Published in final edited form as:

Clin Lab Med. 2013 June ; 33(2): 367–376. doi:10.1016/j.cll.2013.01.001.

ANTICOAGULATION IN MANAGEMENT OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME [APS] IN PREGNANCY

Michael D. Lockshin, MD [Professor of Medicine and Obstetrics-Gynecology]

Weill Cornell Medical College, The Barbara Volcker Center for Women and Rheumatic Disease Hospital for Special Surgery 535 E 70th Street New York, NY 10021 Tel 212-606-1461 Fax 212-774-2374 LockshinM@hss.edu

Synopsis

Our knowledge of antiphospholipid antibodies and their impact on pregnancy continues to evolve. A variety of antiphospholipid antibodies have been identified but not all of them seem to be pathologic for pregnancy outcome. Our understanding of which patients are at high risk for adverse pregnancy outcome and the most effective treatment will require clinical trials based on risk stratification and long term follow-up of infants.

Keywords

Antiphospholipid antibody; Lupus anticoagulant; Systemic lupus erythematosus; Anticoagulation; Pregnancy

1. History and definition

In 1906 Wasserman described a complement fixation test for syphilis that is based on the binding of an IgG or IgM antibody from an infected person to cardiolipin, which is a negatively-charged phospholipid derived from beef hearts.¹ Because patients who could not have contracted syphilis sometimes tested positive, a confirmation test demonstrating the ability of patient serum to immobilize the spirochete, *treponema pallidum* was subsequently devised,² leading to the label of biologic false positive (BFP) reactors for persons whose serum reacted in the cardiolipin (“Wassermann”) test but not in the immobilization test. Initially BFP was a medical curiosity of no known clinical significance, until, in 1952 Conley and Hartman described prolongation of an in vitro clotting test in patients who had systemic lupus erythematosus (SLE), many of whom were also BFP. Because these patients suffered hemorrhage, they named the factor lupus anticoagulant (LAC).³ Work thereafter by Rapaport,⁴ Bowie⁵ and others demonstrated that LAC is an antibody to a phospholipid associated with thrombosis rather than with hemorrhage; it is an antibody that binds and thus sequesters the negatively-charged phospholipids that initiate clotting in the in vitro assays.⁶ Case reports in the 1970s and early 1980s from Sweden, France, and England and Holland suggested an association between LAC, BFP, and fetal death.^{7,8,9,10,11,12,13,14,15,16}

© 2013 Elsevier Inc. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

No conflicts of interest.

No unlabelled drug use discussion.

From the first description until 1983 testing for LAC was tedious, difficult to perform, and unreliable in inexperienced hands. Demonstration of LAC required fresh whole blood specimens for in vitro clotting tests, which began with an abnormal screening test, most often a partial thromboplastin time (PTT) or kaolin clotting time (KCT), but not prothrombin time (PT). Proof that it was an anticoagulant, an inhibitor of clotting, rather than a factor deficiency requires follow-up testing in which patient plasma prolonged the PTT or KCT of normal plasma; if the abnormality is due to deficiency normal plasma will correct the test.

In 1983 Hughes' group in England proposed a simple radioimmunoassay as a proxy for the lupus anticoagulant test.¹⁷ The assay uses cardiolipin as the test antigen, can be done in most clinical laboratories and, most importantly, can be done on stored serum. Within a year the radioimmunoassay was revised to an even simpler and less expensive enzyme linked immunosorbent assay (ELISA). A positive test in this ELISA is now called anticardiolipin antibody (aCL).

In 1990 several groups simultaneously discovered that what is called aCL does not bind cardiolipin directly but requires a cofactor, beta-2-glycoprotein I (β_2 GP-I), also known as apolipoprotein H; an assay for antibody to β_2 GP-I was devised (a β_2 GP-I).^{18,19} Today LAC, aCL, and a β_2 GP-I are collectively known as antiphospholipid antibodies (aPL).

