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## Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis

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**EDITORIAL** by Pinborg and colleagues

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### ABSTRACT

**Objective** To evaluate whether acupuncture improves rates of pregnancy and live birth when used as an adjuvant treatment to embryo transfer in women undergoing in vitro fertilisation.

**Design** Systematic review and meta-analysis.

**Data sources** Medline, Cochrane Central, Embase, Chinese Biomedical Database, hand searched abstracts, and reference lists.

**Review methods** Eligible studies were randomised controlled trials that compared needle acupuncture administered within one day of embryo transfer with sham acupuncture or no adjuvant treatment, with reported outcomes of at least one of clinical pregnancy, ongoing pregnancy, or live birth. Two reviewers independently agreed on eligibility; assessed methodological quality; and extracted outcome data. For all trials, investigators contributed additional data not included in the original publication (such as live births). Meta-analyses included all randomised patients.

**Data synthesis** Seven trials with 1366 women undergoing in vitro fertilisation were included in the meta-analyses. There was little clinical heterogeneity. Trials with sham acupuncture and no adjuvant treatment as controls were pooled for the primary analysis. Complementing the embryo transfer process with acupuncture was associated with significant and clinically relevant improvements in clinical pregnancy (odds ratio 1.65, 95% confidence interval 1.27 to 2.14; number needed to treat (NNT) 10 (7 to 17); seven

trials), ongoing pregnancy (1.87, 1.40 to 2.49; NNT 9 (6 to 15); five trials), and live birth (1.91, 1.39 to 2.64; NNT 9 (6 to 17); four trials). Because we were unable to obtain outcome data on live births for three of the included trials, the pooled odds ratio for clinical pregnancy more accurately represents the true combined effect from these trials rather than the odds ratio for live birth. The results were robust to sensitivity analyses on study validity variables. A prespecified subgroup analysis restricted to the three trials with the higher rates of clinical pregnancy in the control group, however, suggested a smaller non-significant benefit of acupuncture (odds ratio 1.24, 0.86 to 1.77).

**Conclusions** Current preliminary evidence suggests that acupuncture given with embryo transfer improves rates of pregnancy and live birth among women undergoing in vitro fertilisation.

### INTRODUCTION

In vitro fertilisation is expensive, lengthy, and stressful, and new drugs and technologies have been developed to improve success rates. Although some procedures have been shown to improve pregnancy rates in women with a poorer prognosis because of specific conditions, few adjuvant procedures have been shown to be effective for women in general. One exception is luteal phase support, which has been shown to increase pregnancy rates<sup>1</sup> and is routinely used.

Acupuncture has been used in China for centuries to regulate the female reproductive system.<sup>2</sup> Three

potential mechanisms for its effects on fertility have been postulated.<sup>3</sup> Firstly, acupuncture may mediate the release of neurotransmitters,<sup>4</sup> which may in turn stimulate secretion of gonadotrophin releasing hormone, thereby influencing the menstrual cycle, ovulation, and fertility.<sup>5</sup> Secondly, acupuncture may stimulate blood flow to the uterus by inhibiting uterine central sympathetic nerve activity.<sup>6</sup> Thirdly, acupuncture may stimulate the production of endogenous opioids, which may inhibit the central nervous system outflow and the biological stress response.<sup>7</sup>

We conducted a systematic review and meta-analysis of randomised controlled trials to determine whether acupuncture given with embryo transfer improves the rates of pregnancy and live birth among women undergoing in vitro fertilisation.

## METHODS

### Identification of studies

We searched the computerised databases Medline, Embase, Cochrane Central, and the Chinese Biomedical Database from inception to January 2007. We used search terms including acupuncture; auriculotherapy; Medicine, Oriental Traditional; and reproductive techniques, assisted; fertilization in vitro; embryo transfer. We also searched the proceedings of three major annual conferences on assisted reproduction technology for 2001-6. We scanned reference lists of relevant publications.

**Selection criteria, data extraction, and quality assessment** We selected randomised controlled trials that compared acupuncture with sham acupuncture or no adjuvant treatment. We considered only trials in which acupuncture was administered within one day of embryo transfer, with the objective of improving success rates. For trials to be eligible, we had to be able to extract data on at least one of the following outcomes: clinical pregnancy, ongoing pregnancy (pregnancy beyond 12 weeks of gestation), or live birth.

