Women's Issues in Antiphospholipid Syndrome

Emmanouil Papadakis, Anastasia Banti and Anna Kioumi

Hemostasis Unit, Department of Hematology, Papageorgiou Hospital, Thessaloniki, Greece

ABSTRACT: Antiphospholipid syndrome (APS) is an autoimmune systemic disease characterized by vascular thrombosis (arterial or venous) and/or pregnancy complications associated with the occurrence of autoantibodies, specifically lupus anticoagulant, anticardiolipin antibodies, and/or anti-β2 glycoprotein-I antibodies confirmed at least twice over a 12 week period according to the 2006 Sydney criteria. Antiphospholipid antibodies are encountered in the general population with a reported prevalence of 1% to 5% However, APS is far more infrequent with a prevalence of 40–50/100,000 persons and an incidence of about 5 new patients/100,000 persons. APS can be diagnosed in patients with no apparent clinical or laboratory pathology (primary APS) or it may be related to numerous other conditions, autoimmune diseases (usually systemic lupus erythematosus), malignancies, infections and drugs (secondary APS). Women are at risk for APS since the disease is encountered in both the primary and the secondary state in females more often than in men. In addition, women in their reproductive years can develop APS (either classical or obstetric), and special attention is warranted in pregnant women with a diagnosis of APS. The benefits of hormonal therapy in the form of contraception or hormone replacement treatment should be carefully weighed against the increased risk for vascular complications in women with APS.

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KEY WORDS: women, antiphospholipid syndrome (APS), antiphospholipid antibodies (aPL), pregnancy morbidity, thrombosis, risk factors

Antiphospholipid antibodies (aPL) are encountered in the general population, albeit rarely, with a reported prevalence of up to 5% [1]. Antiphospholipid syndrome (APS) is far more infrequent with a prevalence of 40–50/100,000 persons and an incidence of about 5 new patients/100,000 persons. APS can be diagnosed as primary APS or it may be related to numerous other conditions and autoimmune diseases, malignancies, infections and drugs (secondary APS) [2]. A distinct characteristic of APS is the predisposition for both venous and arterial thrombosis. In a cohort of 1000 APS patients [3] stroke was the most common arterial thrombosis (occurring in roughly 20% of the patients) and lower limb thrombosis the most common venous event (observed in 15%). Regarding pregnancy morbidity, recurrent fetal loss was the most common complication, affecting more than 50% of pregnancies in the cohort. Apart from thrombosis and pregnancy complications, several clinical manifestations can be seen in APS patients, namely hemolytic anemia, thrombocytopenia, livedo reticularis, heart valve disease and neurological symptoms [4]. A rare and severe variant of APS is Asherson syndrome, also known as catastrophic antiphospholipid syndrome (*CAPS*); this syndrome encompasses multisystem involvement and microvesicle occlusion which develops rapidly and is lethal for more than 30% of patients [5].

All the aforementioned clinical manifestations have a unifying feature: the persistent presence of aPL antibodies in patients' sera. During the diagnostic process a varied range of diagnoses mimicking APS should be investigated and ruled out. Among them are microangiopathic hemolytic anemias, disseminated intravascular coagulation, and autoimmune diseases such as lupus vasculitis and Behcet's disease.

DIAGNOSIS

After the first diagnostic criteria that were established in 1999 by a consensus of international experts, a second conference for revision of the diagnostic algorithm was held in Sydney in 2006. The revised criteria, referred to as the Sydney criteria, are currently used for APS diagnosis and classification. The criteria are divided into clinical and laboratory. Clinical criteria include thrombosis (arterial, venous, or microvascular) or pregnancy complications (pregnancy loss, prematurity, preeclampsia, or placental insufficiency). Laboratory criteria require positivity for aPL on two or more occasions at least 12 weeks apart. aPL antibodies included in the international consensus criteria are lupus anticoagulant (LA), anticardiolipin (aCL) antibodies (IgG or IgM) > 40 phospholipid units, and anti-β2 glycoprotein-I (anti-β2GPI) antibodies (IgG or IgM) at titers exceeding the 99th percentile. In clinical practice, based on these classification criteria, the following patient categories can be identified:

- Classical APS associated with aPL positivity: thrombotic events in typical sites such as deep vein thrombosis (DVT) of the lower limbs, pulmonary embolism (PE), myocardial infarction (MI), and stroke or typical pregnancy disorders
- Unusual clinical presentation of typical APS: thrombosis in atypical sites, e.g., splanchnic vessels or central nervous venous sinuses

- Incomplete clinical manifestations of obstetric APS with aPL positivity: pregnancy disorders not fulfilling the Sydney criteria (e.g., two consecutive miscarriages before the 10th week of gestation or three or more non-consecutive miscarriages before the 10th week)
- Non-criteria clinical manifestations of APS associated with aPL positivity: for example, non-thrombotic pulmonary or cardiac involvement, and ophthalmic, neurological, hematological and rheumatological manifestations
- CAPS (Asherson syndrome): multiple organ thromboses commonly associated with microangiopathy.

WOMEN AND APS

Female gender dominates antiphospholipid syndrome. In a multinational cohort of 1000 unselected APS patients [3], 820 (82.0%) were women and 180 (18.0%) were men, with a 5:1 ratio of female to male. This predominance was observed not only in secondary APS (usually associated with autoimmune diseases), the ratio being 7:1, but in primary APS as well where the female to male ratio was 3.5:1. Regarding the prevalence of female gender in autoimmune diseases, lupus affects females nine times more often than males; a hormonal influence is apparent in the pathogenesis since autoimmunity peaks in women in their reproductive years [6]. Differences in clinical symptoms and complications were observed to be related to gender in the Euro-Phospholipid Project cohort. Specifically, women experienced more frequent episodes of arthritis (29% vs. 19% in males), livedo reticularis (26% vs. 16%), and migraines (23% vs. 12%), while male patients more frequently presented myocardial infarction (16% vs. 3%), epilepsy (12% vs. 6%), and arterial thrombosis in the lower extremities (11% vs. 3%).

Antiphospholipid syndrome is largely a woman's issue. There are several clinical scenarios in APS, not always related to pregnancy, where a woman will seek medical consultation.

- Management of women with classical vascular APS
- Obstetric APS
- Long-term follow-up of women with obstetric APS
- Hormonal therapy in women with APS
- Management of asymptomatic women with persistent aPL antibodies

MANAGEMENT OF WOMEN WITH VASCULAR APS

Long-term anticoagulant treatment is the mainstay of treatment for thrombotic APS as recommended by medical societies [7]. Conversely, the optimal antithrombotic and anticoagulant treatment and the optimal duration of treatment remain controversial, especially for non-venous thrombotic APS. The balance between thrombosis and hemorrhage in APS patients is important because many patients present thrombocytopenia, coagulopathies and co-morbidities that lead to increased bleeding risk. With the incorporation of direct oral anticoagulants into the management of venous thromboembolism (VTE), rivaroxaban was assessed in APS patients with VTE in the Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial. Rivaroxaban proved to be a safe, non-inferior alternative treatment for APS patients with venous thrombosis [8].

Reducing additional risk factors is essential for the management of patients with thrombotic APS. A retrospective cohort study of 61 patients with APS analyzed factors influencing thrombosis [9]. For arterial thrombotic events, both hypertension and hyperlipidemia were found to be significant risk factors. In addition, smoking was associated with an increased risk of arterial thrombosis with an odds ratio (OR) > 3. On the other hand, diabetes was the only controllable condition found to be significantly associated with VTE. Conversely, a case-control study examined women aged < 50 years who suffered ischemic stroke or MI. This study, called the RATIO study (Risk of Arterial Thrombosis In relation to Oral contraceptives) [10], showed that lupus anticoagulant is a major risk factor for arterial thrombosis in young women, and the presence of other cardiovascular risk factors further increased the risk. In the patient cohort LA was found in 17% of the patients with stroke and in 3% of the patients with MI, and in 0.7% in the control group. The odds ratio for MI was 5.3, which increased to 21.6 in women who used oral contraceptives and 33.7 in those who smoked. The odds ratio for ischemic stroke was 43.1, which increased to 201 in women who used contraceptives and 87 in those who smoked.