2. Biological activity of aPL

All of the terms used to describe aPL are misnomers: except when directed against prothrombin LAC is procoagulant; it is anticoagulant only in vitro. ACL does not directly bind cardiolipin (or other negatively charged phospholipids) but does so through its binding to β_2 GP-I, which itself binds the phospholipid.

β_2 GP-I is a complex molecule with five domains. The fifth domain, in combination with a membrane protein cofactor, most likely Toll-like receptor 2 or 4 (TLR2, TLR4)^{20,21} binds to negatively charged phospholipid, specifically the phosphatidylserine that is exteriorized when a cell is activated or dying. Pathogenic aPL binds to a peptide in the first domain of β_2 GP-I.²² APL binding to β_2 GP-I-TLR4 initiates both intracellular and extracellular processes that result in tissue damage (see below).

Other antibodies commonly associate with aPL, among them antibodies to prothrombin (that, in depleting prothrombin may cause hemorrhage) or to prothrombin-phospholipid complex;^{23,24} the biologic importance of these associated antibodies is now being discovered. Animal models for both thrombosis and pregnancy loss, in which animals are either immunized to produce aPL or have it passively infused, strongly suggest that the aPL itself is directly pathogenic and is not a passive marker or bystander.²⁵

APL can be induced, usually transiently, by several infections, such as EBV, Lyme, leprosy, and, of course, syphilis.²⁶ Some infection-induced aPLs, such as that induced by the syphilis spirochete, bind directly to membrane phospholipid, bypassing the β_2 GP-I pathway, and differ from the pathogenic aPL found in patients with SLE.²⁷ APLs induced by leprosy are likely β_2 GP-I-dependent and pathogenic.

Today the target for pathogenic aPL is thought to be conformationally altered β_2 GP-I bound to TLR4. The pathophysiologic model proposes that the antibody arises, possibly as a result of an (unidentified) infection in a genetically-prepared host; it causes no harm until cell injury, perhaps virally-induced endothelial cell activation, exteriorizes the negatively charged phospholipid phosphatidylserine to the outer cell membrane. At that time β_2 GP-I binds to the cell membrane phosphatidylserine-TLR4 complex and undergoes a

conformational change that activates complement in the extracellular space and/or triggers intracellular activation that results in upregulation of adhesion and other molecules. These events lead to inflammation, thrombosis, and clinically recognized disease.²² APL may also interfere with trophoblast development, maturation, and invasion.²⁸ Under normal circumstances β_2 GP-I is thought to be a molecule that protects endothelial integrity.²⁹

3. Clinical associations

After the introduction of the anticardiolipin ELISA, several papers in the mid-1980s confirmed and strengthened the association between aPL and pregnancy complications, and also between aPL and recurrent venous or arterial thromboses. Initially restricted to fetal death, pregnancy morbidity associated with aPL now includes fetal growth restriction, prematurity, and early or severe pre-eclampsia.

Together with the definition of aPL, a clinical definition of what is now known as antiphospholipid syndrome (APS) evolved. International consensus conferences in 1999 (Sapporo)³⁰ and 2006 (Sydney)³¹ provide these criteria for APS:

- A patient must have both serological and clinical findings.
- Serologic criteria include LAC (positive) and/or high titer (≥ 40 units) IgG or IgM aCL and/or high titer (≥ 40 units) IgG or IgM $\alpha\beta_2$ GP-I
- Tests must be positive on two occasions at least 12 weeks apart
- Clinical criteria include recurrent thromboses and/or recurrent pregnancy losses, defined as at least one loss of an apparently normal fetus after 12 weeks or three consecutive losses of apparently normal fetuses less than 12 weeks, without other causes, such as infection.

