

Antiphospholipid Syndrome in Pregnancy

N BEGUM^a, S GANGULY^b, F ISLAM^c

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Introduction:

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and venous thrombosis, gestational morbidity and presence of elevated and persistently positive serum titers of antiphospholipid antibodies. Antiphospholipid syndrome may exist as an isolated immunologic derangement primary APS (PAPS) or as secondary antiphospholipid syndrome (SAPS) where it occurs in association with autoimmune disease, most commonly SLE. The diagnosis of APS should be suggested whenever patient has history of repeated pregnancy loss without any fetal malformation or foetal death in utero. Other pregnancy complications mainly include intrauterine growth restriction (IUGR), oligohydramnios, preeclampsia, fetal distress, and preterm labor¹. A severe complication of pregnancy, which greatly increases its risk in case of APS, is VTE. Pregnant and postpartum women are approximately 4 to 5 times more likely to develop VTE compared with non pregnant women². Many other clinical manifestations may occur. Pregnant women with APS are considered high-risk obstetric patients, and medical care should be instituted keeping this in mind.

Methods:

The review article is based on systematic search through Pubmed and other search engine like google and google

- a. Dr Nazneen Begum, Assistant Professor, Department of Obst & Gynae, Dhaka Medical College, Dhaka, Bangladesh.
- b. Dr Shikha Ganguly, Associate Professor, Department of Obst & Gynae, Dhaka Medical College, Dhaka, Bangladesh.
- c. Prof. Ferdousi Islam, Professor and Head of the Department of Obst & Gynae, Dhaka Medical College, Dhaka, Bangladesh.

Address of Correspondence: Dr Nazneen Begum, Assistant Professor, Department of Obst & Gynae, Dhaka Medical College, Dhaka, Bangladesh, email: begumnazneen80@gmail.com

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scholar. The materials was mostly taken from Medline databases, Medscape references, the Cochrane databases systematic reviews. The literature search was done focusing more on the latest research. We obtained additional articles from bibliography of the selected manuscripts. We paid attention to systematic reviews, randomised clinical trials, consensus documents and review articles on the diagnosis and therapy of Antiphospholipid Syndrome.

Pathogenesis: APS does not have a known etiology, like other autoimmune disorders. Recently proposed mechanisms are antibody-mediated interference with coagulation homeostasis, platelet activation, endothelial cell activation, placental tissue injury, T-cell immune response and complement activation^{3,4}. The aPL antibodies causes thrombosis most likely by interfering with normal hemostasis by interaction with phospholipids or phospholipid-binding protein components such as β_2 GPI (having anticoagulant properties), prostacycline, prothrombin, protein C, annexin V, and tissue factor. Intraplacental 'thrombosis' is commonly presumed to be the main cause of pregnancy failure and pregnancy complications in women with PAPS. But some authorities have focused on defective endovascular trophoblast invasion for both the occurrence of early pregnancy loss and later pregnancy complications in women affected by PAPS.⁵

Diagnostic Criteria for APS

According to the consensus-derived diagnostic criteria formulated by the Sapporo international workshop, APS is present in patients with 1 clinical and 1 laboratory criterion. Clinical criteria include objectively confirmed arterial, venous, or small-vessel thrombosis, or pregnancy morbidity consisting of recurrent fetal loss before the 10th week of gestation, 1 or more unexplained fetal death at or beyond the 10th week of gestation, or premature birth due to placental insufficiency, eclampsia,

or preeclampsia. Laboratory criteria include medium or high titer IgG or IgM of aCL or the presence of LA on 2 or more occasions at least 6 weeks apart.^{6,7}

Diagnostic criteria were updated in 2006¹, where the clinical criteria remained unchanged; but, two important modifications in laboratory criteria were made: the time elapsed between two positive

determinations was extended to 12 weeks to assure the detection of persistent antibodies only; and anti-beta 2-glycoprotein 1, both IgG and IgM, were added to the laboratory criteria.

