Antiphospholipid Syndrome during pregnancy: the state of the art

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Summary

Obstetric complications are the hallmark of antiphospholipid syndrome. Recurrent miscarriage, early delivery, oligohydramnios, prematurity, intrauterine growth restriction, fetal distress, fetal or neonatal thrombosis, pre-eclampsia/eclampsia, HELLP syndrome, arterial or venous thrombosis and placental insufficiency are the most severe APS-related complication for pregnant women. Antiphospholipid antibodies promote activation of endothelial cells, monocytes and platelets, causing an overproduction of tissue factor and thromboxane A2. Complement activation might have a central pathogenetic role. These factors, associated with the typical changes in the hemostatic system during normal pregnancy, result in a hypercoagulable state. This is responsible of thrombosis that is presumed to provoke many of the pregnancy complications associated with APS. Obstetric care is based on combined medical-obstetric high-risk management and treatment with the association between aspirin and heparin. This review aims to determine the current state of the art of APS by investigating the knowledge achievements of recent years, to provide the most appropriate diagnostic and therapeutic management for pregnant women suffering from this syndrome.

Key Words: Antiphospholipid; Thrombophilia; Hypercoagulability; Thromboprophylaxis.

Introduction

Antiphospholipid Syndrome (APS) is an autoimmune thrombophilic condition that is marked by the presence in blood of antibodies that recognize and attack phospholipid-binding proteins, rather than phospholipid itself (1). The clinical manifestations of APS include vascular thrombosis and pregnancy complications (2), especially recurrent spontaneous miscarriages and, less frequently, maternal thrombosis (3). Many other clinical manifestations may occur (4, 5).
Presence of antiphospholipid antibody (aPL) alone, in the absence of typical clinical complications, does not indicate a diagnosis of APS; long-term asymptomatic aPL-positive patients exist. When diagnosed in patients with underlying autoimmune disease (usually Systemic Lupus Erythematosus, or SLE), APS is termed secondary APS; in otherwise healthy persons it is termed primary APS. Catastrophic Antiphospholipid Syndrome (CAPS) represents the severe end of the spectrum with multiple organ thromboses in a rapid period of time. Multiorgan failure has been described during pregnancy by Asherson (6) and during postpartum by Kochenour (7).
The clinical spectrum of this syndrome has widened (8, 9), with important advances in the knowledge of its pathogenesis and clinical management made during the past several years.

Materials and Methods

In this work, we aimed to offer an up-to-date view of the main pathophysiological, clinical, diagnostic and therapeutic advances in Antiphospholipid Syndrome.
The literature search was done from 2006 to 2011, focusing more on the latest research. The PubMed database was used with the medical subject heading terms "antiphospholipid syndrome" OR "antibodies, antiphospholipid" OR "lupus anticoagulant". The Cochrane database of systematic reviews was searched, with the key word "antiphospholipid". We obtained additional articles from reference sections of the selected manuscripts. We paid special at-

tention to systematic reviews, randomised clinical trials, consensus documents and review articles focused on the diagnostics and therapy of Antiphospholipid Syndrome. Older articles were also included to draw attention to pathogenetic, clinical, and epidemiological issues.

Discussion

Etiology and Pathogenesis

Like other autoimmune disorders, APS does not have a known etiology. There are several hypotheses to explain the probable cause (10):

- Passive transfer of maternal antibodies mediate autoimmune disorders in the fetus and newborn. The mechanism of excess autoantibody production and immune complex formation is not well understood, although current investigation is focused on abnormal regulator functions and the possibility of a slow virus infection.
- Familial occurrence of aPL has been reported, and suggested genetic associations include HLA-DR4, DR7, DRw53 and C4 null allele (11).
- PL molecules are ubiquitous in nature and are present in the inner surface of the cell and in microorganisms. Therefore, during infectious disease processes, including viral (eg, HIV, Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenoviruses), bacterial (eg, bacterial endocarditis, tuberculosis, Mycoplasma pneumonia), spirochetal (eg, syphilis, leptospirosis, Lyme disease), and parasitic (eg, malaria infection), the disruption of cellular membranes may occur during cell damage. PLs release and stimulate aPL antibodies.