We included only trials in which acupuncture involved the insertion of needles into traditional meridian points. The needles could be inserted into tender points in addition to the traditional meridian points, and the needles could also be electrically stimulated. We excluded trials of dry needling or trigger point therapy and laser acupuncture and electro-acupuncture without needle insertion.<sup>8</sup> We imposed no restrictions on publication type or language of publication.

Two authors (EM and GZ) independently selected articles and extracted data. We extracted data pertaining to quality of the methods, participants, interventions, and outcomes. Methodological quality of the trials was evaluated with criteria from the checklist created by the Cochrane menstrual disorders and subfertility group.<sup>9</sup>

### Data synthesis and analysis

The measure of treatment effect was the pooled odds ratio of achieving a clinical pregnancy, ongoing pregnancy, or live birth for women in the acupuncture group compared with women in the control group. We also calculated pooled rate differences between the

acupuncture and control groups and converted these rate differences to numbers needed to treat. For our meta-analyses, we used a random effects model.

All meta-analyses were based on the number of women randomised with the intention to treat approach to analysis.<sup>9,10</sup> All trials reported pregnancy outcomes resulting from a single cycle.

### Subgroup analyses

We performed six subgroup analyses that evaluated whether analyses remained significant when we restricted them to trials judged adequate on six internal validity components.<sup>11</sup> We evaluated heterogeneity. We assessed whether effects of acupuncture varied with three clinical characteristics that might influence success: use of extra acupuncture sessions in addition to the sessions before and after the embryo transfer; eligibility restricted to women with good quality embryos; and low versus high rates of clinical pregnancy in control groups.

## RESULTS

Seven randomised controlled trials with a total of 1366 participants met inclusion criteria.<sup>w1-w7</sup> All trials were published in English since 2002, and conducted in four different Western countries. Four were published as full reports<sup>w2 w4 w6 w7</sup> and three as abstracts.<sup>w1 w3 w5</sup>

All seven trials used a pragmatic design,<sup>12</sup> including typical clinical populations and using typical interventions before and after randomisation. All included a broad selection of women undergoing in vitro fertilisation. The only difference in the inclusion criteria was that two trials<sup>w4 w5</sup> included only women with good quality embryos whereas the five others included women with embryos of varying quality.

In all trials women received acupuncture immediately before or immediately after the embryo transfer. All trials also used a fixed selection of acupuncture points for all patients for the sessions before and after embryo transfer. The fixed selection of points for these sessions was similar in all but one trial.<sup>w2</sup> Three trials also included one extra acupuncture session, in addition to the sessions before and after the embryo transfer.<sup>w2 w6 w7</sup>

