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Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies (Box 1 and Box 2). Diagnosis requires that at least one clinical and one laboratory criterion are met. Because approximately 70% of individuals with APS are female (1), it is reasonably prevalent among women of reproductive age. Antiphospholipid antibodies are a diverse group of antibodies with specificity for binding to negatively charged phospholipids on cell surfaces. Despite the prevalence and clinical significance of APS, there is controversy about the indications for and types of antiphospholipid tests that should be performed in order to diagnose the condition. Much of the debate results from a lack of well-designed and controlled studies on the diagnosis and management of APS. The purpose of this document is to evaluate the data for diagnosis and treatment of APS.

Background

Current evidence suggests that the antigenic determinant for antiphospholipid antibodies that is primarily clinically relevant is β_2-glycoprotein I. This glycoprotein is a ubiquitous, multifunctional plasma protein with an affinity for negatively charged phospholipids. It has a regulatory role in coagulation, fibrinolysis, and other physiologic systems (2). Antiphospholipid antibodies have been associated with a variety of medical problems, including arterial thrombosis and venous thrombosis, autoimmune thrombocytopenia, and fetal loss (3–8). In addition to fetal loss, several obstetric complications have been associated with antiphospholipid antibodies, including preeclampsia, intrauterine growth restriction, placental insufficiency, and preterm delivery (9, 10).

Antiphospholipid Antibodies

The three antiphospholipid antibodies that contribute to the diagnosis of antiphospholipid syndrome are 1) lupus anticoagulant, 2) anticardiolipin, and 3) anti-β_2-glycoprotein I (Box 1). Most experts feel that testing for lupus anticoagulant, which is detected via coagulation assays in plasma, is more specific, but less sensitive than the other two tests (11, 12). Some patients with antiphospholipid syndrome have all three antibodies detected. However, many do not, indicating that the three antibodies are not identical. Thus, the different antiphospholipid antibodies are perhaps best viewed as related but distinctly different immunoglobulins. Because transient positive test results may occur, the diagnosis of APS requires two positive antiphospholipid antibody test results at least 12 weeks apart.

Lupus Anticoagulant

Lupus anticoagulant is present in many individuals without systemic lupus erythematosus and is associated not with anticoagulation but with thrombosis. The presence of lupus anticoagulant is assessed indirectly, and a series of tests are needed for the laboratory diagnosis. The

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Box 1. Laboratory Criteria for the Diagnosis of Antiphospholipid Syndrome

1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart. It is interpreted as either present or absent. Testing for lupus anticoagulant is ideally performed before the patient is treated with anticoagulants, or
2. Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma, present in medium or high titer (ie, greater than 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, or
3. Anti-β_2-glycoprotein I of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma (in titer greater than 99th percentile for a normal population as defined by the laboratory performing the test), present on two or more occasions, at least 12 weeks apart.

Modified from Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

initial laboratory screening test for lupus anticoagulant typically is performed using a combination of sensitive clotting assays, such as a lupus anticoagulant-sensitive activated partial thromboplastin time and dilute Russell's viper venom time. Lupus anticoagulants paradoxically block phospholipid-dependent clotting assays by interfering with the assembly of the prothrombin complex. The sensitivity and specificity of each test for lupus anticoagulant are greatly affected by the reagents used and vary among laboratories.

Because prolonged clotting times in these assays can result from factors other than lupus anticoagulant, such as improperly processed specimens, anticoagulant medications, clotting factor deficiencies, and factor-specific inhibitors, plasma suspected of containing lupus anticoagulant based on a prolonged clotting time is subjected to additional testing. If the prolonged clotting time is caused by a factor deficiency, the addition of normal plasma (containing the missing factor) results in a normal clotting time on repeat testing. In contrast, if an inhibitor such as lupus anticoagulant is present, the clotting time remains prolonged despite the addition of normal plasma. A second confirmatory test, which involves the addition or removal of phospholipid from the assay, has been recommended. For example, preincubation of plasma with phospholipid binds and removes lupus anticoagulant from the sample being tested and normalizes clotting time. Regardless of the assays used, lupus anticoagulant cannot be quantified and is reported only as present or absent.

Anticardiolipin Antibodies

Anticardiolipin antibodies are most commonly detected using enzyme-linked immunosorbent assays. It is recommended that immunoglobulin G (IgG) and immunoglobulin M (IgM) isotypes be measured. The clinical relevance of immunoglobulin A anticardiolipin antibodies remains uncertain, and the diagnosis of APS should not be made on the basis of isolated immunoglobulin A anticardiolipin antibodies. Historically, standardization of anticardiolipin antibody assays has been difficult, resulting in poor concordance between laboratories (13). Consequently, past consensus guidelines have emphasized the use of semiquantitative results (eg, negative, low, medium, or high). This lack of concordance makes clinical interpretation of these guidelines difficult. More recently, however, interlaboratory agreement has seemingly improved (14).