Antiphospholipid antibodies can be broadly categorized into those antibodies that prolong phospholipid-dependent coagulation assays, known as lupus anticoagulants (LA), or anticardiolipin antibodies (aCL), which target a molecular congener of cardiolipin (a bovine cardiac protein). **Lupus Anticoagulants (LA)** reduce the coagulant potential of the plasma and prolong the clotting time in coagulation tests based on the activated partial thromboplastin time (12). Consensus guidelines recommend screening for LA with 2 or more phospholipid-dependent coagulation tests (13). Anticoagulant therapy may interfere with the detection of LA (14). **Anticardiolipin Antibodies (aCL)** share a common in vitro binding affinity for cardiolipin and can be detected using enzyme-linked immunosorbent assays. Enzyme-linked immunosorbent assay tests for aCL are poorly standardized and aCL testing has shown poor concordance between laboratories (12). Both LA and aCL may demonstrate specificity for 2-glycoprotein I (2GPI) (15,16). In fact, even if many other antigenic targets have been described, including proteins C and S, prothrombin (17) and annexin V (18), the major antigen recognized by antiphospholipid (aPL) autoantibodies is 2-glycoprotein I, also known as apolipoprotein H, a member of the complement control protein, or short consensus repeat (SCR), superfamily. The protein has a fishhook shape and binds to anionic phospholipid bilayers through cationic and hydrophobic aminoacids in the fifth of its 5 SCR domains, near the carboxyterminus (19). Recent evidence has indicated that a subset of aPL antibodies (**Anti- 2-glycoprotein I antibodies**) (20,21) associated with increased risk of thrombosis and embolism recognize an epitope in domain I of 2GPI that consists of Gly40-Arg43 (22,23). It has been suggested that antibody-mediated dimerization and pentamerization of 2GPI increase the affinity/aviditity of antibody-2GPI immune complexes for phospholipid and that this increase may be responsible for the pathogenic effects of aPL antibodies (23). The laboratory assay for these antibodies is not standardized, making comparison between studies difficult (16). There is some evidence that these antibodies are more specific for APS (24).

Antiphospholipid antibodies with anti- 2-glycoprotein-1 activity act by multiple mechanisms (25,26):

- APL activate endothelial cells (27) and these express adhesion molecules (such as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin), and (like monocytes) upregulate the production of tissue factor (28).
- APL activate monocytes and induce their increased tissue factor expression (29).
- APL activate platelets that increase expression of glycoprotein 2b-3a and synthesis of thromboxane A2.
  The activation of endothelial cells, monocytes, and platelets by antiphospholipid antibodies, conducting to the increased synthesis of tissue factor and thromboxane A2, induce a procoagulant state (30,31).
- Activation of the complement cascade might close the loop7 and provoke thrombosis and fetal loss (32-35). This occurs often in presence of a second hit (36). Traditional cardiovascular risk factors such as tobacco, inflammation, or oestrogens might have an important role at this point, in fact such risk factors are present in more than 50% of patients with antiphospholipid syndrome. To confirm complement role, studies show that C4d and C3b fragments are deposited in the placentas of patients with antiphospholipid syndrome (37).
- Furthermore, interaction of antiphospholipid antibodies with proteins implicated in clotting regulation, such as prothrombin, factor X, protein C and S (38), and plasmin (39), tissue factor pathway inhibitor (40), might hinder inactivation of procoagulant factors and impede fibrinolysis (28,36).

Interference with annexin A5, a natural anticoagulant that binds to phosphatidylserine exposed during trophoblast syncytium formation, might favour a more direct effect on placental structures, promoting placental thrombosis and fetal loss (18,28,41).

As evidence that thrombosis is the cause of many obstetric complication, abnormalities in placentation have been described in pregnancy loss related to antiphospholipid antibodies (42). 2-glycoprotein 1 directly binds to cultured cytotrophoblast cells and is subsequently recognised by antibodies to 2-glycoprotein 1 (43). Moreover, antiphospholipid antibodies might trigger an inflammatory response mediated by the TLR4/MyD88 pathway resulting in trophoblast damage (44).

Epidemiology of aPL

The prevalence of aCL and LAC in normal healthy populations has been reported to range between 1.0% and 5.6% and between 1.0% and 3.6%, respectively (45-47). The prevalence of elevated aPL antibodies may also increase with age (48). About one-third of SLE patients are aCL positive. LA prevalence is about 15% in SLE patients. A positive LA appears to be more specific for APS than an elevated aCL. The strength of the association between aPL and thrombosis varies. Primarily, aCL are not as strong a

risk factor for thrombosis as LA. Lupus anticoagulant is consistently the most powerful predictor of thrombosis (49-51). About 40% of patients with systemic lupus erythematosus have antiphospholipid antibodies (52), but less than 40% of them will eventually have thrombotic events (49,53). However, thrombotic antiphospholipid syndrome is regarded as a major adverse prognostic factor in patients with lupus (53). Titer and isotype are important: IgG aCL is more strongly associated with clinical events than is IgM aCL, and the risk of thrombosis increases with higher titers (>40 U). Immunoglobulin A aCL and low titers of IgG and IgM aCL are less frequently associated with complications (54). APL account for a significant proportion of thromboses in the general population (55-57).

The presence of additional prothrombotic risk factors in aPL-positive individuals likely influences thrombosis risk. In the currently accepted "second-hit" hypothesis, a second trigger event - such as cigarette smoking, oral contraceptives, surgical procedures, prolonged immobilization, or a genetic prothrombotic state - may increase the likelihood of an aPL positive patient developing a vascular event. Women with pregnancy events alone have a high likelihood of developing thrombosis in later years (58).