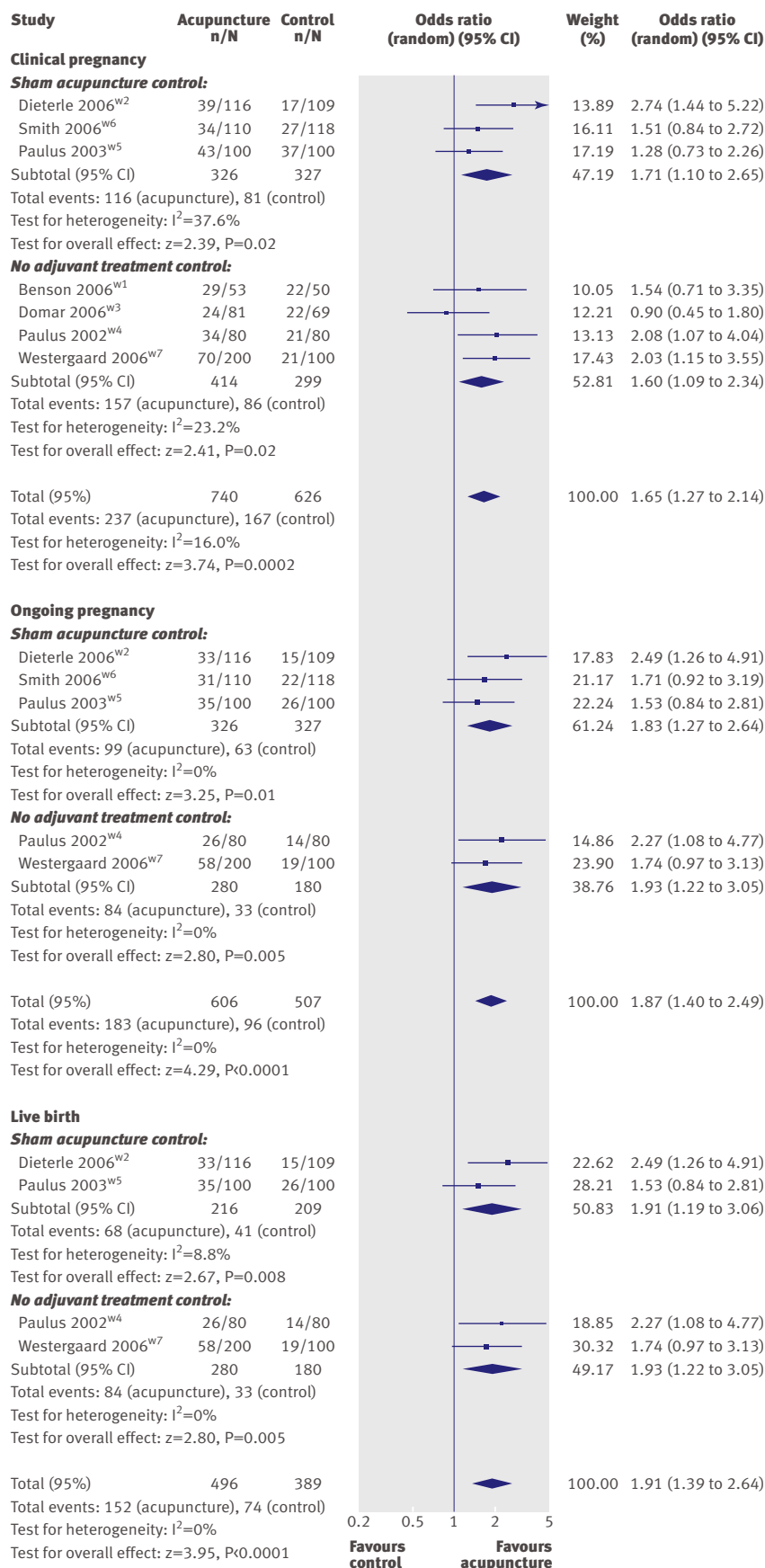
For all trials, there were no significant differences between the randomised groups in the mean numbers of embryos transferred.

### Methodological quality of included studies

The trials generally had high internal validity, in terms of randomisation procedures and follow-up of participants. For all trials but two,<sup>w2 w3</sup> investigators confirmed no losses to follow-up. Three of the trials used a sham acupuncture control,<sup>w2 w5 w6</sup> with one trial<sup>w2</sup> using needles that penetrated the skin at acupuncture points selected not to influence fertility,<sup>13 14</sup> and two<sup>w5 w6</sup> using non-penetrating sham needles. For the four other trials,<sup>w1 w3 w4 w7</sup> women in the control group received no adjuvant treatment.

### Efficacy analysis

Our primary analysis is based on results from all included trials. Embryo transfer with acupuncture was associated with a higher pooled odds for clinical pregnancy (1.65, 95% confidence interval 1.27 to



Effects of acupuncture on clinical pregnancy, ongoing pregnancy, and live birth outcomes

2.14), ongoing pregnancy (1.87, 1.40 to 2.49), and live birth (1.91, 1.39 to 2.64) (figure). The pooled rate differences were 0.11 (0.06 to 0.16) for clinical pregnancy, 0.12 (0.07 to 0.17) for ongoing pregnancy, and 0.12 (0.06 to 0.18) for live birth. The numbers needed to treat were 10 (7 to 17) for clinical pregnancy, 9 (6 to 15) for ongoing pregnancy, and 9 (6 to 17) for live birth. For the clinical pregnancy outcome,  $I^2$  values for heterogeneity were 16% and 4% for the odds ratio and rate difference effect measures, respectively. All of the heterogeneity was caused by a single trial,<sup>w3</sup> which reported only the clinical pregnancy outcome.

