Review Article

Recurrent pregnancy loss and association with anti phospho lipid syndrome

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SUMMARY

Recurrent miscarriage, the occurrence of three consecutive first-trimester losses of pregnancy, affects 1-3 % of pregnant women. The purported causes of recurrent miscarriage include chromosomal abnormalities, thrombophilia, metabolic disorders, anatomical and immunological disturbances. At present, the only recommended investigations are testing for lupus anticoagulant and anticardiolipin antibody levels to diagnose the antiphospholipid syndrome, an acquired thrombophilia and the karyotyping of both parents for chromosomal abnormalities. The Antiphospholipid Syndrome (APS) is an autoimmune disorder characterized by thrombosis, recurrent loss of pregnancy combined with laboratory tests that indicate the presence of antibodies against phospholipid binding proteins.

Clinically relevant antiphospholipid antibodies are mainly anticardiolipin antibodies detected by enzyme linked immuno sorbent assay (ELISA) and lupus anticoagulants demonstrated by in vitro coagulation assay. Women with antiphospholipid syndrome should be offered treatment with aspirin and low subcutaneous heparin. We aimed to summarize current concepts on diagnosis and treatment in recurrent loss of pregnancies and APS.

KEY WORDS: Anti cardiolipin antibody, Anti phospholipid syndrome, Recurrent pregnancy loss.

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INTRODUCTION

Recurrent Pregnancy Loss is a devastating problem for hopeful parents, and it can be a perplexing, often frustrating, clinical challenge for their physicians. Recurrent Pregnancy Loss (RPL) is estimated to occur in 2%–4% of reproductive-age couples.[1] Various etiologies, either alone or in combination, have been proposed to contribute to pregnancy loss; these include chromosomal translocations, uterine abnormalities, endocrine defects, thrombophilias, autoimmune diseases, and infectious agents.[1-3]

APS is one of the autoimmune causes of RPL. There is a tendency of arterial and venous thrombosis in APS. It is assumed that the clinical picture is associated with lupus anticoagulant (LA) and anticardiolipin antibodies (ACA).

The original classification criteria for antiphospholipid syndrome (APS) were formulated at a workshop in Sapporo, Japan, in 1998, during the Eighth International Congress on antiphospholipid antibodies (aPLs), and subsequently published in 1999[4] (Table-I). The APS criteria were revised in 11th International Antiphospholipid Symposium 2006. According to the revised 2006 criteria, the clinical criteria stayed the same, laboratory criteria were

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changed. The laboratory criterion is substantially modified in the revised classification criteria.

Anticardiolipin (aCL) antibodies and lupus anticoagulant (LA) test are required to be positive on >2 occasions at least 12 weeks apart, as opposed to 6 weeks apart in the original criteria. Whereas in the original version aCL IgG / M must be present in medium or high titre, in the revised criteria ''medium or high titre'' is more specifically defined as IgG / M titres of >40 U or >99th centile. Further, the revised classification criteria include anti ß$_2$ glycoprotein I (a ß$_2$GP I) antibody IgG / M isotype as a valid laboratory requirement if titres are >99th centile, on more than two occasions 12 weeks apart. The consensus statement suggests avoiding classification of APS ''if less than 12 weeks or more than 5 years separate the positive aPL tests and the clinical manifestation''.

In addition to the APS classification criteria revision, the consensus paper provides specific definitions for commonly associated clinical manifestations of APS namely, livedo reticularis, cardiac valve disease, thrombocytopenia and nephropathy. However, in the patients who are diagnosed strictly as APS according to the Sapporo criteria, only 59 % of these patients were diagnosed to be APS when the new criteria were applied.[5]

Pathogenesis

Pregnancy is described as a hypercoagulable state accompanied by an increase in clotting factors (factors VIII, IX and X), a 50% increase in ûbrinogen, a decrease in anticoagulant factors (e.g. antithrombin and protein S) and a decrease in fibrinolytic activity. Recurrent miscarriage may be secondary to an exaggerated haemostatic response during pregnancy.

The pathogenesis of APS is not well-known. The APS classification criteria do not specify the pathogenetic pathways. Thrombophilia is part of APS, certainly. Recent work, however, has elucidated multiple pathogenetic mechanisms of antiphospholipid antibodies. In early pregnancy losses, interference with trophoblast invasion, not thrombosis, is more probable. The benefit of heparin in late fetal loss may not be due to its anticoagulant effects, but to its antiinflammatory effects.[6]

The pathophysiological mechanism that underlies pregnancy loss in antiphospholipid syndrome (APS) is not purely thrombotic. This is supported by observations that placental thrombosis is not a characteristic finding in pregnancies complicated by APS, and that defective trophoblast invasion is a feature. In vitro studies have demonstrated that antiphospholipid antibody / a ß$_2$GP I complexes inhibit trophoblast proliferation and invasion of maternal spiral arteries.[7] They were also shown to reduce the synthesis and secretion of human chorionic gonadotrophin.[8] In a dose-dependent manner, heparin interferes with binding between antiphospholipid and trophoblast cells. This process was shown to restore trophoblast invasiveness and differentiation in vivo.[9]

