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## COMMENTARY ON THE COCHRANE REVIEW OF ACUPUNCTURE AND ASSISTED CONCEPTION

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### Abstract

**Background**—Acupuncture has recently been studied in assisted reproductive treatment (ART) although its role in reproductive medicine is still debated.

**Objectives**—To determine the effectiveness of acupuncture in the outcomes of ART.

**Search strategy**—All reports which describe randomised controlled trials of acupuncture in assisted conception were obtained through searches of the Menstrual Disorders and Subfertility Group Specialised Register, CENTRAL, Ovid MEDLINE (1996 to August 2007), EMBASE (1980 to August 2007), CINAHL (Cumulative Index to Nursing & Allied Health Literature) (1982 to August 2007), AMED, National Research Register, Clinical Trials register ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), and the Chinese database of clinical trials.

**Selection Criteria**—Randomised controlled trials of acupuncture for couples who were undergoing ART comparing acupuncture treatment alone or acupuncture with concurrent ART versus no treatment, placebo or sham acupuncture plus ART for the treatment of primary and secondary infertility. Women with medical illness deemed contraindications for ART or acupuncture were excluded.

**Data Collection and Analysis**—Sixteen randomised controlled trials were identified that involved acupuncture and assisted conception. Thirteen trials were included in the review and three were excluded. Quality assessment and data extraction were performed independently by two review authors.

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Meta-analysis was performed using odds ratio (OR) for dichotomous outcomes. The outcome measures were live birth rate, clinical ongoing pregnancy rate, miscarriage rate, and any reported side effects of treatment.

**Main Results**—There is evidence of benefit when acupuncture is performed on the day of embryo transfer (ET) on the live birth rate (OR 1.89, 95% CI 1.29 to 2.77) but not when it is performed two to three days after ET (OR 1.79, 95% CI 0.93 to 3.44). There is no evidence of benefit on pregnancy outcomes when acupuncture is performed around the time of oocyte retrieval.

**Authors' Conclusions**—Acupuncture performed on the day of ET shows a beneficial effect on the live birth rate; however, with the present evidence this could be attributed to placebo effect and the small number of women included in the trials. Acupuncture should not be offered during the luteal phase in routine clinical practice until further evidence is available from sufficiently powered RCTs.

## COMMENTARY

Approximately 7–17% of all couples have difficulty conceiving at some point in their reproductive lives and seek specialist fertility treatment.<sup>1–3</sup> One of the most commonly used conventional treatment options is in vitro fertilization (IVF). In addition to first line conventional therapy, many infertile couples utilize complementary and alternative therapies, such as acupuncture.<sup>4</sup> Several systematic reviews and meta-analyses of randomized controlled trials (RCTs) have investigated whether adding acupuncture to the embryo transfer (ET) procedure of IVF increases the IVF success rate. These meta-analyses have had conflicting findings, and the RCTs they included had heterogeneous methods and results.

The first systematic review and meta-analysis on this topic was published in *BMJ* in February 2008,<sup>5</sup> and concluded that acupuncture given with the ET procedure of IVF increases clinical pregnancy and live birth rates. Six additional meta-analyses have been published since then.<sup>6–11</sup> The first of these additional meta-analyses, published in July 2008<sup>7</sup> found statistically significant pooled benefits of acupuncture as an IVF/ET adjuvant, on the clinical pregnancy outcome. The Cochrane meta-analysis was published in October 2008,<sup>6</sup> and it concluded that acupuncture increases live birth rates but does not increase clinical pregnancy rates. The remaining 4 meta-analyses,<sup>8–11</sup> published between late 2008 and 2010, all concluded that there is no evidence that acupuncture increases either clinical pregnancy or live birth rates. One obvious reason for divergent results is that some of the reviews include the “negative” Craig et al. abstract data<sup>12</sup> and So et al. study.<sup>13</sup>

Notably, after the last published meta-analyses, two more RCTs have been published.<sup>14,15</sup> In the RCT by Moy et al. the aim was to determine whether IVF/ET adjuvant acupuncture in classical acupuncture points together with auricular acupuncture (n= 86) was superior to IVF/ET adjuvant sham needling in non-acupuncture points together with auricular acupuncture in points not related to infertility (n=74).<sup>14</sup> This study found no difference in clinical pregnancy rate between the two treatment groups. In the other study, by Andersen et al., classical acupuncture was compared with placebo acupuncture with needle placement at the same site in both treatment groups.<sup>15</sup> This study also found no difference in clinical pregnancy rate or in live birth rate between the two treatment groups. In total, at least eleven RCTs have investigated the efficacy of acupuncture during ET. Three of them found a statistically significant benefit of acupuncture relative to control,<sup>16–18</sup> six found no statistically significant difference,<sup>14,15,19–22</sup> while two found a statistically significant benefit of the control relative to acupuncture.<sup>12,13</sup> The major question is what might explain the heterogeneity in these results in both the RCTs and in the systematic reviews?

