Review Article

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# Antiphospholipid Antibody Syndrome in Pregnancy

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**Abstract**

APS in pregnancy is one of the important cause of recurrent pregnancy loss, preclampsia and IUGR. Treatment to be started after confirmation of APS with the help of laboratory and clinical criteria.

With the imperfect data that are currently available it is impossible to give evidence based recommendations on how patients with APS should be treated in pregnancy. It is wise to regard pregnancies as being at high risk. Treatment to be started with prepregnancy councelling followed by follow up during pregnancy and treatment .

**Keywords:** APS; Antiphospholipid Antibody (aPL); Recurrent prgnancy loss; Preclampsia.

## Introduction

Antiphospholipid antibody syndrome (APS), also known as Hughes Syndrome is an autoimmune condition that may manifest with recurrent fetal loss, thrombosis (both arterial and venous) and/or autoimmune thrombocytopenia [1].

APS has emerged as the most important treatable cause of recurrent miscarriage, early onset preeclampsia, preterm labor, low birth weight babies and intrauterine growth restriction.

Since the late 1980s some publications have proposed that antiphospholipid antibodies (aPL) may have some relationship with infertility, considering reported deleterious effects that aPL exert on trophoblast proliferation and growth. But available data do not support an association between aPL and infertility, and aPL positivity does not seem to influence IVF outcome [2].

APS is classified as primary or secondary, depending on its association with other autoimmune-disorders.

- Primary APS is diagnosed in patients demonstrating the clinical and laboratory criteria for the disease without other recognized autoimmune disease.
- Secondary APS is diagnosed in patients with other autoimmune disorders, such as systemic lupus erythematosus (SLE).
- Catastrophic Antiphospholipid Syndrome (CAPS) represents the severe end of the spectrum with multiple organ thromboses in a rapid period of time [3]. Multiorgan failure has been described during pregnancy by Asherson [4] and during postpartum by Kochenour [5].

## Pathophysiology

There are several pathological mechanisms by which anti phospholipid antibodies i.e. APAs induce VTEand adverse pregnancy outcomes. These include antibody mediated impairment of endothelial annexin V, thrombomodulin and activated protein C-mediated anticoagulation; induction of endothelial tissue factor expression; impairment of fibrinolysis; and increased platelet

activation.In addition, APA appears to induce complement-mediated inflammationof the decidua and placenta [3].

**Clinical Features**

Clinically, the series of events in APS, which can lead to hypercoagulability and recurrent thrombosis can affect virtually any organ system.Thus, history of any of the following should raise the suspicion for APAS in obstetrician's mind:

- Thrombosis (e.g., deep vein thrombosis, myocardial infarction, transient ischemic attack, cerebrovascular accident, etc.) This is especially important if the episodes are recurrent, occur at an earlier age, or in the absence of other known risk factors.
- History of recurrent miscarriages (especially late trimester or recurrent) [6,7,8].
- History of heart murmur or cardiac valvular vegetations.
- History of hematologic abnormalities, such as thrombocytopenia or hemolytic anemia.
- History of nephropathy.
- Nonthrombotic neurologic symptoms, such as migraine, headaches, chorea, seizures, transverse myelitis, GuillainBarré syndrome, etc.
- Unexplained adrenal insufficiency.
- Avascular necrosis of bone in the absence of other risk factors.
- Pulmonary hypertension [9].

**Effect on Pregnancy**

The presence of a lupus anticoagulant and high ACA IgG levels present the highest risk of adverse pregnancy outcomes. Moreover, APA are present in about 20% of women with recurrent pregnancy loss [8]. Most losses occur after fetal cardiac activity is noted. That these antibodies do not appear to be associated with very early pregnancy loss is suggested by a meta-analysis of seven studies by Hornstein et al., reporting a lack of effect from APA on in vitro fertilization (IVF) outcomes. Moreover, APA can be found in approximately 2% of the general obstetric population [2].

**Diagnosis**

The 1999 "international consensus statement for the diagnosis of antiphospholipid syndrome" provided a set of criteria for the diagnosis of APS. These were updated in 2006 to reflect new insights into the disease.

The diagnosis of APS requires that the patient have at least 1 clinical criterion and 1 laboratory criterion.