IgA antibody does not fulfill the definition for either aCL or $\alpha\beta_2$ GP-I because it is unreliably determined in commercial laboratories. Similarly, assays for antibodies to other phospholipids, such as phosphatidylserine or phosphatidylethanolamine have not undergone rigorous standardization procedures nor clinical association studies and so are not included. Low titer antibody is insufficiently closely associated with clinical events, and may be transient after infection, so does not fulfill criteria for APS.

Many other clinical features occur in patients APS but do not participate in the criteria. These include:

- Thrombocytopenia,
- Livedo reticularis,
- Cardiac valve vegetations,
- Renal thrombotic microangiopathy,
- Cognitive dysfunction,
- Hyperintense non-enhancing white matter lesions on brain MRI, and
- Catastrophic antiphospholipid syndrome (CAPS) in which multiple widespread thromboses occur over a short period of time.³²

Recent papers suggest that patients presenting different manifestations, for instance pregnancy loss or thrombosis, likely represent different subgroups, and that risks faced by one group are not necessarily applicable to another.³³

4. Anticoagulation as treatment

Because historically the recognition of APS evolved from recognizing the relationship between aPL and thrombosis and because the association of aPL with SLE was an early discovery, initial treatment recommendations focused on immunosuppressive therapy for both the thrombotic and the pregnancy morbidity forms of the disease. High dose corticosteroid therapy failed.^{34,35} Because early reports had sought and found placental thrombosis, and because of the association of aPL with peripheral thrombosis, anticoagulation with heparin was introduced, warfarin being disfavored in pregnancy because of teratogenicity. Early papers on pregnancy also emphasized the association of between genetic hypercoagulable states (factor V Leiden, prothrombin 20210, antithrombin III) and recurrent pregnancy loss, and a putative increase in pregnancy failure in patients having both aPL and genetic hypercoagulability, supporting the hypothesis that placental thrombosis was the mechanism at fault.³⁶

The first papers on fetal loss in patients with aCL or LAC did not address therapy.^{13, 37,38} The next generation of papers focused on the (generally negative) results of treatment with high dose corticosteroid.^{34, 35} Thereafter a series of papers, including a few randomized, controlled studies, found better fetal outcome in patients taking heparin and aspirin compared to untreated patients or those treated with aspirin alone,^{39,40,41} but not all investigators agreed.⁴² Studies in patients with genetic thrombopathies or in patients likely to develop pre-eclampsia mostly failed to show efficacy of either aspirin or heparin.⁴³ Some papers emphasized a good prognosis in untreated patients with aPL or APS.^{44,45} The available studies are small; as a rule, they do not stratify patients by either serological or clinical risk profile, nor do they look at different fetal outcomes, such as growth restriction or prematurity, as opposed to fetal death.

The studies that most clearly supported the use of heparin are those of Rai³⁹ and of Kutteh.^{40, 41} Rai prospectively randomized to aspirin or aspirin and heparin treatment pregnant women who had aPL, mostly but not exclusively defined by LAC, and who had had 3 or more miscarriages. Treatment groups had similar numbers of prior miscarriages but were not otherwise described. Forty-five women received 75 mg aspirin plus 5000 units of unfractionated heparin twice daily had a live birth rate of 71% compared to 42% of 45 women who received aspirin alone. Women who received heparin had a median decrease in lumbar spine bone density of 5.4%. Kutteh, using a similar study design and entry criteria, found that 80% of 25 women treated with heparin plus low dose aspirin had viable pregnancies (essentially all at term) compared to 44% of women treated with aspirin alone. He then compared 25 women treated with anticoagulant dose heparin (80% survival) to 25 women treated with low dose heparin (76% survival), concluding, as in the animal experiments, that heparin's efficacy may not reside in its anticoagulant properties. Though less systematic, subsequent studies have argued that low molecular weight heparin is equivalent to unfractionated heparin in efficacy, as it is in the animal model.⁴⁶

