J R Coll Physicians Edinb 2005; 35:337–339

Antiphospholipid syndrome in pregnancy – an update

A Vashisht, L Regan
Department of Obstetrics & Gynaecology, Imperial College at St Mary's Hospital, London, England

ABSTRACT The presence of aPL has been clearly shown to have an adverse effect on pregnancy outcome. These effects may be apparent in the first trimester, presenting as recurrent pregnancy loss, or may be associated with the later development of PET, IUGR, placental abruption, pre-term delivery, and intrauterine death. What appear to be most important in the aetiology, initially, are factors that disturb the vital interaction between the embryonic trophoblastic tissue and the host (maternal) endometrial tissue. It seems that the presence of aPL may impair trophoblastic invasion, thus interfering with implantation and subsequent placental development. As the pregnancy advances, women are more prone to thrombosis in the uteroplacental vasculature. Indeed, women with PAPS suffer from a live birth rate as low as 10% in the absence of pharmacological intervention.

Dramatic improvements in pregnancy outcome can be achieved by a combination of aspirin and heparin. However, although the live birth rate is increased sevenfold, it should be acknowledged that these births are associated with an increased rate of prematurity and possible neonatal complications. The increased incidence of pregnancy-related complications necessitates the need for careful antenatal surveillance, and for delivery to be conducted in a unit with facilities for operative delivery and neonatal intensive care. For the women themselves, the significance of aPL outside pregnancy is far from clear, and the ideal management for optimising long-term health is yet to be determined.

LIST OF ABBREVIATIONS Activated partial thromboplastin time (APTT), anticardiolipin antibodfies (aCL), antiphospholipid antibodies (aPL), antiphospholipid syndrome (APS), ß2-glycoprotein I (ß2GPI), bone mineral density (BMD), dilute Russell's viper venom time (dRVVT), enzyme-linked immunosorbent assay (ELISA), immunoglobulin G (IgG), immunoglobulin M (IgM), intrauterine growth restriction (IUGR), lupus anticoagulant (LA), pre-eclampsia (PET), pre-term birth (PTB), primary antiphospholipid syndrome (PAPS), prolonged pre-term rupture of membranes (PPROM), systemic lupus erythematosus (SLE)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***May 2005***

Correspondence to ***L Regan, Department of Obstetrics and Gynaecology, St Mary's Campus, Imperial College London***

tel. ***+44(0)20 7886 1731***

e-mail ***l.regan@imperial.ac.uk***

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INTRODUCTION

Since its original description over 15 years ago, the effects of APS on pregnancy have been increasingly recognised. The condition is known to play a major role in the aetiology of recurrent miscarriage, PET, IUGR, placental abruption, and PTB.

The PAPS refers to the association between aPL with recurrent miscarriage, late pregnancy loss, and/or thrombosis and thrombocytopenia. Although more than 20 antibodies directed against phospholipid-binding proteins have been described, in terms of pregnancy morbidity only the aCL and LA antibodies are thought to be clinically relevant. The binding of both LA and aCL to phospholipid is co-factor dependent. The co-factor for LA is prothrombin and that for aCL is a naturally occurring anticoagulant, ß2GPI. Women with PAPS do not have any of the clinical or serological features of SLE, and it is only aPL-positive SLE sufferers who experience fetal loss.

INVESTIGATION AND TESTING FOR ANTIBODIES

Testing for aPL is fraught with difficulties if standardised laboratory criteria are not employed for their detection and because of the fluctuating levels of these antibodies in individuals at different times. To make a positive diagnosis of APS, aPL antibodies must be detected on two separate occasions at least six weeks apart to preclude any transient false-positive or false-negative results secondary to intercurrent infection, laboratory error, or sample preparation. It is important that samples are collected with minimal venous stasis to avoid platelet activation, that they are double-centrifuged within two hours of collection, and that the assays used conform to internationally agreed guidelines

(see BCSH Haemostasis and Thrombosis Taskforce). Lupus anticoagulant is detected on its ability to prolong *in vitro* phospholipid-dependent coagulation tests. The dRVVT with a platelet neutralising procedure appears to be the test of choice for the identification of LA, having been shown to be significantly more sensitive than either the APTT or the kaolin clotting time. A standardised ELISA is used to assay aCL (IgG and IgM). The presence of later pregnancy complications is higher in women carrying LA or high titre IgG aCL. It has been suggested that low titre levels of IgM do not need any therapy, although it is our experience that these antibodies may be associated with repeated pregnancy loss and therefore do require treatment.

OCCURRENCE OF APL

As well as being found in 15% of women with recurrent first trimester miscarriage and 21% of women with mid-trimester miscarriage, the presence of aPL is also associated with subsequent PET, IUGR, and placental abruption, suggesting some form of disturbance in trophoblastic function. In comparison, less than 2% of the normal, low risk obstetric population will have these antibodies. A family history of thrombosis, cardiovascular disease, epilepsy, or migraine may be suggestive of the presence of aPL in a woman presenting with any of the above obstetric conditions. Those women with a personal history of systemic thromboses are most likely to have a positive aPL status.

TREATMENT OF PAPS IN PREGNANCY

Various treatments have been proposed including aspirin, heparin, steroids, and immunoglobulins. The latter two have been widely disregarded, with steroids in particular being shown to be associated with adverse maternal and fetal morbidity, including pre-term delivery and maternal gestational diabetes. The current treatment for women who are known to have PAPS is to take low dose aspirin as soon as they become pregnant, and to add in daily subcutaneous injections of heparin once an intrauterine pregnancy is confirmed on ultrasound scan.

