and assessing the influence of this procedure on clotting time, the theoretical underpinning being that if prolongation of clotting time is the result of a coagulation factor deficiency, it will correct to normal, whereas with LA, correction requires larger volumes of normal plasma[29] (Table 4 from Rand with permission). Although ELISA-based methods were developed to detect aPLAb, LA detected by coagulometric tests has been shown to be strongly associated with thrombosis[6]. There is growing belief that β2-GPI-dependent aPLAbs are strongly associated with thrombosis[5,6]. For this reason, various attempts have been made to specifically detect β2-GPI-dependent LAs. Two methods of β2-GPI-dependent LA identification were described[30,31]. The aβ2-GPI antibodies may be divided into high and low avidity and the former is associate with thrombosis[29]. In the obstetric APS, testing positive on all 3 assays (LA, β2-GPI, and aCL-ELISAs) is associated with a greater risk for thrombosis[7,6]. In the update criteria, it is recommended that patients be divided into classes according to the type and number of antibodies. Patients are classified as class I when they posses more than one type of antibody. The group with all three types of antibodies (LA, aCL, and aβ2-GPI) were connected with the highest risk of pregancy loss[31]. The IgG rather the IgM isotype is significantly associated with the clinical events for both aCL and aβ2-GPI antibodies[28]. Patients with both LA and aβ2-GPI IgG or LA and aCL IgG positivity may represent the subgroups at the highest risk of thrombotic complications[28].

Table 4 Tests used for diagnosis of the antiphospholipid syndrome.

Immunoassays
Biologic flase-positive serologic test for syphilis
Anticardiolipin antibodies (cofactor-dependent assay)
Anti-β2GpI antibodies
Antiphosphosphatidylserine antibodies
Antiprothombin antibodies
Coagulation tests
Dilute Russel viper venom time (DRVVT) with confirmatory tests
aPTT:
evidence of inhibitor with mixing studies
panel of aPL-sensitive and insensitive aPTT reagents
platelet neutralization procedure
Kaolin clotting time
Tissue thromboplastin inhibition test
Hexagonal phase array test
Textarin/ecarin test

These observations support the suggestion to simplify the laboratory work-up of aPLAbs, excluding IgM from the ELISA mesurement of aCL and aβ2-GPI antibodies[27]. Conversely, both retrospective and prospective studies of women with pregnancy morbidity, particulary pregnancy loss, suggest that elimination of aCL and IgM aβ2-GPI from APS laboratory diagnostic criteria would lead to a failure to diagnose the syndrome in a significant proportion of women who could be regarded to have obstetric APS[3].

TREATMENT OF OBSTETRIC APS

In three meta-analyses of randomized trials in women with APS, the combination of LDA plus LMWH reduced pregnancy loss (RR 0.46)[32] or first-trimester loss (OR 0.39)[33] and increased live births than with aspirin alone (RR2.3)[34]. The British Committee for Standards in Hematology (BCSH)[35] and American College of Chest Physicians (ACCP)[36] guidelines provide recommendations on the management of women who fulfil the clinical and laboratory international consensus criteria for obstetric APS, based on a history of recurrent miscarriages. The BCHS guidance recommendes antenatal administration of heparin combined with LDA throughout pregnancy, in general starting as soon as pregnancy is confirmed and continuing until six weeks post-partum. The ACCP guidelines also recommend that women with obstetric APS should be treated with prophylactic or intermediate dose unfractionated heparin (UHF) or prophylactic dose LMWH combined with LDA (75 to 100 mg/daily) in the antepartum period as soon as pregnancy is confirmed[37] (Table 5). Although direct comparison studies are lacking, LMWH has superseded the use of UHF in pregnancy (ACCP 2012) because of safety and convenience[3,7]. LMWH may promote extravillous trophoblast development, being able to stimulate their invasive properties[38]. The classic complement pathway inhibition in pregnant women treated with LMWH may also be relevant, altered complement regulation being the role in PE[38]. The ACCP guidelines recommend LDA alone throughout pregnancy, starting from the second trimester for women considered at risk for PE. The BCSH guidelines also recommend LDA alone for women with APS and a history of PE[3]. Despite the use of aspirin and heparin treatment for women with obstetric APS, live birth rates remain suboptimal[7]. This suggest that the antithrombotic treatment may be inadequate: higher dose of LMWH and/or aspirin might be more effective, and indeed, the optimal doses have not been established[7]. Theoretically, women with recurrent pregnancy loss refractory to treatment with aspirin and heparin may benefit from immunosuppression, because of the complement-mediate placental damage, to maintain a viable pregnancy[39]. Bramham *et al*[39] suggest that low-dose prednisolone (10 mg daily) taken until 14 weeks'gestation in addition to aspirin and heparin may be benefit in women with APS refractory to standard treatment[39]. Prednisolone such as heparin inhibits activation of complement allowing adequate trophoblast invasion and placentation[39]. This study is worthy of further assessment because prednisolone is associated with significant side effects such as increased risk of gestational diabetes, elevations in blood pressure during pregnancy, asymptomatic infections, and preterm deliveries[38].

TREATMENT OF NON-CRITERIA OBSTETRIC APS

Prospective[40] and retrospective[41-43] cohort studies in patients with non-criteria laboratory manifestations of obstetric APS (OMAPS) suggest that they may have similar pregnancy outcomes with standard

treatment for obstetric APS as women who fulfil international consensus criteria for obstetric APS. Such studies also suggest that women with OMAPS may benefit from standard treatment for obstetric APS with LMWH plus LDA, with good pregnancy outcomes. The role of post-partum thromboprophylaxis in this patient group is not etsablished.