Diagnosis of APS (59)

Criteria

In 1998, the preliminary classification criteria for antiphospholipid syndrome were proposed at Sapporo, Japan (60). Classification for this syndrome needed at least one clinical manifestation together with positive tests for circulating antiphospholipid antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values, detected at least twice in 6 weeks. In 2006,classification criteria were updated (61) and are listed in Table 1.

Essentially, the clinical criteria remained unchanged; however, two important modifications were made: the time elapsed between two positive determinations was extended to 12 weeks to assure the detection of persistent antibodies only; and anti- 2-glycoprotein 1, both IgG and IgM, were added to the laboratory criteria. Medium titres of anticardiolipin, or anti- 2-glycoprotein 1, were defined as more than 40 GPL or MPL or higher than the 99th percentile. Notably, IgA isotypes, antiprothrombin antibodies, and antibodies directed against phosphatidylserine-prothrombin complex remained excluded from the criteria. These modifications have been criticised (63), and the debate about the clinical implications of different antiphospholipid antibodies is still open.

You can recognize different kind of APS. See Table 2.

Overview of laboratory tests

The laboratory tests that are frequently used to diagnose this condition are shown in Table 3.

The first test that identified this condition was the biologic falsepositive (BFP) syphilis test, which actually reported autoantibody recognition of phospholipid-binding proteins, primarily 2GPI (in contrast to true-positive syphilis tests in which antibodies recognize phospholipid directly). The BFP syphilis test was first refined into a quantitative anticardiolipin immunoassay[64] and then included immunoassays that used other phospholipids, such as hosphatidylserine, and immunoassays that detected antibodies against the putative antigens, primarily 2GPI. A second avenue of diagnostic testing conducted to tests that report interference with phospholipid-dependent coagulation reactions, causing a prolonged clotting times with any of the following tests: activated partial thromboplastin time (aPTT), the dilute Russell Viper venom time (dRVVT), kaolin clotting time, plasma clotting time. These prolongations should be confirmed with mixing studies with normal plasma (clotting time will remain prolonged with LA) or with platelet neutralization test.

Table 1 - Summary of the Sydney Consensus Statement on Investigational Classification Criteria for the APS (61).

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical criteria

Vascular thromboses:

1. One or more documented episodes of arterial, venous, or small vessel thrombosis - other than superficial venous thrombosis - in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
   (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 the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, or
   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

These criteria for laboratory testing are consistent with current American Congress of Obstetricians and Gynecologists clinical management guidelines.(62)

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipiddependent antibodies).(61)
2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-b2-glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL present alone; IIc, anti- b2GPI antibody present alone.

Table 2 - Types of patients having antiphospholipid (aPL) antibodies.

I. Antiphospholipid syndrome
   A. "Primary" – in the absence of SLE
   B. "Secondary" – in patients with SLE

II. aPL antibodies stimulated by infection
   A. No known association with thrombosis (e.g., syphilis, Lyme disease, cytomegalovirus, Epstein-Barr virus)
   B. Possible association with thrombosis (e.g., varicella, HIV, hepatitis C)

III. Drug-induced aPL antibodies (e.g. chlorpromazine and other phenothiazines)

IV. aPL antibodies prevalent in the general population

Table 3 - Tests used for diagnosis of the antiphospholipid syndrome.

Immunoassays
Biologic false-positive serologic test for syphilis
Anticardiolipin antibodies (cofactor-dependent assay)
Anti-b2GPI antibodies
Antiphosphatidylserine antibodies
Antiprothrombin antibodies
Coagulation Tests
Dilute Russell 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
Plasma clotting time

High-affinity (avidity) phospholipid-binding antibody-cofactor-phospholipid complexes are the likely basis for the LA phenomenon. Both of the approaches - immunoassay and LA testing - may be considered to be empirically derived surrogate tests for the syndrome. The sensitivities and specificities of the tests are variable, and a single negative test cannot rule out the diagnosis in a patient. It is generally recommended that a panel of tests be done to attempt to exclude the diagnosis. Specific ELISA for antibodies directed against the domain 1 of 2-glycoprotein is one of the new expected tests that will need assessment (65).

The presence of more than one class of antiphospholipid antibodies increased thrombotic risk (20). Patients who test positive for all three of the major assays - positive LAC, elevated anticardiolipin antibodies and elevated anti- 2GPI antibodies (referred to as "triple positivity"), are at markedly increased risk for thrombosis (66-68) and for pregnancy complications (69).

These tests are not useful for screening asymptomatic general medical or obstetrical populations. At the present time, testing for aPL antibodies should usually be restricted to patients who have had thrombosis, embolism, or pregnancy complications that may be attributable to APS, and to patients with SLE even if they have not have any of the above manifestations. A panel of tests should always be done when APS is suspected since individual tests may yield false negatives. Persistence of the abnormal test should be confirmed after 12 weeks.