Animal models demonstrate both that aCL has a direct, causative role in fetal loss and that heparin prevents fetal loss. A particularly informative set of experiments in mice further demonstrates that heparin, but not fondaparinux or warfarin, prevents aCL-induced fetal resorption, and that complement deficiency or inactivation is equally protective.⁴⁷ Kutteh's low dose heparin trial (inactivating complement but not preventing thrombosis) would seem to confirm, and Rai used subanticoagulant doses as well. These data are consistent with the hypothesis that heparin's efficacy is due to its anticomplement activity and thus place complement activation and inflammation at the head of the pathogenetic line, with thrombosis being a downstream, terminal event. More recent human studies question whether genetic hypercoagulable states truly lead to pregnancy loss and whether they need

be treated at all,^{43, 44} again diminishing the prothrombotic theory of recurrent pregnancy loss.

5. Treatment Recommendations

Standard treatment to prevent adverse pregnancy outcome, based mostly on consensus data rather than on clinical trials, continues to be:

- Prophylactic doses, e.g., 0.5 mg/kg/d of low molecular weight heparin (enoxaparin) or 5000 u twice daily unfractionated heparin plus low dose (81 mg) aspirin for patients who have not had prior thrombosis. It is best to consider checking, once or twice during treatment, an anti-Factor Xa four hours after last dose for level of 0.2 – 0.6 U/ml.
- Full anticoagulant doses, e.g., 1 mg/kg every 12 hours of enoxaparin, or 10-12,000 units unfractionated heparin every 12 hours in those who have had prior thrombosis. Treatment dose must be monitored by anti-Factor Xa activity, since PTT is usually abnormal in patients with LAC. Target anti-Factor Xa four hours after last dose for 0.5 – 1.1 U/ml if bid dosing or 1.0 – 2.0 U/ml if once a day dosing.
- Treatment begins at conception and continues for 6-12 weeks post partum if there is no history of thrombosis and indefinitely if there is.
- Dosing will need to be reduced if there is renal impairment.

6. Risk-stratification

A difficulty in interpreting the available data is that recent work strongly suggests that not all patients with aPL are at equal risk for pregnancy loss, and that past studies that did not risk-stratify may be invalid. Papers discussing aPLs have not clearly distinguished risks that might be differently distributed among the different antibodies, aCL, a β_2 GP-1 and LAC, nor have treatment studies attempted to risk-stratify according to clinical diagnosis.

Only recently have studies begun to stratify patients according to pre-pregnancy risk profile. In its setting criteria for the classification of APS, an international consensus team emphasized risk is increased only by sustained high titer aCL and a β_2 GP-1, of IgG or IgM isotype, and as opposed to low titers of IgA aCL, or transient high titers of IgG aCL or IgM aCL.³¹ Concomitantly, clinical studies confirmed the increased risk attributable to coexisting SLE, prior thrombosis history, smoking, and trigger factors (such as surgery, trauma, oral contraceptive therapy, and sepsis).⁴⁸ Systematic risk stratification analyses for pregnancy treatment studies are unavailable.

A parallel literature on aPL-associated thrombosis began to argue that risk could be graded by serological profile: depending on investigator, high titer, “triple” (aCL, a β_2 GP-1 and LAC) positivity, a β_2 GP-1 alone, LAC alone, or antibody to a peptide found in domain 1 (of 5 domains) of β_2 GP-1 more precisely predicted thrombotic risk.⁴⁹ Other investigators focused on clinical risk profile: occurrence of trauma, surgery, or delivery; smoking; pre-existing atherosclerosis; and prior thrombi.⁴⁸

Until recently, no study has been large enough, or has considered a sufficient number of variables, to allow determination of treatment efficacy in a risk-stratified patient group.

