How to treat women with antiphospholipid antibodies in pregnancy?

The persistent presence in plasma of medium to high levels of IgG and/or IgM class anticardiolipin antibodies (aCL) and/or the lupus anticoagulant (LAC) is associated with both “recurrent pregnancy loss” and venous and arterial thrombosis. This clinicossenological entity, first described in the early eighties in patients with systemic lupus erythematosus was termed the antiphospholipid syndrome (APS). The recognition that APS also occurs in otherwise healthy people led to the term primary antiphospholipid syndrome. The classic laboratory markers of APS, aCL, and LAC belong to the family of so-called antiphospholipid antibodies (aPL). Clinical studies indicate that aPL are related to both early pregnancy losses and fetal demise in advanced pregnancy and that placental thrombosis and infarction are common findings in aPL related intrauterine fetal deaths. Studies in animal models for APS support a causative role for aPL in pregnancy loss. Prospective clinical studies have confirmed that aPL are risk factors for pregnancy loss, both in patients with systemic lupus erythematosus (60% versus 13% pregnancy loss) and in healthy nulliparous women (16% versus 7% pregnancy loss). In women with a history of three or more consecutive pregnancy losses persistently positive tests for aPL are found in up to 15%, and in these, subsequent fetal loss rates up to 60–90% are noted without specific treatment. Apart from being risk factors for fetal demise, aPL associate with high frequencies of pre-eclampsia, intraterine growth restriction, fetal distress, and premature delivery.

Laboratory tests

aCL are detected with enzyme linked immunosorbent assays (ELISAs), in which the negatively charged phospholipid cardiolipin is coated on plastic plates, whereas LAC refers to antibodies which prolong the clotting time of phospholipid-dependent coagulation tests by competing with coagulation factors for binding to the catalytic phospholipid template. aCL and antibodies causing LAC do not react with phospholipids themselves but with phospholipid-binding plasma proteins (cofactors). Established cofactors are β2-glycoprotein I for the aCL ELISA, and both β2-glycoprotein I and prothrombin for antibodies causing LAC. This explains earlier notions that aCL and LAC refer to related, but not necessarily similar, antibodies. To classify a patient as having APS both aCL and LAC assays have to be performed. It is important to note that different laboratories often use different criteria to score a sample positive for aCL or LAC. Specialised laboratories can reach reasonable agreement upon classification of selected samples into normal, low, medium, and high positive for aCL levels, but the situation is worse in daily practice where different cut off points for positivity are used and serious interlaboratory differences are noted frequently. It is hoped that at least part of the methodological problems with the aCL ELISA will be solved, when stable standards for aCL measurement, such as the recently described constructs of chimeric antibodies, find universal application. For the detection of LAC internationally accepted guidelines are available which deal with collection and processing of platelet poor test plasma, and with screening and confirmatory steps in coagulation tests, but many laboratories fail to adhere to these. The current situation is that different laboratories often use a different test for first line screening for LAC and that these assays vary widely in sensitivity for the effects of antibodies. Obviously, a non-uniform classification of patients as positive or negative for aPL hinders comparison of results from different clinical studies, and contributes to discrepant findings on the association between aPL and pregnancy outcome and to the wide variation in reported frequencies of aPL in different populations.

