Sir,

We read with great interest the article by So et al. (2009), in which they evaluate the efficacy of acupuncture in in vitro fertilization (IVF) treatment. This is a very controversial issue. Four meta-analyses have been published over the last year (El-Toukhy et al., 2008; Manheimer et al., 2008; Ng et al., 2008; El-Toukhy and Khalaf, 2009) leading to opposite conclusions. Three of these conclude that there is no evidence of acupuncture efficacy (El-Toukhy et al., 2008; Manheimer et al., 2008; El-Toukhy and Khalaf, 2009), whereas another one concludes that acupuncture improves the rates of pregnancy and live birth (Manheimer et al., 2008). Unfortunately, the paper by So et al. (2009) does not provide useful elements to sort out the issue. The real conclusion of this study should be that in order to significantly increase the IVF pregnancy rate, placebo acupuncture should be introduced in clinical practice rather than verum acupuncture. This paradoxical conclusion, obviously, needs some comments. Several perplexities arise from a careful evaluation of the study design and results.

First, the study enrolled 30% of women with repeated IVF cycles. Ideally, when evaluating therapeutic efficacy, the patients should be receiving treatment for the very first time in order to reduce any potential bias. In fact, it is possible that women with previous IVF failure belong to a different prognostic group than those undergoing treatment in their first cycle (Daya et al., 2003). Furthermore, the authors do not report how many previous cycles the patients underwent.

Second, the authors use the overall pregnancy rate as primary outcome measure, defined by a positive urinary pregnancy test. This is an unacceptable primary outcome measure (Barlow, 2003, 2004; Daya et al., 2003; Vail and Gardener, 2003; Griesinger et al., 2004; Arce et al., 2005). Reporting of biochemical pregnancy might be misleading because of the possible carry-over effect from exogenously administered hCG that could be detected in the urinary test (Daya et al., 2003). It should be noticed that in the study by So et al. (2009), over two-thirds of patients received hCG for luteal support.

Third, the sample size calculation is very confusing. The authors use the results of the study by Paulus et al. (2002) to calculate the sample size. They state that the pregnancy rates found by Paulus et al. (2002) in the acupuncture group and the control group were 42.5% and 26.3%, respectively, but omit that these were ongoing pregnancy rates. Thus, they use ongoing pregnancy rates to calculate sample size in a study where biochemical pregnancy rate is the primary outcome. Furthermore, they state that in their unit, in 2005, pregnancy rate per transfer was 35%, but do not specify if it was ongoing or biochemical pregnancy rate. In addition, the study by Paulus et al. (2002) cannot be considered the best reference study because women in the control group received no adjuvant treatment. The authors had better to refer to the subsequent study by Paulus et al. (2003), which has a design more similar to theirs; indeed, a sham acupuncture control was used (Paulus et al., 2003). As a matter of fact, in this study, no significant difference was found in the pregnancy rate between placebo needling and real acupuncture ($P = 0.39$) (Paulus et al., 2003).

Finally, the authors state that ‘placebo acupuncture was associated with a significantly higher pregnancy rate in IVF treatment when compared with real acupuncture’. This is not quite correct since only biochemical but not clinical ongoing live birth rate was higher in the placebo acupuncture group.

In conclusion, apart from the flaws of the design study, it still fails to answer the crucial question: does acupuncture actually increase the pregnancy rates in IVF? We believe that until truly evidence-based answers are provided, every study investigating this issue will have a fundamental bias. We also consider that in order to definitively clarify the role of acupuncture in IVF treatment, a carefully designed three-arm randomized controlled trial, including real acupuncture, placebo acupuncture and no adjuvant treatment arm, should be performed.

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Reply: RCT of real versus placebo acupuncture in IVF

Sir,

We refer to the letter from Ricci, Bello and Skerk addressed to our recent publication on the use of acupuncture in IVF treatment (So et al., 2009) and would like to answer some concerns about our study.

1) Four meta-analyses (Cheong et al., 2008; El-Toukhy et al., 2008; Manheimer et al., 2008; Ng et al., 2008) on the role of acupuncture in IVF were published in 2008. Indeed, three meta-analyses (Cheong et al., 2008; Manheimer et al., 2008; Ng et al., 2008) showed that acupuncture improved rates of pregnancy and live birth in women undergoing IVF treatment, contrary to what has been stated in the letter. The meta-analysis by El-Toukhy et al. (2008) is the only one which did not find any improvement in pregnancy and live birth rates following acupuncture. This group published another meta-analysis (El-Toukhy and Khalaf, 2009) in 2009 and the findings were in line with their previous one after adding our study.

2) In our study, we recruited patients undergoing the first cycle and repeated cycles. We are aware of the impact of the cycle number on the success rate and stratified the randomization sequence according to the cycle number, i.e. the first cycle and repeated cycles. This achieved a nearly identical proportion of the first cycle and repeated cycles in both real and placebo acupuncture groups. We do not feel that the inclusion of those undergoing repeated cycles would affect the conclusion as this is more reflective of the real clinical situation. However, we would agree that further studies should be conducted to find out if acupuncture may work in certain subgroups of patients. The subgroup analysis of the review paper by Manheimer et al. (2008) suggests that the benefit of acupuncture may not be observed in studies with high baseline pregnancy. Therefore, it may be more logical to examine the use of acupuncture in patients undergoing repeated IVF cycles without success.

3) We fully agree that the best primary outcome is the live birth rate but the live birth rate may not be available because of incomplete data collection. Therefore, we used the most easily available outcome in this study, i.e. the proportion of a positive pregnancy test, but we followed the outcome until the delivery of patients. A urine pregnancy test was checked 10 days after the last dose of hCG as the luteal phase support and it is unlikely that the positive pregnancy test is related to the hCG injection.

4) Clinical pregnancy rate defined as the presence of a fetal sac during an ultrasound examination of 6 weeks after embryo transfer was given in the paper by Paulus et al. (2002). We agree that we should use the clinical pregnancy rate in the sample size calculation. When we designed our study, we were not aware of the study by Paulus et al. (2003), which appeared as an abstract and did not have details about the placebo needle.

5) We are very cautious about our conclusion that should read as ‘Placebo acupuncture was associated with a significantly higher overall pregnancy rate when compared with real acupuncture’. The overall pregnancy rate that was defined by a positive urinary pregnancy test.

We are aware of the shortcomings of our study design and agree that a three-armed RCT consisting of no treatment, real acupuncture and placebo acupuncture should be performed to address the role of acupuncture in IVF treatment. The contribution of our study (So et al., 2009) is that placebo acupuncture performed in the manner described in our study should not be considered to be inert and those in the placebo group should not be taken as controls.

References


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