Class Room

Recurrent Pregnancy Loss - Obstetric Anti - Phospholipid Syndrome

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Chettinad Health City Medical Journal 2016; 5(3): 157 - 163

Introduction

Recurrent pregnancy loss contributes to 1% of total pregnancies.[1] 20% of the recurrent pregnancy loss is due to anti-phospholipid antibodies (aPL) and 6% of pregnancy morbidity is seen with aPL positivity.[1] Anti-phospholipid Syndrome (APS) poses a major challenge not only to the mother and fetus, but also to the treating specialist.

Definition

APS is an autoimmune disorder of recurrent vascular thrombosis and/or pregnancy loss associated with persistently elevated levels of anti-phospholipid antibodies. It can be primary or secondary.

Primary APS is the most common acquired cause of thrombophilia and accounts for 10 to 15% of women with recurrent fetal loss.[2] It occurs in the absence of connective tissue disorders (CTD).

The secondary form occurs in a background of CTDs like Systemic Lupus Erythematosus (SLE), Sjogren Syndrome, Mixed Connective Tissue Disorder (MCTD), Rheumatoid arthritis (RA), Progressive systemic sclerosis(PSS) etc. The main culprits are the anti-phospholipid antibodies which induce both a pro-coagulant and a pro-inflammatory state, end result of which is vascular thrombosis and pregnancy morbidity.

Pathogenesis of APS

I) Anti-phospholipid antibodies usually bind to endothelial cells, platelets and monocytes inducing a pro-inflammatory and pro-thrombotic state[2].

II) During early placental development, the cytotrophoblast differentiates into two cell types, the villous trophoblast (VT) and the extravillous trophoblast (EVT).[3] The VT forms the syncytiotrophoblast which acts as protective barrier between mother and fetus and the EVT invades the endometrium and anchors the embryo (as shown in Figure 1). In pregnancy, aPLs target the cytotrophoblast cells of the placenta.

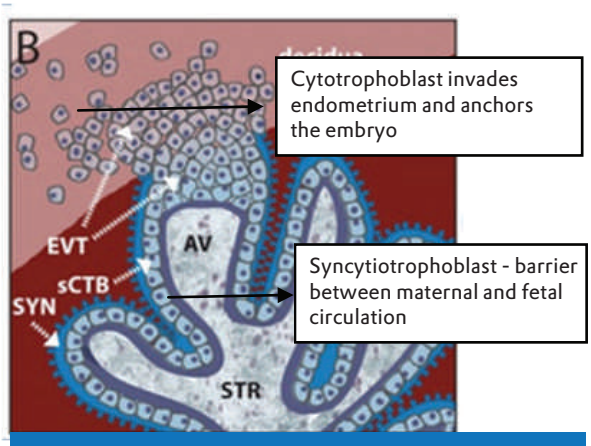


Fig 1 : Trophoblast differentiation during placental development Source: https://embryology.med.unsw.edu.au/

III) The main pathogenic antigen for aPL antibodies is the Beta2 glycoprotein 1 (β2 GP1), a cationic protein present on the cytotrophoblast cells. It is composed of 5 homologous domains with 60 amino acids, each of which have a closed conformation in the plasma. Domains I & V are positively charged. Domain I is pathogenic[4] and activates platelets whereas domain V binds to phospholipids. The pathogenicity of anti-β2 GP1 antibodies (anti Domain I) is due to increased resistance against Annexin A5, activated protein C, increased concentration of von Willebrand factor (vWF).

Iv) During apoptosis of the cytotrophoblast, the negatively charged phospholipid which gets exposed from the inner surface of the cell membrane to the outer side. Domain V of β2GP binds to the phospholipid and allows domain I to be bound with the antibody. Anti-domain I antibodies release vWF from the endothelium and also inhibit ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 activity), causing platelet aggregation and a prothrombotic state.[4]They also activate the complement cascade leading to C4 deposition in placenta.[5,6] Inhibition of protein C, S and anti-thrombin III by the aPLs also contribute to the activation of the coagulation cascade.

v) The role of annexin V is to prevent exposure of phospholipids to the outer surface of the trophoblast layer and anti-annexin V antibodies expose the phospholipids activating coagulation cascade.

vi) Antiphospholipid antibodies impair invasion and proliferation of trophoblastic cells. Antiphosphatidyl serine antibodies are responsible for syncytiotrophoblast fusion impairments.[7] Serum beta human Chorionic Gonadotropin levels have been found to be decreased in patients with APS.

