Singapore Med J 1998; Vol 39(7):331-334

Antiphospholipids and Pregnancy – A Review

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ABSTRACT

The presence of antiphospholipid antibodies is associated with a clinical syndrome characterised by thrombocytopenia, recurrent arterial and venous thromboses and recurrent fetal loss. The etiology is unknown but leads to an abnormal autoimmune response. Platelet aggregation and thrombosis follow. The mainstay of treatment is low dose aspirin, heparin and corticosteroids.

Keywords: antibodies, antiphospholipid, thrombocytopenia, fetal loss, thrombosis

INTRODUCTION

The antiphospholipid syndrome (APS) is a clinical syndrome characterised by thrombocytopenia, recurrent arterial and venous thrombosis and recurrent fetal loss. More specifically in pregnancy, it is related to a variety of obstetric complications including pre-eclampsia, intrauterine growth retardation and intrauterine death. Indicators of the disease include the presence of moderate to high levels of antiphospholipid antibodies in the serum of these patients[1]. Among these antibodies currently detectable in the laboratory are the lupus anticoagulant and anticardiolipin antibodies.

In 1952, Conley and Hartmann[2] described two SLE patients with plasma prolonged whole blood clotting time but not thrombin clotting time of normal blood samples. The term lupus anticoagulant was later used by Feinstein and Rapaport in 1972[3] to describe acquired circulating agents which inhibited coagulation tests *in vitro*. The lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) have since been shown to be immunoglobulins (IgM, IgG or both) which bind to negatively charged phospholipids and were therefore termed antiphospholipid antibodies (aPL).

Antiphospholipid syndrome may occur as a primary condition, with no other autoimmune diseases associated with it, or as a secondary condition in patients with autoimmune disease, in particular, systemic lupus erythematosus (SLE). Meta-analysis of 21 studies of SLE patients showed that the prevalence of aCL in these patients was 44% while that of LA was 34%[4]. Fifty-nine percent of patients with SLE and LA also had aCL while 45% of patients with SLE and aCL had LA. The presence of antiphospholipid antibodies in patients with SLE carries a higher risk for obstetric complications.

Antiphospholipid antibodies can be found in the normal population, especially in low serum concentrations and the significance of this in the absence of clinical features is uncertain.

The overall prevalence of aPL in an unselected antenatal population was of the order of 2%: aCL was found in 1% while LA was present in 1.2%. 0.2% of patients had both antibodies[5,6].

Laboratory detection of antiphospholipid antibodies

Antiphospholipid antibodies which have been associated with adverse pregnancy outcome include anticardiolipin antibodies and the lupus anticoagulant. These antibodies recognise similar antigenic determinants and bind strongly to negatively charged phospholipids. The lupus anticoagulant can only be recognised indirectly, by its ability to prolong phospholipid dependent clotting tests. The term "lupus anticoagulant" is misleading: while the activated partial thromboplastin time (aPTT) is prolonged *in vitro* by interaction between an antiphospholipid antibody in the patient's serum and the test substrate of cardiolipin, its effect *in vivo* is to cause arterial and venous thromboses. LA also reacts with phospholipids of platelet membranes and this results in incomplete generation of the prothrombin activator complex (factor Xa, factor V, and platelet phospholipid in the presence of calcium ions). β2-glycoprotein I, a circulating anticoagulant, may act as an important cofactor for the binding of LA to phospholipids[7].

A panel of tests are generally used to detect LA and these include aPTT, kaolin clotting time (KCT), direct Russell viper venom time (DRWT) and tissue thromboplastin inhibition time. The aPTT is phospholipid dependent and is irreversibly prolonged by the presence of the LA.

Although the aPTT is the most commonly used screening test, it is non-specific as antibodies to other clotting factors would give similar results. In addition, the aPTT test is relatively insensitive, because the patients must have enough antiphospholipid antibodies to unmask an abnormal biologic phenomenon in a test system.

The KCT is simply an aPTT with phospholipids completely removed from the system, thus making this test especially sensitive to prolongation by LA. The DRWT is based on direct activation of factor

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X by a trace component of the venom. It is more specific for LA than the aPTT since deficiencies of factors VIII and IX and other contact factors will not influence results. However, these tests are not widely available and not easily automated.

As many as 20% of patients with SLE have a false-positive Venereal Disease Research Laboratory (VDRL) test for syphilis[8] and are also positive for the lupus anticoagulant. This is because phospholipid substrates are used to detect syphilis antibodies and to obtain the aPTT. However, not all patients with LA or aCL have a false positive VDRL since the antiphospholipid antibodies are diverse and cardiolipin is just one of the many targets. Other membrane phospholipids which are being evaluated as antigens include phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, phosphatidylglycerol and phosphatidic acid.

