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Management of Antiphospholipid Syndrome in Pregnancy

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Antiphospholipid antibody syndrome is one of the most important acquired causes of hypercoagulability and pregnancy loss [1]. Antiphospholipoid syndrome (APS) patients are prone to arterial as well as venous thrombosis [2]. Pregnancy itself is a procoagulant state, to compensate for excessive maternal bleeding during delivery. In addition, venous stasis due to venous dilation and compression of the uterus [3] occurs, leading also to a higher risk of thrombosis. 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.

Pathogenesis

Understanding of the pathogenesis of pregnancy loss in APS would ultimately lead to scientifically derived, rather than empiric, therapy. The most important advance in this area has been in a murine model of APS pregnancy loss. In this model, complement activation is a necessary step, and blocking complement activation or complement deficiency is protective [4]. At least in the mouse, this work suggests that complement activation, and not thrombosis, is the pathogenetic mechanism of APS pregnancy loss. This has been further confirmed by studies of different anticoagulants. Levels of heparin, which block complement activation but do not achieve anticoagulation, are able to protect against APS pregnancy loss [5]. A national multicenter study is now underway, called PROMISSE, to determine

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if complement activation precedes pregnancy loss in pregnant women with antiphospholipid antibodies versus pregnant controls.

If complement activation proves to be the major mechanism of pregnancy loss in women with APS, it would have implications for treatment. First, it would suggest that prophylactic doses of heparin would be effective (without aspirin). Second, it would suggest that prednisone might have a role, after decades in which prednisone has been discouraged because of its maternal morbidity, and, especially, its role in increasing pre-eclampsia. Finally, specific blockade of complement activation could be on the research horizon, through monoclonal antibodies or other inhibitory techniques.

Before the work on complement activation shook the field, a large body of work already existed on effects of antiphospholipid antibodies that could be injurious to pregnancy. Early pregnancy loss is still poorly understood. Antiphospholipid antibodies may affect implantation [6]. Interleukin 3, for example, may be important in early pregnancy loss, and might be one of the benefits of aspirin therapy [7]. Antiphospholipid antibodies could lead to later pregnancy loss through multiple mechanisms of injury to the uteroplacental unit, including interfering with annexin V [8].

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.

Clinical trials of aspirin

Many APS pregnancy trials have included aspirin (Table 1). However, many have included aspirin in both arms of the trial, so that no conclusion regarding the benefit (or harm) of aspirin alone can be ascertained. Several trials, however, contained an ''aspirin alone'' arm.

Aspirin has been compared with placebo in several APS pregnancy trials. Tulppala and colleagues [9] compared aspirin 50 mg daily versus placebo in 66 women. Only 12 had antiphospholipid antibodies, however. Aspirin had no benefit over placebo. Cowchock and colleagues [10] compared aspirin 81 mg daily versus usual care in 19 pregnancies. Aspirin had no advantage. Pattison and all [11] compared aspirin 75 mg daily versus placebo in 50 pregnancies. No difference was found in either antenatal or neonatal morbidity.

Kutteh, in 1996 [12], compared aspirin 81 mg as a sole therapy versus aspirin plus unfractionated heparin. The aspirin was started preconception. Heparin was started at 10,000 units subcutaneously in two divided doses,

Table 1
APS pregnancy trials including aspirin

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Cowchock [15]	1992	45	Randomized multicenter	Prednisone 20 mg Aspirin 80 mg	Heparin 10,000 units twice daily Aspirin 80 mg	No difference (75% live births) in pregnancy success. More maternal morbidity and preterm delivery with prednisone/aspirin
Silver [30]	1993	34	Randomized	Aspirin 81 mg	Prednisone 20 mg with subsequent adjustment based on anticardiolipin level Aspirin 81 mg	No difference in pregnancy success (100%). Preterm delivery was higher with prednisone/aspirin ($P = 0.003$).
Kutteh [44]	1996	50	Prospective unicenter Consecutive assignment	Aspirin 81 mg High-dose heparin	Aspirin 81 mg Low-dose heparin	No difference
Kutteh [12]	1996	50	Prospective unicenter	Heparin initiated at 10,000 units daily in two divided doses Aspirin 81 mg/d	Aspirin 81 mg	Heparin/aspirin was better
Rai [13]	1997	90	Randomized	UF Heparin 5000 units twice daily Aspirin 75 mg	Aspirin 75 mg	Aspirin/Heparin had better pregnancy outcome as compared to aspirin alone
Tulppala [9]	1997	66 (only 12 had anticardiolipin)	Placebo controlled randomized.	Aspirin 50 mg	Placebo	No difference
Cowchock [10]	1997	19	Randomized	Aspirin 81 mg	Usual care	No difference