Obstetric Complications

The antiphospholipid syndrome causes several clinical manifestations. See Table 4.

Obstetric complications are the other hallmark of antiphospholipid syndrome.

The risk of thrombosis among women with antiphospholipid antibodies may be increased (58). Thrombosis is presumed to cause many of the pregnancy complications associated with APS. The most common obstetric manifestation of this syndrome is recurrent miscarriage. Recurrent miscarriage occurs in about 1% of the general population attempting to have children (70). About 10-15% of women with recurrent miscarriage are diagnosed with antiphospholipid syndrome (71,72). Fetal loss (≥10 weeks of gestation) is more strongly associated with aPL than are earlier pregnancy losses (73). Lupus anticoagulant has been strongly associated with recurrent miscarriage before the 24th week of gestation (74). Overall, approximately half of aPL-associated pregnancy losses occur in the first trimester (pre-embryonic and embryonic loss, < 10 weeks of gestation) (75). The diagnosis of APS should be made only with three or more consecutive losses in the ab-

Table 4 - Clinical manifestations of Antiphospholipid Syndrome.

Arterial thrombosis:	Cerebral vascular accident; extremity gangrene; mesenteric infarction; aortic occlusion
Venous thrombosis:	Deep venous thrombosis; pulmonary emboli; mesenteric, hepatic, or renal vein thrombosis; adrenal insufficiency
Obstetric complications:	Fetal loss, recurrent pre-embryonic/embryonic losses; pre-eclampsia; intrauterine growth retardation
Hematologic:	Thrombocytopenia; hemolytic anemia; Evans syndrome; thrombotic microangiopathic hemolytic anemia
Cutaneous:	Livedo reticularis; cutaneous necrosis; pyoderma-like ulcerations; digital gangrene
Neurologic complications (non-stroke):	Seizures; chorea; transverse myelitis; multiple sclerosis-like syndrome
Renal complications:	Nephropathy with glomerular thrombosis; cortical necrosis; renal infarction
Cardiac complications:	Mitral and/or aortic insufficiency; intracardiac thrombosis, coronary artery thrombosis
Avascular necrosis	
Catastrophic APS:	With multisystem failure

sence of other identifiable etiologies. The two greatest risk factors for fetal loss are high titer IgG aCL and a history of previous fetal loss. These patients have up to 80% risk of current pregnancy loss (76). Both IgG and IgM anticardiolipins are associated with an increased risk of miscarriage, albeit to a lesser degree than lupus anticoagulant (74). The clinical relevance of anti- 2-glycoprotein I antibodies also is uncertain; in three systematic reviews (16,50,74). these antibodies were not associated with either thrombosis or recurrent early miscarriage, in others (23,77,78). they showed an increased risk for obstetric complications and thrombosis. Also the risk of fetal loss among asymptomatic women who have antiphospholipid antibodies appears to be increased (58, 79-82). Although fetal death is linked to antiphospholipid syndrome (83), the overall contribution of this syndrome is uncertain, partly because of the effect of other possible contributing factors such as underlying hypertension or pre-existing comorbidities such as systemic lupus erythematosus or renal disease.

Obstetric manifestations of APS are not restricted to fetal loss (8,58,75,84-86). Current APS criteria include early delivery, oligohydramnios, neonatal complications (such as prematurity -estimated at 30-60% and more common in SLE patients-, intrauterine growth restriction - IUGR -, fetal distress (60) and rarely fetal or neonatal thrombosis) (87), associated maternal obstetric complications (like preeclampsia/eclampsia and HELLP syndrome - hemolytic anemia, elevated liver enzymes, and low platelet counts, arterial or venous thrombosis) and other aPL-related complications (placental insufficiency) (75). The association between antiphospholipid antibodies and the risk of premature birth due to eclampsia or preeclampsia and intrauterine growth restriction remains controversial; studies contributing data to this area tend to be small, retrospective, and have conflicting results (88,89). Furthermore, the toxicity of treatments evaluated in these studies may contribute to pregnancy loss or complication and may confound the association between antiphospholipid antibodies and adverse pregnancy outcomes (90).

Screening of healthy pregnant women is not indicated (91). While both aCL and LA predict fetal loss, concordance is incomplete, so both must be tested if APS is suspected. Other aPLs are not as helpful in predicting risk. In fact, antibodies directed against other phospholipids, such as antiphosphatidylserine or antiphosphatidylethanolamine, do not generally identify additional patients (92). It is not clear if anti- 2GPI antibodies add significant predictive value to aCL and LA in identifying patients at risk for fetal loss (93), although occasional patients may present with these antibodies alone. Exclusion of confounding conditions is important in aPLpositive patients with pregnancy morbidities. Gynecologic conditions may include uterine abnormalities, hormonal imbalance (eg, luteal phase defect), maternal and paternal karyotype abnormalities, or fetal genetic abnormalities. In addition, presence of a heritable procoagulant state, such as factor V Leiden, may mimic APS (94).