OBSTETRIC APS

Obstetric APS is characterized by pregnancy complications along with the presence of antiphospholipid antibodies. Although the exact incidence of APS in pregnancy is not known, APS is widely recognized as the most common thrombophilic state associated with recurrent fetal loss and pregnancy complications. APS in pregnancy affects both mothers and developing fetuses. Mothers are at increased risk of thrombosis, thrombocytopenia and complications like preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). APS can cause fetal loss, recurrent early miscarriages and stillbirths, intrauterine growth restriction, and prematurity.

Although the exact prevalence of aPL antibodies is not accurately estimated in pregnancy and pregnancy complications, it is reported that in obstetric populations the prevalence of LA is about 0.3% and of aCL can reach 9% (2.2–9.1%) [11]. In a retrospective review of a cohort of women without SLE, the prevalence of aPL was 20% in women with recurrent fetal losses compared with only 5% in healthy women [12].

APS can impact on pregnancy from the pre-conception period – although still widely debated – through implantation failures, until postpartum. Obstetric APS is even implicated in neuropsychological developmental disorders of infants [13] and in the long-term increased risk for vascular complications in mothers.

In the Euro-Phospholipid Project cohort consisting of 590 women, 71.9% experienced one or more pregnancies (1–23), and 437 of them (74.1%) succeeded in having one or more live births (mean 1.7, range 1–8). The most common obstetric complications in the mothers were preeclampsia (9.5% of pregnant women), eclampsia (4.4%) and abruptio placentae (2.0%). The most common fetal complications were early fetal loss (35.4% of pregnancies), late fetal loss (16.9%) and prematurity (10.6% of live births). In a survey of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) [14] in a cohort of 247 APS pregnancies, live births were achieved in 192 of the 247 cases (77.7%), but not in 55 (22.3%). Of the 192 successful cases, 174 (89.7%) received treatment and 18 (10.3%) did not. Thirty-eight (69%) of the remaining 55 women who did not achieve live births received treatment and 17 (31%) did not. Obstetric complications occurred in 129/247 cases (52.2%), although not all ended in fetal loss. Fetal loss was the most frequent (17.80%) complication followed by miscarriage (16.27%), with stillbirth being relatively infrequent (4.69%). Prematurity was the most common non-fatal complication (47.28%). Early and severe preeclampsia together with HELLP syndrome occurred in more than 18% of these women. Fetal growth restriction complicated 15.50% of cases.

■ Obstetric APS: Maternal complications

Manifestations affecting pregnant women with APS include thrombotic events as well as obstetric pathologies. Pregnancy is a hypercoagulable state, predisposing particularly to venous thrombosis. Pregnant women indeed have a five- to sixfold increased risk of venous thrombosis compared with non-pregnant women of the same age [15]. Arterial thrombosis can also be observed in APS pregnancies [16] in the form of stroke, transient ischemic attack, and amaurosis fugax (temporary loss of vision). In the NOHAPS study, cerebrovascular events were significantly higher in obstetric APS patients compared with controls (0.32% vs. 0.09%) [17]. Although serious, thrombotic events in APS pregnancies often do not receive adequate care. The coexistence of thrombotic events and miscarriage is estimated at around 2.5–5% of APS pregnancies [18]. APS during pregnancy can present symptoms like thrombocytopenia or livedo reticularis in 20% of cases. Thrombocytopenia (< 100 g/L) can be difficult to manage, especially in women receiving anticoagulant treatment. Livedo reticularis is a dermatologic condition encountered in APS where the skin appears violaceous, red or blue, in a reticular or mottled pattern, and is persistent and irreversible with warming (i.e., does not regress after skin warming).

