Reply to Heparin’s ‘potential to improve pregnancy rates and outcomes’ is not evidence-based

Sir,

We would like to thank Ricci et al. for their interesting comments. Firstly they suggest that at present there is insufficient evidence to support the use of heparin in women with recurrent implantation failure and thrombophilia. We agree that the trial data as summarized by us and substantiated by Ricci and colleagues are limited (Nelson and Greer, 2008). In the context of our review, we therefore highlighted repeatedly the necessity for further adequately powered randomized controlled trials to address this important clinical question. Specifically, we stated that ‘Further study of heparin, both in terms of mode of action and its potential therapeutic role in women with thrombophilia and implantation failure are warranted, with multicentre trials required to achieve meaningful numbers’.

Notably we did not place particular weight on any individual study and recommend a treatment regimen consistent with the need for further studies. However, further comment on the individual merits of these studies is warranted to address the issue that our review was not evidence based as demonstrated by the title of their letter. Firstly, the study by Kutteh et al. (1997) is inadequately powered with only 36 antiphospholipid positive women and this small study shows a numerically higher rate of clinical pregnancy in women with antiphospholipid antibodies (52.6 versus 47.0%) with unfractionated heparin and aspirin treatment, but this was not statistically significant. In reality the number of participants were far too small, indeed the authors themselves highlighted the need for a prospective multicentre randomized clinical trial.

The study by Stern et al. (2003) examined 143 women treated with unfractionated heparin and aspirin. This incorporated women seropositive for antinuclear antibodies as defined as a titre of ≥1/80, with 65% of all women affected, and for 22.4% of patients this was the only positive antinuclear antibody (ANA) test. It is now clear that up to 30% of healthy individuals have an ANA positive test at a titre of 1:40 and 5% at a titre of 1:160 (Malleston et al., 1997). Therefore given that ANA seropositivity alone characterized a significant proportion of the patients, this study was again underpowered to detect a difference between the groups.

The larger non-randomized study by Sher et al. (1994) demonstrated that unfractionated heparin and aspirin treatment in 169 antiphospholipid antibody positive women was associated with a 49% pregnancy rate as compared with 16% in the seropositive women not exposed to treatment and 27% in the seronegative controls. Logarithmic regression estimated the odds ratio of pregnancy rates (treated/untreated) in seropositive women as 3.02, with 95% confidence limits of 1.09–8.40. Notably comparison of treated antiphospholipid antibody positive against antiphospholipid antibody negative controls was also associated with improved outcome odd ratio 1.79 (95% CI 1.24–2.59), which may reflect a bias associated with the lack of randomization, antiphospholipid antibody positive status being beneficial or a treatment effect.

A subsequent article (Sher et al., 1998b), which although using the same recruitment start date as the 1994 article, was one of three published from the group in 1998 all of which incorporated unfractionated heparin in differing treatment protocols (Sher et al., 1998a, b, c). It is unclear as to whether the same patient groups were partially and repeatedly reported in the much larger study of 603 antiphospholipid antibody positive women undergoing 923 IVF cycles where unfractionated heparin was administered, or the 84 antiphospholipid antibody positive women who had 127 IVF cycles without treatment. Treatment with unfractionated heparin and aspirin was associated with a significant increase in live birth rate (46 versus 17%; P < 0.0001). We accept that this was not a randomized study; however, the emphasis placed by Ricci on the type of infertility influencing the outcome is probably excessive. This is because analysis of 8457 first cycles demonstrated that although there was a significant association between the cause of infertility (unexplained 17.8%, tubal pathology 14.6%) and live birth rates on univariate analysis, this was lost after adjustment for confounders OR 0.86 (95% CI 0.70–1.01) (Lintsen et al., 2005).
A parallel non-randomized study by this group examined the combination of unfractionated heparin, aspirin and immunoglobulin in women with recurrent implantation failure who were seropositive for antiphospholipid antibodies, and again treatment in 52 antiphospholipid antibody seropositive women was associated with an improved live birth rate (42%) relative to 37 seronegative untreated patients (19%) *(P = 0.02)* (Sher et al., 1998c). We appreciate that once again this is not a randomized trial and the appropriateness of the control group can be questioned. However, despite the methodological concerns and even leaving aside the study by Schenk, which cannot be fully evaluated, collectively four of the five studies all suggest a beneficial effect of heparin in women with acquired thrombophilia with or without recurrent implantation failure. We believe that such a suggestion of benefits from this preliminary evidence requires formal testing of this hypothesis in adequately powered randomized controlled trials.

With respect to inherited thrombophilia the literature is even more limited with Ricci et al. highlighting some of the potential deficiencies of the study by Qublan and colleagues (2008). A striking feature of this study is that in women who had previously experienced three failed IVF attempts, irrespective of whether any individual thrombophilia was associated with recurrent implantation failure, treatment with low molecular weight heparin rather than placebo injections, was associated with a significant improvement in live birth rate (23.8 versus 2.4%; *P < 0.01*). Furthermore this study used low molecular weight heparin, which despite different biological characteristics to unfractionated heparin as used in the historical studies, an effect was still observed. We are aware of a further pilot trial that has taken the pragmatic view of examining the phenotype of recurrent implantation failure rather than any underlying thrombophilic state, which also demonstrates a trend towards a benefit with low molecular weight heparin and combined with the study by Qublan will inevitably help inform the design of definitive trials.

On the basis of the above preliminary evidence and biological plausibility of an effect (Nelson and Greer, 2008), we believe that the possible beneficial effect of heparin in women with thrombophilia and recurrent implantation failure should now be tested in adequately powered randomized trials. Thus we are in agreement with Ricci et al. on the need for such trials. We also proposed the hypothesis of possible benefit of heparin in all women undergoing IVF. This hypothesis requires to be tested. We are therefore surprised that Ricci et al. suggest that our approach is not evidence based—we synthesized the available evidence, described biological plausibility and preliminary but limited clinical data of possible benefit with heparin treatment in assisted conception, proposed a testable null hypothesis and the need to examine this in adequately powered randomized trial in suitable patient groups. These are key components of the science of evidence based medicine.

References


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