Standard, reference reagents for anticardiolipin antibodies are available, and results are typically reported in international standard units, designated "GPL" for IgG phospholipid and "MPL" for IgM phospholipid. Despite the accuracy and reliability of quantitative anticardiolipin antibody results historically being somewhat limited, current consensus guidelines suggest that a positive anticardiolipin result is greater than 40 GPL or 40 MPL (ie, greater than the 99th percentile) (15).

Anti-β_2-Glycoprotein I Antibodies

As with anticardiolipin antibodies, anti-β_2-glycoprotein I antibodies are most commonly detected using enzyme-linked immunosorbent assays. Both IgG and IgM anti-β_2-glycoprotein I isotypes should be measured. Anti-β_2-glycoprotein I antibodies are reported most commonly in international standard units known as "SGU" or "SMU" for IgG and IgM, respectively. Current consensus guidelines suggest that a positive result is greater than the 99th percentile (15).

Other Antiphospholipid Antibodies

The revised criteria for antiphospholipid syndrome (15) indicate that only three antiphospholipid antibodies—1) lupus anticoagulant, 2) anticardiolipin, and 3) anti-β_2-glycoprotein I—can be used to establish the diagnosis. Some laboratories offer testing, often in a panel of tests, for other antiphospholipid antibodies. Results from such assays do little to improve the accuracy of the diagnosis of APS and testing for such antibodies is not recommended (16).

Medical Complications of Antiphospholipid Syndrome

The most common and serious complications associated with APS are venous thrombosis and arterial thrombosis (5, 6, 17). Most thrombotic events (65–70%) are venous (18, 19). Approximately 2% of all patients with venous thrombosis will test positive for lupus anticoagulant antibodies (20). Although the most frequent site of venous thrombosis is a lower extremity, thrombosis can occur in almost any blood vessel in the body, and occlusions in unusual locations should prompt clinicians to consider the diagnosis of APS. It is estimated that less than 1% of the asymptomatic nonpregnant adults incidentally found to have antiphospholipid antibodies eventually will develop thromboses each year (21). One retrospective cohort study of 147 participants found a thrombosis recurrence rate of 25% per year in untreated patients with antiphospholipid syndrome, but also showed that recurrence can be minimized with anticoagulation (18).

The risk of thrombosis is significantly increased during pregnancy in patients with APS. In a large cohort study, up to 25% of thrombotic events in patients with APS occurred during pregnancy or the postpartum period (22). These findings were confirmed in prospective studies indicating a 5–12% risk of thrombosis during pregnancy or the puerperium in women with antiphospholipid syndrome (9, 10).

Arterial thrombosis also is associated with antiphospholipid antibodies and can occur in atypical sites, such as the retinal, subclavian, digital, or brachial arteries. Stroke is the most common consequence of an arterial occlusion, with the most frequently involved vessel being the middle cerebral artery. Transient ischemic attacks and amaurosis fugax also are associated with antiphospholipid antibodies (22, 23). Antiphospholipid antibodies are present in 4–6% of otherwise healthy individuals with stroke who are younger than 50 years (24, 25). Coronary occlusions also have been reported (4). Individuals with unexplained arterial thrombosis, stroke, amaurosis fugax, or transient ischemic attacks should undergo testing for antiphospholipid antibodies.

Autoimmune thrombocytopenia occurs in 40–50% of individuals with APS (3, 4, 26). Thrombocytopenia associated with antiphospholipid antibodies is extremely difficult to distinguish from idiopathic thrombocytopenic purpura (ITP), although the pertinent platelet antigens appear to differ in APS and ITP. Thrombocytopenia caused by APS is treated the same as thrombocytopenia caused by ITP.

A variety of other medical conditions have been associated with antiphospholipid antibodies, including autoimmune hemolytic anemia, livedo reticularis, cutaneous ulcers, chorea gravidarum, multi-infarct dementia, and transverse myelitis (3, 4). A condition termed catastrophic APS occurs in some individuals who develop progressive thromboses and multiorgan failure (27). Others have a severe illness postpartum primarily consisting of cardiopulmonary failure, fever, as well as renal insufficiency, and multiple thromboses (28–30).