The most common obstetric manifestation is preeclampsia which can affect up to 10% of APS pregnancies [3]. Preterm delivery which is encountered in 20% of APS pregnancies is usually associated with hypertension/preeclampsia. The relationship between aPL and preeclampsia is still unclear, with conflicting data from different studies. Women with high titers of aPL had an increased risk of preeclampsia or eclampsia (adjusted OR 2.93), placenta insufficiency (adjusted OR 4.58), and prolonged hospitalization (> 3 days, adjusted OR 3.93) in a cross-sectional study of 141,286 pregnancies [19]. Preeclampsia in women with APS occurs earlier (< 34 weeks) and is more severe. aCL is more strongly linked to preeclampsia (OR 2.73) than lupus anticoagulant (OR 1.45), while the presence of more than one type of aPL increases the risk of pregnancy-induced hypertension and predisposes to severe preeclampsia. In women with SLE and prior thrombosis the rate of preeclampsia can reach 32–50%. Complications of preeclampsia include rarer and more serious conditions such as eclampsia and HELLP syndrome. The incidence of HELLP syndrome in APS patients is difficult to determine; it seems more severe and occurs earlier in APS pregnancy than in pregnancies not affected by aPL [20]. HELLP syndrome is a harbinger for catastrophic APS which represents 1% of APS and can occur outside of pregnancy as well. CAPS is defined as a "thrombotic storm" secondary to diffuse microvascular thrombosis leading to multiorgan failure. It was reported that 6% of CAPS is associated with pregnancy and postpartum, but this is probably an underestimation [21]. Early diagnosis and management of CAPS is crucial since mortality is high for both mothers (46%) and babies (54%) even after aggressive therapy is started [21]. CAPS differential diagnosis, including HELLP syndrome, thrombocytopenic thrombotic purpura (TTP) and disseminated intravascular coagulation (DIC), can be challenging during pregnancy.

■ Obstetric APS: Fetal complications

APS may be the cause for diverse fetal development and growth impairment in every stage of pregnancy. Although in the general population a miscarriage can occur in one of five pregnancies, recurrent fetal loss affects only 1% of pregnancies. The main recognizable cause for recurrent fetal loss is fetal chromosomal abnormalities; however, aPL are observed in 15% of recurrent fetal losses, indicating that APS constitutes one of the main acquired causes for recurrent miscarriages [22]. Fetal loss can occur in any trimester of pregnancy, as documented in the Euro-Phospholipid series [3], although the frequency was higher before the 10th week of gestation than after (35.4% vs. 16.9% respectively) in the same cohort. In the report of the EUROAPS registry stillbirth was observed at a lower frequency (< 5%) [14]. Premature births are reported at 10–20% of live births in APS pregnancies and are usually associated with hypertension/preeclampsia. A meta-analysis of 25 studies reported that LA has the strongest association with late fetal loss (OR 7.79, 95% confidence interval 2.30–26.45) [23], while there is debate regarding the association between anti-β2GPI antibodies and pregnancy complications. Poor placentation results in fetal growth restriction. In a review analyzing three prospective studies that investigated the prevalence of

aPL among pregnant women with fetal growth restriction the overall prevalence of aPL was 9.5% [24].

■ Obstetric APS: Uncharted manifestations

Whether APS has a causal relationship with infertility and IVF failures is still a matter of debate. The incidence of aPL in women with unexplained infertility and in vitro fertilization (IVF) failure seems significantly increased compared to controls [25]. However, due to the lack of well-designed studies, there is insufficient solid evidence of aPL association with implantation or IVF outcome. Furthermore, precautions should be taken when interpreting positive aPL test results [25].

■ Obstetric APS: Management

APS pregnancies represent real challenges for clinicians and should therefore be planned. Careful counseling [Table 1] is required and multidisciplinary surveillance [Table 2] is the key to a successful pregnancy. Women with APS already on oral anticoagulation should be informed of potential teratogenic effects. Once pregnancy is confirmed, oral anticoagulation should be immediately switched to low molecular weight heparin (LMWH) combined with low dose aspirin for the rest of the pregnancy. Even under treatment the chance of an uneventful pregnancy can reach 70% [3,14]. The EUROAPS has shown that if first-line treatment is administered according to existing guidelines, 87.1% of APS pregnancies will be successful. Ruffati et al. [26] found that risk factors for pregnancy failure were: the presence of SLE or other autoimmune diseases (OR 6.0), a history of both thrombosis and pregnancy morbidity (OR 12.1), and triple antibody positivity (OR 4.1).

