Review Article

Antiphospholipid Syndrome in Pregnancy and its Management

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Abstract:
Antiphospholipid syndrome (APS) is an autoimmune condition, in which antiphospholipid antibodies (aPL) cause clinical features including thrombosis, fetal loss, and preterm delivery. Antiphospholipoid syndrome (APS) patients are prone to arterial as well as venous thrombosis the fetal loss in patients with APS is not caused primarily by thrombosis, but by a number of biological effects of aPL that affect implantation of the embryo. The established management of pregnancy in patients with known obstetric APS is to give daily low-dose oral aspirin plus daily subcutaneous heparin. The goal of treatment of APS in pregnancy is to protect the mother from thrombosis and to reduce the risk of fetal loss. This article will review current treatment options for antiphospholipid antibodies in pregnancy. There is no definite evidence supporting the use of heparin plus aspirin in patients who are aPL-positive, but who have never suffered any problems in pregnancy. However, patients taking long-term warfarin for thrombotic APS should have this changed to heparin during pregnancy.

Keywords: Antibodies, antiphospholipid syndrome (APS), heparin, pregnancy, trophoblast

Received: May 18, 2017; **Accepted:** June 05, 2017

Introduction:
The antiphospholipid syndrome (APS) is an autoimmune condition, in which antiphospholipid antibodies (aPL) interact with phospholipid-binding proteins in the body, of which the most important is beta-2-glycoprotein I (β2GPI). The aPL-β2GPI complexes then bind to the surface membranes of target cells (which are composed of phospholipids) and this leads to changes in the behavior of those cells [1]. This cellular dysfunction, in turn, leads to the clinical features of APS.

The currently accepted criteria are summarized in (Table-1) and stipulate that the patient must have suffered either arterial thrombosis or venous thrombosis or pregnancy loss or a combination of these and must also have persistently positive serological tests for aPL [2].

It is important to remember that Miyakis et al. criteria are primarily designed for classification in research studies and not for diagnosis [2]. Thus, it is not always necessary to wait for two positive aPL tests before making the diagnosis of APS. Although only thrombosis and pregnancy loss are included in the criteria, patients with APS can develop many other clinical features. For example, a retrospective study of 1000 European patients (Euro-Phospholipid study) with APS reported that arthritis, epilepsy, and livedo reticularis were all common clinical features and occur in PAPS as well as SLE-associated APS [3]. Antiphospholipid antibodies could lead to later pregnancy loss through multiple mechanisms of injury to the uteroplacental unit, including interfering with annexin V [4].

The Effect of Antiphospholipid Syndrome on Pregnancy:
Without treatment, APS is a major risk factor for recurrent miscarriage [5]. Since first-trimester miscarriages are common even in healthy women, the criteria specify that there must be at least three successive first-trimester pregnancy losses or at least one fetal loss from later in pregnancy. Furthermore, there must be no other cause for the miscarriage (e.g., chromosomal abnormality).

The burden of pregnancy morbidity in patients with APS is underlined by the findings of the Euro-Phospholipid study [3]. Of 1580 pregnancies in 590 women, 560 pregnancies ended in early fetal loss (before 10 weeks), 267 in late fetal loss, and 80 in premature births. Preeclampsia occurred in 9.5% of pregnant women, eclampsia in 4.4%, and placental abruption in 2% [3].

In a subsequent prospective study following the same patients between the years 1999 and 2004, 77 women (9.4% of female patients) had one or more pregnancies. Of these pregnancies, 17.1% ended in early fetal loss and 35% in premature birth [6].

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Table-1: Revised classification criteria for antiphospholipid syndrome

APS is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met[a]:

Clinical criteria

1. Vascular thrombosis[b]

One or more clinical episodes[c] of arterial, venous, or small-vessel thrombosis[d] in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (unequivocal findings of appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy-related morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasonography or by direct examination of the fetus, *OR*

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (i) eclampsia or severe preeclampsia described according to standard definitions *OR* (ii) recognized features of placental insufficiency[e] *OR*

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.[f]

Laboratory criteria[g]

All laboratory criteria should be present on 2 or more occasions, at least 12 weeks apart.