The single most clear cut recent advance in the investigation and treatment of couples with recurrent miscarriage has been the identification of the role of aPL. In women with PAPS who are untreated, the miscarriage rate has been reported to be as high as 90%. This contrasts with a live birth rate of 66% among a control group of aPL-negative women with a history of recurrent miscarriage. A prospective randomised study has shown the beneficial effects of giving a combination of low dose aspirin (75 mg) and heparin (5,000 U subcutaneously 12-hourly) up to 34 weeks' gestation to improve pregnancy outcome in women with recurrent pregnancy loss and APS. In this group of women, the live birth rate was found to be 71%, compared with 42% in the group taking low dose aspirin alone. Interestingly, there was no significant difference in live birth rate between the two treatment groups once the pregnancy had advanced beyond 13 weeks, indicating that heparin is most likely to be beneficial during the first trimester. This is the time when initial trophoblastic invasion of maternal decidua and spiral arterioles occurs. Indeed, proposed mechanisms accounting for the high rate of obstetric complications associated with aPL have centred around both thrombosis in the uteroplacental vasculature and, latterly, impairment of embryonic implantation. Interference with trophoblastic invasion into the maternal decidua, and hence defective placental function, seems likely if one looks at the clinical sequelae of PAPS. Defective trophoblastic invasion into the maternal spiral arteries is well noted to be associated with early pregnancy failure, PET, IUGR, placental abruption, pre-term rupture of membranes, and pre-term delivery.

The therapeutic benefit of heparin is thought to arise from its ability to bind aPL. By doing so, the pathological interaction between aPL and the trophoblast and maternal decidual vessels is inhibited, and placentation is more likely to be successful. Later in pregnancy the anticoagulant properties of heparin are likely to be beneficial in reducing the risk of placental thrombosis and infarction. Aspirin, by inhibiting platelet aggregation, also has a favourable thromboprophylactic effect. Unfractionated and low molecular weight heparins have been shown to be equally beneficial in the treatment of women with PAPS, the latter having the advantage of being a once daily injection. Women may also be reassured that the modest loss in BMD observed with heparin therapy is not significantly different from the natural physiological loss in BMD seen in normal pregnancy.

COMPLICATIONS

It is important to remember that although aspirin and heparin may allow the progression of a pregnancy, the pregnancy remains at risk of potential complications. Once the pregnancy advances beyond the first trimester vigilance should be paid to potential symptoms or signs of IUGR and PET. In a prospective study of 1,600 women with no previous history of pregnancy loss, those with a positive test for ß2GPI-dependent aCL at 10 weeks' gestation had a significantly increased risk of adverse pregnancy outcome compared with those who were aCL-negative. The former group had a 52-fold increased relative risk for intrauterine death, 18-fold increased relative risk for IUGR, and 22-fold increased risk for developing PET compared with those women who were aCL-negative.

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MONITORING

The optimal way of monitoring pregnant women with PAPS, or indeed of predicting poor outcome or complications, is uncertain. One prospective study looking at 170 women with recurrent miscarriage and aPL found that uterine artery notching, as measured by Doppler assessment at 22–24 weeks, predicted PET and small for gestational age babies in pregnancies associated with LA but not in those associated with aCL. Although promising as a potential screening tool, the numbers of women in the study were too small to make firm recommendations.

OUTCOMES

Aspirin and heparin treatment appears to reduce the severity of the defective endovascular trophoblastic invasion, but this may be superseded by later problems related to the underlying uteroplacental vasculopathy. Even in treated women with PAPS the prevalence of placental infarction is noted to be around 8%, compared with 1% in the unselected obstetric population. The improved live birth rate by itself is not the only yardstick by which to judge obstetric outcome; the incidence of PTB, with its associated adverse sequelae, is known to be increased. In a study of 150 women with aPL-related recurrent miscarriage treated with aspirin and heparin, 24% of deliveries occurred pre-term, prior to 37 completed weeks. This is approximately four times the incidence occurring in the normal obstetric population. The causes of PTB were spontaneous pre-term labour (24%), PPROM (20%), severe PET or IUGR necessitating elective early delivery (32%), and emergency delivery for placental abruption or fetal distress (24%). In this particular cohort of women, over two-thirds of the pre-term deliveries occurred after 34 weeks' gestation, accounting for the excellent infant survival seen. Prolonging treatment beyond 34 weeks does not significantly alter the late obstetric complications of PAPS.

ANTIPHOSPHOLIPID SYNDROME AND THE NON-PREGNANT WOMAN

Outside of pregnancy it is widely agreed that women with persistent aPL titres are at increased risk of thrombotic complications. There is known to be increased thrombin generation in these women, although whether continuous thromboprophylaxis should be advised is controversial. The results of long-term follow-up studies of women first identified with aPL as a result of pregnancy complications is urgently required in order to optimise their future health.

KEYPOINTS

- Antiphospholipid syndrome is an important treatable cause of recurrent miscarriage.
- Combination therapy with low dose aspirin and heparin is currently the gold standard for treatment.
- Clinicians need to be aware that, despite treatment, these women remain at risk of late pregnancy complications including pre-eclampsia, pre-term labour, placental abruption, and fetal growth restriction.
- Strict laboratory methodology is required to minimise false-positive and false-negative test results for antiphospholipid antibodies.
- The long-term sequelae of antiphospholipid syndrome in women whose first presenting symptom is adverse pregnancy outcome are unclear. This is an area that requires further multidisciplinary research.

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