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Table 1 (*continued*)

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Branch [27]	2000	16	Randomized	Aspirin 81 mg Heparin 15,000–20,000 units	Aspirin 81 mg Heparin 15,000–20,000 units IVIG 1 g/kg for 2 consecutive days every 4 weeks	No difference
Pattison [11]	2000	50	Randomized placebo controlled	Aspirin 75 mg	Placebo	No difference: 85% pregnancy success in placebo versus 80% with aspirin
Pauzner [25]	2001	57	Observational	Enoxaparin Aspirin	Warfarin between weeks 15 to 34	No difference: 86% successful pregnancy with warfarin vs 87% in nonwarfarin
Farquharson [14]	2002	98	Randomized placebo controlled	LMW Heparin 5000 units Aspirin 75 mg	Aspirin 75 mg	No difference
Stephenson [23]	2004	28	Randomized	LMW Heparin Aspirin	Unfractionated Heparin Aspirin	No difference
Jeremic [28]	2005	40	Observational	LMW Heparin Aspirin	LMW Heparin Aspirin Intravenous immunoglobulin	No difference: successful pregnancy in 85% heparin/aspirin and 90% heparin/ aspirin/IVIG

Abbreviations: IVIO, intravenous immunoglobulins; LMW, low molecular weight; UF, unfractionated.

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. Similarly, Rai and colleagues, in 1997 [13], compared aspirin 75 mg as a sole therapy with unfractionated heparin 5000 units subcutaneously twice daily with aspirin. The aspirin was begun after a positive pregnancy test. Heparin was started at the time a fetal heart beat was demonstrated on ultrasound. Ninety women were randomized. As with the Kutteh trial, the heparin and aspirin group did better than the aspirin-alone group. The very similar results from these two trials suggest that heparin dosing does not need to be adjusted for any certain aPPT.

A third trial, done by Farquharson and colleagues, that compared aspirin alone versus heparin and aspirin, reached a different conclusion from Kutteh and Rai and colleagues [14]. Aspirin 75 mg daily as a sole therapy was compared with aspirin 75 mg plus low molecular weight (LWM) heparin 5000 units subcutaneously daily. Ninety-eight women participated in this randomized placebo-controlled trial. In this study, aspirin and heparin/aspirin were equal in successful pregnancies.

Clinical trials of heparin

Heparin has been studied in multiple APS pregnancy trials (Table 2). One of the most pivotal clinical trials compared prednisone and aspirin with unfractionated heparin and aspirin [15]. In this multicenter trial, both arms had equal pregnancy success. Maternal morbidity, however, including gestational diabetes and preterm birth, due largely to pre-eclampsia, was increased in the prednisone/aspirin arm. This trial had immediate impact on clinical obstetric practice, with heparin/aspirin becoming the ''gold standard'' treatment.

Subsequent trials (also reviewed under ''Clinical Trials of Aspirin'') compared whether heparin added benefit over aspirin alone (Table 3). These three clinical trials, Kutteh [12], Rai and colleagues [13], and Farquharson and colleagues [14] reached different conclusions, with Kutteh and Rai and colleagues finding superiority of heparin/aspirin and Farquharson and colleagues finding no difference. There were design differences between the trials. Both Kutteh and Rai and colleagues used unfractionated heparin, whereas Farquharson and colleagues used LMW heparin. Kutteh started aspirin before conception, whereas Rai and Farquharson and colleagues started it after conception. Kutteh adjusted the heparin dose. Rai and colleagues started heparin after the finding of a fetal heart beat on fetal ultrasound. However, none of these design differences appears to explain the contrasting results.