Clinical criteria

- Vascular thrombosis: one or more clinical episodes of arterial or venous thrombosis or thrombosis of small vessels of any organ or tissue, confirmed on Doppler or histopathology, vasculitis being excluded;
- Gestational morbidity:
 - One or more unexplained deaths of a morphologically normal fetus after the 10th gestational week, confirmed on ultrasound or by examining the fetus;
 - One or more premature births of a morphologically normal fetus before the 34th gestational week due to eclampsia, preeclampsia or causes of placental insufficiency;
 - Three or more unexplained spontaneous abortions before the 10th gestational week, with neither maternal hormonal nor anatomical abnormalities, paternal and maternal chromosomal causes excluded.

Laboratory criteria

- Presence of lupus anticoagulant antibody (LA) in the plasma on two or more occasions at a minimum 12-week interval, detected according to the recommendations of the International Society on Thrombosis and Hemostasis (ISTH);
- Moderate (> 40) to high (> 80) titers of IgG or IgM anticardiolipin antibodies (ACL) on two or more occasions at a minimum 12-week interval, detected by using standard ELISA test;
- IgG or IgM anti-beta 2-GPI antibodies in the plasma on two or more occasions at a minimum 12-week interval, detected by using standard ELISA test.

Anticoagulant therapy may interfere with the detection of LA⁸. Enzyme-linked immunosorbent assay tests for ACL are poorly standardized and aCL testing has shown poor concordance between laboratories⁹. The presence of more than one class of antiphospholipid antibodies increased thrombotic risk¹⁰.

The association between antiphospholipid antibodies and thrombosis is stronger with LA than with aCL. Both ACL and LA predict fetal loss. The association between antiphospholipid antibodies and fetal loss is strongest for loss occurring after 10 weeks¹¹. Obstetric manifestations of APS are not restricted to fetal loss.^{12,13,14} Early delivery, oligohydramnios, pre-eclampsia/eclampsia and HELLP syndrome, arterial or venous thrombosis and placental insufficiency, neonatal complications (such as prematurity-estimated at 30-60% and more common in SLE patients, intrauterine growth restriction - IUGR, fetal distress¹⁵ and rarely fetal or neonatal thrombosis)¹⁶ are described.

Management of APS in Pregnancy:

The goals of treatment in pregnant women with antiphospholipid syndrome are to improve maternal and fetal/ neonatal outcomes by preventing morbidity, including, preeclampsia, placental insufficiency, fetal growth restriction, fetal loss and iatrogenic preterm birth¹⁷. Also to reduce or eliminate aPL antibodies that induce the disease. With proper management, more than 70% of pregnant women with antiphospholipid syndrome will deliver a viable live infant¹⁸, compared to 10% without treatment¹⁹.

Prepregnancy:

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 pulmonary hypertension because of the high risk of maternal mortality²⁰, and should be postponed in uncontrolled hypertension or recent thrombotic events eg, stroke²⁰. A complete profile of antiphospholipid antibodies, including repeated anticardiolipin and lupus anticoagulant, should be available before pregnancy is planned. 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.

Antenatal:

Frequent prenatal visits, at least every 2-4 weeks before mid-gestation and every 1-2 weeks thereafter is recommended. 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, 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. Decreased fetal growth may reflect uteroplacental insufficiency in patients with APS. Colour doppler examination of early uteroplacental blood flow, may identify abnormal intervillous flow patterns prior to pregnancy failure and hence provide useful prognostic and therapeutic information⁵. Uterine and umbilical artery Doppler velocimetry can assess the risk for preeclampsia, placental insufficiency, and fetal growth restriction after the 20th week of gestation, and normal result have high negative predictive values.²¹

Antithrombotic management of patients with APS is mainly based on, antiaggregation (aspirin) or anticoagulation (unfractionated or low molecular weight heparin) agents and immunomodulatory (prednisolone, intravenous immunoglobulins, plasma exchange. Most studies have shown that the best therapy of APAS is offered by aspirin (60 to 100 mg) and heparin of LMW (an injection a day in preventive dose). A meta-analysis²² of randomized controlled trials examined the outcomes of various treatments –including aspirin, steroids, intravenous globulin and heparin–given to improve pregnancy outcome of women with recurrent miscarriage associated with antiphospholipid antibodies. This meta-analysis reported that the only treatment or treatment combination that leads to a significant increase in the live birth rate among women with antiphospholipid syndrome is aspirin plus unfractionated heparin. This combination therapy significantly reduced the foetal loss by 54%.²² Aspirin should be started when she

plans conception and low-molecular-weight heparin in prophylactic doses should be started when a viable intrauterine pregnancy is documented. The aspirin should be stopped by the 35th weeks of pregnancy, while the heparin is continued during 6 weeks after the childbirth. This treatment seems to be deprived of major maternal or foetal complication.