Pregnancy loss nomenclature

Next to these methodological technical problems, the interpretation of the literature on aPL and pregnancy loss is also hindered by different definitions for pregnancy loss, and differences in comorbidity and obstetric histories in the populations studied. The latter is important as previous pregnancy loss is an independent risk factor for subsequent loss. Traditionally, in the US, pregnancy losses before 20 weeks’ gestation are grouped together as “abortions” and death in utero thereafter as “stillbirth” or “fetal death”, whereas European obstetricians used trimesters, where fetal demise before 16 weeks’ gestation is termed “abortion” and losses thereafter “fetal deaths”. Recurrent pregnancy loss is defined heterogeneously in published reports on APS, partially owing to this different terminology. In future studies this should be overcome by making use of recently introduced new obstetrical nomenclature which gives credit to current knowledge on reproductive biology by distinguishing losses in the (pre-)embryonic period from fetal death. The (pre-)embryonic period lasts from conception to three weeks of gestation (similar to about five weeks from the first day of the last menstrual period), and is followed by the embryonic period, which goes to the end of the ninth week of gestation. Up to 12% of normal pregnancies end with a loss before 10 weeks’ gestation (so-called (pre-)embryonic losses), and their most common cause is fetal chromosomal abnormality. In the new nomenclature the period from 10
weeks to delivery is termed the fetal period and loss in that period fetal death. It is certain that a conceptus has entered this stage when a fetal length of at least 30 mm is documented (macroscopically or with ultrasound), or when fetal cardiac activity is found at or beyond 10 weeks’ gestation. In healthy women the occurrence of fetal death (loss after ≥10 weeks’ gestation) is rare and usually unrelated to chromosomal abnormalities. Even women with recurrent (pre-)embryonic losses have over 80% chance for a live birth when fetal cardiac activity is shown at or beyond 8–10 weeks’ gestation.

**Thrombosis**

Several case reports and small case series suggest that treatment of women with APS during pregnancy with high dose intravenous immunoglobulin reduces the rates of aPL related pregnancy complications. However, a recently published unique randomised, double blind study found no improved obstetric or neonatal outcomes beyond those achieved with a heparin and low dose aspirin regimen. This strongly argues against a place for this expensive treatment in the treatment of aPL related pregnancies. Both pregnancy and the postpartum period are thrombogenic periods. In the general population venous thromboembolic events occur during pregnancy and the puerperium at a rate of one and two per 1000 deliveries, respectively. Ischaemic stroke, the most common thrombotic manifestation at the arterial site in pregnancy, occurs in 4–5 per 100 000 deliveries and is not infrequently related to (pre-)eclampsia. Conceivably, the presence of aPL in a pregnant woman further increases the risk for venous and arterial thrombosis, as aPL are a risk factor for both thrombosis and (pre-)eclampsia. However, the extent to which aPL increase those risks has not been evaluated in controlled studies.

Many patients with aPL related thrombosis are treated outside pregnancy with oral anticoagulants for prolonged periods to prevent recurrences. In patients who need anticoagulation during pregnancy, it is common practice to change from oral anticoagulants to heparin before conception or at the latest within two weeks of the missed period, because oral anticoagulants cross the placenta, are teratogenic when given between 6 and 12 weeks’ gestation, and may cause intracranial bleeding in the fetus. There are no published prospective data on pregnancy outcome in aPL positive women with a thrombotic history, and the question whether a thrombotic history further increases the risk for adverse pregnancy outcome in aPL positive women cannot be answered.

**Recommendations**

With the imperfect data that are currently available it is impossible to give evidence based recommendations on how patients with aPL should be treated in pregnancy. It is wise to regard aPL pregnancies as being at high risk for complications and to offer careful follow up by a team of doctors from different specialties. Medical treatment should be individualised, taking into account the obstetric history, presence or absence of a personal or family history of thromboembolic events, comorbidity, current drugs, and thrombotic risk factors other than aPL. In cases of recurrences were (pre-)embryonic losses one should always exclude genetic, anatomical, and other causes. With a personal history of thromboembolic events one should consider their number, nature, and severity, as well as the circumstances in which such events occurred.