LMW heparin may offer an advantage over unfractionated heparin in terms of convenience, less osteoporosis [16–18], and less thrombocytopenia [19,20]. There is disagreement over whether LMW heparin can or should be

Table 2
APS pregnancy trials including heparin

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Cowchock [15]	1992	45	Randomized multicenter	Prednisone 20 mg Aspirin 80 mg	Heparin 10,000 units twice daily Aspirin 80 mg	No difference (75% live births) in pregnancy success. More maternal morbidity and preterm delivery with prednisone/aspirin
Kutteh [12]	1996	50	Prospective unicenter	Heparin initiated at 10,000 units daily in two divided doses Aspirin 81 mg	Aspirin 81 mg	Heparin/aspirin was better
Rai [13]	1997	90	Randomized	UF Heparin 5000 units twice daily Aspirin 75 mg	Aspirin 75 mg	Heparin/aspirin had better pregnancy outcome as compared to aspirin alone
Branch [27]	2000	16	Randomized Trial	Aspirin 81 mg Heparin 15,000–20,000 units	Aspirin 81 mg Heparin 15,000–20,000 units IVIG 1g/kg for 2 consecutive days every 4 weeks	No difference
Pauzner [25]	2001	57	Observational	Enoxaparin Aspirin	Warfarin between weeks 15 to 34	No difference: 86% successful pregnancy with warfarin versus 87% in non-warfarin
Farquharson [14]	2002	98	Randomized placebo Controlled	LMW Heparin 5000 units Aspirin 75 mg	Aspirin 75 mg	No difference
Triolo [45]	2003	40	Randomized	LMW Heparin 5700 units Aspirin 75 mg	IVIG 400 mg/kg/d for 2 days then once every month	IVIG was inferior (57% successful pregnancies vs 84% with heparin/aspirin)

Malinowski [46]	2003	148	Randomized	Aspirin 75 mg	LMW Heparin Group 3: LMW Heparin Aspirin 75 mg	No difference: aspirin (89.3%), heparin (81.1%), aspirin/ heparin (92.5%) Pregnancy loss was statistically higher in the lupus anticoagulant group (21.2%) versus anticardiolipin (6.7%)
Ensom [22]	2004	15	Pharmacokinetic randomized study	Various doses of dalteparin	Various doses of UF Heparin	Dalteparin dosing requires adjustment during pregnancy: 2500 units daily pre- and postpregnancy; 5000 units daily in pregnancy
Stephenson [23]	2004	28	Randomized	LMW Heparin Aspirin	Unfractionated Heparin Aspirin	No difference
Jeremic [28]	2005	40	Observational	LMW Heparin Aspirin	LMW Heparin Aspirin Intravenous immunoglobulin	No difference: successful pregnancy in 85% heparin/aspirin and 90% heparin/ aspirin/IVIG
Noble [24]	2005	50	Randomized	LMW heparin Aspirin	UF heparin Aspirin	No difference: 84% live birth with LMWH vs 80% with UF heparin

Abbreviations: IVIO, intravenous immunoglobulins; LMW, low molecular weight; UF, unfractionated.

Table 3
Comparison of heparin/aspirin versus aspirin for APS pregnancies

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Kutteh [12]	1996	50	Prospective unicenter	Heparin initiated at 10,000 units daily in two divided doses Aspirin 81 mg/d	Aspirin 81 mg	Heparin/aspirin was better
Rai [13]	1997	90	Randomized	UF Heparin 5000 units twice daily Aspirin 75 mg	Aspirin 75 mg	Heparin/aspirin had better pregnancy outcome as compared to aspirin alone
Farquharson [14]	2002	98	Randomized Placebo Controlled	LMW Heparin 5000 units Aspirin 75 mg	Aspirin 75 mg	No difference

Abbreviations: IVIO, intravenous immunoglobulins; LMW, low molecular weight; UF, unfractionated.