- The clinical criteria include:

Thrombosis diagnosed by diagnostic imaging or histology involving one or more venous, arterial, or small vessels but not including superficial venous thrombosis;

Adverse pregnancy outcome including unexplained fetal death at 10 weeks of gestation or more of a morphologically normal fetus, *or* 1 or more preterm birth(s) prior to 34 weeks due to preeclampsia or placental insufficiency, or 3 or more unexplained embryonic losses;

- The criteria for laboratory testing, which are consistent with current clinical management guidelines from the American Congress of Obstetricians and Gynecologists (ACOG), include the following [10]:

1. Anticardiolipin antibodies - Anticardiolipin (aCL) IgG or IgM antibodies present at moderate or high levels (ie, >40 GPL or MPL or >99th percentile) in the blood on 2 or more occasions at least 12 weeks apart.
2. Lupus anticoagulant - LAC detected in the blood on 2 or more occasions at least 12 weeksapart, according to the guidelines of the International Society on Thrombosis and Hemostasis.
3. Anti-beta 2 -glycoprotein I antibodies IgG or IgM - In titer above the 99th percentile for normal asdefined by the laboratory performing the test, on 2 or more occasions at least 12 weeks apart [11,12,13].

- Other Investigation to rule out other system involvement-In a 3-year retrospective analysis by the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), the investigators indicated that all relevant laboratory studies should be obtained to avoid false-negative diagnoses and that levels may act as serologic markers for some cases [14].

1. Prolongation of the following clotting assays due to the presence of lupus anticoagulant:
   - Kaolin clotting time,
   - Dilute Russell viper venom time (DRVVT)
   - Activated partial thromboplastin time (aPTT)
2. Serologic test for syphilis (false positive result)
3. CBC count (thrombocytopenia, hemolytic anemia):

Thrombocytopenia is fairly common in persons with APS.

4. Imaging studies are helpful for confirming a thrombotic event, for e.g. the use of CT scanning or MRI of the brain (cerebrovascular attack), chest (pulmonary embolism), or abdomen (Budd-Chiari syndrome).
5. Doppler ultrasound studies are recommended for possible detection of DVT.
6. Two dimensional echocardiography(2D-ECHO) may help demonstrate an asymptomatic valve thickening, vegetations orvalvular insufficiency. Aortic or mitral insufficiency is the most common valvular defect found in persons with Libman Sacks endocarditis [15].

**Treatment**

With the imperfect data that are currently available it is impossible to give evidence based recommendations on how patients with APS should be treated in pregnancy. It is wise to regard pregnancies as being at high risk for complications and to over careful follow up by a team of doctors from different specialties [16]. Consultations with specialists like rheumatologist, hematologist, neurologist, cardiologist, pulmonologist, hepatologist, ophthalmologist, etc may be required depending on clinical presentation [17].

- The prophylactic measures comprise of elimination of various risk factors, such as oral contraceptives, smoking, hypertension or hyperlipidemia.
- For women with known antiphospholipid antibody syndrome, it is recommended that pre-pregnancy counseling is given to the woman and that she be monitored closely from the beginning of the pregnancy.
- Medical treatment should be individualised, taking into account the obstetric history, presence or absence of a personal or family history of thromboembolic events, comorbidity, current drugs, and thrombotic risk factors other than aPL.
- In cases of recurrent (pre-) embryonic losses one should always exclude genetic, anatomical, and other causes. With a personal history of thromboembolic events one should consider their number, nature, and severity, as well as the circumstances in which such events occurred [1].

The following treatment options can be considered:

- *Thromboprophylaxis (primary prevention):* Because of the controversial results of thromboprophylaxis (primary prevention) in patients positive for antiphospholipid antibodies, the continuous administration of aspirin and/or coumarins cannot be recommended to those patients, their use being reserved to situations with an elevated risk of thrombosis like pregnancy and postpartum [18].
- *The thromboprophylaxis of patients with APS and previous thrombosis:* The use of low molecular weight heparin subcutaneously (dalteparin, 5,000 IU/day or enoxaparins, 1 mg/kg/day, doubling one or the other after the 16th week) associated with aspirin (100 mg/day) during pregnancy and after delivery reduces the occurrence of maternal thrombosis and fetal loss. Warfarin is the option after the 13th gestational week. Most obstetricians prefer to avoid the use of warfarin (coumadin) during pregnancy as it can cross the placental barrier and produce teratogenic changes in the fetus. The patient must be educated about anticoagulation therapy and explained the importance of planned pregnancies so that long term warfarin can be switched to aspirin and heparin before pregnancy is attempted [17]. Despite the lack of good quality scientific evidence, the authors recommend, based on case series, case reports and personal experience, that pregnant patients with APS and previous thrombosis maintain full dose and nonprophylactic low molecular weight heparin associated with aspirin during pregnancy due to the high risk of new thromboembolic events in that period.
- The thromboprophylaxis of patients with APS and previous venous thrombosis recommends maintaining long-term anticoagulation with oral anticoagulants, aiming at an INR between 2.0 and 3.0 .
- The treatment of patients with antiphospholipid antibody and history of arterial thrombosis should be long and performed with warfarin (INR between 2.0 and 3.0 or INR > 3.0) either associated or not with antiplatelet agents. The prospective studies that found no difference between high-intensity warfarin and standard INR included a small group of patients with arterial thrombosis, hindering, thus, definitive conclusions. The authors suggest long-term anticoagulation with high-intensity warfarin [19,20]. Despite treatment, there is a significant risk for pregnancy complications in APS patients with previous CVE. Especially in the context of preeclampsia, anticoagulation should be given rigorously to prevent recurrence of CVE [21].
- The Thromboprophylaxis of Patients with APS and exclusive presence of obstetric events Patients