TREATMENT OF THROMBOTIC APS

APS is an important predictor of subsequent VTE[8]. Management currently depends on expert opinion and on the perception of the physician. According to the sixth ACCP guidelines for antithrombotic therapy for the prevention and treatment of thrombosis, the mainstay of treatment of arterial or venous thrombosis in patients with established APS is LMWH followed by oral anticoagulation with a targeted INR of 2-3[5]. The use of long term LDA is often applied in clinical practice. LDA has no effects on the prevention of subsequent VTE whereas there may be a potential beneficial effect on the prevention of TIA or stroke[2]. However, the risk-benefit ratio in the prevention of arterial thrombosis should be evaluated by randomized clinical trials. Given the higher risk of venous and arterial thrombosis in women with purely obstetric APS, should we use long-term anticoagulants for primary prophylaxis? At present there are no data on the risk-to-benefit ratio of this approach[2]. Whether administration of continuous primary prophylaxis can be considered in the presence of high-titer LA (or triple aPLAbs positivity) and of additional risk factors for thrombosis including inherited thrombophilia as well as what optimal regimen is for on-demand prophylaxis in situations at risk for women with purely obstetric APS, are still open questions. In the meantime, the decisions up to the treating physicians and the patients based on a careful evaluation and counseling on the thrombosis risk according to available data from the literature[2]. Interestingly, Schmidt-Tanguy *et al*[44] assessed the efficacy of hydroxychloroquine (HCQ) as a new therapeutic approach in primary thrombotic APS for secondary venous thrombosis prophylaxis in a small cohort of patients. HCQ is an antimalarial drug that has several antithrombotic effects[45-47] and its administration is associated with increased survival. The results are encouraging but should be confirmed in a randomized controlled trial of HCQ for thrombosis prevention in primary APS. (Table 5 from Soch MC et al with permission).

CONCLUSION

APS probably constituites the single most recognisable risk factor in the majority of cases of recurrent pregnancy loss and late placenta-mediated obstetric morbidity. The pathogenetic mechanisms underlying pregnancy complications in women with APS may differ from those in thrombotic APS. The BCSH[35] and ACCP[36] recommendations support that women with obstetric APS who meet International consensus criteria should be treated with prophylactic or intermediate dose UHF or prophylactic LMWH combined with LDA, in the antepartum period as soon as pregnancy is confirmed. Women

Table 5 Overview of the Therapeutic Options Used in Antiphospholipid Syndrome Pregnancy.

Drug	Use	Evidence	Safety in pregnancy	Safety in breast-feeding
Aspirin 75-100 mg daily from conception until ≥ 36 weeks gestation.	Reduction of fetal loss Prevention of eclampsia Antiplatelet effect.	No randomized controlled trials of aspirin for preventing VTE; Some evidence for aspirin use in improving pregnancy outcomes, specifically reduction in rates of preeclampsia.	Will cross the placenta; human data inconsistent, but risk is likely low; Some first-trimester analyses have shown small increased risk of gastroschisis.	Does enter breast milk, but al low doses; should be safe.
Warfarin Discontinue as soon as pregnancy is confirmed.	Not recommended in pregnancy unless; LMWH may be less effective (e.g., prosthetic heart valves).	Teratogenic between 6-12 weeks of gestation; switch to LMWH before 6 weeks of gestation.	Teratogenic	Not excreted in breast milk.
Unfractionated heparin (UHF)	May be used in event of massive pulmonary embolism; If rapid reversal of anticoagulation is needed during peripartum period or operative procedures.	Most studies using UHF have been Superseded by studies using LMWH	Safe	Not excreted in breast milk
LMWH	Drug of choice for women on warfarin, women who have had VTE or arterial thrombosis during pregnancy, women with previous pregnancy complications, or women who require thromboprophylaxis.	Evidence for its role in preventing first-trimester controversial loss remains.	Does cross placenta.	Does enter breast milk, but of little concern due to low bioavailability.
Steroids (e.g., prednisone)	Little evidence for benefit in APS; used in immune thrombocytopenia associated with APS or SLE.	Minimal evidence of therapeutic benefit; Benefit outweighted by its adverse effects (e.g., preeclampsia, gestational diabetes, increased risk of preterm deliveries).	Cleft palate reported with first trimester use.	Low concentrations in breast milk.
Intravenous immunoglobulins.	Used in a small number of women with APS as therapy for concomitant, immune-mediated thrombocytopenia.	No addiotional benefit when added to conventional therapy with ASA and LMWH.	Crosses placenta after 30 weeks of gestation.	Excetion is unknown.
Hydroxychloroquine (HCQ).	Used when women have coexisting SLE.	Mild antithrombotic effects; Decreased risk of congenital heart block in women on HCQ in case-controlled studies.	No reports of fetal toxicity.	Considered safe despite excretion in breast milk.

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with non-criteria clinical and/or laboratory onstetric APS (OMAPS) may benefit from standard treatment for obstetric APS with LMWH plus LDA, with good pregnancy outcomes. Women with obstetric APS appear to be at higher risk than other women of PE, placenta-mediated complications and neonatal morbidity. Accurate diagnosis of obstetric APS is a prerequisite for optimal clinical management, and thereby, the potential prevention of long-term disability as a result of placenta-mediated obstetric complications. Women with obstetric APS also appear to be at increased long-term risk of thrombotic events.

CONFLICT OF INTERESTS

The Authors have no conflicts of interest to declare.

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