A severe complication of pregnancy, which greatly increases its risk in case of APS, is VTE.

Pregnancy and the postpartum period, in fact, carry an increased risk of VTE, with an incidence between 0.61 and 1.72 per 1000 deliveries (95,96). Compared with non pregnant women, pregnant and postpartum women are approximately 4 to 5 times more likely to develop VTE (97). Virchow's triad describes 3 elements that contribute to the development of thrombosis: (a) stasis, (b) vascular trauma, and (c) hypercoagulability. These elements are all present during pregnancy and the postpartum period. Lower extremity venous stasis has been demonstrated during pregnancy (98). Venous flow velocity decreases with advancing gestation, and is lower in the left compared with the right lower extremity. When DVT presents during pregnancy, it is more likely to be in the left lower extremity (95,99). Predominance of left lower extremity clot formation may be due to compression of the left common iliac vein by the enlarging gravid uterus (100). In addition, venous distention has been demonstrated, which may result in endothelial damage and prothrombotic changes in the endothelium (101). Lower extremity venous flow velocity increased and vessel diameter decreased between 4 and 42 days postpartum (102). Venous flow velocity and diameter returned to levels observed in early pregnancy at the 42-day measurement (101,102). In addition to mechanical compression of pelvic veins, increased circulating levels of estrogen and local production of prostacyclin and nitric oxide increase deep venous capacitance during pregnancy (103). Moreover, normal pregnancy is accompanied by changes in the hemostatic system that would seem to result in a hypercoagulable state for the prevention of hemorrhage at the time of delivery:

- Factors II, VII, VIII, IX, XII, and von Willebrand factor increase (104).
- Fibrinogen levels increase to levels that are almost twice that of the nonpregnant state (104,105).
- Free and total protein S antigen levels decrease, as well as decreased activity, occurring very early in pregnancy.
- Although protein C levels remain unchanged (104,106), an overall increase in activated protein C resistance is present, with the degree of resistance dependent on several modifiers, including the presence of the Factor V Leiden mutation (FVLM), thrombin generation, and the presence of antiphospholipid antibodies (107). Fibrinolysis is decreased, predominantly due to diminished tissue plasminogen activator activity.
- Other markers of a hypercoagulable state include increased thrombin-antithrombin complexes, prothrombin fragments 1 and 2, peak thrombin generation, and increased D-dimer levels (104-106).

During pregnancy may occur also a vascular trauma in the form of endothelial damage due to venous distention (101), or may occur during conditions such as preeclampsia where vascular endothelial activation is present (108).

During normal delivery, venous compression may occur. Operative and assisted deliveries are thought to contribute to vascular trauma, also possibly contributing to the risk of thrombosis in the postpartum period; this is especially true for cesarean delivery.

Testing for antiphospholipid syndrome (via lupus anticoagulant, anticardiolipin, and anti- 2-glycoprotein I) is common practice in a first-episode VTE because patients with antiphospholipid syndrome should be considered for long-term anticoagulation (109). It is important to rule out antiphospholipid syndrome, as this diagnosis would alter pregnancy care as well as be an indication for heparin use.

Management and Antithrombotic Treatment of APS in Pregnancy

With proper management, more than 70% of pregnant women with antiphospholipid syndrome will deliver a viable

live infant (110). Ideally, preconception counseling gives the physician the opportunity to understand the specific context of each patient with the syndrome and to outline the risks of pregnancy and treatment. Pregnancy should be discouraged in all women with important pulmonary hypertension because of the high risk of maternal death (111), and should be postponed in the setting of uncontrolled hypertension or recent thrombotic events, especially stroke (111). A complete profile of antiphospholipid antibodies, including repeated anticardiolipin and lupus anticoagulant, should be available before planning of pregnancy. However, these tests do not need to be repeated during pregnancy, since subsequent negative results (after diagnostic, repeatedly positive tests) do not eliminate the risk of complications (111).

Patients should be counseled in all cases regarding symptoms of thrombosis and thromboembolism and should be educated regarding, and examined frequently for, the signs or symptoms of thrombosis or thromboembolism, severe preeclampsia, or decreased fetal movement. We recommend frequent prenatal visits, at least every 2-4 weeks before mid-gestation and every 1-2 weeks thereafter.