Of the nine subgroup analyses on clinical and methodological variables, only the subgroup analysis on the rates of clinical pregnancy in the control group showed a significant effect modification ( $P=0.04$ ). Restriction to the three trials with the higher rates of clinical pregnancy in the control group suggested a smaller non-significant benefit of acupuncture (odds ratio 1.24, 0.86 to 1.77). No other subgroup restriction resulted in a change to a non-significant effect. There were no significant adverse effects of acupuncture reported in the two trials that reported on this outcome.<sup>w2 w6</sup>

## DISCUSSION

This review suggests that acupuncture given with embryo transfer improves rates of pregnancy and live birth among women undergoing in vitro fertilisation. The strengths of this review include the number of trials and their relatively large sample sizes; pooled odds ratios that are highly significant; fairly consistent effect sizes across trials; homogeneity of the acupuncture protocols; use of objective and clinically relevant outcomes; adherence to the intention to treat approach for all meta-analyses; and overall high validity of the trials, as well as robustness of the results to sensitivity analyses on the effects of study validity variables.

### Methodological strengths and limitations of included trials

The included trials generally had sound methods. In terms of randomisation, six out of the seven trials<sup>w2-w7</sup> used an allocation procedure that would be considered as concealed.<sup>9 15</sup> Four of these six trials,<sup>w2 w3 w6 w7</sup> however, concealed allocation by using sealed envelopes managed by clinical investigators. This is not ideal because of the greater potential for subversion and errors than use of off site treatment allocation.<sup>16</sup>

As for blinding, three trials<sup>w2 w5 w6</sup> used a sham control and four<sup>w3 w4 w7</sup> did not blind women to treatment assignment. The necessity to blind participants, however, is arguable when the outcomes are entirely objective, such as in these trials.<sup>17</sup>

Three of the seven trials did not blind the physicians.<sup>w1 w6 w7</sup> However, considering the cost of embryo transfer and the importance of successful transfers to maintaining high pregnancy rates at clinics, we think that physicians would be motivated primarily to perform a successful procedure for all patients making blinding of patients or physicians less critical.

For all trials but one,<sup>w3</sup> the data were reported in sufficient detail to allow us to conduct full intention to treat analyses for clinical pregnancies.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

In vitro fertilisation is lengthy, expensive, and stressful

Safe, low cost, adjuvant treatments to improve success rates would benefit patients and reduce costs

**WHAT THIS STUDY ADDS**

Current evidence from methodologically sound trials showed an odds ratio of more than 1.6 for clinical pregnancy after in vitro fertilisation with adjuvant acupuncture

On average, 10 women would need to be treated with acupuncture to bring about one additional clinical pregnancy

The magnitude of this effect depended on the baseline pregnancy rate

**Limitations of the systematic review and meta-analysis**

Limitations of the meta-analysis include heterogeneity of baseline rates across trials, as well as the potential for publication and orientation biases.<sup>18</sup> This heterogeneity is probably not caused by differential selection of patients across trials because each trial was pragmatic, including typical clinic patients with minimal inclusion or exclusion criteria applied. While distribution of other factors—such as fertilisation procedure—varied somewhat across trials, such factors have not been shown to be strong predictors of pregnancy rates.<sup>12</sup> In this review, the country of the trial seemed to be a determinant of the success rates of pregnancy in the control group.<sup>19–21</sup> Because of the heterogeneity in baseline rate, the pooled estimates should be interpreted with caution and might not be directly applicable to any specific clinical population.

Although we conducted extensive searches to identify relevant studies and funnel plots did not suggest that there were small studies with negative results that were unpublished or not identified, we cannot rule out publication bias and this must be acknowledged as a potential limitation.

**Clinical implications**

The odds ratio of 1.65 suggests that acupuncture increased the odds of clinical pregnancy by 65% compared with the control groups. It is important to note that the odds ratio significantly overestimates the rate ratio when the event (pregnancy) is relatively frequent. In absolute terms, the number needed to treat was 10. These are clinically relevant benefits.<sup>22</sup> The subgroup analysis restricted to three trials with the higher pregnancy rates at baseline<sup>w1 w3 w5</sup> suggested a smaller non-significant benefit of acupuncture. A possible explanation for this non-significant finding is that in in vitro fertilisation settings, where the baseline pregnancy rates are already high, the relative added value of additional cointerventions may be reduced.

