Update on the Latest Research in Patients With APS

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Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thrombosis or pregnancy complications combined with the persistent presence of antiphospholipid antibodies (aPL). Ronald HWM Derksen, MD, PhD, University Medical Center, Utrecht, The Netherlands, gave an overview of the latest research in APS.

Serologic studies are required for the diagnosis of APS. Lupus anticoagulation (LAC), anti-cardiolipin (aCL), and anti-β_2-glycoprotein I (anti-β_2-GPI) assays are typically used to determine whether a patient has APS. Several studies have found that a positive LAC test correlates better with thrombosis and pregnancy loss than the aCL assay, but performing these tests can be challenging. Although there are numerous LAC assays, no single test has 100% sensitivity and specificity. The LAC tests cannot be performed in patients receiving anticoagulation therapy, and there is no standardized definition of a positive test. In addition, a high degree of inter-laboratory variability has been observed in aCL tests, standards have a lot-to-lot variability, and no universally accepted, clinically relevant level currently exists. The anti-β_2-GPI assay is also problematic, as there are no uniformly accepted calibrators and units, and a clinically relevant cut-off has not been defined.

In an attempt to better define patients with APS, a group of international experts developed a formal list of APS classification criteria in 1999, which was updated in 2006 [Myakis S et al. *J Thromb Haemost* 2006]. The APS classification requires one clinical and one laboratory criterion, as summarized in Table 1.

Table 1. Classification Criteria for Antiphospholipid Syndrome

Clinical	**Laboratory**
Thrombosis ▪ One or more episodes of arterial, venous, or small vessel thrombosis in any organ or tissue ▪ Thrombosis confirmed by objective validated criteria (i) Using histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall And/or:	The following present for at least 12 weeks or longer: ▪ Lupus anticoagulant positivity according to the International Society of Thrombosis and Hemostasis criteria ▪ Anti-cardiolipin antibodies IgG and/or IgM isotype in medium or high titer (>40 GPL or MPL units or >99th percentile) ▪ Anti-β_2 glycoprotein-I antibodies IgG and/or IgM isotype (in titer >99th percentile)
Pregnancy complications ▪ Three or more consecutive unexplained losses under 10 weeks' gestation ▪ One or more unexplained fetal deaths with normal morphology beyond 10 weeks' gestation ▪ One or more premature births under 34 weeks' gestation of a morphologically normal neonate because of: (i) Eclampsia or severe preeclampsia (ii) Recognized features of placental insufficiency	
Categories	
Category I	More than one laboratory criterion present in any combination
Category IIa	Lupus anticoagulant test present alone
Category IIb	Anti-cardiolipin antibody present alone
Category IIc	Anti-β_2 glycoprotein-I antibody present alone

IgG=immunoglobulin G; IgM=immunoglobulin M.

Source: Myakis S et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006.

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Whereas the original intent was to use these criteria in research studies to determine the serological profile and clinical characteristics of patients at the highest risk for complications and, thus, ascertain the optimal treatment plan, these criteria are often used for diagnosing APS. The presenters stated that the presence of non-aPL risk factors for thrombosis does not preclude the diagnosis of APS. In a study of 183 patients with aPL-associated thrombosis, more than 50% of patients had coexisting or inherited non-aPL risk factors for thrombosis [Kaul M et al. *Ann Rheum Dis* 2007]. Examples of non-APL thrombosis risk factors include hypertension, diabetes mellitus, high cholesterol levels, family history of cardiovascular disease, obesity, cigarette smoking, oral contraceptive use, and coexisting autoimmune disease, such as systemic lupus erythematosus (SLE). The frequency of these risk factors requires they be considered to judge the thrombotic risk in aPL patients, noted Prof. Derksen.

Some believe that the 99th percentile cut-off for APS may be set too high. A recent study of 145 APS patients found that ~50% of those patients with obstetric APS had low levels of aCL or anti-β_2-GPI (between the 95th and 99th percentile) [Gardiner C et al. *Lupus* 2013]. These data show that patients with non-obstetric, thrombotic APS have much higher levels of these antibodies, indicating a difference between the obstetric and thrombotic subsets, stated Prof. Derksen. Gardiner and colleagues recommended a cut-off at the 95th percentile to diagnose obstetric APS.

The importance of the serological profile in APS patients has been demonstrated in several studies. In a prospective study of 200 women, 53 were classified with obstetric APS and followed for 7 years [Ruffatti A et al. *Thromb Haemost* 2006]. The authors reported that LAC, aCL, and anti-β_2PI positivity (triple positivity) had a significant association with late pregnancy loss (OR, 16.2; 95% CI, 0.9 to 292; p=0.01) and thrombosis (OR, 122.5; 95% CI, 16 to 957; p<0.001). In addition, the immunoglobulin (Ig) G-aCL and IgG anti-β_2-PI levels were significantly higher in triple-positive patients when compared with double-positive patients. Sixteen triple-positive patients and 37 double-positive patients (no positivity for LAC) were followed for a mean 6.3 years (range, 0.5 to 15 years). A total of 47 patients became pregnant and were treated with aspirin and low molecular weight heparin. Seven pregnancies were unsuccessful (15%), and triple positivity or previous thromboembolism were independent markers for pregnancy failure (OR, 34.4; 95% CI, 3.5 to 335.1; p=0.003). There was a new thrombotic episode in 8 patients, and a significant association was seen between thrombotic events and triple positivity or thromboembolism (OR, 57.5; 95% CI, 2.7 to 1160; p=0.0004).

In another multicenter study of obstetric APS, the following independent risk factors for pregnancy failure were identified: history of thrombosis and pregnancy morbidity (OR, 12.1; 95% CI, 1.3 to 115.3; p=0.03), presence of SLE or other autoimmune diseases (OR, 6.0; 95% CI, 1.7 to 20.8; p=0.01), and triple positivity (OR, 4.1; 95% CI, 1.0 to 16.7; p=0.05) [Ruffatti A et al. *Rheumatology (Oxford)* 2011]. In addition, babies born to women who were triple positive were more likely to have a low birth weight and Apgar score, be small for their gestational age, require resuscitation, require neonatal intensive care unit admission, and have infections [Ruffatti A et al. *Arthritis Care Res* 2010].

In the Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Antiphospholipid Syndrome study [PROMISSE; Lockshin MD et al. *Arthritis Rheum* 2012], 144 pregnant patients with aPL were treated with aspirin and heparin and followed prospectively. Out of 144 pregnancies, 28 (19%) were not successful. The authors reported that adverse pregnancy outcomes (APO) were not associated with IgM-aCL at any level, IgG- or IgM anti-β_2-PI, or a combination of aCL or anti-β_2-GPI. Instead, LAC positivity was the primary predictor of APO and was the only component of triple positivity that had predictive value. The differences in the findings between this study and that by Ruffatti and colleagues may be due to the cut-off values used for the assays, stated Prof. Derksen.

In his concluding remarks, Prof. Derksen emphasized that well-designed studies are needed to define which aPL profiles are the most important in regard to treatment decisions and which require long-term or short-term thromboprophylaxis, among other issues.