Ruffatti, emphasizing serology, retrospectively compared 57 women with APS who either lost pregnancies or delivered before 34 weeks (“unsuccessful”) to 57 women with APS who had successful pregnancies.⁵⁰ To isolate predictive clinical features, this study matched

successful and unsuccessful pregnancies according to heparin, aspirin, or both together. Ruffatti concluded that triple positivity was the best predictor of fetal loss. Concerns about this conclusion are: the patients were collected between 1986 and 2009 ($\alpha\beta_2$ GP-1 was not identified until 1990^{18, 19} and did not become a clinical assay until several years later); only 38 of the 57 (67%) women with unsuccessful pregnancies and 45 of the 57 (79%) with successful pregnancies in fact had all three tests done; and those with unsuccessful pregnancies differed from those with successful pregnancies in having much more associated autoimmune disease (49% versus 12%), prior thrombosis (49% versus 21%), both pregnancy morbidity and prior thrombosis (32% versus 4%), and other APS-related manifestations (35% versus 12%).

Our own studies⁵¹ show similar outcomes but lead to different conclusions. Between 2003 and 2011 we enrolled 144 pregnant patients with aPL into a prospective observational study; all were tested for aCL, $\alpha\beta_2$ GP-1 and LAC at core laboratories at enrollment, at each trimester, and 3 months postpartum; LAC was determined by three separate methods (screening with PTT, dilute Russell's Viper Venom time, or dilute prothrombin time). We did not analyze pregnancies lost before 12 weeks, nor did we alter therapy chosen by the treating physician. Fifty-seven of the 144 patients had SLE. Using multivariate analysis we concluded that the most powerful predictor of adverse pregnancy outcome (fetal death, prematurity, growth restriction, and/or pre-eclampsia) is lupus anticoagulant. Other adverse predictors include diagnosis of SLE, prior thrombosis, and young maternal age. Surprisingly, neither adverse prior pregnancy history nor high titer aCL or $\alpha\beta_2$ GP-1, IgG or IgM (without concomitant LAC) added to the prediction model. Triple positivity was no more predictive than its dominant component, LAC. The study was not a treatment trial and we cannot exclude confounding bias by treatment indication; however, when only LAC positive patients are considered, heparin therapy was not associated with improved outcome, while aspirin was. Patients without LAC had uniformly good outcomes whether or not heparin or aspirin were administered.

Our review of available information to date suggests the following: aPL is associated with recurrent pregnancy loss; among aPLs, LAC is the most powerful predictor; other clinical features, especially coexisting SLE, contribute to pregnancy risk; and no study to date has sufficiently stratified patients to support an unequivocal recommendation of heparin treatment for prophylaxis against pregnancy loss, nor are clear guidelines for either dose or type of heparin available.

7. Future treatments and trial design

The biology of aPL-associated tissue damage suggests alternatives to anticoagulation as treatment for APS.^{29, 52} If complement activation is truly a critical early step in the process that leads to fetal death, as it seems to be in animal models, products that prevent complement activation may be of benefit; eculizumab, a C5 inhibitor, successfully interrupted recurring catastrophic syndrome in one patient.⁵³ Experimental animal models indicate that peptides that block the binding of antibody to β_2 GP-1 are also effective.⁵⁴ It may be possible to remove or block aPL synthesis, or to prevent upregulation of the adhesion molecules that, presumably, are the final step in vascular insufficiency and placental failure. Other, anecdotal, treatments include plasmapheresis and intravenous immunoglobulin. These new treatment opportunities and others have been reviewed elsewhere.^{29, 5556}

It will, however, be difficult to design safe and ethical clinical trials. Most clinics now achieve >80% fetal survival in women who do not have SLE and who have had two or more consecutive fetal losses, implying that, if positive aPL, history of recurrent fetal loss, and no

underlying illness are the only entry criteria, very large numbers of patients will have to be treated to demonstrate success, and the safety of an intervention will have to be guaranteed at a very high level. If studies are restricted to women stratified to be at very high risk (history of prior losses, co-existing SLE, lupus anticoagulant positive, history of prior thrombosis), very few study subjects will be available, but few will be needed to prove efficacy. Because modern neonatology permits survival of very premature or ill infants, outcome criteria for clinical trials will have to include prematurity, growth restriction, and pre-eclampsia as well as death, which will add variables to the analysis; similarly, analysis will not truly be complete until the infants have reached at least school age and possibly their teens to determine long-term outcomes of the intervention. It will be difficult to fulfill these rigorous criteria, but couples suffering repeated pregnancy loss continue to plead for the challenges to be met.