Safety and costs are other considerations. Two large prospective surveys of practitioners show that serious adverse events after acupuncture are rare.<sup>23,24</sup> In vitro fertilisation is an expensive procedure, costing an average of \$12 400 (£6300, €8480) per cycle in the United States.<sup>25</sup> If acupuncture increased the likelihood of success of an individual cycle, then the need for a subsequent cycle would be reduced, and overall costs would be decreased.

**Conclusion and future research**

Although current estimates of the effects of adjuvant acupuncture on in vitro fertilisation are significant and clinically relevant, they are still preliminary. Additional randomised trials are needed to quantify findings further and investigate the relation between baseline rate of pregnancy and the efficacy of adjuvant acupuncture.

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## Commentary: Good, but not perfect

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In commenting on the systematic review by Eric Manheimer and colleagues of the effects of acupuncture for women undergoing in vitro fertilisation (IVF),<sup>1</sup> I have focused on the methods used in the review. My commentary stems from issues raised when the manuscript was refereed and, perhaps, a wish to have an independent opinion on the reliability of the findings. Having accepted this challenge, I set out to assess whether the review provides knowledge of a sufficient standard to influence decisions.

The eligible interventions were specific types of acupuncture, used close to the time of embryo transfer, compared with sham acupuncture or no adjuvant treatment. Other aspects of care were the same for women within each trial. The trials were randomised and the population studied was women trying to get pregnant through IVF. Whether it is appropriate to combine trials using sham acupuncture and no adjuvant treatment is dealt with by presenting results for the two types of trial separately and together. This showed little difference in the point estimates for the effects of acupuncture or the finding of significance, whichever way the analyses were done.

No reviewers can search absolutely everywhere for potentially eligible studies. This would be a never ending task, accompanied by diminishing returns of eligible studies. The compromise is a balance between the pragmatic and the perfect by searching various sources likely to provide a reasonable yield of eligible studies while minimising the impact of publication bias. Manheimer et al did this, as they have in other systematic reviews.<sup>2</sup> And, although they might still be missing some studies, this is a problem for all reviews and will remain so until trial registration and the availability of trial findings become the norm.<sup>3</sup>

Each trial was assessed in a standard way. Most were judged to be satisfactory for methodological features related to the risk of bias. These features included concealment of allocation, which was "adequate" in six of the seven included trials, although the reviewers do express some concerns about the preference for sealed envelopes, rather than more secure off-site processes.

The authors sought to supplement published information with data from the original researchers. They were successful to some extent—for example, they obtained unpublished data on live births from three trials. They conducted their analyses in a standard way (odds ratios and a random effects model), and their findings would have been similar had they used other approaches, such as risk ratios or the fixed effect model. One potential problem is with their subgroup analysis

based on the proportion of women in the control group who became pregnant. Although this analysis was prespecified and used a predefined threshold of 28%, splitting a meta-analysis on the basis of outcome data from one intervention group to investigate the comparative effect against the other group can lead to bias. Focusing on trials that found good prognosis for the control group tends to produce a lower effect estimate than using the prognosis for both groups combined. Hence, it might be preferable to apply the pregnancy threshold to each trial as a whole. If this is done, I calculate that five trials would be in the subgroup analysis for "higher pregnancy" and the odds ratio for clinical pregnancy would be 1.52 (95% confidence interval 1.13 to 2.05,  $P=0.006$ ).

The review supplements the calculated odds ratios, which are difficult to interpret, with a number needed to treat to estimate how many women would need to receive acupuncture during one cycle of IVF to become pregnant. The authors veer on the side of caution by basing some of the discussion on the upper end of the confidence interval and note that 17 women would need to be treated for one more to become pregnant. Whether or not 17 is "too many" for acupuncture to be judged to be a clinically useful intervention is debatable.

So is this review by Manheimer and colleagues a well conducted review, worthy of consideration when making decisions about IVF? Yes. Is it perfect? No. However, several thousand systematic reviews are published each year in health care,<sup>4</sup> and none of them is likely to be perfect. This one seems as good as many. Unless, of course, you know differently?

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