**Guidelines for treatment**

As a guideline for the treatment of pregnant patients with aPL we propose the following:

1. **Treatment**
   - Treatment of pregnant, aPL positive women to improve pregnancy outcome is completely empirical. In 1983 Lubbe et al showed that five out of six women with LAC and poor obstetric histories gave birth to live infants when they were treated during pregnancy with prednisone (40–60 mg daily) and low dose aspirin (75 mg daily).
   - From that time on such treatment has been applied in many variants worldwide, with live births reported in 30 to 100% of pregnancies thus treated. The rationale for the use of prednisone was suppression of aPL levels, whereas aspirin may be beneficial by irreversibly blocking the action of cyclo-oxygenase in platelets, thereby inhibiting platelet thromboxane A2 synthesis and preventing thrombosis of the placental vasculature. However, corticosteroids used for prolonged periods in pregnancy have significant side effects, like diabetes, hypertension, osteoporosis, (pre-) eclampsia, and preterm delivery secondary to premature ruptured membranes, as shown by Cowchock et al. The latter study was a randomised trial comparing prednisone (40 mg) with unfractionated heparin (both combined with low dose aspirin). Both treatments resulted in 75% live births, but in the group treated with heparin there were significantly fewer complications. Since 1992 heparin, combined with low dose aspirin, has replaced prednisone for treatment of pregnant aPL positive women in many centres. A recent prospective study, in which aPL positive pregnant women with at least three spontaneous consecutive miscarriages were alternately assigned to low dose aspirin alone or aspirin plus subcutaneous heparin twice daily, found 44% live births for women treated with aspirin alone and 80% for those treated with the combination. A randomised, but otherwise comparable, trial also found aspirin alone inferior to aspirin plus heparin (42% versus 71% live births). Illustrative of the heterogeneous definition of aPL in the literature is that the study of Kutteh excluded women with LAC, whereas in the study of Rai et al 80% of the patients had LAC in the absence of aCL. Doubt as to whether heparin is always needed comes from an uncontrolled prospective study with 91% live births with low dose aspirin alone in aPL positive pregnant women with a minimum of two spontaneous abortions and a history of only 6% live births. Probably, differences in the inclusion and exclusion criteria used in different studies are the major cause of such discordant findings.

   Although the safety of low dose aspirin during the first trimester of pregnancy still is a subject of debate, treatment with aspirin is started in aPL positive pregnancies before conception, or when a pregnancy test is positive. Treatment with heparin is started when there is a positive pregnancy test, or fetal heart activity. All prospective studies on the efficacy of heparin in aPL related pregnancies used unfractionated heparin. However, over the past few years a lot of experience has been gained with the use of low molecular weight heparin given during pregnancy for prevention and treatment of venous thrombosis, or for improvement of pregnancy outcome in aPL positive women. Compared with unfractionated heparin, low molecular weight heparin is more comfortable for the patient as it usually needs only one subcutaneous injection a day. Furthermore, it is associated with less bone loss and smaller risks for bleeding and heparin induced thrombocytopenia. However, the experience with the use of high doses of low molecular weight heparin in pregnancy is still limited.

2. **Guidelines**

   - Thrombosis
   - Several case reports and small case series suggest that treatment of women with APS during pregnancy with high dose intravenous immunoglobulin reduces the rates of aPL related pregnancy complications. However, a recently published unique randomised, double blind study found no improved obstetric or neonatal outcomes beyond those achieved with a heparin and low dose aspirin regimen. This strongly argues against a place for this expensive treatment in the treatment of aPL related pregnancies.
   - Both pregnancy and the postpartum period are thrombogenic periods. In the general population venous thromboembolic events occur during pregnancy and the puerperium at a rate of one and two per 1000 deliveries, respectively. Ischaemic stroke, the most common thrombotic manifestation at the arterial site in pregnancy, occurs in 4–5 per 100 000 deliveries and is not infrequently related to (pre-)eclampsia. Conceivably, the presence of aPL in a pregnant woman further increases the risk for venous and arterial thrombosis, as aPL are a risk factor for both thrombosis and (pre-)eclampsia. However, the extent to which aPL increase those risks has not been evaluated in controlled studies.
   - Many patients with aPL related thrombosis are treated outside pregnancy with oral anticoagulants for prolonged periods to prevent recurrences. In patients who need anticoagulation during pregnancy, it is common practice to change from oral anticoagulants to heparin before conception or at the latest within two weeks of the missed period, because oral anticoagulants cross the placenta, are teratogenic when given between 6 and 12 weeks’ gestation, and may cause intracranial bleeding in the fetus. There are no published prospective data on pregnancy outcome in aPL positive women with a thrombotic history, and the question whether a thrombotic history further increases the risk for adverse pregnancy outcome in aPL positive women cannot be answered.