REFERENCES

1. Wassermann A, Neisser A, Bruck C. Eine serodiagnostische Reaktion bei Syphilis. *Deutsche medizinische Wochenschrift*, Berlin. 1906; 32:745–6. http://en.wikipedia.org/wiki/Wassermann_test.
2. Nielsen HA, Reyn A. The Treponema pallidum immobilization test. *Bull World Health Organ*. 1956; 14:263–288. [PubMed: 13329850]
3. Conley CL, Hartmann RC. A hemorrhagic disorder caused by circulating anticoagulants in patients with disseminated lupus erythematosus. *J Lab Clin Invest*. 1952; 31:621–2.
4. Mueh JR, Herbst KD, Rapaport SI. Thrombosis in patients with the lupus anticoagulant. *Ann Intern Med*. 1980; 92:156–9. [PubMed: 7352719]
5. Bowie EJW, Thompson JH, Pascuzzi CA, et al. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. *J Lab Clin Med*. 1963; 62:416–430. [PubMed: 14061973]
6. Thiagarajan P, Shapiro SS, De Marco L. Monoclonal immunoglobulin M lambda coagulation inhibitor with phospholipid specificity. Mechanism of a lupus anticoagulant. *J Clin Invest*. 1980; 66:397–405. [PubMed: 6772673]
7. Nilsson IM, Åstedt B, Hedner U, Berezin D. Intrauterine death and circulating anticoagulant (“antithromboplastin”). *Acta Med Scand*. 1975; 197:153–9.
8. Soulier J-P, Boffa M-C. Avortements à répétition, thromboses et anticoagulant circulant anti-thromboplastine: trois observations. *Nouv Presse Med*. 1980; 9:859–64.
9. Firkin BG, Howard MA, Radford N. Possible relationship between lupus inhibitor and recurrent abortion in young women. *Lancet*. 1980; 2:366. [PubMed: 6105497]
10. Abramowsky CR, Vegas ME, Swinehart G, et al. Decidual vasculopathy of the placenta in lupus erythematosus. *N Engl J Med*. 1980; 303:668–72. [PubMed: 6995842]
11. Carreras LO, Defreyn G, Machin SJ, et al. Arterial thrombosis, intrauterine death and “lupus” anticoagulant: detection of immunoglobulin interfering with prostacycline formation. *Lancet*. 1981; 1:244–6. [PubMed: 6109901]
12. De Wolf F, Carreras LO, Moerman P, et al. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss and a lupus anticoagulant. *Am J Obstet Gynecol*. 1982; 142:829–34. [PubMed: 6801984]
13. Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *Br Med J (Clin Res Ed)*. 1983; 287(6399):1088–9.
14. Lubbe WF, Palmer SJ, Butler WS, et al. Fetal survival after prednisone suppression of maternal lupus anticoagulant. *Lancet*. 1983; 1:1361–3. [PubMed: 6134138]
15. Reece EA, Romero R, Clyne LP, et al. Lupus-like anticoagulant in pregnancy. *Lancet*. 1984; 1:344–5. [PubMed: 6141412]
16. Gårdlund B. The lupus inhibitor in thromboembolic disease and intrauterine death in the absence of systemic lupus. *Acta Med Scand*. 1984; 215:293–8. [PubMed: 6428168]