vii) Anti - phospholipids also interfere with endometrial differentiation and angiogenesis. Anti β2 GP1 antibodies inhibit angiogenesis, vascular endothelial growth factor (VEGF) secretion and NFkB (Nuclear Factor Kappa B) activation.[8] The placenta is made dysfunctional by thrombosis and fibrin deposits. It appears shrunken, hemorrhagic and edematous.

viii) Innate immunity also plays a major role. Toll - like receptor 2 (TLR2) and TLR 4 pathologically activate endothelial cells, monocytes and platelets.[8-13] Translocations of TLR 7 and TLR 8 have been noted in endosomes of human monocytes.[14]

ix) HLA associations include HLA DR7, HLA DR4 and HLA DR3. Epitope mimicry is also thought to play a role in producing the autoimmune status.[15]

x) Exposure of tissue factor, increased plasminogen activator inhibitor I and induction of apoptosis of cytotrophoblasts predisposes to APS.

Hence obstetric APS is not a single disease entity. Multiple factors play a role on the placental as well as the endometrial cells as follows

a. Mechanisms on placental cell[5]

i) Thrombosis by aspecific mechanism

ii) Inflammation and complement activation

iii) TLR 4 (Toll Like Receptor 4) activation by a PL8 - 13

iv) Defective placentation

(a) Migration: decrease in IL-6 and STAT3 expression[16]

(b) Invasion: decrease in integrin expression

(c) Differentiation: decrease in β-hCG secretion and decrease in fusion

b. Mechanisms on endometrial cells[5]

i) Angiogenesis inhibition by decrease in VEGF (Vascular Endothelial Growth Factor) secretion

ii) Inhibition of NFκB (Nuclear Factor Kappa B) activation[8].

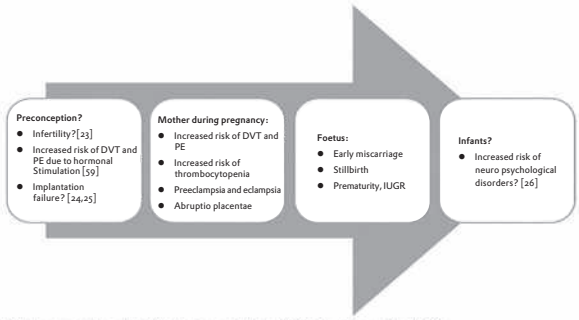
Clinical Manifestations

Majority of the patients present with recurrent fetal loss beyond 20 weeks and may exceed 90% in untreated patients.[17] Aspirin and heparin can reduce the fetal loss by 25%.[7] Other manifestations include severe pre-eclampsia and preterm birth, before 34th week of gestation. Severe preeclampsia manifests as central nervous system symptoms like headache, visual disturbance, liver dysfunction, blood pressure greater than 160/110 mmHg, thrombocytopenia with platelets less than 1 lakh/mm^3, renal dysfunction and pulmonary edema.

These patients are at high risk of placental insufficiency leading to Intra uterine growth restriction(IUGR) and oligohydramnios. Placental insufficiency is assessed by an abnormal or non-reassuring Non stress test (NST). An abnormal Doppler wave study indicates an increased resistance to blood flow which reflects as fetal hypoxia. Amniotic fluid index (AFI) less than 5 indicates oligohydramnios and post natal birth weight might be less than the 10th percentile for the gestational age.

Previous fetal loss is a compounding risk factor for further fetal loss, preeclampsia, premature birth and placenta mediated complications in patients with obstetric anti phospholipid syndrome. Multiorgan failure during pregnancy has been described by Asherson[18] and by Kochenour[19] in the post-partum period.

Obstetric APS is more than a single disease entity affecting both mother and the child as depicted in Figure 2. Other features include thrombosis, both venous and arterial. It can occur in Inferior vena cava (IVC), pulmonary veins, hepatic, renal veins, leg veins, cerebral arteries, coronaries, brachial, mesenteric & extremity arteries. Catastrophic events like strokes, pulmonary hypertension, pulmonary infarct, ARDS & diffuse alveolar hemorrhage can occur.



Dvt: deep venous thrombosis; PE: pulmonary embolism; IUGR: Intrauterine growth restriction

Fig 2: Obstetric APS more than a single disease entity[5]

Gangrene, livedo reticularis, cutaneous ulcers are the skin manifestations. Eye involvement in the form of Central retinal artery or venous occlusions can occur. Avascular necrosis of bones and renal involvement are other manifestations. Chorea gravidarum, autoimmune hemolytic anemia and thrombocytopenia, positive direct Coomb's test can occur along with prolonged activated partial thromboplastin time (aPTT) or prothrombin time (PT).