1. LA present in plasma, detected according to the guidelines of the ISTH (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (> 40 GPL or MPL, or > 99th percentile), measured by a standardized ELISA.
3. Anti-ß2GP1of IgG and/or IgM isotype in serum or plasma (in titer > 99th percentile), measured by a standardized ELISA, according to recommended procedures.

APS, antiphospholipid syndrome; LA, lupus anticoagulant; ISTH, International Society on Thrombosis and Haemostasis; aCL, anticardiolipin; GPL, IgG phospholipid; MPL, IgM phospholipid; ELISA, enzyme-linked immunosorbent assay; anti-ß2GP1, anti-ß2 glycoprotein-1; aPL, antiphospholipid antibodies; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; GFR, glomerular filtration rate.

[a] Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test result and the clinical manifestation.

[b] Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, 2 subgroups of patients with APS should be recognized, according to (a) the presence and (b) the absence of additional risk factors for thrombosis. Such cases include age (> 55 years in men and > 65 years in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension; diabetes mellitus; elevated LDL or low HDL cholesterol level; cigarette smoking; family history of premature cardiovascular disease; BMI, ≥ 30 kg/m²; microalbuminuria; estimated GFR, < 60 mL/min/1.73 m²; inherited thrombophilias; oral contraceptives; nephrotic syndrome; malignancy; immobilization; and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

[c] A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

[d] Superficial venous thrombosis is not included in the clinical criteria.

[e] Generally accepted features of placental insufficiency include (i) abnormal or nonreassuring fetal surveillance test(s), eg, a nonreactive nonstress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, eg, an amniotic fluid index of ≤ 5 cm; *OR* (iv) a postnatal birth weight < the 10th percentile for the gestational age.

[f] In studies of populations of patients who have more than 1 type of pregnancy-related morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

[g] Investigators are strongly advised to classify patients with APS in studies into 1 of the following categories: I, more than 1 laboratory criterion present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-ß2GP1 antibody present alone.

It seems more likely that the problem lies in an effect of aPL on implantation of the embryo in the uterus. This effect is probably multifactorial and involves inflammation at the fetal-maternal interface, inhibition of migration of trophoblast cells, and impaired expression of endometrial differentiation markers 5. Studies in vitro have shown effects of aPL on both trophoblast and endometrial cells [5,7,8,9].

The monoclonal antibodies inhibited the ability of the trophoblast cells to migrate through a membrane [7]. Poulton et al. showed that polyclonal IgG from patients with obstetric APS, but not IgG from patients with thrombotic APS, inhibited migration of human trophoblast cells [9]. In a series of experiments in a murine model of APS pregnancy, Girardi et al. showed that infusing a large amount of IgG from patients with APS to mice early in pregnancy caused a significant decrease in the number of viable fetuses [10].

Furthermore, whereas heparin (the most commonly utilized treatment for APS pregnancy) could also reverse these effects of the APS-IgG on fetal loss, an alternative anticoagulant called hirudin could not [10].

Evidence-based management:

Clinical trials of treatment of APS pregnancy suffer from common weaknesses. First, there is not a uniform definition of early pregnancy losses, nor stratification by history of early versus late losses. Second, there is not a stratification by anticardiolipin versus lupus anticoagulant positivity, nor proof of persistence of antiphospholipid antibodies. Third, there is no agreement on whether treatments should be started pre- or postconception, or whether some should be stopped before delivery.

The aims of management of APS in pregnancy are threefold:

1. To maximize the chance of successful fetal outcome.
2. To prevent thrombosis and other clinical manifestations of APS in the mother.
3. To ensure good counseling and planning for future pregnancies.

Clinical trials of aspirin:
Aspirin has been compared with placebo in several APS pregnancy trials. Tulppala and colleagues compared aspirin 50 mg daily versus placebo in 66 women [11]. Only 12 had antiphospholipid antibodies, however. Aspirin had no benefit over placebo.