The majority of existing guidelines suggest using the combination of low dose aspirin and subcutaneous LMWH for first-line treatment of APS pregnancy, which improves both fetal and mother outcomes [9th ACCP, BCSH-RCOG guidelines]. Even with optimal management, around 10–20% of APS pregnancies will not be uneventful. In these cases second-line treatment is justified often in combination with first-line treatment. Of the modalities that have been used in the past, like steroids, intravenous immunoglobulin, plasmapheresis procedure, and hydroxychloroquine (HCQ), the latter seems to be the more promising and safer approach. HCQ initially used in SLE yields promising results and in an experimental model reduced the binding of anti-β2GP1 at the surface of trophoblastic cells [27]. Since there is a paucity of well-designed trials on second-line treatments for APS pregnancies, caution should be exerted prior to their administration.

LONG-TERM FOLLOW-UP OF WOMEN WITH A HISTORY OF OBSTETRIC APS

Women with purely obstetric APS carry an increased risk both for venous thromboembolism and arterial thrombosis that persists over years. As Gris and colleagues demonstrated in the NOH-APS study [17], purely obstetric APS patients (n=517) had an increased risk of thrombosis including DVT (1.46%), PE (0.43%) and superficial vein thrombosis (0.44%), even though they received low dose aspirin treatment, compared with controls (n=796, with 0.43%, 0.12%, 0.14%, respectively). The annual rate for subsequent cerebrovascular events (0.32% vs. 0.09% for control) was found significantly elevated in asymptomatic women with aPL antibodies than in the control group. Based on the findings of the NOH-APS study that obstetric and classical APS share common thrombotic mechanisms, clinicians are urged to conduct a long-term follow-up for any vascular incident in women with purely obstetric APS.

Table 1. Counseling for pregnancy in APS

• Pregnancy should be discouraged in all women with severe pulmonary hypertension due to the high risk of maternal mortality. If a patient has uncontrolled hypertension or recent thromboembolism, especially stroke, pregnancy should be postponed
• Information should be provided regarding risks of fetal loss, increased risk of preeclampsia and HELLP syndrome, risk of thrombosis (both arterial and venous), risk of fetal growth restriction and small for gestational age, and the likelihood of a preterm delivery
• A complete and repeated profile of antiphospholipid antibodies should be available before planning a pregnancy. Testing is not required during pregnancy since subsequent negative results (after diagnosis, repeatedly positive tests) do not eliminate the risk of complications

Table 2. Antenatal monitoring of APS pregnancies

• Women with APS should be monitored every 4–6 weeks for preeclampsia, fetal growth restriction after 20 weeks and maternal disease activity monitoring (especially if APS is not primary)
• Early dating scans and screening for any chromosomal abnormalities are recommended
• Women should be made aware of the symptoms of thrombosis and preeclampsia, and should have their blood pressure measured and urine checked for proteinuria at each visit
• Uterine artery waveforms are usually assessed between 20 and 22 weeks gestation for evidence of fetal growth restriction
• There should be a low threshold for diagnosis of preeclampsia or HELLP
• Routine measurement of anti-Xa activity for women receiving LMWH for thromboprophylaxis is not required
• Women with concurrent SLE will need other disease-specific measures if there is any evidence of a flare
• An increase of anti-dsDNA antibodies and a decrease of complement levels is suggestive of a flare of SLE