LMWH does not cross the placenta and is safe for both mother and fetus. Various clinical studies have demonstrated its function in improving live birth rates in patients with APS^{23,24}. Initiation of heparin in the face of a failing pregnancy should be undertaken with caution due to risks of bleeding. The treatment by the heparin requires a weekly supervision of platelet especially during first weeks of the treatment.²⁵ The patient should be counseled regarding potential adverse effects of heparin. Heparin-induced osteoporosis occurs in 1-2% of cases. Bone density studies should be considered. This may be most important in women who have been treated in a previous pregnancy or are planning pregnancy. Calcium supplementation and weight bearing exercise is to be encouraged.

Treatment for APS with recurrent pregnancy loss with combination of high dose prednisone and low-dose aspirin, has successful outcome in 75% of treated pregnancies, but high maternal and fetal morbidity resulted, including gestational diabetes, hypertension, and premature rupture of membranes. A randomized controlled study showed low-dose subcutaneous heparin and low-dose aspirin to be equally efficacious with less morbidity in comparison with prednisone and aspirin.

Intravenous immunoglobulin (IVIg) contains anti-idiotypic antibodies, has an immunomodulatory action and may be used to treat autoimmune diseases. There are numerous case reports of successful pregnancy outcomes after treatment with IVIg. Some studies indicate that LMWH and IVIg may be more efficient^{23,24}. 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.²² Jing Xiong et al.²⁶ evaluated the effect of traditional treatment (prednisone and aspirin) and comprehensive treatment [prednisone, aspirin, low molecular weight heparin (LMWH) and IVIg] on the pregnancy outcome, obstetric complications and

fetal outcome in women with antiphospholipid syndrome (APS) and found that in traditional treatment group and comprehensive treatment group, the live birth rate was 83.91% and 97.62% ($P < 0.05$), respectively, and the obstetric morbidity was 22.99% and 7.14% ($P < 0.05$), respectively. The neonatal weight in the comprehensive treatment group was increased compared with the traditional treatment group ($P < 0.05$), however, no differences were found in gestational age at delivery or preterm labor. Comprehensive treatment improved the result of gestation and reduced obstetric complications, and is a more effective treatment for APS than the traditional method of using prednisone and aspirin. The combination of heparin, particularly low molecular weight heparin (LMWH) and aspirin is considered superior to prednisone and aspirin, not because it achieves higher live birth rates, but because it causes less maternal morbidity.

Several potential new therapeutic approaches for APS are emerging. The only new drugs for APS that pregnant women can use are dipyridamole and hydroxychloroquine. Hydroxychloroquine is safe for the fetus and neonate²⁵ and the absence of associated bleeding, hydroxychloroquine can be considered for an adjuvant antithrombotic agent in patients with systemic lupus erythematosus who are positive for antiphospholipid antibodies.

Labour and delivery:

Labour and delivery of women with APS should be managed like a patient at high risk for preeclampsia and uteroplacental insufficiency. Pregnancy to be terminated near term, postdates to be avoided. Continuous electronic fetal monitoring is recommended during labour. Patients on heparin should withhold at the onset of labour. Heparin should be discontinued 24 hours before planned induction of labour or caesarean section.

Postpartum:

Heparin and LMWHs are not secreted into breast milk and can be safely administered to nursing mothers. Warfarin does not induce an anticoagulant effect in the breast-fed infant when the drug is given to a nursing mother. Warfarin may be substituted for heparin during the postpartum period to limit further risk of heparin-induced osteoporosis and bone fracture. Therefore, women using this drug should be encouraged to breast feed. Oral contraceptives containing estrogen is absolutely contraindicated in women with APS.

Conclusion:

APS pregnancies are regarded as being at high risk for complications and should be treated and follow up by a team of doctors from different specialties. 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, so that the miseries of pregnant women with APS can be minimized.

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