As noted above, one possible explanation for divergent results across meta-analyses is that a “negative” trial,<sup>12</sup> which found that acupuncture significantly *decreases* clinical pregnancy rates relative to a no treatment control, was presented at a conference in October 2007, too late for inclusion in the first 2 meta-analyses to be published. The Cochrane meta-analysis was able to include the clinical pregnancy outcome data from this “negative” Craig et al trial, but did not include the Craig et al trial live birth outcome data because the live birth outcome data were not reported in the Craig et al published abstract. Because the Cochrane meta-analysis authors were not able to obtain or include the live birth outcome data from the “negative” Craig et al, the Cochrane meta-analysis for the live birth outcome was still statistically significant, and the Cochrane meta-analysis authors therefore concluded in their abstract that “Acupuncture performed on the day of ET shows a beneficial effect on the live birth rate”.

Subsequent meta-analyses included both the Craig et al clinical pregnancy outcome data, and also the Craig et al live birth outcome data. Even though the pooled results from the first 7 RCTs to be published on acupuncture for IVF showed significant and clinically relevant benefits of adjuvant acupuncture, because the Craig et al trial had quantitatively and qualitatively different results from the 7 previous RCTs, adding the Craig et al RCT data for clinical pregnancies (and subsequently also live births) into a meta-analysis with the other 7 RCTs resulted in very high heterogeneity, and this greatly increased the width of the pooled 95% confidence intervals (CIs), so much so that the pooled CIs crossed the meta-analytic “line of no effect”. Therefore, in the Cochrane meta-analysis and its subsequent update, as well as in all subsequent meta-analyses, the review authors included the clinical pregnancy data from the first 7 published RCTs, added the Craig et al clinical pregnancy rate data, ran the meta-analysis, and found that the confidence intervals crossed the line of no benefit, and therefore concluded, for example in a 2010 update of the Cochrane meta-analysis, that “the results provided no evidence of benefit in the use of acupuncture during assisted conception”.<sup>11</sup> With such extreme heterogeneity, however, it is questionable to report the pooled meta-analysis of all the trials as the primary result. If a meta-analysis is conducted, it should not necessarily be considered the sole finding (i.e. no evidence of benefit for acupuncture), but rather used primarily to assess the consistency of effects and better understand the impact of moderator variables.

What might explain the negative results in the Craig et al trial? In the Craig et al trial, the women receiving the acupuncture needed to drive to the acupuncturist’s office both before and after the ET procedure, while in all the other trials, the acupuncture was administered onsite at the IVF clinic, immediately before and after the ET procedure. That is, while all the other trials have been efficacy trials, conducted to test whether adjuvant IVF is helpful under controlled conditions in which the acupuncture was administered onsite at the IVF clinic, the Craig et al trial was an effectiveness trial, designed to test whether adjuvant acupuncture was still helpful if delivered offsite, which might better approximate every day, “real life” conditions.<sup>23</sup> Indeed, Craig et al explicitly stated this to be the objective of their RCT in their abstract, as follows: “Objective: Acupuncture performed onsite before and after embryo transfer has been reported to improve in vitro fertilization (IVF) outcome in patients with good quality embryos. The purpose of this investigation was to evaluate whether acupuncture before and after embryo transfer would alter pregnancy rates in patients undergoing IVF regardless of embryo quality if the treatment was performed offsite.”<sup>12</sup> By receiving acupuncture off-site, the patients were required to drive from the IVF clinic to their acupuncturist’s office, both before and after their embryo transfer, and this additional stress and activity on the day of embryo transfer, which is already a stressful day, may partially explain the lowered pregnancy rates in the acupuncture group of the Craig et al RCT. Because the Craig et al trial tests a different research question than all the other trials (i.e. offsite versus on-site acupuncture), relevant decision makers (e.g. patients, IVF clinics,

policy makers) may be better served if they are provided separate evidence for these 2 distinct research questions. Namely, the available evidence suggests that acupuncture may be more effective than no adjuvant treatment if the acupuncturist is located on-site and administers acupuncture immediately before and after ET at the IVF clinic, but that acupuncture is not effective and may even be harmful if the acupuncturist cannot administer the acupuncture at the IVF clinic and instead the patients need to drive to the acupuncturist's office both before and after the ET. This may be a more nuanced and clinically relevant interpretation of the data than an interpretation based on pooling all the data from the heterogeneous trials.

