

Acupuncture in *in vitro* fertilisation: why do reviews produce contradictory results?

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Keywords

- Acupuncture
- clinical pregnancy
- embryo transfer
- *in vitro* fertilisation treatment

Introduction

In the past decade acupuncture has attracted much interest in *in vitro* fertilisation (IVF) treatment. Historically, acupuncture first became associated with IVF treatment when electroacupuncture was reported to increase uterine artery blood flow in women with high blood flow impedance undergoing IVF and embryo transfer (ET) treatment.¹ Subsequently, electroacupuncture in combination with paracervical blockade was shown to be as effective in relieving pain as fast-acting opiates in combination with paracervical blockade.² An interesting observation made in that study was that the pregnancy rate was significantly higher in the electroacupuncture group. However, the number of patients was too small ($n=150$) and the power of the findings therefore insufficient for this observation to be statistically confirmed. Another early study showed that acupuncture administered before, during, and after ET increased pregnancy rates.³ No power calculation was presented in the study; because of an insufficient number of patients ($n=180$), the results might be misleading and should be interpreted with caution. A larger number of patients is required in order to determine whether there is a true difference in pregnancy rates between groups.

These initial acupuncture trials of IVF treatment have received much attention in debate and review articles and further RCTs have been

published on the topic.² Many researchers claim that the higher pregnancy rates in the acupuncture groups compared with the experimental and control groups may be due to placebo effects. As a result of methodological limitations and lack of knowledge about the physiological effects of acupuncture, much scepticism about the alleged effects of acupuncture remains, and there is reason for a serious discussion about their scientific documentation and validation. Furthermore, many of the trials are underpowered and the study designs vary between trials, which makes it difficult to interpret the data.

Review of reviews

In 2008, four systematic reviews were published, all with the aim of systematically reviewing the effects of acupuncture on the outcomes of IVF treatments.^{16,19} These reviews have, however, produced contradictory results. Manheimer *et al.*¹⁸ concluded that current preliminary evidence suggests that acupuncture administered before and after ET improves pregnancy and live birth rates among women undergoing IVF. Ng *et al.*¹⁹ concluded that pregnancy rates of IVF treatment are increased when acupuncture is administered on the day of the ET, but its effectiveness remains controversial. El-Toukhy *et al.*¹⁷ concluded that there is no difference in the clinical pregnancy rate or live birth rate when acupuncture is performed for pain relief during oocyte aspiration or around the time of ET; they further concluded that the current available literature does not provide sufficient evidence that adjuvant acupuncture improves IVF outcomes. The fourth and last systematic review is a Cochrane Review published in October 2008.¹⁶ It concluded that there is evidence of benefit for live birth rates when acupuncture is performed on the day of ET but not 2 - 3 days after ET or during oocyte aspiration. The authors also stress that based on the current evidence, these effects can be attributed to placebo effects and/or the small number of patients included in the trials.

Overall, three out of four systematic reviews favour acupuncture when performed around the day of ET. But how can systematic reviews addressing the same question produce such different answers? Systematic reviews are regarded as the most reliable tool for summarising the existing evidence.²⁰ They often show, however, discrepancies in results and conclusions. The most common reasons for discrepancies are differences in inclusion criteria, methods of literature searching, data extraction and data analysis.²⁰ Taking all these issues into account, seemingly small decisions in the review process can have a major impact.²⁰

To what extent do the inclusion and exclusion criteria differ between reviews?

Manheimer *et al.*¹⁸ focused on acupuncture during ET and included seven trials with 1366 women; Ng *et al.*¹⁹ included 10 trials, five of which employed acupuncture during oocyte aspiration ($n=460$) and five around ET ($n=606$);¹⁹ El-Toukhy *et al.*¹⁷ included 13 trials, five of which employed acupuncture during oocyte aspiration ($n=455$) and eight around ET ($n=844$); and Cheong *et al.*¹⁶ included 13 trials and performed a number of different subgroup analyses, but do not provide numbers for each analysis (see [Table 1](#)).

See [Table 1: Included trials in each systematic review and number of women in each study](#).

The trials included in the four systematic reviews differ slightly. The review by Ng *et al.*¹⁹ includes only 10 trials as the search date for trials was August 2006. It can be questioned whether a systematic review should be accepted for publication if the last search was performed one and a half years earlier. The review by Manheimer *et al.*¹⁸ did not include the abstract published by Craig *et al.*,⁴ whereas El-Toukhy *et al.*¹⁷ and Cheong *et al.*¹⁶ included the same trials in their reviews.

El-Toukhy *et al.*¹⁷ discussed two reasons for the difference between their review and the review by Manheimer *et al.*¹⁸ First, their search identified an additional trial,⁴ which was not included in the earlier review. Second, they included all five study arms of the study by Benson *et al.*,¹⁵ whereas Manheimer *et al.*¹⁸ only included study arms related to needle acupuncture.

The two systematic reviews by El-Toukhy *et al.*¹⁷ and Cheong *et al.*¹⁶ include the same trials and could therefore be compared directly. Interestingly, they arrive at different conclusions. These two reviews will be compared and discussed in the following paragraphs.