Diagnosis of APS

The Sapporo criteria for classification of anti-phospholipid syndrome was amended in May 2012 and presented in Sydney, The Sydney Classification criteria[20]. This includes both clinical and laboratory criteria for classifying APS as follows:

Clinical Criteria

1.Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed by Imaging, Doppler, or histopathological examination (without significant vessel wall inflammation)

2. Pregnancy morbidity (normal morphology on ultrasonography or direct examination findings) with either of the following

- One or more unexplained fetal deaths at > 10 weeks gestation
- One or more premature births at <34 weeks gestation due to severe preeclampsia, eclampsia, or placental insufficiency.
- Three or more unexplained consecutive spontaneous abortions at <10 weeks gestation, excluding maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes

Laboratory Criteria

- Anticardiolipin (aCL) antibody
- IgG / IgM isotype in medium/high titer [>40 IgG phospholipid units (GPL), >40 IgM phospholipid units (MPL)] on 2 or more occasions 12 weeks apart
- Anti - β2-GP1
- IgG or IgM isotype in serum or plasma (in titers> 99thpercentile) measured by ELISA on 2 or more occasins 12 weeks apart.
- Lupus anticoagulant on 2 or more occasions at least 12 weeks apart.

Diagnosis

One clinical criteria and one laboratory criteria should be satisfied on 2 occasions more than 12 weeks apart and < 5years before the clinical episode classifies the patient to have APS. Lupus anticoagulant (LA) carries the highest risk of arterial and venous thrombosis. Those with "Triple positive" antibodies i.e aCL, LA and Anti β2GP1 are at highest risk for thrombosis.[21]

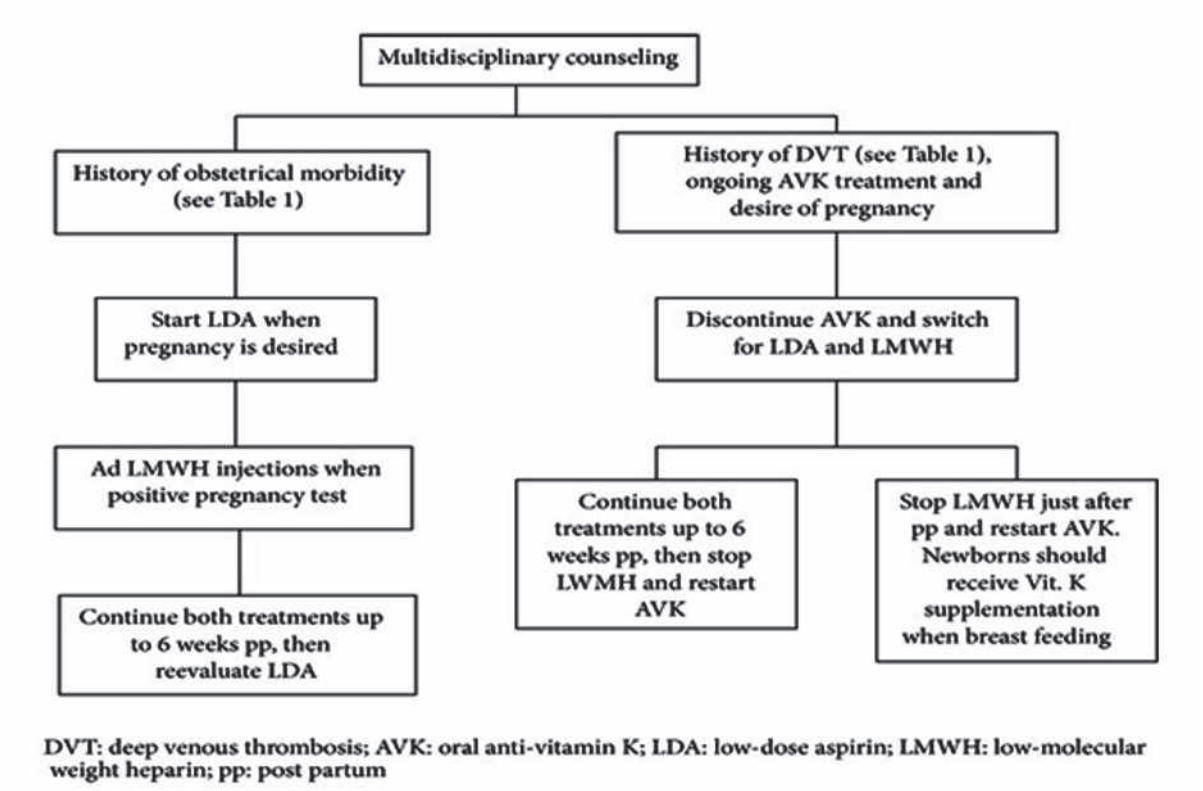
The differential diagnosis for catastrophic anti-phospholipid syndrome include thrombotic thrombocytopenic purpura(TTP), Hemolytic anemia with elevated Liver enzymes and low platelets (HELLP syndrome) and Acute Fatty Liver of Pregnancy(AFLP).[22] (as shown in Table 1)