Kutteh, in 1996, compared aspirin 81 mg as a sole therapy versus aspirin plus unfractionated heparin [12]. The aspirin was started preconception. Heparin was started at 10,000 units subcutaneously in two divided doses, and was adjusted to keep the activated partial thromboplastin times (aPTT) at 1.2 to 1.5. This was a one center trial, with 50 women. The heparin and aspirin group did better than the aspirin alone group.

Clinical trials of heparin:
Low MW heparin may offer an advantage over unfractionated heparin in terms of convenience, less osteoporosis, and less thrombocytopenia [13,14,15]. There is disagreement over whether LMW heparin can or should be used as once daily dosing when being given in prophylactic or therapeutic doses for APS pregnancy. Many units, including our own, believe that twice daily dosing is preferable [16,17,18].

One randomized study of pharmacokinetics determined that dalteparin required one dose pre- and post-pregnancy and another dose during pregnancy [19].

Clinical trials of warfarin:
In the United States, because of concern about warfarin teratogenicity, pregnant women are switched to heparin.

Clinical trials of intravenous immunoglobulin:
In most APS pregnancy trials, only 75% to 80% pregnancy success is obtained, regardless of treatment arm. Women with failed pregnancies on standard treatments such as heparin and aspirin need additional options. Intravenous immunoglobulin (IVIG) is of interest because it reduces levels of anticardiolipin. One mechanism is that saturation of the IgG transport receptor leads to accelerated catabolism of pathogenic antiphospholipid antibodies [20].

Clinical trials of a complement modulating agents:
Thus, this group suggested that complement activation in the placenta plays a major role in APS pregnancy morbidity and this would fit with other work showing that endometrial biopsies from patients with APS had reduced expression of complement regulatory proteins [5]. However, complement modulating agents are not being used routinely in the management of APS pregnancy.

Clinical trials of prednisone:
In the landmark trial of Cowchock and colleagues, however, the prednisone/aspirin arm had more maternal morbidity in terms of diabetes mellitus and pre-eclampsia [21]. Subsequently, Silver and colleagues showed that prednisone/aspirin led to more preterm birth [22]. Prednisolone is not recommended. An early trial in twenty patients by Cowchock et al. compared treatment with low-dose heparin and treatment with oral corticosteroids (40 mg prednisone daily) [21].

Both treatment groups received low-dose aspirin. Live birth rate was 75% in each group, but the patients treated with prednisone had significantly higher rates of maternal morbidity and preterm birth.A later review in 2014 included ten RCTs including all those studied by Mak et al. [23] .The later review did not restrict the analysis to trials that compared heparin plus low-dose aspirin to aspirin alone (for example, they included studies comparing heparin to corticosteroids or intravenous immunoglobulin) [24]. They found that live birth rate in patients treated with aspirin alone (seven studies had an aspirin alone arm with a median number of subjects 25) ranged from 42% to 80%. In comparison, live birth rate in patients treated with aspirin plus heparin (eight studies had a heparin plus aspirin arm with a median number of subjects 29.5) ranged from 71% to 85%.

Overall, the authors concluded that the evidence did justify the use of heparin plus low-dose aspirin in patients with recurrent early miscarriage and positive aPL though they also stressed the need for larger well-designed studies [24].

Conclusion:
APS pregnancy losses are one of the most common treatable causes of recurrent pregnancy loss. Clinical trials have helped in delineating the dangers of prednisone use in pregnancy, and suggest that heparin and aspirin regimens are preferred. Since APS was first described as a separate condition, pregnancy loss and pregnancy complications have been among the major clinical features. It is important to recognize that many women who test positive for aPL are not at increased risk of pregnancy loss and so aPL tests should not be done routinely in all pregnant women. Routine testing of that kind would lead to many false-positive results and cause unnecessary concern and possibly unnecessary treatment in those expectant mothers. Thus, aPL tests are primarily justified in patients who have either thrombotic or obstetric history suggestive of APS or in patients with SLE. Further research may lead to the development of new treatment for APS pregnancy such as complement modulators.

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Citation of this article:
Arzoo S, Akter MS, Afroz S, Begum SA. Antiphospholipid Syndrome in Pregnancy and its Management. Eastern Med Coll J. 2017; 2 (2): 22-26.