Human chorionic gonadotropin (hCG) values in the first trimester can be followed to evaluate the viability of the pregnancy. If hCG levels are increasing normally (ie, doubling every 2 d) in the first month of pregnancy, a successful outcome is predicted in 80-90% of cases. However, when the increases are abnormal (ie, slower), a poor outcome is predicted in 70-80% of cases. In patients with poor obstetric histories, evidence of preeclampsia, or evidence of fetal growth restriction, ultrasonography is recommended every 3-4 weeks starting at 18-20 weeks' gestation. The objectives of prenatal care in the second and third trimesters are close observation for maternal hypertension, proteinuria and other features of preeclampsia, frequent patient assessment, obstetric ultrasound to assess fetal growth and amniotic fluid volume, and appropriate fetal surveillance testing. Surveillance testing should begin at 32 weeks' gestation, or earlier if the clinical situation for placental insufficiency is suspected, and should continue at least every week until delivery. Regular and coordinated medical consultation every 2-4 weeks, especially in women with systemic lupus erythematosus, is recommended. In patients with uncomplicated APS, ultrasonography is recommended at 30-32 weeks' gestation to assess fetal growth. Lagging fetal growth may reflect uteroplacental insufficiency in patients with APS (10). Uterine and umbilical artery Doppler assessments are widely used in Europe to assess the risk for pre-eclampsia, placental insufficiency, and fetal growth restriction after the 20th week of gestation, and normal examinations have high negative predictive values (112).

The goals of treatment in pregnant women with antiphospholipid syndrome are to improve maternal and fetal-neonatal outcomes by keeping to a minimum the risks of the recognised complications of the disorder, including maternal thrombosis, fetal loss, preeclampsia, placental insufficiency, and fetal growth restriction, and the need for iatrogenic preterm birth (75).

The optimal treatment of pregnant women with antiphospholipid antibodies and 1 or more fetal losses after 10 weeks' gestation without thrombosis is controversial (113). Earliest treatment for recurrent pregnancy loss associated with aPL was a combination of high dose prednisone and low-dose aspirin, with successful outcome in 75% of treated pregnancies. High maternal and fetal morbidity resulted, however, including gestational diabetes, hypertension, and premature rupture of membranes. A randomized controlled study of prednisone and aspirin as compared with heparin and aspirin showed low-dose subcutaneous heparin with low-dose aspirin to be equally efficacious with less morbidity (114). Moreover, a Cochrane analysis concluded that intravenous immunoglobulins were associated with an increased risk of pregnancy loss or premature birth, compared with heparin and low-dose aspirin (115).

Then the studies focused on the effectiveness of therapy with UFH, LMWH and low-dose aspirin and their possible association, lead to conflicting results. In two trials (116,117), the proportion of successful pregnancies substantially improved with the addition of unfractionated heparin to low-dose aspirin. Two other randomised trials (118,119), both using low-molecular-weight heparin, proved negative. Additionally, two studies recorded no differences in pregnancy outcomes when comparing unfractionated heparin with low-molecular-weight heparin, both combined with aspirin (120,121). Moreover, low doses of subcutaneous unfractionated heparin (5000 units twice daily) appear to be as effective as high-dose heparin (10 000 units twice daily) (117,122). Finally, several observational studies have reported pregnancy success rates of 79-100% with low-dose aspirin alone (123-129). Other available studies indicated that aspirin (50-81 mg/d) compared with placebo or usual care did not reduce the rate of pregnancy loss (130,131). Despite the obvious controversies raised by these trials, a 2005 Cochrane systematic review concluded that women with recurrent miscarriage and antiphospholipid syndrome should be given a combination of heparin 5000 IU subcutaneously twice daily and low-dose aspirin (115). Expert guidelines recommend the combination of aspirin with either low-dose heparin or low-molecularweight heparin (132).

Heparin is the anticoagulant drug of choice during pregnancy (133). Heparin does not cross the placenta and is widely considered safe for the embryo-fetus. Of the 2 clinically available forms, the low molecular weight heparin (LMWH) preparations offer some advantages over unfractionated heparin (UFH). Both UFH and LMWH act primarily by binding to antithrombin to catalyze the molecule binding to and altering the activity of serine protease procoagulants. UFH enhances the activity of antithrombin for Factor Xa and thrombin, whereas the predominant effect of LMWH is via antithrombin- mediated anti-Factor Xa activity. UFH has complex pharmacokinetics that ultimately leads to a somewhat unpredictable anticoagulant response. Also, the bioavailability of the UFH after subcutaneous (SC) injection is reduced compared with intravenous infusion. LMWH, in contrast, is less likely to bind nonspecifically to various circulating protein or cell surfaces and so has improved pharmacokinetics and bioavailability when given SC. In addition, LMWH is less likely than UFH to cause heparin-induced thrombocytopenia (HIT) and osteoporosis, though the latter is infrequent (1-2% of cases) in women treated during pregnancy (100,103). Importantly, counsel the patient regarding potential adverse effects of heparin. Bone density studies should be considered in patients receiving anticoagulation with heparin or LMWH may be important in women who have been treated in a previous pregnancy or are planning pregnancy. For the most part, the longer half-life of LMWH is seen as an advantage because it allows once- or twice-daily dosing regimens to be used.

Pregnant patients with antiphospholipid syndrome can be classified in:

- Patients affect by antiphospholipid syndrome without a previous thrombotic event (diagnosed because of obstetric event(s):
  (a) patients with recurrent early (preembryonic or embryonic) miscarriage and no other features of antiphospholipid syndrome, or
  (b) those with one or more previous fetal deaths (at more than 10 weeks' gestation) or previous early delivery (at less than 34 weeks' gestation) because of severe pre-eclampsia or placental insufficiency.
- Patients with acute VTE within several months of conception or during pregnancy or Recurrent VTE (2 or more prior VTEs).