Features	TTP	CAPS	HELLP	AFLP
Fever	+++	+	-	++
Microangiopathic hemolytic anemia (MAHA)	+++++	+	+++++	+
Thrombocytopenia	+	+++	+++	-
Renal	++	++++	+++	+++++
Hypertension	+++	+	++++	++
Hepatic	+	+	+	+++++
Hypoglycemia	-	-	-	+++
Hepatic infarcts	-	+	+	-
Pulmonary	-	+++++	-	-
Disseminated intravascular Coagulation	-	+	+++	++++
ADAMTS13 <5%	+++++	-	-	-

Table 1: Differential diagnosis of Catastrophic APS[23]

Treatment

Treatment of obstetric APS requires, preventing thrombus development, giving safe drugs before and during pregnancy and in the postpartum period to prevent complications. The proposed management for APS is described. (Flow chart 1 and Tables 2, 3 and 4)



DVT: deep venous thrombosis; AVK: oral anti-vitamin K; LDA: low-dose aspirin; LMWH: low-molecular weight heparin; pp: post partum

Flowchart 1: Proposed line of management of APS :[5]

Feature	Management	
	Pregnant	Non pregnant
APS with prior fetal death or recurrent pregnancy loss	Heparin in prophylactic doses (15,000-20,000 U of unfractionated heparin or equivalent per day) administered subcutaneously in divided doses with low-dose aspirin daily Calcium and vitamin D supplementation	Optimal management uncertain; options include no treatment or daily treatment with low-dose aspirin
APS with prior thrombosis or stroke	Heparin to achieve full anticoagulation (does not cross the placenta)	Warfarin administered daily in doses to maintain international normalized ratio of 2.5 and in recurrent thrombosis INR is maintained between 3-4 with the addition of low dose aspirin
APS without prior pregnancy loss or thrombosis	No treatment or daily treatment with low-dose aspirin or daily treatment with prophylactic doses of heparin plus low-dose aspirin; optimal management uncertain	No treatment or daily treatment with low - dose aspirin; optimal management uncertain
aPL Antibodies Without APS		
LAC or medium to high level of aCL IgG	No treatment	No treatment
Low levels of aCL IgG, only aCL IgM, or only aCL IgA without LA, aPL, or aCL	No treatment	No treatment

Table 2 : Proposed Management For Women With Apl Antibodies5,[30]

Scenarios	Management
APS with thrombosis on warfarin	Continue warfarin. Stop warfarin within 14 days of missing period and check pregnancy and start heparin at therapeutic doses once pregnancy is confirmed
APS with thrombosis and pregnancy morbidity	As above + start low dose aspirin
APS with pregnancy morbidity alone	Start low dose aspirin preconceptionally start heparin at prophylactic doses once pregnancy is confirmed
aPL antibodies+	No treatment

Table 3 : Pre-conceptional management of APS[5,30]

Scenarios	Management
APS with thrombosis	UFH/LMHW therapeutic doses
APS with thrombosis and pregnancy morbidity	UFH/LMWH therapeutic doses + low dose aspirin
APS with pregnancy morbidity alone	UFH/LMHW prophylactic doses + low dose aspirin
APS antibodies+Pregnancy	Low dose aspirin

Table 4 : Ante partum management of APS [5,30]

Drugs

Drugs approved during pregnancy include low dose aspirin, unfractionated heparin, low molecular weight heparin (LMWH) and newer anticoagulants Danaparoid (Heparinoid) and Fondaparinaux (anti Xa). Warfarin is indicated only in the second trimester and postpartum period.