To what extent does the review process differ?

The ultimate primary endpoint of IVF treatment is live birth rates. However, most studies included in the reviews do not present live birth rates. Instead, ongoing pregnancy rates and clinical pregnancy rates are presented as IVF outcome variables. As previously mentioned, the same trials were included in the reviews by El-Toukhy *et al.*¹⁷ and Cheong *et al.*,¹⁶ and the major difference lies in the way the data were analysed.

Regarding the effects of acupuncture in relieving pain during oocyte aspiration, data on clinical pregnancy rates were available from all five trials included.^{2, 79, 12} Both reviews presented the pooled results of these five trials and the clinical pregnancy rates do not differ between the acupuncture and the control groups.

Regarding the effect of acupuncture around the time of ET on clinical pregnancy rates, the analyses differ between the two systematic reviews.^{16, 17} El-Toukhy *et al.*¹⁷ pooled the results for clinical pregnancy rates from all eight trials,^{36, 10, 1315} whereas Cheong *et al.*¹⁶ only pooled the results from six trials.^{3, 6, 10, 1315} The reasons why the trials by Dieterle *et al.*⁵ and Craig *et al.*⁴ are not included in the pooled results of clinical pregnancy rates are not provided.

Cheong *et al.*¹⁶ state under data collection and analysis that subgroup analyses would be performed if there was significant clinical or statistical heterogeneity. This is the most reasonable explanation for the different results and conclusions in the two systematic reviews. This raises the question of which review performed the most appropriate analysis? Should trials be included in the analysis if they exhibit significant clinical or statistical heterogeneity? The most sensible solution may be to pool all trial data and if there is heterogeneity they should be presented together with subgroup analyses and explained in detail. In their present form, it is almost impossible to judge which of the reviews gives the most accurate picture.

To what extent do the two trials not included in the clinical pregnancy analysis by Cheong *et al.*¹⁶ differ?

The results of the two trials not included in the clinical pregnancy rate analysis are contradictory. The study by Craig *et al.*⁴ randomly assigned 107 women to acupuncture vs. control. Patients in the acupuncture group received treatment by one of two licensed acupuncturists at an off-site location before and after ET according to a modified version of the protocol used by Paulus *et al.*³ When an interim analysis found a significantly higher pregnancy rate in the control group compared with the acupuncture group (78.3% vs. 52.1%), the researchers stopped the enrolment of patients. This trial has substantial limitations due to: (1) the number of patients - it is questionable whether the limited number had statistical power; (2) the choice of treatment site - the patients may have found it stressful to receive acupuncture off-site compared with

patients in all other reviewed studies who received it on-site; and (3) the control group's pregnancy rate - 78% is exceptional; is this the average pregnancy rate at this clinic?

Dieterle *et al.*⁵ randomly assigned 225 women to acupuncture or placebo acupuncture in points that (ideally) do not influence fertility. Both groups received two acupuncture treatments, first after ET and then again 3 days later. The pregnancy outcome was significantly higher in the acupuncture group than the placebo group (28.4% vs. 13.8%). This trial has substantial limitations due to: (1) the number of patients - it is questionable whether the limited number had statistical power; (2) the choice of control - how do they know that needling non-acupuncture points would not influence fertility?; and (3) the placebo group's pregnancy rate - 13.8% is very low; what is the average pregnancy rate at this clinic? The results from these two trials diverge considerably and it is not clear how to interpret the data.

It is not obvious why these trials were excluded in the review by Cheong *et al.*¹⁶ As Cheong *et al.*¹⁶ and El-Toukhy *et al.*¹⁷ included the same trials but performed different subgroup analyses and used different statistical methods, it would be of great interest to get the results from Cheong *et al.*¹⁶ of clinical pregnancy rates when all eight trials around ET are pooled - we might then get a clearer idea of the results. Also, one additional RCT was published after the last systematic review, which may further affect the outcome of a meta-analysis.¹¹

What needs to be done?

Despite the increasing number of trials, there is still no large, adequately powered RCT evaluating the effect of acupuncture performed on-site to reduce stress and other confounding factors before and after ET. Interestingly, a comment in the *British Medical Journal* reports that a Danish RCT of adjuvant acupuncture before and after ET including more than 600 women undergoing IVF (twice as many as in the largest RCT included in the meta-analysis) is currently underway.²¹

Furthermore, to enable comparisons between studies, it is important that study protocols are fixed - that the number of needles, stimulation type (manual and/or electrical), and treatment duration are the same, and control situations are similar.²²

Important issues from a patient perspective are safety and cost and these need to be addressed. A large survey of practitioners shows that serious

adverse events after acupuncture are rare and none of the published articles within IVF/ET treatment report any adverse events.²³

Conclusion

Acupuncture may or may not have specific effects and a place within IVF/ET treatment, but there are compelling reasons for the scientific community to elucidate the issue further. The question as to whether acupuncture should be recommended as adjuvant therapy during IVF/ET treatment remains unanswered. The results from the systematic reviews published in 2008 are confusing, and clarifications as well as large, adequately powered RCTs are required.

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