

Review Article

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Beyond Heparin and Aspirin: Evolving Paradigms in Anticoagulant Management of Obstetric Antiphospholipid Syndrome

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ABSTRACT

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.

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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. 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, 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) Work thereafter by Rapaport, Bowie 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. Case reports in the 1970s and early 1980s from Sweden, France, and England and Holland suggested an association between LAC, BFP, and fetal death [1-7].

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. 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) [8].

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 2GP-I), also known as apolipoprotein H; an assay for antibody to β 2GP-I was devised (a β 2GP-I). Today LAC, aCL, and a β 2GP-I are collectively known as antiphospholipid antibodies (aPL) [9,10].

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 2GP-I, which itself binds the phospholipid.

β 2GP-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) 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 2GP-I. APL binding to β 2GP-I-TLR4 initiates both intracellular and extracellular processes that result in tissue damage (see below) [11,12].

Other antibodies commonly associate with aPL, among them antibodies to prothrombin (that, in depleting prothrombin may cause hemorrhage) or to prothrombin-phospholipid complex; 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 [13-15].

APL can be induced, usually transiently, by several infections, such as EBV, Lyme, leprosy, and, of course, syphilis. Some infection-induced aPLs, such as that induced by the syphilis spirochete, bind directly to membrane phospholipid, bypassing the β 2GP-I pathway, and differ from the pathogenic aPL found in patients with SLE. APLs induced by leprosy are likely β 2GP-I-dependent and pathogenic [16,17].

Today the target for pathogenic aPL is thought to be conformationally altered β 2GP-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 2GP-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. APL may also interfere with trophoblast development, maturation, and invasion. Under normal circumstances β 2GP-I is thought to be a molecule that protects endothelial integrity [18-20].

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) and 2006 (Sydney) provide these criteria for APS [21, 22]:

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 β 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 a β 2GP-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. [23]

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 [24].

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. 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 [25-27].

The first papers on fetal loss in patients with aCL or LAC did not address therapy. The next generation of papers focused on the (generally negative) results of treatment with high dose corticosteroid. 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, but not all investigators agreed. Studies in patients with genetic thrombopathies or in patients likely to develop pre-eclampsia mostly failed to show efficacy of either aspirin or heparin. Some papers emphasized a good prognosis in untreated patients with aPL or APS. 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 [28-35].

The studies that most clearly supported the use of heparin are those of Rai and of Kutteh. 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 [36-39].

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. Kutteh's low dose heparin trial (inactivating complement but not preventing thrombosis) would seem to confirm, and Rai used sub anticoagulant 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 again diminishing the prothrombotic theory of recurrent pregnancy loss [40-42].

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.

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, $\alpha\beta 2$ 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 $\alpha\beta 2$ GP-1, of IgG or IgM

isotype, and as opposed to low titers of IgA aCL, or transient high titers of IgG aCL or IgMaCL.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, $\alpha\beta 2$ GP-1 and LAC) positivity, $\alpha\beta 2$ GP-1 alone, LAC alone, or antibody to a peptide found in domain 1 (of 5 domains) of $\beta 2$ GP-1 more precisely predicted thrombotic risk. Other investigators focused on clinical risk profile: occurrence of trauma, surgery, or delivery; smoking; preexisting atherosclerosis; and prior thrombi [43,44].

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, 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%). [45,46]

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.

Future Treatments and Trial Design

The biology of aPL-associated tissue damage suggests alternatives to anticoagulation as treatment for APS. 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. Experimental animal models indicate that peptides that block the binding of antibody to $\beta 2$ 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 [47-51].

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 [52-56].

Conclusion

In summary, primary prevention of thrombosis is generally not recommended in asymptomatic aPL-positive women, although anticoagulation should be considered in high-risk conditions. LDA is recommended before conception and during pregnancy to improve pregnancy outcomes. For selected high risk patients, 6 weeks of LDA is recommended for vaginal delivery, and LDA plus a prophylactic dose of LMWH are recommended for cesarean section during the postpartum period. In patients with obstetric APS, LDA is recommended before pregnancy and LDA plus a prophylactic dose of LMWH during pregnancy and for 6 weeks after delivery. In patients with a history of premature birth due to uteroplacental insufficiency but no history of fetal loss, LDA alone is acceptable. Women of childbearing age with vascular APS should be treated with warfarin with frequent pregnancy tests. These patients should be switched immediately to LDA and a therapeutic dose of LMWH when pregnancy is confirmed. The treatment of APS in women of childbearing age depends on the types of prior obstetric and/or vascular complications. In addition, traditional risk factors for thrombosis should also be considered before deciding medical treatment. Current review has limitations. First, it did not address extra criteria clinical manifestations in the diagnosis of APS. Second, the study suggested a general approach in all races, despite the varying risk of thrombosis among different races. Lastly, the options of direct-acting oral anticoagulants (DOACs) in the selection of anticoagulants were not addressed. However, there are not enough data to judge the safety of DOACs during pregnancy. Although this review outlines treatment guidelines, a tailored approach and patient-oriented treatment are mandatory.

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