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 [21]. One randomized study of pharmacokinetics determined that dalteparin required one dose pre- and postpregnancy and another dose during pregnancy [22].

Two clinical trials have compared unfractionated heparin versus LWM heparin in terms of APS pregnancy efficacy. Stephenson and colleagues compared LMW heparin/aspirin with unfractionated heparin/aspirin in 28 pregnancies and found 69% live births with LMW heparin/aspirin versus 31% with UF heparin/aspirin (not statistically different) [23]. In a second trial, Noble and colleagues found 84% live births with LMW heparin/aspirin versus 80% with unfractionated heparin/aspirin, with 25 pregnancies in each arm [24].

Clinical trials of warfarin

In the United States, because of concern about warfarin teratogenicity, pregnant women are switched to heparin. However, in other countries, warfarin is used, sometimes throughout pregnancy and sometimes after organogenesis. Pauzner and colleagues [25] (Table 4) compared enoxaparin versus warfarin in an observational study in 57 pregnancies and found no difference in outcome.

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 [26].

IVIG has been studied in three APS pregnancy trials (Table 5). In comparison to LMW heparin and aspirin, IVIG is inferior. In two trials [27,28],

Table 4
APS pregnancy trials including warfarin

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Pauzner [25]	2001	57	Observational	Enoxaparin Low-dose aspirin	Warfarin between weeks 15 to 34	No difference: 86% successful pregnancy with warfarin versus 87% in non-warfarin

Table 5
APS pregnancy trials including intravenous immunoglobulin

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Branch [27]	2000	16	Randomized	Aspirin 81 mg Heparin 15,000–20,000 units	Aspirin 81 mg Heparin 15,000–20,000 units IVIG 1g/kg for 2 consecutive days every 4 weeks	No difference
Triolo [45]	2003	40	Randomized	LMW Heparin 5700 units Aspirin 75 mg	IVIG 400 mg/kg/d for 2 days then once every month	IVIG was inferior (57% successful pregnancies vs 84% with heparin/aspirin)
Jeremic [28]	2005	40	Observational	LMW Heparin Aspirin	LMW Heparin Aspirin Intravenous immunoglobulin	No difference: successful pregnancy in 85% heparin/aspirin and 90% heparin/aspirin/IVIG

Abbreviations: IVIG, intravenous immunoglobulins; LMW, low molecular weight; UF, unfractionated.

IVIG offered no advantage over heparin and aspirin. Given the expense of IVIG, the lack of positive clinical trials suggests it should be reserved for accepted indications in pregnancy, such as thrombocytopenia.

Clinical trials of prednisone

Prednisone was the original APS pregnancy therapy studied by Lubbe [29]. 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 [15]. Subsequently, Silver and colleagues showed that prednisone/aspirin led to more preterm birth [30]. Finally, Laskin and colleagues [31], in a study of 202 pregnancies (not all of which were antiphospholipid antibody positive), determined that prednisone/aspirin was inferior to placebo in terms of preterm birth (Table 6).

Management

Management is summarized in Table 7.

Antiphospholipid antibody positivity with a history of thrombosis but no pregnancy loss

Patients with antiphospholipid antibodies and a first episode of thrombosis have a high rate of recurrent thrombosis [3,32,33]. The Swedish Duration of Anticoagulation Study found an increased mortality as well [34]. For this reason, APS thrombosis is treated with long-term anticoagulation. The targeted degree of anticoagulation has changed, however. Initially, the targeted international normalized ratio (INR) was 3 to 4 (''high intensity''), based on the largest retrospective study [3]. Subsequently, two randomized clinical trials [35,36] have demonstrated that an INR target of 2 to 3 is equally effective as the more dangerous 3 to 4 target.

However, warfarin can be teratogenic in pregnancy. Therefore, as soon as pregnancy is identified, the warfarin is stopped and therapeutic doses of heparin are substituted.

