

# Antiphospholipid Syndrome in Pregnancy

Anisur Rahman

Department of Rheumatology, University College London, London, United Kingdom

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**Address for correspondence:**

Prof. Anisur Rahman,  
Centre for Rheumatology Research,  
Division of Medicine, University  
College London, Room 412,  
Rayne Institute, 5 University Street,  
London WC1E 6JF, United Kingdom.  
E-mail: [anisur.rahman@ucl.ac.uk](mailto:anisur.rahman@ucl.ac.uk)

## Abstract

Antiphospholipid syndrome (APS) is an autoimmune condition, in which antiphospholipid antibodies (aPL) cause clinical features including thrombosis, fetal loss, and preterm delivery. Studies in large numbers of patients with APS show that they suffer both early and late fetal loss as well as complications of pregnancy such as preeclampsia. 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. These factors are not yet understood fully but include effects on trophoblast cell viability and migration, inflammation at the fetal-maternal interface, and activation of complement. The established management of pregnancy in patients with known obstetric APS is to give daily low-dose oral aspirin plus daily subcutaneous heparin. This gives a live birth rate of over 70%. The trials that led to this form of management being adopted were small but overall do support the use of the heparin/aspirin combination over aspirin alone. 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.

**Key Words:** Antibodies, antiphospholipid syndrome, heparin, pregnancy, trophoblast

## What is the Antiphospholipid Syndrome?

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 ( $\beta$ 2GPI). The aPL- $\beta$ 2GPI 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.<sup>[1]</sup> This cellular dysfunction, in turn, leads to the clinical features of APS.

APS was initially described by Hughes in 1983 as a subset of patients with systemic lupus erythematosus (SLE).<sup>[2]</sup> These patients were characterized by vascular thromboses and/or pregnancy loss and their blood tested positive for aPL. Subsequently, it was discovered that APS can also occur in patients who do not have SLE (primary APS [PAPS]). Classification criteria for APS were developed and updated. 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.<sup>[3]</sup> The serological tests most commonly used are the anticardiolipin enzyme-linked immunosorbent assay (ELISA) and the lupus anticoagulant (LA) test. In some units, a third assay, the anti- $\beta$ 2GPI ELISA is also available. The name "LA" is a confusing one. It is not a test for lupus. Most patients who are LA-positive do not have SLE and most patients with SLE are not LA-positive. LA is a test for APS. LA-positivity is caused by aPL in blood which tends to inhibit clotting of blood in a test tube (this is why it is called the LA test) but has the opposite effect, causing increased clotting, in the human body.

It is important to remember that Miyakis *et al.* criteria<sup>[3]</sup> are primarily designed for classification in research studies and not for diagnosis. 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

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**Table 1: Summary of classification criteria for antiphospholipid syndrome (modified from Miyakis *et al.*<sup>[3]</sup>)**

Vascular thrombosis criteria	Arterial thrombosis Venous thrombosis Small vessel thrombosis NB must be confirmed by imaging or histopathology
Pregnancy criteria	Three or more unexplained consecutive spontaneous abortions before week 10 of gestation One or more unexplained deaths of a morphologically normal fetus at or beyond week 10 of gestation One or more premature births of a morphologically normal fetus before week 34 of gestation because of preeclampsia, eclampsia, or placental insufficiency Note in the case of spontaneous abortion or fetal death, other causes such as maternal anatomical or hormonal abnormalities or parental chromosomal causes must be excluded
Serological criteria	Elevated IgG anticardiolipin antibody (>40 GPLU or >99 <sup>th</sup> percentile of healthy controls) Elevated IgM anticardiolipin antibody (>40 MPLU or >99 <sup>th</sup> percentile of healthy controls) Elevated IgG anti- $\beta$ 2GPI antibody (>99 <sup>th</sup> percentile of healthy controls) Elevated IgM anti- $\beta$ 2GPI antibody (>99 <sup>th</sup> percentile of healthy controls) Positive lupus anticoagulant assay NB one or more of these tests must be positive on at least two occasions at least 12 weeks apart

APS can be diagnosed if the patient meets at least one of the serological criteria plus at least one vascular thrombosis criterion and/or one pregnancy criterion.  $\beta$ 2GPI: Beta-2-glycoprotein I, APS: Antiphospholipid syndrome

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.<sup>[4]</sup>

### What is the Effect of Antiphospholipid Syndrome on Pregnancy?

Without treatment, APS is a major risk factor for recurrent miscarriage.<sup>[5]</sup> As shown in Table 1, the classification criteria for APS are very specific about the number and type of miscarriages that must be reported to have a confirmed diagnosis of APS.<sup>[3]</sup> 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). Premature births before the 34<sup>th</sup> week of gestation can also be included in the definition of pregnancy morbidity included in these criteria.

