

## Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss: Results from the HepASA Trial

To the Editor:

Laskin, *et al*<sup>1</sup> claim that low molecular weight heparin and aspirin (LMWH/ASA) did not confer incremental benefit compared to ASA alone in women with recurrent pregnancy loss and either autoantibodies or a coagulation abnormality. However, the inclusion criteria were so wide as to preclude any significant results. Patients with 2 unexplained consecutive pregnancy losses prior to 32 weeks' gestation have an 80% chance of a subsequent live birth. No treatment will significantly increase the live birth rate over 80%. Blighted ova resulting in first-trimester abortions and pregnancy losses at 32 weeks starting with contractions are not identical and should probably not be considered together. Although the authors claim that the prognosis is similar after 2 or 3 miscarriages, above 3 miscarriages the most important feature to predict the subsequent prognosis is the number of previous pregnancy losses<sup>2</sup>. Hence, the European Society of Human Reproduction and Embryology (ESHRE) protocol<sup>3</sup> recommends that the number of previous miscarriages and maternal age are the most important covariates and they have to be taken into account when planning therapeutic trials. The ideal trial should have stratification for the number of previous miscarriages and maternal age, with randomization between control and experimental treatments within each stratum. However, Laskin, *et al*<sup>1</sup> did not stratify for the number of previous miscarriages. Hence, no subgroup analysis is possible. In "evidence-based" terms, "the design of the trial prevents any meaningful result."

References are cited that coagulopathy is not the only mechanism of placental ischemia, and that immune-mediated inflammatory mechanisms may also contribute to fetal loss. Hence 15 patients with antinuclear antibody (ANA) alone were included in the trial. The only publication to report on the subsequent abortion rate in patients with ANA alone is that of Ogasawara, *et al*<sup>4</sup>. Abortion occurred in 6 of 39 patients with recurrent miscarriage (15.4%), which was not significantly different from the 23.1% found in ANA-negative patients. The authors concluded that ANA-positive recurrent aborters with no evidence of antiphospholipid antibodies do not require medication because the presence of antibodies does not predict subsequent pregnancy loss. Further, there is no evidence in the literature that aspirin or dalteparin act on patients with ANA as a sole finding. Including these patients may obscure any possible effects that LMWH may have in patients with antiphospholipid syndrome (APS) or hereditary thrombophilias.

To date there are 3 reports comparing heparin and aspirin to the effect of aspirin alone<sup>5-7</sup> in a much more closely defined group of women, with APS and 3 or more miscarriages. When the 3 trials are combined in a meta-analysis there was a common odds ratio of 2.63 in favour of heparins (95% CI 1.46-4.75)<sup>8</sup>. Hence, when APS is combined with hereditary thrombophilias and ANA and not matched for predictive factors such as number of losses, etc., the possible beneficial effect of LMWH may be obscured.

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