diagnosed with APS and exclusive presence of obstetric events should undergo long-term thromboprophylaxis with low-dose aspirin, aiming at reducing thrombotic events, especially the arterial ones. Pregnant patients with antiphospholipid antibody and history of early or late abortions should be treated with heparin (unfractionated or low molecular weight) and aspirin. It is also concluded that thrombosis or infarctions are prominent features in placentae from patients with anti-phospholipid antibodies and intra-uterine fetal death. Consequently, antithrombotic treatment during pregnancy forms a rational approach in these patients [22]. Since long term use of heparin can cause osteoporosis, When heparin is used for prolonged periods consider giving extra oral calcium (1000 mg/day) , vitamin D supplementation and control platelet counts regularly.

- *Treatment of patients with CAPS.* There are no good quality studies confirming the benefit of the association of other medications with anticoagulants in the treatment of patients with CAPS. Despite the limited good quality scientific evidence, the authors recommend, based on case series, case reports and personal experience, the association of corticosteroid, plasmapheresis and/or rituximab with anticoagulant therapy, because of the high mortality of that condition. In patients for whom the treatment with aspirin and heparin is not successful, use of intravenous immunoglobulins (IVIG) can be used. At this time, the studies suggest this may be helpful in refractory cases, but is not recommended for use on a routine basis.
- Some researchers have examined the use of combination: comprising of aspirin and prednisone during pregnancy. Most of the studies suggest that complications associated with prednisone use usually outweigh the benefits associated. Thus prednisone must not be used in addition to aspirin.
- In patients with SLE, hydroxychloroquine, which may have intrinsic antithrombotic properties, can be considered.
- Pregnancy monitoring

1 Level II ultrasonography at 18 weeks.

2. Fetal growth should be monitored every 4–6 weeks beginning at 20 weeks for any patient on anticoagulation; ultrasonographic assessment should be more frequent if fetal growth restriction is suspected or documented; in such a case, Doppler flow studies may be useful in determining the optimal timing of delivery.
3. Office visits as often as every 2 weeks beginning at 20 weeks to screen for preeclampsia.
4. Nonstress tests (NST) and/or biophysical profiles (BPP) weekly beginning at 36 weeks in uncomplicated cases or earlier as clinically indicated.

- *Timing of delivery:* If the pregnancy is complicated by fetal growth restriction or preeclampsia, antenatal testing and maternal status will guide the timing of delivery. If the pregnancy is uncomplicated, delivery can be delayed until 39 completed weeks provided that antenatal surveillance (NST/BPP) is reassuring. Therapy is usually withheld at the time of delivery and is restarted after delivery [17].
- *Postpartumcare:* Pneumatic compression boots should be used during labor and delivery or at cesarean delivery. Either unfractionated heparin or low-molecular weight heparin can be restarted 6 hours after vaginal delivery or 12 hours after cesarean delivery. This should be continued until at least 6 weeks postpartum. If the patient has a history of VTE, long-term prophylaxis is required as there is as high as a 30% recurrence risk for VTE in an APA-positive patient with a prior VTE. In this case, warfarin is to be started on day 2, and both heparin and warfarin are to be continued for 5 days and until the INR is therapeutic (2–3) for 2 consecutive days [23]. Breastfeeding women may be administered the combination of heparin and warfarin. If warfarin therapy is instituted, the patient must be instructed to avoid excessive consumption of foods that contain vitamin K.

## Discussion

Antiphspholipid syndrome is important cause of preclampsia, IUGR, RPL.Diagnosis depends on laboratory and clinical criteria. Treatment needs multidisciplinary approach. Consultations with specialists like rheumatologist, hematologist, neurologist, cardiologist, pulmonologist, hepatologist, ophthalmologist, etc may be required depending on clinical presentation. Treatment to be started with prepregnancy counceling.

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