Obstetric Complications

Fetal and Recurrent Pregnancy Loss

A large proportion of pregnancy losses related to antiphospholipid antibodies occur in the fetal period (greater than 10 weeks of gestation). However, fetal deaths at these gestational ages normally account for only a small proportion of all pregnancy losses in the general population, which occur more frequently before 10 weeks of gestation (7). In a cohort of 76 women with antiphospholipid antibodies, 50% of pregnancy losses occurred during the fetal period compared with 10% in those women without antiphospholipid antibodies; also, 84% of women with antiphospholipid antibodies had at least one fetal death compared with 24% of women without antiphospholipid antibodies (31).

Although antiphospholipid antibodies also are not associated with sporadic embryonic pregnancy loss, they have been associated with recurrent embryonic or fetal loss or both. Observational studies have consistently documented positive test results for antiphospholipid antibodies in a higher proportion of women with recurrent spontaneous pregnancy loss than in controls (32–40). Most studies report positive test results for antiphospholipid antibodies in 5–20% of women with recurrent pregnancy loss, although concerns about whether or not cases would meet current international criteria for the diagnosis of APS remain a subject of debate among experts (41).

Preeclampsia

Preeclampsia is associated with APS (9, 10). Although 11–17% of women with preeclampsia will test positive for antiphospholipid antibodies (42–45), the association is strongest in women with severe preterm preeclampsia (less than 34 weeks of gestation). In addition, a prospective evaluation of more than 1,000 women found that women with antiphospholipid antibodies had an increased risk of pregnancy-induced hypertension (odds ratio 5.5) and severe pregnancy-induced hypertension (odds ratio 8.1) (46).

Intrauterine Growth Restriction

Intrauterine growth restriction (IUGR) complicates pregnancies in women with APS, occurring in 15–30% in most series (9, 10, 34, 47). Although APS is associ-

ated with IUGR, there is conflicting evidence of the link between antiphospholipid antibodies alone and IUGR (48). Although some studies have not found a correlation between antiphospholipid antibodies and IUGR (49, 50), this discrepancy may result from the inclusion of some women with low-positive test results for antiphospholipid antibodies (10, 34, 51).

Clinical Considerations and Recommendations

▶ *Who should be tested for antiphospholipid antibodies?*

Clinical criteria proposed for the diagnosis of APS are listed in Box 2. The principal manifestations of antiphospholipid syndrome are venous or arterial thromboses, specific pregnancy morbidities, and fetal or recurrent pregnancy loss. Testing for antiphospholipid antibodies should be performed in women with a prior unexplained arterial or venous thromboembolism, or a new arterial or venous thromboembolism during pregnancy, or a history of venous thromboembolism who have not been tested previously. Obstetric indications for antiphospholipid antibody testing include a history of one fetal loss or three or more recurrent embryonic or fetal losses. Although preterm severe preeclampsia and early onset placental insufficiency are indicated as clinical criteria for the diagnosis of APS by expert consensus, insufficient evidence currently exists to support that screening and treatment of women with these conditions improves subsequent pregnancy outcomes. Studies in this area have been small with poorly characterized obstetric details.

Other conditions associated with APS include, hemolytic anemia, autoimmune thrombocytopenia, amaurosis fugax, livedo reticularis, systemic lupus erythematosus, and a false-positive rapid plasma reagin result. These conditions are not considered clinical criteria for APS; therefore, testing individuals with these isolated conditions is not recommended. Clinicians who test for antiphospholipid antibodies in women without clinical features of APS may be left with an uninterpretable positive test result and a management dilemma. It is best to avoid such problems by testing only patients with disorders clearly related to antiphospholipid antibodies.

Box 2. Clinical Criteria for Diagnosis of Antiphospholipid Syndrome

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ, or
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 eclampsia or severe preeclampsia, or features consistent with placental insufficiency, or
   c) Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

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▶ *What laboratory criteria are used for the diagnosis of antiphospholipid syndrome?*

Testing for APS should include lupus anticoagulant, anticardiolipin antibodies (IgG and IgM) and anti-β_2-glycoprotein I antibodies (IgG and IgM) (Box 1). Initially, positive test results should be confirmed after an interval of 12 weeks or more (15). Persistence of positive results upon repeat testing is confirmatory of the syndrome.