   - **Recommendations**
   - With the imperfect data that are currently available it is impossible to give evidence based recommendations on how patients with aPL should be treated in pregnancy. It is wise to regard aPL pregnancies as being at high risk for complications and to offer careful follow up by a team of doctors from different specialties. Medical treatment should be individualised, taking into account the obstetric history, presence or absence of a personal or family history of thromboembolic events, comorbidity, current drugs, and thrombotic risk factors other than aPL. In cases of recurrences were (pre-)embryonic losses one should always exclude genetic, anatomical, and other causes. With a personal history of thromboembolic events one should consider their number, nature, and severity, as well as the circumstances in which such events occurred.

   - **Guidelines for treatment**
   - As a guideline for the treatment of pregnant patients with aPL we propose the following:
1 aPL positive patients without a thrombotic history

- Always give prophylactic treatment with low molecular weight heparin for six weeks in the postpartum period to prevent venous thromboembolic events.
- With a history of no more than two unexplained (pre-)embryonic losses there is no need for medical treatment during pregnancy.
- With a history of three or more consecutive (pre-)embryonic losses or at least one fetal death (with normal morphology) start aspirin and a prophylactic dose of low molecular weight heparin when pregnancy is confirmed. The rationale for the use of heparin is that this drug, apart from its anticoagulant action, seems to promote successful implantation in early pregnancy. The explanation for this observation may be that heparin binds aPL, and thus prevents aPL reducing the physiological coverage of trophoblast cells with the potent anticoagulant protein annexin V. This may be confirmed by laboratory data.
- When heparin is used for prolonged periods, especially in the postpartum period, in patients with aPL, control platelet counts regularly.
- Do not give low molecular weight heparin for at least 12 hours before and four hours after spinal or epidural analgesia.

2 aPL positive patients with a thrombotic history

- Always give prophylactic treatment with low molecular weight heparin for six weeks in the postpartum period to prevent venous thromboembolic events. When there is an indication for long term oral anticoagulation before the current pregnancy this treatment should be resumed.
- With a history of venous thromboembolic events: give prophylactic anticoagulation during pregnancy. This means a standard prophylactic dose of low molecular weight heparin for most patients. Details of the personal thrombotic history and presence of additional risk factors for venous thromboembolic events can result in the use of higher doses of low molecular weight heparin. The obstetric history will determine the use of aspirin.
- With a history of arterial thrombosis it is impossible to give a general advice. The kind of prophylactic treatment used outside pregnancy (aspirin or anticoagulation set at a certain intensity) and the obstetric history will determine whether aspirin or low molecular weight heparin, or both, or anticoagulation at high intensity seems most appropriate. In the latter situation for some patients a switch from high dose heparin to oral anticoagulants between 16 and 36 weeks of gestation may be an attractive and safe alternative to treatment with heparin throughout pregnancy.

R H W M DERKSEN
Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, The Netherlands

Haemostasis and Thrombosis Laboratory, University Medical Centre Utrecht, The Netherlands

Department of Haematology, University Medical Centre Utrecht, The Netherlands

Department of Obstetrics and Gynaecology, University Medical Centre Utrecht, The Netherlands

Ph G DE GROOT
H K NIEUWENHUIS
G C M L CHRISTAENES

Correspondence to: Dr R H W M Derksen, Department of Rheumatology and Clinical Immunology, University Medical Centre, PO Box 85800, 3508 GA Utrecht, The Netherlands

r.h.w.m.derksen@digd.azu.nl