Table 5 summarises recommended treatments for these groups.

So the Evidence-Based Clinical Practice Guidelines of American College of Chest Physicians (132) suggest that women with antiphospholipid antibodies and a history of 2 or more early pregnancy losses or 1 or more late pregnancy losses who have no prior history of thrombosis receive treatment with combination aspirin and heparin (unfractionated or lowmolecular-weight) during pregnancy. Aspirin (81 mg/d) should be started with attempted conception; most investigators recommend, in fact, preconceptional aspirin because of its possible beneficial effect on early stages of implantation (123). Heparin (5000-10 000 units every 12 hours) or low-molecular-weight heparin in prophylactic doses (Enoxaparin 40 mg SC every 24 h) should be started when a viable intrauterine pregnancy is documented and continued until late in the third trimester (134). Patients with a history of thrombosis should be fully anticoagulated with an adjusted-dose UFH or LMWH regimen (UFH SC every 12 h or Enoxaparin 1 mg/kg SC every 12 h) for at least 6 months from the initial presentation with VTE. Women who are on warfarin should discontinue the warfarin before 6 weeks of gestation. Some clinicians favor discontinuing the warfarin when the patient initiates attempting to conceive, replacing it with UFH or LMWH. If the patient reaches 6 months of anticoagulation during the pregnancy, consideration of reducing the degree of anticoagulation (eg, to prophylactic UFH or LMWH) is reasonable, especially in preparation for epidural anesthesia. Following delivery, the UFH or LMWH should be restarted and bridged to warfarin.

About Peripartum Heparin Management, as Cesarean delivery has been cited as a risk for VTE (96,107). Recommendations for thromboprophylaxis (132,133). suggest that those women receive thromboprophylaxis with prophylactic LMWH or UFH, or by mechanical prophylaxis with lower extremity compression devices while hospitalized. Low- to moderate-risk patients on LMWH can be transitioned to UFH (because of its shorter half-life) at 36 to 37 weeks' gestation in an effort to improve the likelihood of epidural anesthesia if preterm labor occurs. Patients should be advised that if they suspect spontaneous labor, heparin should be discontinued. For induction or scheduled cesarean, adjusted-dose heparin and intermediate-dose LMWH should be discontinued 24 hours before the scheduled admission. Prophylactic heparin should be discontinued at least 12 hours prior. For high-risk patients, reasonable options include reducing the heparin dose to 5000 units SC twice a day or using a judiciously applied continuous infusion of heparin during labor, with discontinuation when delivery is estimated to be 1 to 2 hours away. In most cases, heparin should be restarted 6 to 8 hours following delivery or cesarean section. Regarding high-risk patients, continuous infusion should be restarted after delivery when the risk of bleeding has decreased (usually 2 to 4 hours after delivery). The American Society of Regional Anesthesia (ASRA) has made recommendations regarding anticoagulation and regional anesthesia. Regional anesthesia is contraindicated in patients less than 24 hours from their last dose of twice-daily LMWH. For prophylactic LMWH, regional anesthesia can be placed 10 to 12 hours' dura-

Table 5 - Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy.

Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage →Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses: Enoxaparin 40 mg SC every 24 h). Following delivery, postpartum thromboprophylaxis with warfarin or LMWH is indicated.
Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency → Low-dose aspirin plus unfractionated heparin (7500–10 000 IU subcutaneoulsy every 12 h in the first trimester; 10 000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1・5 times the control mean) or LMWH (usual prophylactic doses: Enoxaparin 40 mg SC every 24 h). Following delivery, postpartum thromboprophylaxis with warfarin or LMWH is indicated.
Antiphospholipid syndrome with thrombosis → Low-dose aspirin plus unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the midinterval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range) or LMWH (usual therapeutic dose-eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1・5 mg/kg/day subcutanously, or dalteparin 200 U/kg/day subcutaneously)†

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

Data from American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition).(132)