The burden of pregnancy morbidity in patients with APS is underlined by the findings of the Euro-Phospholipid study.<sup>[4]</sup> 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%.<sup>[4]</sup> 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.<sup>[6]</sup>

The mechanism by which aPL causes pregnancy morbidity in patients with APS is not understood fully. Although it was initially thought to be due mainly to intraplacental

thrombosis, this does not appear to be the case. Sebire *et al.* carried out a histological study of the products of conception comparing miscarriages from patients with and without APS and found no difference in the frequency of placental thrombosis between the groups.<sup>[7]</sup>

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.<sup>[5]</sup> Studies *in vitro* have shown effects of aPL on both trophoblast<sup>[8-10]</sup> and endometrial<sup>[5]</sup> cells. Trophoblast expresses  $\beta$ 2GPI and exogenous  $\beta$ 2GPI can bind to the surface of trophoblast cells.<sup>[9]</sup> Thus, aPL can bind to  $\beta$ 2GPI on trophoblast and exert pathogenic effects. For example, Mulla *et al.* showed that murine anti- $\beta$ 2GPI antibodies and polyclonal human IgG from patients with APS affect viability and cytokine production of human trophoblast cells.<sup>[9]</sup> The monoclonal antibodies inhibited the ability of the trophoblast cells to migrate through a membrane.<sup>[8]</sup> These authors suggested that the mechanism of action is the production of uric acid and activation of the inflammasome leading to inflammation at the fetal-maternal interface.<sup>[11]</sup> 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.<sup>[10]</sup>

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.<sup>[12]</sup> This effect, however, was reduced

in complement-deficient mice<sup>[13]</sup> or in the presence of complement inhibitors.<sup>[14]</sup> 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.<sup>[12]</sup> Heparin, but not hirudin, blocks the activation of complement. 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.<sup>[5]</sup> However, complement modulating agents are not being used routinely in the management of APS pregnancy.

### Which Pregnant Women should be Tested for Antiphospholipid Antibodies?

It is important to note that positive tests for aPL may occur in approximately 5% of the population<sup>[15]</sup> and that these “nonpathogenic” aPL do not carry increased risk of thrombosis or pregnancy morbidity. The binding properties of pathogenic and nonpathogenic antibodies differ. Notably, whereas nonpathogenic antibodies bind phospholipids in the absence of serum cofactors, pathogenic antibodies require cofactors of which the most important is  $\beta$ 2GPI.<sup>[16]</sup>

Thus, there is no indication for routine testing of all pregnant women for APS and a recent review stated that evidence does not support routine testing of aPL in patients with infertility.<sup>[17]</sup>

Testing for aPL can be recommended in patients whose clinical history suggests that APS is a likely diagnosis, for example, those with two or more early miscarriages<sup>[18]</sup> or in patients with unexplained late miscarriage. In addition, aPL tests are routinely carried out in patients with SLE due to the high prevalence of aPL-positivity in those patients (about 25%).<sup>[15]</sup>

### How should Pregnant Women with Antiphospholipid Syndrome be Managed?

Prednisolone is not recommended. An early trial in twenty patients by Cowchock *et al.*<sup>[19]</sup> compared treatment with low-dose heparin and treatment with oral corticosteroids (40 mg prednisone daily). 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.

The standard management of pregnant women with obstetric APS is with daily low-dose aspirin plus daily subcutaneous heparin [Table 2]. This was originally based on the results of two randomized controlled trials (RCTs) published in the 1990s, which showed that the live birth rate was significantly higher in APS patients treated with the heparin/aspirin combination than in those treated with aspirin.<sup>[20,21]</sup> It should be noted, however, that these were small studies with fewer than 100 patients included in each case and both used unfractionated heparin (UFH). Subsequent studies using low molecular weight heparin (LMWH) did not show a significant difference between the heparin plus aspirin and aspirin alone groups.<sup>[22,23]</sup> These studies were also small, and it is important to note that the outcomes in heparin plus aspirin groups were not worse than in the two earlier studies.<sup>[20,21]</sup> The lack of statistical significance between groups was because the response in the aspirin alone groups was better in the later trials.<sup>[22,23]</sup> A meta-analysis of the literature on this subject in 2010 identified only five suitable RCTs,<sup>[24]</sup> which were overall of poor quality and included a total of 334 patients (171 on heparin plus aspirin and 163 on aspirin alone). Combining all the trials, the live birth rate was 74.27% (127/171) in patients on heparin plus aspirin compared to 55.83% (91/163) in patients on aspirin alone giving an odds ratio of 1.3 (95% confidence

