

# Antithrombotic therapy for pregnancy complications: let's not throw the baby out with the bath water

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**Commentary on:** Schisterman EF, Silver RM, Leshner LL, *et al.* Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 2014;384:29–36.

## Context

Placenta-mediated pregnancy complications, ranging from miscarriage to growth restriction and pre-eclampsia, collectively affect more than 25% of pregnancies. While the aetiology of pregnancy complications is heterogeneous, it is plausible that common processes such as inflammation and activation of the coagulation system play key roles. Therefore, antithrombotic treatments, specifically low-dose aspirin (LDA) and low molecular-weight heparin (LMWH), have been used for these conditions, usually following the diagnosis of pregnancy. There are biological data indicating that LDA can improve endometrial growth and vascularisation in women undergoing assisted conception, suggesting that treatment-initiated preconception could influence pregnancy outcomes. There is limited information on preconceptional use of such agents. The Effects of Aspirin in Gestation and Reproduction (EAGeR) study examined the effects on live birth rate of LDA started preconceptionally in women with previous pregnancy loss.

## Methods

This was a multicentre, randomised, double-blind placebo-controlled trial in women aged between 18 and 40 years. Recruited women were planning to conceive and were stratified to those with one loss at 20 weeks gestation and those with one or two previous losses with no restriction of gestational age at the time of the loss. Daily LDA plus folic acid was administered preconceptionally and compared with placebo plus folic acid. Both were given for up to six menstrual cycles pending conception. Where conception occurred the study treatment was continued until 36 weeks gestation.

## Findings

Overall, 1078 women (of 1228 recruited) completed the trial—535 in the LDA group and 543 in the placebo group. Fifty-eight per cent of the women in the LDA group had a live birth, compared with 53% of the placebo group ( $p=0.0984$ ). Pregnancy loss occurred in 13% of women in the LDA group versus 12% in the placebo group ( $p=0.7822$ ). However, when analysis was restricted to the original stratum of women with one

loss at less than 20 weeks gestation there was a significant difference in live birth rate between the groups (62% of the LDA group vs 53% of the placebo group ( $p=0.0446$ )). In contrast, in the expanded stratum there was no significant difference between the groups in terms of live births. There was no evidence of major event rates between the groups. Although LDA was associated with increased vaginal bleeding, this was not associated with pregnancy loss.

## Commentary

These data do not support the preconceptional use of LDA to prevent pregnancy complications, and pregnancy loss in particular. This resonates with other trials that also showed no general benefit, including the ALIVE trial, where LDA and LMWH were used in women with recurrent pregnancy loss with preconceptional LDA use.<sup>1</sup> Thus, EAGeR and a number of other trials show no benefit from antithrombotic interventions starting either before or following conception.

Should we now abandon such treatment as being ineffective? Although there is no consistent benefit from antithrombotic interventions for pregnancy complications in these trials, others have reported positive results.<sup>1</sup> Therefore, it is important to make a better assessment of where the treatment is best employed, based on biological plausibility for effectiveness, before rejecting antithrombotics for prevention of pregnancy complications. As these conditions are heterogeneous in their mechanisms, the lack of specificity in patient selection is liable to dilute the sample to include those with underlying factors that would not benefit from such therapies. Thus, better targeting of specific disease processes amenable to antithrombotic therapy is required.<sup>1</sup>

We should focus on obtaining better precision by stratifying patients. In support of this is the positive finding in the EAGeR study in the original stratum of patients with a single pregnancy loss at less than 20 weeks, as well as the further finding that LDA had significant effects on positive urine pregnancy tests, suggesting a biologically favourable effect on implantation. These findings led the authors of the EAGeR studies to conclude that their trial should be regarded as hypothesis generating. This emphasises the need for better stratification of these patients, ideally through biomarkers, to add to the clinical phenotype to achieve optimum stratification. This would allow us to target specific disease processes amenable to antithrombotic therapy and test these in adequately controlled trials starting at preconception.

Thus, the EAGeR trial further fuels the need for a more precise approach to the stratification of pregnancy complications based on the underlying disease mechanism rather than the clinical outcome. In the mean time, it would be premature to abandon such therapy; until better stratified randomised controlled trials are available we should resist throwing the baby out with the bath water.

**Competing interests** None.

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## Reference

1. Greer IA, Brenner B, Gris JC. Antithrombotic treatment for pregnancy complications: which path for the journey to precision medicine? *Br J Haematol* 2014;165:585–99.