tion from the last dose of LMWH heparin. The neuraxial catheter should be removed 2 hours before the first LMWH dose. Intravenous heparin can be initiated 1 hour following neuraxial anesthesia, with catheter removal 2 to 4 hours after the last heparin dose. SC heparin dosed twice daily with a total dose less than 10,000 units of UFH per day is not a contraindication to neuraxial anesthesia. However, neuraxial anesthesia at doses greater than 10,000 units of UFH or dosing at a frequency greater than twice daily dosing has not been established to be safe (135). Therapy (including aspirin and heparin) can reduce the rate of fetal loss to 25%, as described by Cowchock et al. (114). In order to reduce the risk of postpartum deep vein thrombosis, antithrombotic coverage of the post-partum period is recommended in all women with antiphospholipid syndrome, with or without previous thrombosis (132). Generally, women with previous thrombosis will need long-term anticoagulation, and most experts prefer switching the treatment to warfarin, as soon as the patient is clinically stable after delivery, to limit further risk of heparin-induced osteoporosis and bone fracture. In patients with no previous thrombosis, the recommendation is prophylactic dose heparin or low-molecular-weight heparin therapy for 4-6 weeks after delivery (132), although warfarin is an option. Both heparin and warfarin are safe for breast-feeding mothers (136). A retrospective study of subsequent thrombosis in 65 patients with prior pregnancy events not routinely treated with prophylaxis after the immediate post-partum period, has shown such patients to have a 59% rate of thrombosis over 10 years of follow up; patients who continued on low-dose aspirin, however, had a rate of 10% (58). Based on these data, the current recommendation may be low-dose aspirin postpartum indefinitely.

About the other pregnancy complications, data from meta-analysis (137) have shown their significant reduction in women at high risk for pre-eclampsia who were given antiplatelet agents (mostly aspirin). In all clinical trials, maternal and fetal-neonatal outcomes in pregnancies progressing beyond 20 weeks'gestation were benign, with the frequencies of fetal death, pre-eclampsia, severe placental insufficiency, and iatrogenic preterm birth close to those of the general obstetric population. Results from randomised trials do not define optimum treatment for women with fetal death (>10 weeks' gestation) or previous early delivery (<34 weeks' gestation) due to severe pre-eclampsia or placental insufficiency. Most experts recommend low-dose aspirin and either prophylactic or intermediate-dose heparin (75,115,132). Vitamin K antagonists are teratogenic and should be avoided between 6 and 12 weeks' of gestation. Because of the risk of fetal bleeding thereafter (132,136) warfarin after 12 weeks' gestation should be given only in exceptional circumstances.

Probably there is a relationship of aPL to infertility but it has been controversial until now. Although prevalence of aPL antibodies is increased in patients undergoing in vitro fertilization (IVF), a recent prospective study found that aspirin and heparin treatment of IVF patients with positive aPL antibodies and history of failed IVF cycles does not improve IVF cycle outcome (138).

Future therapies

Several potential new therapeutic approaches for APS are emerging (Table 6).

But most of these possible future therapies (clopidogrel, rivaroxaban, statins, rituximab, and other new anticoagulant drugs) are for non-pregnant patients. The only new drugs for APS that pregnant women can use are dipyridamole and hydroxychloroquine.

Combination treatment with aspirin plus dipyridamole have shown higher efficacy than has aspirin alone in patients with stroke. Such combination might be considered in selected patients with antiphospholipid syndrome in whom warfarin is not effective or safe. Observational studies have suggested an antithrombotic effect of hydroxychloroquine in patients with antiphospholipid antibodies, most of whom have systemic lupus erythematosus (49,139,140). Furthermore, results from basic studies have shown a dose-dependent reduction by hydroxychloroquine of platelet activation and clotting induced by antiphospholipid antibodies (141,142). Hydroxychloroquine directly inhibits the binding of antiphospholipid antibody- 2-glycoprotein-1 complexes to phospholipid surfaces (143). An additional and previously unrecognised role of hydroxychloroquine in prevention of pregnancy loss is suggested by the description of its protective effect of the annexin A5 shield formed over phospholipid bilayers from damage induced by antiphospholipid antibodies (144). In view of the excellent safety profile, including the absence of any adverse effects on the fetus-neonate (145), and the absence of associated bleeding, hydroxychloroquine should be considered for an adjuvant antithrombotic role in patients with systemic lupus erythematosus who are positive for antiphospholipid antibodies. Patients with primary antiphospholipid syndrome and recurrent thrombosis despite adequate anticoagulation, who have difficulty maintaining adequate anticoagulation intensity, or have a high-risk profile for major haemorrhage, might also benefit from hydroxychloroquine treatment.

Furthermore, recent data from an experimental model of aPL antibody-induced pregnancy losses in mice (33) suggest that the therapeutic effect of heparin in the disorder might be due to the inhibition of complement rather than its inhibition of coagulation. These data, if generalizable to human APS-related pregnancy losses, have raised the intriguing possibility of novel non anticoagulant approaches to treatment.

Conclusion

Obstetricians and gynecologists have the means to prevent thrombosis and the related pregnancy complications associated with APS in the obstetric patients. Attaining the ability to identify patients at risk, determine who is a candidate for thrombophilia screening, and who may warrant thromboprophylaxis, is important to this end. In addition, it is fundamental to understand various thromboprophylaxis regimens and peripartum anticoagulant management. Other

Table 6 - Potential future therapies for antiphospholipid syndrome.

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

well-designed prospective studies are required to complete the understanding of the optimal treatment of patients with antiphospholipid antibodies and APS, especially to reach detailed and well standardized recommendations regarding precise intensity and duration of anticoagulation.

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