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Preventing recurrent pregnancy loss: time to rethink the standard of care?

Aspirin in combination with heparin is the accepted treatment for pregnant women with a history of recurrent pregnancy loss (RPL) who are positive for antiphospholipid antibodies (aPL). A randomized controlled trial by Carl Laskin and colleagues, however, found that the effect of this treatment on pregnancy outcomes is no different than that of treatment with aspirin alone, adding to the growing body of evidence that questions the need for thromboprophylaxis in pregnancy.

The cause of RPL, which can be classified on the basis of two or more consecutive losses, is unknown in many cases, although hypercoagulability is implicated in patients with inherited thrombophilias or aPL. The combination of low-dose aspirin and prophylactic heparin emerged as the 'standard of care' for this population of patients on the basis of the results of several studies published in the 1990s. Conclusive evidence supporting the practice was lacking, however, owing to small sample sizes or design inconsistencies between studies. In addition, explains Laskin, "my experience seemed to indicate that heparin may not be essential." The present study was undertaken, therefore, to explore in a randomized controlled trial the effect of treatment on live birth rates in women with a history of RPL.

The investigators aimed to enroll 200 pregnant women over the duration of the study, selected on the basis of the presence of a history of RPL and at least one of aPL, inherited thrombophilia or antinuclear antibody. During 2000–2004, 859 patients were recruited and screened, but only 88 were randomly allocated to one of two treatment arms. The patients then received treatment with either low-molecular-weight heparin (LMWH) in combination with aspirin or aspirin alone throughout pregnancy until 35 weeks' gestation or delivery. The study was ended

after the planned 4-year period, but without the enrolment target being met, on the basis of an interim analysis that revealed no difference in live birth rates between the two treatment groups. The decision to terminate the study was also influenced by the observed rate of pregnancy loss in patients in the aspirin-only group, which was much lower than predicted.

In the LMWH plus aspirin group, 35 (77.8%) of 45 pregnancies resulted in a live birth; in the aspirin-only group, 34 (79.1%) of 43 pregnancies were successful. Stratification by the presence or absence of aPL revealed no correlation between outcome and aPL status. Similarly, live birth rates were not affected by the number of pregnancies previously lost or by a history of early versus late loss. No serious adverse effects were observed in either group, and bone mineral density did not differ by group. Overall, and despite the small sample size, the results suggest that the addition of heparin does not improve pregnancy outcomes in this patient population, a conclusion that seems consistent with the uncontrolled observations that prompted the study.

The inclusion criteria comprised not only aPL but antibodies characteristic of systemic lupus erythematosus (SLE). The rationale for including these was derived from the association of SLE with an increased frequency of RPL, which suggested to the authors that women without clinical SLE but positive for autoantibodies typical of the disease could have pregnancy outcomes similar to patients with SLE. From the results, however, it seems that autoantibodies characteristic of SLE are not markers of pregnancy outcome for women with RPL who do not have clinical SLE.

One of the main limitations of the study is its sample size. The frequency of aPL and inherited thrombophilias in women with RPL was lower than the authors anticipated, which they suggest could account for the

slower-than-expected enrolment rate. The authors also point out that the difficulty of recruiting patients highlights the need to consider collaboration between research groups. Some potential collaborators approached for this study, however, were reluctant to withhold LMWH from those patients in the aspirin-only treatment arm. "We had planned to expand the study into a multicenter project," explains Laskin. "However, the use of aspirin plus heparin had become so widely accepted that we could not get any other center to collaborate." Whether the results of this and other recent studies will encourage participation in large, multicenter investigations of RPL treatment remains to be seen.

Regardless of these limitations, the results of this study suggest that aspirin plus heparin does not seem to be as beneficial as previously thought for the treatment of RPL. Although these findings sit in contrast to the few studies published before 2000 on which the current standard of care is based, they are consistent with other studies published after this period. This growing body of evidence could lead to a change in the way clinicians approach the problem of RPL.

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