Assessment of Thrombophilia

Thrombophilia leads to decidual arterial and venous thrombosis and finally placental infarcts occur. Preeclampsia, uteroplacental deficiency and fetal demises can occur as a result of thrombotic events. Placental circulation does not develop in the first trimester. Therefore, first trimester pregnancy losses are not associated with congenital thrombophilia. The relationship between congenital thrombophilia and RPL and the related studies are controversial[10-12] and there is no randomized controlled study. Therefore, routine thrombophilia screening is not recommended in clinical practice.[13-15]

APS is an acquired thrombophilia and one of the RPL causes. The women with a history of complying with Sapporo criteria should be investigated in relation with APS.[4] Thrombus formation occur in intervilleus space and normal functions of the trophoblasts are influenced in APS. These changes lead to disruption of fetoplacental circulation. The other probable factors are increased tissue factor expression, protein C activation, activated protein C inhibition and prostacyclin-thromboxan in balance.[16,17] The antiphospholipid antibodies increase the platelet aggregation and interaction of platelet-endothelium. Annexin V expression is found to be decreased in cases with APS.[18,19]

Treatment

There is no concensus about treatment, because most studies are not randomized and do not include appropriate controls. In addition, the serologic criteria for ACA, the clinical definitions of APS, and the dosing regimens for treatments vary greatly among studies. Treatment of patients with APS who have had previous fetal losses seems to improve pregnancy rates, but fetal loss may occur despite treatment. Overall, most studies report increased pregnancy survival in women undergoing treatment for APS.[20-23] Treatment options include, subcutaneous heparin, low-dose aspirin, prednisone and immunoglobulins. Several well-controlled studies showed that subcutaneous heparin (5000 U) given twice a day with low-dose aspirin 81 mg/d increases fetal survival rates from 50% to 80% among women who have had at least two losses and who have unequivocally positive results for ACA. It was found to be equally

Table-I: Sapporo criteria. At least one clinical and one laboratory criterion must be required for diagnosis.

* They must found to be positive in two or more measurement with at least 6 months intervals.

Clinical Criteria

1. Thrombosis: One or more clinical attack which can lead arterial, venous or capillary thrombosis.
2. The morbidity of pregnancy:

a) One or more unexplained deaths of a morphologically normal neonate, or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus.

b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (1) eclampsia or severe pre-eclampsia defined according to standard definition or (2) recognised features of placental insufficiency.

c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory Criteria

1. Anticardiolipin immunoglobulin M (Ig M) or Ig G positivity with moderate or high titers*.
2. Anticardiolipin antibody (ACA) positivity*.

a) Prolongation of coagulation tests which dependent phospholipid (activated partial thromboplastin time, kaolin clotting time, diluted Russel's viper venom time, diluted prothrombin time, textarin time).

b) Not to improved screening test when the mixture was mixed with poor thrombocyte normal plasma.

c) Normalization of the screening test with phospholipid addition test.

d) Exclusion of the other coagulopathies.

effective and less toxic than prednisone (40 mg/d) plus aspirin.

In 1992, Branch et al reviewed 82 consecutive 54 pregnant women with APS who were treated during the pregnancy with the following: (1) prednisone and low-dose aspirin; (2) heparin and low-dose aspirin; (3) prednisone, heparin, and low-dose aspirin; or (4) other combinations of these medications or immunoglobulins. The overall neonatal survival rate was 73%, but fetal and neonatal treatment failures occurred in all treatment groups. Patients with successfully treated pregnancies had fewer previous fetal deaths than those with unsuccessfully treated pregnancies. In addition, outcomes did not significantly differ among the four treatment groups.[24]

It has been proven that the glucocorticoid treatment is not useful.[25,26] A previous metaanalysis about intravenous immun globulin (IVIG) stated an increase in pregnancy loss and preterm birth.[23] On the other hand, IVIG could lead to anticardiolipin (aCL) and lupus anticoagulant (LA) inhibition and increase aCL antibody clearance.[27]

CONCLUSION

The management of women with recurrent miscarriage continues to be a major challenge. According to the definition of recurrent miscarriage, investigation and treatment (if appropriate) should only start after three consecutive losses. Currently, the only recommended investigations are testing for lupus anticoagulant and anticardiolipin antibody levels. There is no evidence based treatment of RPL. The studies which seem to be as efficient lack important points. Only thromboprophylactic therapy in APS has been shown to be of proven benefit in improving subsequent pregnancy outcome. Women with antiphospholipid syndrome should be offered treatment with aspirin and low molecular weight heparin.

Conflict of Interest: There is no contribution of colleagues or institutions. There is no relationship between authors and industrial foundations. The protocol for the research project was approved by our institution's Ethics Committee.

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