17. Harris EN, Gharavi AE, Boey ML, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet*. 1983; 2:1211–4. [PubMed: 6139567]
18. Galli M, Comfurius P, Maassen C, et al. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma cofactor. *Lancet*. 1990; 335:1544–7. [PubMed: 1972485]
19. McNeil HP, Simpson RJ, Chesterman CN, et al. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid binding inhibitor of coagulation: b2 Glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci USA*. 1990; 87:4120–4. [PubMed: 2349221]
20. Allen KL, Fonseca FV, Betapudi V, et al. A novel pathway for human endothelial cell activation by antiphospholipid/anti- β 2 glycoprotein I antibodies. *Blood*. 2011; 119:884–93. [PubMed: 22106343]
21. Mulla MJ, Brosens JJ, Chamley LW, et al. Antiphospholipid antibodies induce a pro-inflammatory response in first trimester trophoblast via the TLR4/MyD88 pathway. *Am J Reprod Immunol*. 2009; 62:96–111. [PubMed: 19614626]
22. Salmon JE, Girardi G, Lockshin MD. The antiphospholipid syndrome as a disorder initiated by inflammation: implications for the therapy of pregnant patients. *Nat Clin Pract Rheumatol*. 2007; 3:140–7. [PubMed: 17334336]
23. Erkan D, Bateman H, Lockshin MD. Lupus anticoagulant-hypoprothrombinemia syndrome associated with systemic lupus erythematosus: report of 2 cases and review of literature. *Lupus*. 1999; 8:560–564. [PubMed: 10483036]
24. Amengual O, Atsumi T, Koike T. Pathophysiology of thrombosis and potential targeted therapies in antiphospholipid syndrome. *Curr Vasc Pharmacol*. 2011; 9:606–18. [PubMed: 21692741]
25. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nat Med*. 2004; 10:1222–6. [PubMed: 15489858]
26. Ribeiro SL, Pereira HL, Silva NP, et al. Anti- β 2-glycoprotein I antibodies are highly prevalent in a large number of Brazilian leprosy patients. *Acta Reumatol Port*. 2011; 36:30–7. [PubMed: 21483278]
27. Levy RA, de Meis E, Pierangeli S. An adapted ELISA method for differentiating pathogenic from nonpathogenic aPL by a beta 2 glycoprotein I dependency anticardiolipin assay. *Thromb Res*. 2004; 114:573–7. [PubMed: 15507293]
28. Han CS, Mulla MJ, Brosens JJ, et al. Aspirin and heparin effect on basal and antiphospholipid antibody modulation of trophoblast function. *Obstet Gynecol*. 2011; 118:1021–8. [PubMed: 22015869]
29. Meroni PL, Borghi MO, Raschi E, et al. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol*. 2011; 7:330–9. [PubMed: 21556027]
30. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum*. 1999; 42:1309–1311. [PubMed: 10403256]
31. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006; 4:295–306. [PubMed: 16420554]
32. Erkan D, Lockshin MD. Non-criteria manifestations of antiphospholipid syndrome. *Lupus*. 2010; 19:424–7. [PubMed: 20353981]
33. Meroni PL, Raschi E, Grossi C, et al. Obstetric and vascular APS: same autoantibodies but different diseases? *Lupus*. 2012; 21:708–10. [PubMed: 22635208]
34. Lockshin MD, Druzin ML, Qamar T. Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody. *Amer J Obstet Gynecol*. 1989; 160:439–44. [PubMed: 2916633]
35. Cowchock ES, Reece EA, Balababan D, et al. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low dose heparin treatment. *Am J Obstet Gynecol*. 1992; 166:1313–23.
36. Bradley LA, Palomaki GE, Bienstock J, et al. Can Factor V Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes?: Results from a targeted evidence-based review. *Genet Med*. 2012; 14:39–50. [PubMed: 22237430]