Antiphospholipid antibody positivity and no prior pregnancies

As many as 7.5% of normal controls have antiphospholipid antibodies [37]. On occasion, antiphospholipid antibodies may have been checked and found to be abnormal in a woman with no prior pregnancies nor thrombosis. Possible scenarios include a woman with lupus, a woman with infertility, or a woman with a strong family history of lupus or APS.

If the woman has lupus, and is on hydroxychloroquine for systemic lupus erythematosus (SLE) disease activity, there is a general consensus that hydroxychloroquine can be continued during pregnancy. Although hydroxychloroquine does cross the placenta, and there is the potential for

Table 6
APS pregnancy trials including prednisone

Author	Year	Size	Study design	Comparison arm 1	Comparison arm 2	Study outcome
Cowchock [15]	1992	45	Randomized multicenter	Prednisone 20 mg Aspirin 80 mg	Heparin 10,000 units twice daily Aspirin 80 mg	No difference (75% live births) in pregnancy success. More maternal morbidity and preterm delivery with prednisone/aspirin
Silver [30]	1993	34	Randomized	Aspirin 81 mg	Prednisone 20 mg with subsequent adjustment based on anticardiolipin level Aspirin 81 mg	No difference in pregnancy success (100%). Preterm delivery was higher with prednisone/aspirin ($P = 0.003$).
Laskin [31]	1997	202	Randomized placebo controlled (not all had anticardiolipin or lupus anticoagulant)	Prednisone (0.5 to 0.8 mg/kg) Aspirin 100 mg	Placebo	No difference in pregnancy success (65% with prednisone/aspirin vs 57% placebo). Preterm births were increased with prednisone/aspirin (62% versus 12%, $p < 0.001$), as were hypertension ($p = 0.05$) and diabetes mellitus ($p = 0.02$)

Table 7
Current treatment recommendations for APS pregnancy

Condition	Pregnancy	Postpregnancy
Women with previous thrombosis	Unfractionated or LMW Heparin in therapeutic range	Return to warfarin
Women with antiphospholipid antibodies but no history of pregnancy loss or thromboembolism.	Low dose aspirin	Low-dose aspirin
Women with medium to high titer anticardiolipin, anti-beta2glycoprotein 1, or lupus anticoagulant, and 2–3 (or more) first trimester losses or one or more fetal deaths or one or more very preterm births due to placental insufficiency	Low dose aspirin AND Prophylactic unfractionated or LMW heparin	Continue unfractionated or low molecular weight heparin for 6 weeks postpartum Continue low-dose aspirin life-long

Abbreviations: IVIO, intravenous immunoglobulins; LMW, low molecular weight; UF, unfractionated.

deposition in the fetal eye or ear, a large published experience has not found problems in children exposed in utero [38–40]. Hydroxychloroquine reverses platelet activation induced by human IgG anticardiolipin [41] and reduces thrombosis size in an animal model [42]. If the woman has lupus, low-dose aspirin would be added.

If the woman does not have lupus, most physicians would start low dose aspirin (81 mg), not just during the pregnancy, but as a life-long prophylactic treatment to reduce the risk of future thrombosis. It is important to acknowledge, however, that aspirin has yet to be proven effective as a prophylactic therapy for APS thrombosis. In fact, the randomized prospective clinical trial of Doruk Erkan and colleagues [43] has not shown benefit, although the trial is still ongoing.

Antiphospholipid antibody positivity and one first trimester loss

Although not specifically addressed in clinical trials, the fact that first trimester losses are commonly found in normal women means that first trimester pregnancy loss cannot always be ascribed causally to APS. Thus, most would only recommend low dose aspirin.

Antiphospholipid antibody positivity and multiple first trimester losses or one late fetal loss

The predominance of clinical trial evidence supports the use of prophylactic doses of heparin and aspirin. LMW heparin is equally effective as unfractionated heparin. Twice-daily versus once-daily dosing has not been adequately studied.

Summary

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. However, the clinical trials suffer from the lack of uniform definition of antiphospholipid antibody positivity, from inclusion of women with different past pregnancy histories, and from different timing of the onset of the therapeutic modalities tested. New research on the role of complement activation in murine APS pregnancy loss may change therapeutic options in the future.

Acknowledgments

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