**Table 2: Summary of management in patients testing positive for antiphospholipid antibodies**

Type of patient	Management
aPL-positive – Low-titer or transient with no history of thrombosis or pregnancy problems	No indication for treatment with heparin or aspirin
aPL-positive – High-titer or multiple positive tests which are persistently abnormal, but no history of thrombosis or pregnancy loss	No definite evidence supporting the use of heparin or aspirin but can be considered on a case-by-case basis. For example, where a mother has had difficulty becoming pregnant or is so old that there may not be another chance of pregnancy
Confirmed thrombotic APS – Patient has suffered thrombosis but has either never been pregnant or has had only normal pregnancies	These patients will normally be on long-term anticoagulation with warfarin. This should be changed to heparin for the duration of the pregnancy
aPL-positive – Patient has suffered pregnancy loss but does not fulfill the pregnancy criteria for APS (e.g., only one or two spontaneous abortions before week 10 of gestation)	Although the patient does not fulfill the classification criteria for APS, many physicians would treat with heparin and aspirin as in cases of confirmed APS
Confirmed APS and fulfills pregnancy criteria (i.e., known obstetric APS)	Daily low-dose aspirin and daily subcutaneous heparin throughout pregnancy

aPL: Antiphospholipid antibodies, APS: Antiphospholipid syndrome

interval: 1.040–1.629) in favor of the combination.<sup>[24]</sup> There were no significant differences between the groups in secondary outcome measures such as preeclampsia and birth-weight. This review noted the lack of a trial comparing UFH and LMWH, which was important given that LMWH is increasingly the preferred choice in many clinical scenarios within and outside the field of APS.

Subsequently, in 2011, an Egyptian group published a study of sixty women with a history of three or more consecutive spontaneous abortions and persistently positive serological tests for aPL who were randomized to UFH 5000 units twice daily plus low-dose aspirin or LMWH (enoxaparin 40 mg) daily plus low-dose aspirin.<sup>[25]</sup> There was no significant difference between the live birth rates in the two groups (80% for LMWH vs. 66.7% for UFH,  $P = 0.243$ ).

A later review in 2014 included ten RCTs including all those studied by Mak *et al.*<sup>[24]</sup> The later review<sup>[17]</sup> 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). 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.<sup>[17]</sup>

### **How should Pregnancy be Managed in Antiphospholipid Antibodies-positive Women who do not have a History of Pregnancy Morbidity?**

This situation might arise in patients who have suffered vascular thrombosis due to APS and are taking warfarin. Warfarin should be stopped and converted to LMWH, to be continued throughout the pregnancy [Table 2]. This is to prevent thrombosis rather than pregnancy loss, and thus there is no definite indication to add aspirin. Warfarin cannot be used in pregnancy because it is teratogenic.

The decision is more difficult in a pregnant patient who has been found to have aPL but has neither a thrombotic nor an obstetric history of clinical features of APS. This might happen in a patient with SLE whose aPL was measured as part of routine screening. There is no definite evidence to support the use of heparin plus aspirin or even aspirin alone in such a pregnancy. However, in a large recent study (PROMISSE) in 385 women with low activity SLE, Buyon *et al.* showed that LA-positivity was one of the strongest predictors of adverse pregnancy outcomes.<sup>[26]</sup>

### **Conclusion**

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, however, 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.

The mechanism by which aPL causes pregnancy morbidity is not fully understood and is multifactorial. It is not due simply to placental thrombosis. Further research may lead to the development of new treatments for APS pregnancy such as complement modulators.

The established treatment for pregnant women with a history of obstetric APS is daily low-dose aspirin plus daily subcutaneous heparin. Although the trial evidence is limited, perhaps the most important point is that this combination treatment gives a live birth rate of 70% or above. This fact is not disputed (though whether aspirin alone would give the same result is disputed), and thus it remains prudent to offer the combination regimen to all pregnant women with obstetric APS unless there is a strong reason to the contrary (e.g., high risk of bleeding).

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### **Conflicts of interest**

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