Anticoagulation during pregnancy needs to be taken care specially, taking into consideration the maternal peripartum state, fetal safety etc. Heparins are commonly used as they do not cross the placenta. Among these, the choice would be Low molecular weight heparin(LMWH) except during the final weeks of pregnancy, as they are easily administered, do not require monitoring and have a more predictable response than unfractionated heparin(UFH).[23]

Unfractionated heparin is cost effective and is the drug of choice during labour, perioperative period and when creatinine clearance is < 30ml/min.[23]

Danaparoid is a heparinoid but considered as a LMWH by some. It acts by inhibiting activated factor X (Xa). It does not cross the placenta and is reserved for patients with heparin induced thrombocytopenia.[23]

Warfarin is better avoided in pregnancy, as it is teratogenic; with the highest risk between 6 and 12 weeks of gestation. It can cause embryopathy, fetal bleeding and miscarriage. When there is no other choice, it may be relatively safe during the second trimester only [24-27] and in the post-partum period. Warfarin should be titrated to an INR (International Normalized Ratio) of 2.0-3.0.[28] To counteract bleeding, vitamin K and fresh frozen plasma can be given.

How and when to start heparin? A baseline platelet count and serum creatinine are mandatory. Platelet counts are assessed on day 3, weekly during first two weeks and monthly thereafter, when on heparin. LMWH are preferred as they do not cross the placenta and are safe for the fetus.[29] For those requiring anticoagulation during pregnancy, LMWH is the preferred drug. It is started after confirmation of pregnancy. Both LMWH and prophylactic unfractionated heparin are given subcutaneously although the latter can be given intravenously when constant levels need to be maintained and when rapid discontinuation is necessary (eg. delivery, surgery). Prefilled preservative free syringes are better since preservative containing heparins are contra indicated in pregnancy.

For LMWH, therapeutic dosage is based on body weight and anti-factor Xa levels. It is administered subcutaneously 12th hourly (eg.Enoxaparin 1mg/kg or dalteparin 100 units/kg). If necessary, peak anti-factor X a activity levels are tested 4-6 hours after the last dose (recommended levels are 0.6 to 1.0 units/ml). For unfractionated heparin therapeutic dosage is administered intravenously and is adjusted to maintain an activated partial thrompoplastin time 1.5 to 2.5 times baseline.[29]

Prophylactic LMWH is administered as a single subcutaneous dose of 40 mg every day. Prophylactic

subcutaneous injection starting from 5000 units in the first trimester and increasing by 2500 units every trimester.

Switching from subcutaneous to intravenous heparin should be done prior to labor in patients requiring continuous anticoagulation. At the onset of labor heparin is discontinued and resumed 4 to 6 hours after normal delivery and 6 to 12 hours after caesarean in prophylactic dose.

In the event of bleeding with heparin, protamine sulphate may have to be given intravenous at a dose of 1-1.5mg IV for every 100 units of heparin and aPTT is monitored 15min after protamine and again after 6-8 hours.[23,28]

IVIG (Intravenous Immunoglobulin) is another drug which can modulate aCL levels in refractory APS and so is plasma exchange. For patients with SLE, immunosuppression is required, the safest drugs are hydroxychloroquine and azathioprine. Plasma exchange is in the investigational phase.

Precautions

Obstetric patients who were recently treated with steroids should take steroid supplementation during labor. Pregnancy by itself does not harm the mother or fetus.[30]

In the event of a low platelet count, epidural anesthesia should not be given and use of forceps or vacuum extractor should be done with discretion.[30]

Counseling and patient education are very important. USG is done every 3-4 weeks starting from 20 weeks. Viability of pregnancy can be assessed by USG. Screening should be done to rule out thrombosis, thromboembolism, decreased fetal movement or severe preeclampsia. In patients with refractory thrombocytopenia either during early second trimester or during Caesarean section, splenectomy may be considered.[30]

Conclusion

Obstetric anti-phospholipid syndrome is a great challenge to the mother and fetus. A better understanding of the pathological mechanisms is needed for therapeutic interventions. Screening for anti-phospholipid syndrome improves pregnancy outcomes. SLE with APS requires both thromboprophylaxis and immunosuppression. Multidisciplinary management with a strict follow up is needed.

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Answer to : **Diagnose the Condition**

ECG discussion

The ECG shows a intermittent CHB with ventricular paced rhythm - Bipolar VVI pacemaker. Ventricular rate 90/mt. Sinus capture beats(4th, 6th and 8th QRS complexes) seen. The P wave preceding the capture beat is fused with the preceding T wave. The pause following the capture beat is long signifying ventricular sensing and appropriate inhibition by the pacemaker, thus ruling out pacemaker dysfunction. The pacemaker was checked and found that the rate was set at 90/mt. It was readjusted to 70/mt, following which patient symptoms improved.

- Dr.M.Chokkalingam, Consultant Cardiologist, CSSH