Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant

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Limited evidence suggests that combined unfractionated heparin and aspirin may reduce pregnancy loss. Many aspects of antiphospholipid antibody syndrome remain poorly understood. To develop guidance on the best treatment options, well-designed randomized trials evaluating unfractionated and low-molecular-weight heparin and aspirin are urgently needed.

RHL Commentary by Mathai E

1. EVIDENCE SUMMARY

This Cochrane review includes randomized or quasi-randomized controlled trials on pregnant women with at least one fetal loss, evidence of Antiphospholipid (APL) antibodies and receiving any type of therapy; women with false-positive VDRL tests were also included in the trials. A total of 13 trials involving 849 participants satisfied the review’s broad inclusion criteria.

The only significant benefit of therapy observed was that the combination of unfractionated heparin and aspirin reduced pregnancy loss by 54% (Relative Risk [RR] 0.46, 95% Confidence Interval [CI]: 0.29 to 0.71) compared with aspirin alone. When low-molecular-weight (LMW) heparin and unfractionated heparin studies were pooled, there was a 35% reduction in pregnancy loss or preterm delivery (RR 0.65, 95% CI: 0.49 to 0.86). The different dosages of heparin used in the studies reviewed did not alter the outcomes. Therefore, the optimal dose of heparin—one that would yield maximum benefit with minimum harm—is still unknown. None of the other interventions tested had any significant beneficial effects on pregnancy outcome compared with placebo although, a small benefit from aspirin cannot be excluded. In contrast, intravenous immunoglobulin (IVIG) and prednisone did not show benefits, but had adverse effects. Adverse outcomes like pregnancy loss and preterm delivery were more in women treated with prednisone. This group of mothers also had significantly more gestational diabetes, and infants born to them were of low birth weight and were more frequently admitted to intensive care units. Pre-eclampsia and hypertension also appeared to be more common in these women. IVIG was also associated with increased risk of pregnancy loss or preterm delivery. Therefore, these two agents may have no role in the treatment of recurrent pregnancy loss associated with APL. However, when other indications are present, for example, active systemic lupus erythematosus, the potential benefits should be weighed against the potential harms. The review did not include any trials of plasmapheresis. The trials lacked sufficient data to draw any conclusions regarding hypertension, pre-eclampsia or the long term effects (like osteoporosis) of the therapies studied.

In addition, the numbers studied were small, limiting the precision of all estimates. The quality of trials was
also variable. Some studies did not conceal allocation and in certain others it was not clear whether the analyses were performed by ‘intent to treat’ and the number of women with a history of miscarriages presenting themselves at the health care facility during the recruitment phase was not available. Although the review shows benefit only with the combination of unfractionated heparin and aspirin, in treating women with APL and recurrent pregnancy loss, this is unlikely to be the final word since the evidence base at the present time is small.

2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

The risk of recurrent fetal loss is significantly higher in pregnant women with APL antibodies or lupus anticoagulant (LA) (1, 2, 3, 4). Anticardiolipin (ACL) antibodies—the most frequently measured APL antibodies—are present in less than 10% of normal pregnant women (2, 3, 5). Women with ACL antibodies have 3–9 times greater risk of fetal loss (2, 3, 6) than those who do not have them. APL antibodies facilitate arterial and venous thrombosis.

However, the magnitude of the problem caused by APL is largely unknown, especially in developing countries. One reason for this is that the diagnosis of APL is problematic. Laboratory tests for APL are expensive and not easily available. Also, there is a lack of uniformity in the criteria used by different centres for diagnosing the APL syndrome. Since diagnostic criteria include fetal loss, the syndrome can be diagnosed only after fetal loss has occurred. Moreover, since some form of therapy is initiated in most women with APL and pregnancy loss, it is nearly impossible to assess the effects of these antibodies on pregnancy outcome (if APL were left untreated). One study from India reported a 40% prevalence of ACL among women with recurrent pregnancy loss (7). In an ongoing study at our centre, 7% of normal pregnant women had ACL compared with 15% with recurrent pregnancy loss.

2.2. Applicability of the results

The different diagnostic criteria used in the included studies to determine the study population makes it difficult to generalize the findings. The applicability of the conclusions drawn may need to be reassessed in situations where criteria for diagnosis of antiphospholipid antibody syndrome—at least three consecutive early (< 10 weeks) fetal loss or at least one late fetal loss and higher ACL cut off values—are strictly applied. Pregnant women with low positive ACL or LA may be at lower risk of adverse outcomes. Such differences in the populations can affect the interpretation of the effectiveness of a therapy. Benefits of any form of therapy in low risk pregnancies remain to be proved.

2.3. Implementation of the intervention

Given the prevailing conditions in most developing countries, only a small proportion of pregnant women with recurrent pregnancy loss will benefit from the evidence presented. One reason for this is that laboratory testing for ACL or LA is a prerequisite for initiating treatment, and this requires at least two visits to the antenatal care services early in pregnancy. This requirement may limit the number of women who can benefit from this intervention as many women in resource-poor settings do not receive any antenatal care at all or receive it only later in pregnancy.

Heparin preparations are expensive and may not be safe enough to be dispensed through primary care centres in resource-poor settings: misuse of treatment regimens by practitioners not fully aware of the indications for treatment and the risk of side-effects constitutes an important risk.

3. RESEARCH
Many issues about APS remain poorly understood. This includes basic concepts in pathogenesis, diagnostic criteria and optimum modalities of therapy for maximum benefits. To develop guidance on the best treatment options, well-designed randomized trials evaluating unfractionated and LMW heparin and aspirin are urgently required.

References