Antithrombotic Therapy for Recurrent Miscarriage?
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Recurrent miscarriage is a major health problem, with 5% of women of reproductive age having two or more miscarriages and approximately 1% having three or more.¹ Most of these pregnancy losses remain unexplained, and there is no effective treatment; many hormonal and immune therapies have been tried, despite a lack of evidence of efficacy. Conditions that are associated with recurrent miscarriage include the antiphospholipid syndrome,²⁻³ acquired thrombophilia, and heritable thrombophilias, such as factor V Leiden and the prothrombin G20210A mutation.⁴ Moreover, there is evidence that miscarriage attributable to the antiphospholipid syndrome is amenable to treatment with antithrombotic therapies.²⁻³ These findings have raised the possibility that unexplained recurrent miscarriage may reflect a prothrombotic phenotype. Miscarriage in affected women may result not only from thrombosis but also from adverse effects of coagulation-cascade activation on the developing trophoblast. These possible mechanisms suggest the potential for antithrombotic therapy to have benefits beyond its anticoagulant effect in reducing the rate of recurrent miscarriage.⁵

Many clinicians have prescribed antithrombotic therapies for women with recurrent miscarriage on the basis of the association between this condition and thrombophilia, the success of antithrombotic treatment in the antiphospholipid syndrome, and the safety of aspirin and low-molecular-weight heparin in pregnancy.⁶ However, good evidence from randomized trials to indicate benefit has been lacking. Such an approach to therapy for recurrent miscarriage appeared logical, but was it premature?

In this issue of the Journal, Kaandorp et al.⁷ describe their findings regarding the use of aspirin combined with low-molecular-weight heparin in the Anticoagulants for Living Fetuses (ALIFE) study (Current Controlled Trials number, ISRCTN58496168). Women with a history of two or more unexplained miscarriages who were attempting to conceive or who had been pregnant for up to 6 weeks were randomly assigned to receive low-dose aspirin combined with low-molecular-weight heparin (nadroparin), low-dose aspirin alone, or placebo. Of 364 women who underwent randomization, 299 became pregnant. Aspirin was started at the time of randomization in the aspirin-only and combination-therapy groups, and low-molecular-weight heparin was started at 6 weeks of gestation in the combination-therapy group after confirmation of a viable pregnancy. The trial was halted early on the basis of futility. Neither aspirin combined with nadroparin nor aspirin alone improved the rates of live births, as compared with placebo, in these women. Live-birth rates in women who became pregnant were 69.1% (relative risk, 1.03; 95% confidence interval [CI], 0.85 to 1.25) in the combination-therapy group and 61.6% (relative risk, 0.92; 95% CI, 0.75 to 1.13) in the aspirin-only group, as compared with 67.0% in the placebo group. No major safety issues with antithrombotic treatment in pregnancy were identified, which was consistent with previous evidence,⁶ but there were substantial numbers of side effects, such as injection-site reactions and bruising.

Recurrent miscarriage is a heterogeneous condition. Although a full investigation is usually not advocated until three pregnancy losses have occurred, women are increasingly being treated after two such events. Thus, this trial is directly applicable to current practice. It is possible that certain subgroups of women with recurrent miscarriage — such as those with three or more losses, those with heritable thrombophilia, and those with no history of successful pregnancy — may represent homogeneous
groups that might have a different response to antithrombotic treatment. In prespecified analyses of such subgroups in the ALIFE study, there were no significant differences in outcome according to study group, but the study was not powered for such analyses (e.g., only 16% of the women had an identified thrombophilia). The results of similar trials that were targeted specifically to women with thrombophilia are awaited. 

The findings of the ALIFE study are supported by the results of another multicenter, randomized, controlled trial, the Scottish Pregnancy Intervention Study (ISRCTN06774126). In this trial, investigators compared intensive pregnancy surveillance alone (i.e., without medical therapy) with a combination of low-molecular-weight heparin (enoxaparin) and low-dose aspirin in 294 women with a history of two or more miscarriages. There was no significant reduction in the rate of miscarriage associated with the antithrombotic intervention, as compared with surveillance alone (odds ratio, 0.91; 95% CI, 0.52 to 1.59).

In the ALIFE study, low-molecular-weight heparin was not given until 6 weeks of gestation; if the intervention were to act through protective effects on the trophoblast, then treatment at an earlier stage might be required. Many assisted-conception units are now prescribing low-molecular-weight heparin pragmatically after embryo transfer because of possible beneficial effects on the trophoblast that might increase the rates of successful pregnancy, but this practice is not supported by evidence from controlled trials. The findings of the ALIFE study underscore the need for randomized, controlled trials of antithrombotic treatment in women undergoing assisted conception before this intervention is adopted in routine practice.

In conclusion, the findings of Kaandorp et al. and other available data provide good evidence that antithrombotic intervention should not be advocated for unexplained recurrent miscarriage, although further data are needed in women with thrombophilia or with three or more miscarriages. The widespread use of antithrombotic interventions for women with two or more miscarriages appears to be no more than another false start in the race to identify an effective intervention for this distressing condition that affects so many women.

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