To the Editor:

We read with interest Dr. Carp's comments regarding the HepASA trial. The questions he raises about our inclusion criteria and conclusions are those that have surrounded therapeutic trials for recurrent pregnancy loss (RPL) with or without antiphospholipid antibodies (aPL) for decades.

Dr. Carp suggests that stratification for this patient population should include age and number of previous losses. The issue of evaluating and treating women with a history of 2 versus 3 losses continues to be debated, and evidence supporting both contentions is available and used by investigators according to their convictions. As noted, we and others have observed that causes of RPL are similar in women with 2 or 3 losses^{1,2}. Brigham, *et al*, in a longitudinal study of 325 patients with idiopathic RPL, found that women with a history of 2 versus 3 previous losses had the same chances of success in a subsequent pregnancy (76% vs 79%)³. Intuitively, therefore, if, in the absence of an identifiable etiology, there is no difference in subsequent pregnancy outcome and if there is no difference in the distribution of known etiologies of loss between women with 2 versus 3 losses, it is acceptable to include both groups without stratifying by number of losses. Indeed, our analysis supported this inference, as we found no difference in outcome when comparing women with 2 versus 3 previous losses⁴. As Dr. Carp noted, and as supported by Brigham's large prospective study³, maternal age has a profound influence on future pregnancy success, and appears to be the most significant factor in predicting subsequent pregnancy outcome in women with RPL. Age was not a discriminating factor in our trial, as there was no significant difference between the 2 treatment groups (33.8 vs 34.6 yrs). The issues of number of losses and age have already been thoroughly addressed with regard to this population. Our trial design incorporated 2 of the strata that have not yet been adequately investigated with regard to the treatment efficacy of heparin and aspirin (ASA) for RPL: the effect of aPL positivity and a history of early versus late losses.

Regarding the inclusion of women positive for antinuclear antibodies (ANA) as well as aPL in our trial, we discussed the controversial status of the decision in our report. However, as we stratified the 2 treatment groups on the presence of aPL positivity, we were able to analyze the (apparently) more interesting aPL subgroups without interference from the inclusion of ANA-positive women. We reiterate that investigating a broader spectrum of autoantibodies than just aPL for women with RPL in the absence of connective tissue disease may be important, as it is emerging that in patients with primary antiphospholipid syndrome (APS), there may be an inflammatory component to the RPL with an etiology that remains to be elucidated⁵.

Dr. Carp mentions 3 reports that have evaluated heparin and ASA versus ASA alone, and cites them as a "more closely defined group of women with antiphospholipid syndrome and 3 or more miscarriages." Unfortunately, this is not the case. Kutteh, *et al*⁶ specifically excluded women with the lupus anticoagulant (a classification criterion for APS) and studies by both Rai, *et al*⁷ and Farquharson, *et al*⁸ included women with such low levels of anticardiolipin antibodies (IgG > 5 and IgM > 3⁷; and IgG > 9 and IgM > 5⁸) that they would not have fulfilled classification criteria for APS regardless of the number of miscarriages. As discussed in our report, Rai and Kutteh's studies, both completed and published more than 10 years ago, have the lowest birthrates in their ASA-only treatment groups in the literature, and they are the only studies that found a significant dif-

ference in pregnancy outcome with the addition of heparin. Because they were the earliest trials reported for this population, the results became the basis for clinical decision-making that has not assimilated new data published over the intervening decade. Subsequent trials that have reported much higher success rates in their ASA-only treatment arms and detected no significant improvement in pregnancy outcome with anticoagulant therapy have been largely disregarded or misconstrued. For example, in his letter, Dr. Carp cites Farquharson, *et al*'s report⁸ as evidence supporting the continued use of heparin and ASA despite their conclusion to the contrary — that no benefit was conferred by the addition of heparin to ASA treatment.

Regardless of treatment regimen, number of prior losses, history of early versus late losses, or aPL positivity, almost 80% of our patients had a live birth. While we clearly conceded the weaknesses in our trial, we stand by our contention that for women with RPL, aPL, and no history of thrombosis, there is insufficient evidence for recommendations for thromboprophylaxis in pregnancy. Unfortunately, this treatment has become entrenched and continues as an example of eminence- rather than evidence-based medicine.

CHRISTINE A. CLARK, Research Associate; KAREN A. SPITZER, MS; CARL A. LASKIN, MD, University of Toronto and LifeQuest Centre for Reproductive Medicine, Suite 1800, 655 Bay Street, Toronto, Ontario, Canada. Address correspondence to C. Clark; E-mail: cclarksolo@aol.com

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