Identification of aCL, which reacts with cardiolipin present on microtiter plates, is carried out by enzyme linked immunosorbent assay (ELISA). Results are expressed in standardised aCL IgG (GPL) and aCL IgM (MPL) units: each unit has the binding activity of 1 μg/mL of purified aCL. ELISA is a hundred times more sensitive than the aPTT and has greatly facilitated diagnosis of antiphospholipid syndrome.

The significance of antiphospholipids other than aCL will become clearer as assays for these antibodies improve and become more widely available. It has been suggested that one or more of these antiphospholipids could be responsible for abnormal lupus anticoagulant tests in patients who are aCL-negative.

Etiology

The etiology of APS is not known. It has been suggested that this form of autoimmunity could result from exposure to viruses or bacteria that have an antigenic similarity to host cellular phospholipids. A genetic predisposition may precipitate and perpetuate the abnormal autoimmune response and HLA DR7, DR4, DRw7 and DRw53[9] have been reported to be more common in affected individuals.

Pathophysiology

The exact mechanism of action of antiphospholipid antibodies remains unknown. By binding to the platelet membrane, aPL may cause activation and release of thromboxane, with resultant platelet aggregation and thrombosis. Alternatively, aPL may bind to endothelial cells and inhibit prostacyclin production[10]. Prostacyclin deficiency in placental vessels could result in vasoconstriction and thrombus formation, with consequent gestational proteinuric hypertension, growth retardation and fetal loss. The increased tendency towards thrombosis may also be due to a number of other factors associated with the presence of aCL. These include prekallikrein, protein C and S deficiencies and reduced antithrombin III activity[11].

Clinical features and associations

Antiphospholipid syndrome comprises a clinical triad of recurrent arterial and venous thromboses, thrombocytopenia and fetal loss. Other clinical associations include migraine, chorea, strokes, epilepsy, livedo reticularis[12], transverse myelitis and haemolytic anaemia.

Arterial and venous thromboses

Recurrent arterial and venous thromboses are major features of the APS. Vessels of all sizes may be involved. While arterial thromboses are about half as frequent as those in the venous system, the consequences of the former are generally more profound. Between 26% – 58% of patients with lupus anticoagulant developed recurrent arterial or venous thromboses[13]. While there was a 46% prevalence of thrombotic events in patients with SLE and aCL, this was lower (4.5% – 18%) in those with SLE but without aCL[14]. In patients with rheumatological disorders and aCL, thromboses occurred in about 50%. Higher levels of IgG aCL were associated with a greater risk of thromboses: more than 75% in patients with high levels of IgG anticardiolipin antibodies[15].

Other clinical problems seen in association with the APS include myocardial infarction[16], pulmonary hypertension, renal vein thrombosis, malignant hypertension, cerebral ischaemia, migraine, epilepsy, chorea and other movement disorders, gut ischaemia, hepatic thromboses and the Budd-Chiari syndrome[17].

Thrombocytopenia

While thrombocytopenia is frequently seen in SLE patients with APS, the precise mechanism by which this occurs is unknown. Harris and the Kingston antiphospholipid study group[18] found aCL in 31% of patients with idiopathic thrombocytopenic purpura (ITP).

Recurrent fetal loss

In 1975, Nilsson et al[19] associated the APS with recurrent fetal loss. Recurrent spontaneous abortion, IUGR and fetal loss associated with aPL syndrome probably result from placental vessel thromboses and ischaemia which may start from very early on in pregnancy. The prevalence of APS in women with three or more first trimester miscarriages varied between 14% – 42%[20,21]. LA activity was associated with a 91% rate of adverse pregnancy outcome (ie. spontaneous abortions and stillbirths) in untreated patients. Both LA and aCL have equal predictive values for poor obstetric outcome. Higher levels of IgG aCL have been reported in second and third trimester fetal losses[22]. The three major patterns of fetal loss observed in women with aPL include recurrent first trimester miscarriages, late second trimester miscarriages and third trimester fetal losses, with or without evidence of growth retardation.

In late fetal losses complicated by growth retardation, placentae were generally small with

multiple infarcts and calcifications. In late losses of normally grown fetuses, placentae were generally of normal size. Characteristically however, the spiral arterioles showed evidence of inadequate development, similar to that found in pre-eclamptic pregnancies.

Postnatal syndrome

Severe coagulopathy may manifest in the postpartum period. In addition to the coagulopathy, myocarditis, ascites, vasculitis and pleuritis may be seen in the postpartum period[23].

Catastrophic antiphospholipid syndrome

The catastrophic antiphospholipid syndrome is an acute disseminated vasculopathy characterised by non-inflammatory vascular occlusion and is often fatal. The syndrome is associated with high titres of anticardiolipin antibody, a positive lupus anticoagulant, low-titre antiDNA antibodies and multi-organ failure[24]. Patients often develop malignant hypertension, oliguria and DIVC. Death may be due to intravascular fibrin thrombi involving the kidneys, central nervous system and heart.