▶ *How should antiphospholipid syndrome be managed during pregnancy and the postpartum period?*

The goals of treatment for APS during pregnancy are to improve maternal and fetal–neonatal outcome. Two reviews (52, 53) have emphasized that case series and treatment trials tend to include individuals whose APS diagnosis falls into one of two groups: 1) those with a history of thrombotic events and 2) those without a history of thrombotic events. For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum (54). Patients enrolled in most published series also received low-dose aspirin, but the benefit of adding aspirin for this indication is unknown. Anticoagulation should be continued for a minimum of 6 weeks postpartum to minimize the risk of maternal thromboembolism (52). After

delivery, this prophylaxis can be safely accomplished with coumarin.

The optimal treatment of women with antiphospholipid syndrome without a preceding thrombotic event has not been well studied. However, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted (54). A meta-analysis suggested that, for women with recurrent pregnancy loss and antiphospholipid antibodies, prophylactic use of heparin and low-dose aspirin may reduce pregnancy loss by 50% (55). This combined therapy appears superior to low-dose aspirin alone or to prednisone. Therefore, for women with a history of sporadic fetal loss or any type of recurrent pregnancy loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks postpartum should be considered.

Other therapies that have been suggested for treatment of pregnant women with antiphospholipid syndrome include corticosteroids and intravenous immunoglobulin (IVIG). Several case series using historical self-comparison have reported a 60–70% rate of successful pregnancies in women with antiphospholipid syndrome treated with prednisone and low-dose aspirin (56). However, a meta-analysis of therapeutic trials showed no reduction in pregnancy loss in women treated with prednisone and low-dose aspirin (55). Direct comparison of studies is difficult because participants had different clinical and laboratory features and dose regimens, and many trials were nonrandomized and poorly controlled. The efficacy of prednisone in pregnancies complicated by APS remains uncertain and, because of the risks associated with the prophylactic use of prednisone for this indication, its use is discouraged solely for the treatment of APS.

Treatment with IVIG has been evaluated in a small number of cases in which adverse outcomes have been refractory to heparin or prednisone treatment (57–59). Obstetric complications have been rare in patients treated with IVIG (59, 60). However, most of the women who received IVIG also were treated with heparin or prednisone and low-dose aspirin. A small randomized controlled study demonstrated no greater benefit from IVIG (plus heparin and aspirin) than from heparin and aspirin alone (61). Because the efficacy of IVIG has not been proved in appropriately designed studies and the drug is extremely expensive, its use is not recommended.

▶ *Should women with antiphospholipid syndrome have antepartum surveillance?*

Antepartum testing has been suggested because of the potential risk of fetal growth restriction and stillbirth in pregnancies of women with APS. The data are insufficient to support or refute a specific practice, but many experts recommend serial ultrasonographic assessment and antepartum testing in the third trimester.

▶ *What is appropriate long-term management of antiphospholipid syndrome?*

Long-term risks for women with antiphospholipid syndrome include thrombosis and stroke. In studies of women with antiphospholipid syndrome, including studies of women without prior thrombosis, one half developed thromboses during 3–10 years of follow-up and 10% developed systemic lupus erythematosus (22, 62, 63). The studied populations were highly selected referral populations and, thus, may have been biased toward including women with severe disease. However, no method currently predicts which patients with antiphospholipid syndrome using anticoagulants will develop recurrent thrombosis once treatment is discontinued. In addition, no evidence exists to support long-term treatment when thrombotic events occur in the presence of other risk factors (62). Therefore, for long-term management postpartum, patients with antiphospholipid syndrome should be referred to a physician with expertise in treatment of the syndrome, such as an internist, hematologist, or rheumatologist.

Pregnancy and the use of estrogen-containing oral contraceptives appear to increase the risk of thrombosis in women with APS. Experts concur that women with APS should not use estrogen-containing contraceptives (64), but that progesterone–only forms of contraception are appropriate.

Summary of Recommendations and Conclusions

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Obstetric indications for antiphospholipid antibody testing should be limited to a history of one fetal loss or three or more recurrent embryonic or fetal losses.
- Testing for antiphospholipid antibodies should be performed in women with a prior unexplained venous thromboembolism, a new venous thromboembolism during pregnancy, or in those with a history of venous thromboembolism but not tested previously.

- In women with APS and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- For women with APS who have had a thrombotic event, most experts recommend prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks postpartum.
- For women with APS who have not had a thrombotic event, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted.
- For long-term management postpartum, patients with APS should be referred to a physician with expertise in treatment of the syndrome, such as an internist, hematologist, or rheumatologist.
- Women with APS should not use estrogen-containing contraceptives.

Proposed Performance Measure

Many experts recommend serial ultrasonographic assessment and antepartum testing in the third trimester for women with APS.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–November 2009. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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