HORMONAL TREATMENT IN WOMEN WITH APS

■ Contraception in women with APS

Pregnancy outcome in APS is optimized when pregnancy is timely planned. Therefore, effective and safe contraception methods are warranted. Pregnancy, especially in secondary APS, should be avoided during active autoimmune disease or when the patient is on pregnancy-incompatible medications. Apart from natural and mechanical barrier methods which are the least effective, every other method of contraception carries thrombotic risk (arterial and venous), the highest being combined estrogen-progestone oral contraceptives (three- to fivefold risk). In women receiving combined oral contraceptives, the presence of additional prothrombotic factors increases the risk for thrombosis. Given the multifactorial nature of VTE disease combined oral contraceptives are generally not advised in women with APS. Long-acting forms of contraception such as the progesterone intrauterine device (IUD) or subdermal implant are preferable for most patients [28]. The levonorgestrel IUD is a good alternative for many APS patients and is usually effective in reducing menstrual blood loss. It is prudent to avoid depot medroxyprogesterone acetate (DMPA) in corticosteroid-treated or other patients at risk for osteoporosis. Progesterone-only contraceptives probably represent the best option for aPL-positive patients, maximizing both safety and efficacy.

■ Hormone replacement therapy in women with APS

There are very few data regarding HRT in women with APS, with most studies focusing on HRT administration in lupus. Women with secondary APS (SLE related) are more likely to experience premature menopause, osteoporosis and cardiovascular disease. Cardiovascular disease is a major cause of death in SLE. HRT can induce SLE flares and thromboembolic events, and estrogen might be implicated in disease flares. In autoimmunity-related APS, hormonal treatment depends on the status of the autoimmune disease [29].

- **Inactive disease:** If the woman has experienced no flare, the disease is inactive, has no aPL antibodies and is on low dose and stable glucorticoid treatment (or none) for more than one year, the lowest dose of transdermal estrogen combined with natural progesterone, dydrogesterone or close progestogen derivatives can be used
- **Mild disease:** Non-estrogenic agents should be tried as a first-line treatment; in case of failure, low dose transdermal estrogen can be used with close follow-up
- **Active disease:** Non-estrogenic drugs should be used as first-line treatment. These include SSRIs and SRNIs, such as fluoxetine and paroxetine. Progesterone can alleviate hot flushes and may have beneficial effects on sleep disorders; they can be used without concern in SLE
- **History of VTE and persistent aPL antibodies:** These are a contraindication to both estrogen and raloxifene.

MANAGEMENT OF ASYMPTOMATIC WOMEN WITH PERSISTENT aPL ANTIBODIES

Primary thromboprophylaxis in asymptomatic aPL women is still a matter of debate. The presence of one factor on the multifactorial ladder to thrombosis seems insufficient, but an additional trigger may be needed to develop a vascular event in aPL carriers. It has been demonstrated that aPL-positive patients have a risk of thrombosis reaching 3.8% [30]. The type of aPL present must be taken into account. Thus, triple positivity, i.e., the presence of LA combined with aCL and anti-β2GPI, or the presence of persistently positive aPL at high levels is considered a high risk serological profile. Another group of aPL carriers who might benefit from primary prophylaxis with low dose aspirin are aPL-positive women with pregnancy morbidity not fulfilling the Sydney criteria. A retrospective study in aPL-positive women who only experienced a fetal loss [31] demonstrated that low dose aspirin significantly reduced the incidence of vascular thrombosis after pregnancy: the event incidence was 10% in those receiving low dose aspirin vs. 59% in the untreated group. Reversible vascular risk factors should be corrected, and during periods of increased thrombotic risk (i.e., surgery or prolonged immobilization) thromboprophylaxis with aspirin or LMWH appears to be effective in reducing thrombotic complications in asymptomatic aPL women [32]. In asymptomatic women with SLE, aspirin and hydroxychloroquine may be beneficial based on observational data. Recently the American Society of Hematology [33] produced evidence-based guidelines on thromboprophylaxis of aPL carriers.

Correspondence
Dr. E. Papadakis
Paraskeuopoulou 45, 55133 Kalamaria, Thessaloniki, Greece
Phone: +30 231 063-9211
Fax: +30 231 069-3293
email: emmpapadoc@yahoo.com

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