Differential diagnoses of this condition include disseminated intravascular coagulation, sepsis, thrombotic thrombocytopenic purpura and vasculitis.

Early therapeutic intervention is necessary to control the accelerated clotting cascade and anticoagulation or plasmapheresis may be essential. High dose steroids and cytotoxics are not usually effective. Decreased tissue plasminogen activator may accelerate the clotting cascade, so fibrinolytic therapy may be helpful.

DIAGNOSIS

Diagnosis of the antiphospholipid syndrome is based on the presence of at least one clinical feature and one serological feature[25].

Clinical features	Serological features
Recurrent venous or arterial thromboses	IgG aCL > 20GPL
Recurrent fetal loss	LA
Thrombocytopenia	IgM ACL > 20MPL, plus LA

Differential diagnosis

Drugs which have been associated with both LA and aCL expression include chlorpromazine, hydralazine, propranolol, procainamide, quinidine, dilantin, valproic acid, amoxycillin and streptomycin.

Infections such as measles, mumps, varicella, parvovirus, adenovirus, Epstein Barr virus, pneumococcal pneumonia, mycoplasma, Lyme disease and malaria, may do likewise.

The lupus anticoagulant has been found in a wide spectrum of clinical conditions including myeloproliferative disorders, carcinoma, lymphoma, drug-induced lupus syndrome and other connective tissue diseases like polyarteritis nodosa, rheumatoid arthritis and pulmonary vasculitis.

Who should be investigated

Every pregnant patient with SLE should be evaluated at least once, preferably in the first trimester, because the presence of aCL and LA confer an unfavourable prognosis. Additionally, aCL and LA should be excluded in severe early onset pre-eclampsia and in any patient whose two most recent pregnancies ended in spontaneous miscarriage of unknown cause. Those with a false positive VDRL or RPR test are especially at high risk of aCL.

It is also appropriate to test patients who give an atypical history, for example, a premenopausal woman with a myocardial infarction. Patients who, for no obvious reason, manifest a seizure disorder or any other neurological insult – stroke, chorea, presenile dementia – should also be tested for aCL and LA.

Management

Although the presence of aPL confers high pregnancy loss rates, successful outcomes have been reported without therapy. The heterogeneous nature of these antibodies and the lack of controlled trials make therapeutic decisions difficult. In general, treatment decisions should be influenced by past obstetric history (for example, two or more proceeding pregnancy losses). Improved pregnancy outcomes have been reported using corticosteroids, aspirin, heparin, warfarin, azathioprine, plasmapheresis, immunoglobulin or combinations of the above.

Thromboses

Retrospective studies demonstrated that thromboses recurred in patients with antiphospholipid antibodies. Warfarin and low molecular weight heparin were effective in preventing recurrent thromboses[26]. Prolonged prophylactic anticoagulation should therefore be instituted in patients with APS who have a previous episode of thrombosis. Since patients may be at risk for several years, steroids and other immunosuppressive agents to suppress antibody production have not generally been advised. However, these should not be withheld if thromboses were to occur despite adequate anticoagulation therapy.

There is no justification for administering prophylactic treatment to patients who have not had a previous history of thrombosis since the thrombotic effect of antiphospholipid antibodies is not invariable.

Recurrent fetal loss

The association between antiphospholipid antibodies and fetal loss led to several uncontrolled trials to evaluate different therapeutic regimes. Many of these treatments which included among them, aspirin, heparin, steroids and high doses of intravenous human IgG, were associated with significant decreases in the rate of fetal loss[27,28].

While some studies with high-dose corticosteroids resulted in a decrease in fetal loss rates, long-term treatment with such drugs during pregnancy have been associated with pre-eclampsia, increased infection rates, gestational diabetes, cushingnoid features and osteoporosis.

Rosove et al demonstrated that the use of prophylactic subcutaneous heparin resulted in a significant decrease in fetal loss. For women with three or more miscarriages and detectable aPL on at least two occasions (two to four months apart), prophylaxis with low dose subcutaneous heparin and/or low dose aspirin for subsequent pregnancies may be offered. A recent randomised controlled trial showed that combined treatment with low dose aspirin and prophylactic doses of subcutaneous heparin resulted in a higher rate of live births than with aspirin alone[29].

A few anecdotal case reports with the use of intravenous IgG have also resulted in improved fetal salvage[30].

CONCLUSION

Antiphospholipid antibodies are heterogeneous and are sometimes associated with adverse pregnancy outcome. The significance of the presence of these antibodies needs to be correlated with the individual clinical presentation.

Maternal and fetal surveillance for known obstetric complications is essential. Treatment should be reserved for those with a prior history of fetal loss or thrombosis. Further research to facilitate understanding of the balance between anti-coagulation and immunosuppression in such patients would improve therapeutic decisions.

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