Recurrent pregnancy loss with antiphospholipid antibody: a systematic review of therapeutic trials
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Authors' objectives
To assess the effects of interventions to improve pregnancy outcome in women with antiphospholipid (APL) antibodies.

Searching
The Cochrane Controlled Trials Register (2000), the Cochrane Pregnancy and Childbirth Group's Specialised Register (1999), MEDLINE (from 1966 to 1999) and EMBASE (from 1988 to 1999) were searched without language restrictions. In addition, bibliographies, Lupus (vol. 1 to 8, 1991 to 1999) and conference proceedings from the International Symposium on APL Antibodies were searched and experts were contacted for further studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible for inclusion.

Specific interventions included in the review
Studies of any intervention to prevent pregnancy loss were eligible for inclusion. The included studies compared aspirin with placebo or usual care; heparin or calcium heparin plus aspirin versus aspirin; high-dose heparin plus aspirin versus low-dose heparin plus aspirin; prednisone plus aspirin versus aspirin or placebo; intravenous immunoglobulin plus aspirin and heparin versus placebo plus aspirin and heparin.

Participants included in the review
Studies in pregnant women with at least one previous pregnancy loss and serologic evidence of APL antibodies were eligible for inclusion. Two trials in which some participants had not experienced a pregnancy loss were included in the review (less than 2% of all women included in the review). In the included studies, the mean pregnancy loss per woman was 0.6 to 4 and the proportion with a previous successful pregnancy ranged from 26 to 42%. Anticardiolipin levels and the proportion of women with lupus anticoagulant varied between the trials.

Outcomes assessed in the review
The primary outcome was pregnancy loss. The secondary outcomes included pre-term delivery (before 37 weeks), Caesarean delivery, small for gestational age (birth weight below the 10th percentile), admission to neonatal intensive care, birth weight, neonatal bleeding or bruising, plus six maternal outcomes including death, and intervention-related side-effects.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion and resolved any disagreements by discussion.

Assessment of study quality
Study quality was assessed on the basis of the method of randomisation, allocation concealment, blinding, loss to follow-up and use of intention-to-treat analysis. Two reviewers independently assessed study quality and resolved any disagreements by discussion.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements by discussion. Investigators were contacted for missing information. Data were extracted to calculate the risk for dichotomous outcomes and the weighted mean difference (WMD) for birth weight.
Methods of synthesis
How were the studies combined?
A random-effects meta-analysis, weighted by the inverse variance, was used to combine studies grouped by treatment. The relative risk (RR) or absolute risk reduction was used according to which one showed the least statistical heterogeneity.

How were differences between studies investigated?
Statistical heterogeneity was assessed by examination of the fixed-effect and random-effects meta-analyses and the Q statistic.

Results of the review
Ten studies were included: 6 RCTs (n=442), 3 quasi-randomised trials (n=166) and 1 that did not describe the method of randomisation (n=19).

No statistically significant reduction in pregnancy loss was shown between aspirin and placebo or standard care (RR 1.05, 95% CI: 0.66, 1.68), based on 135 women in 3 trials (one of which was an RCT, n=50). Heparin plus aspirin compared with aspirin alone did significantly reduce pregnancy loss (RR 0.46, 95% CI: 0.29, 0.71) among 140 women in 2 trials (one an RCT, n=90). However, no difference was shown between prednisone plus aspirin and placebo or aspirin (RR 0.85, 95% CI: 0.53, 1.36; 2 RCTs, n=122), or between prednisone plus aspirin and heparin plus aspirin (RR 1.17, 95% CI: 0.47, 2.93; 1 RCT, n=45). There were no pregnancy losses in the trial of immunoglobulin (n=16).

On pooling 3 RCTs, a statistically significant increase in premature birth was associated with prednisone plus aspirin compared with placebo, aspirin, or heparin plus aspirin (RR 4.83, 95% CI: 2.85, 8.21). The small immunoglobulin trial (n=16) also showed a statistically significant increase in premature birth when that intervention was added to heparin plus aspirin. One RCT (n=202) showed a significant increase in admission to neonatal intensive care with prednisone plus aspirin versus placebo (RR 9.00, 95% CI: 2.14, 37.78). Another RCT (n=34) showed a reduction in mean birth weight when prednisone was added to aspirin (WMD 552.0 g, 95% CI: -1,064.8, -39.2). None of the trials showed a significant difference in Caesarean rates or foetal growth restriction. There were no maternal deaths.

Three women out of 120 treated with prednisone developed cataracts and prednisone was associated with an increased risk of gestational diabetes.

Authors' conclusions
The authors concluded that aspirin plus heparin may reduce pregnancy loss by 54% among women with APL antibodies, but highlighted that this was based on 2 trials, one of which had inadequate randomisation.

CRD commentary
The question addressed in this review was clear. The search for studies covered various sources and was designed to minimise language bias. Steps were also taken to minimise bias in the study selection, quality assessment and data extraction processes. The characteristics of the individual included studies were clearly presented. Clinical and statistical heterogeneity were considered to inform the pooling of studies, and study quality was taken into account when interpreting the findings. Although there were a lot of outcome measures (which can increase the probability of obtaining a statistically significant result by chance), the available data limited the number of analyses that were possible. The authors' conclusions appear to be an accurate reflection of the evidence reviewed.

Implications of the review for practice and research
Practice: The authors stated that the optimum dose of heparin to maximise benefit and minimise harm is unknown. Also, that prednisone appears to have no role in the treatment of recurrent pregnancy loss associated with APL antibodies because of the increased risk in adverse outcomes observed.

Research: The authors stated that further RCTs are needed to assess the adverse effects of aspirin and heparin, and that
these trials need to be large and have adequate concealment of allocation.

**Bibliographic details**

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**Other publications of related interest**

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