37. Lockshin MD, Druzin ML, Goei S, et al. Antibody to cardiolipin predicts fetal distress or death in pregnant patients with systemic lupus erythematosus. *New Engl J Med.* 1985; 313:152–6. [PubMed: 3925336]
38. Branch DW, Scott JR, Kochenour NK, et al. Obstetric complications associated with the lupus anticoagulant. *N Engl J Med.* 1985; 313:1322–6. [PubMed: 3932854]
39. Rai R, Cohen H, Dave M, et al. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ.* 1997; 314:253–7. [PubMed: 9022487]
40. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol.* 1996; 174:1584–9. [PubMed: 9065133]
41. Kutteh WH, Ermel LD. A clinical trial for the treatment of antiphospholipid antibody-associated recurrent pregnancy loss with lower dose heparin and aspirin. *Am J Reprod Immunol.* 1996; 35:402–7. [PubMed: 8739461]
42. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol.* 2002; 100:408–13. [PubMed: 12220757]
43. Manuck T, Branch DW, Lai Y, et al. Antiphospholipid antibodies and pregnancy outcomes in women heterozygous for factor V Leiden. *J Reprod Immunol.* 2010; 85:180–5. [PubMed: 20439118]
44. Cohn DM, Goddijn M, Middeldorp S, et al. Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy. *J Thromb Haemost.* 2010; 8:2208–13. [PubMed: 20704646]
45. Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol.* 2009; 36:279–87. [PubMed: 19208560]
46. Check JH. The use of heparin for preventing miscarriage. *Am J Reprod Immunol.* 2012; 67:326–33. [PubMed: 22435784]
47. Salmon JE, Girardi G. Antiphospholipid antibodies and pregnancy loss: a disorder of inflammation. *J Reprod Immunol.* 2008; 77:51–6. [PubMed: 17418423]
48. Erkan D, Yazici Y, Peterson MG, et al. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford).* 2002; 41:924–9. [PubMed: 12154210]
49. Ioannou Y, Rahman A. Domain I of beta2-glycoprotein I: its role as an epitope and the potential to be developed as a specific target for the treatment of the antiphospholipid syndrome. *Lupus.* 2010; 19:400–5. [PubMed: 20353977]
50. Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with antiphospholipid syndrome treated with conventional therapies: a multicentre, case-control study. *Rheumatology (Oxford).* 2011; 50:1684–9. [PubMed: 21652586]
51. Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum.* 2012; 64:2311–8. [PubMed: 22275304]
52. Gelber SE, Salmon JE. Autoimmunity: effectiveness of treatments for pregnant women with APS. *Nat Rev Rheumatol.* 2010; 6:187–9. [PubMed: 20357787]
53. Shapira I, Andrade D, Allen SL, et al. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum.* 2012; 64:2719–23. [PubMed: 22354668]
54. de la Torre YM, Pregnotato F, D'Amelio F, et al. Anti-phospholipid induced murine fetal loss: novel protective effect of a peptide targeting the β 2 glycoprotein I phospholipid-binding site. Implications for human fetal loss. *J Autoimmun.* 2012; 38:J209–15. [PubMed: 22196923]
55. Erkan D, Lockshin MD. New approaches for managing antiphospholipid syndrome. *Nature Clinical Practice Rheumatology.* 2009; 5:160–70.
56. Pierangeli SS, Erkan D. Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet? *Lupus.* 2010; 19:475–85. [PubMed: 20353991]

Key points

- Antiphospholipid antibody (anticardiolipin, antibody to β_2 glycoprotein I, lupus anticoagulant) are associated with fetal death, prematurity, growth restriction, and pre-eclampsia.
- Among the antiphospholipid antibodies, lupus anticoagulant is the best predictor of adverse outcome.
- Co-existing systemic lupus erythematosus and/or history of prior thrombosis worsen pregnancy prognosis.
- Although heparin and aspirin are considered standard therapy, treatment trials have not been done in risk-stratified populations; recommended therapies may therefore be less effective than thought.
- Low dose heparin (in patients without a history of thrombosis) is as effective as full anticoagulant doses; low molecular weight heparin is likely as effective as unfractionated heparin.
- Many new therapy options are under investigation, but doing clinical trials in this population will be difficult.