Reviewer's report

Title: Acupuncture to improve live birth rates for women undergoing in vitro fertilisation: a protocol for a randomised controlled trial

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Reviewer: John Norrie

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Acupuncture to improve live birth rates for women undergoing in vitro fertilisation: a protocol for a randomised trial

Statistical / methodological review

Discretionary revisions

The authors provide a very clear protocol on an interesting topic. The design seems rigorous and the statistical methods seem appropriate for the design. There are several minor issues to consider, as follows:

1. The justification for another (large) randomised trial needs to be made more clearly – the authors state (page 5) ‘The first systematic review was published in 2008 and this review found that acupuncture as an adjunct to ET was associated with statistically and clinically significant increases in the pregnancy, ongoing pregnancy, and live birth rates’ ... but they go on ‘over the last 3-4 years several new trials and systematic reviews have been published. To date many trials are heterogeneous and results inconsistent. There remains insufficient evidence ...‘ – this is a bit confusing:
   a. If the first review was finding clinically and statistically significant benefit, why the additional trials in the first place?
   b. And given these trials took place, what was the explanation for the heterogeneity e.g. populations, interventions, controls, outcomes – in respect of informing the design of the current trial, avoid repeating methodological mistakes etc
   c. And specifically rather than just calculating a sample size to address a certain change, what about designing a study that would definitely address the heterogeneity and thus settle the doubts, given the literature that exists?

2. It would be useful for the authors to justify the inclusion criteria in a bit more detail – they say (Page 3) ‘ ... <43 years old, undergoing a fresh cycle, and restricted to women with potential for a lower live birth rate defined as 2 or more previous unsuccessful ET, and unsuccessful clinical pregnancies of quality embryos ...’:
   a. Specifically, why restrict to those women with a lower chance – is this simply to create room for a large treatment effect, or is this a groups specifically identified in the meta-analyses as most likely to benefit? Isn’t there a danger of missing out on demonstrating a treatment effect in those at medium or even low
risk of failure?
b. And why <43 years old – this seems a restriction in the other direction, of excluding those at higher risk of failure?
c. And how many ‘unsuccessful clinical pregnancies of quality embryos’ – 2 or more?
d. And how do the inclusion/exclusion criteria fit with global settings for IVF, outside Australia and New Zealand?

3. The rationale for the non-randomised cohort - to look at ‘a baseline pregnancy rate’ – could be made clearer – for example, why would those who refused to take part in the RCT be representative of the ‘baseline’?

4. The power calculation for the non-randomised cohort likewise could be clearer – the authors indicate that there will be 449 women per group and inflated that to 584 to allow 30% non treatment – but then they say 231 vs. 495 for the acupuncture group? Where has the 495 come from?

5. The authors say that the patient will be blinded to the intervention – but surely if the placebo needle does not penetrate the skin, won’t they know? That they haven’t previously had acupuncture won’t necessarily protect them from becoming aware that they haven’t had the real acupuncture, you feel?

6. Page 7 – what is ‘practitioner intent’?

7. Page 7 ‘De qi will be maintained during the initial treatment ...’ perhaps need to explain ‘de qi’?

8. Page 9 ‘Any imbalances at randomisation will be adjusted for in subsequent analysis’ – this doesn’t sound like good statistical practice – the covariates to be adjusted for should be pre-specified, on the basis of being strongly related to outcome, and not on the basis of any chance imbalance in the dataset at hand?

9. Useful to include a CONSORT type statement with details of numbers, randomised groups, timelines for assessments etc.