Another possible reason for the qualitatively and quantitatively different results in the Craig et al trial is that this trial had an extraordinarily high clinical pregnancy rate in the control group (i.e. 69.6%), and a statistically significantly lower, but still very high, clinical pregnancy rate in the acupuncture group (i.e. 43.8%). Indeed, the very high control group clinical pregnancy rate in the Craig et al trial, which was more than twice as high as the control group clinical pregnancy rate in the other 7 trials included in the first systematic reviews (i.e. average of 28%), may be another reason that acupuncture was not effective in the Craig et al trial. The same holds for two other trials, not included in the early systematic reviews, one of which is a negative RCT<sup>13</sup> and the other is a 'no difference' RCT.<sup>14</sup> That is, it may be that in IVF settings where the baseline pregnancy rates (as estimated by the control group rates) are already high, probably because of multiple embryos being transferred,<sup>5</sup> the relative added value of additional co-interventions, such as acupuncture, may be reduced. In such settings where multiple embryos are transferred, it may be that pregnancy rates are already at their limit, and adding acupuncture or other co-interventions cannot increase the rates further. Or it may be that adjuvant acupuncture promotes success of a single embryo transfer, but not a multiple embryo transfer/multiple pregnancy.

Another source of heterogeneity in acupuncture for IVF meta-analyses may be the different controls used in the RCTs. The controls ranged from IVF alone and no acupuncture, to needling non-acupuncture points, to the use of the so called placebo needles placed at acupuncture points or at non-acupuncture points, and this may explain the large heterogeneity in the results. A recent review investigated whether effects associated with sham acupuncture differed from other "physical placebo" procedures and it was concluded that sham acupuncture interventions may be associated with larger effects than both pharmacological and physical placebos.<sup>24</sup> Two of the three RCTs statistically significantly favouring acupuncture compared it with IVF alone (no sham acupuncture),<sup>17,18</sup> while most of the RCTs that compared acupuncture with some kind of sham acupuncture found no statistically significant differences between the study groups, thus suggesting that different sham acupuncture procedures might influence the pregnancy outcome. The question is then, can it be concluded from trials where an "active" sham procedure has been used as a control that acupuncture has no effect since it does not differ from the sham? Most of the sham-controlled RCTs lacked a standard care treatment group (i.e. IVF alone with no acupuncture), which, if included, would have helped to address this question.

From a scientific perspective, the sham-controlled trials are methodologically sound in almost all ways, with state of the art methods of randomization and zero drop-outs. But, the use of the sham control in these trials may have unnecessarily complicated rather than clarified the existing evidence base. While in RCTs of acupuncture for pain-related conditions, sham controls are necessary to guard against placebo effects, defined as "the impact of expectation on subjective outcomes",<sup>25</sup> it may be argued that in RCTs of acupuncture for IVF, placebo effects are much less of a concern because the outcomes are entirely objective. That is, in acupuncture for pain trials, patients know they are getting acupuncture and might expect it to benefit them, and therefore they may rate themselves as

feeling less pain on post-treatment questionnaires, regardless of whether or not the acupuncture worked. However, it seems much less likely that a patient's knowledge of whether she was receiving acupuncture would affect her ability to become pregnant. Using sham controls in IVF RCTs, while probably not necessary for reducing bias, would still not increase the risk of bias if sham controls were inert placebos. However, sham controls used in recent acupuncture for IVF RCTs may not be inert and their use in RCTs may increase the risk of bias.

For example, in 3 of the recent sham-controlled RCTs of acupuncture for IVF,<sup>13,15,26</sup> the sham control involved placing non-insertive, but pricking, "sham" needles at the same acupuncture points that were used in the true acupuncture group. These "sham" needles gave patients a pricking or penetrating sensation on their skin indistinguishable from that of a true acupuncture needle,<sup>27</sup> throughout the duration of the acupuncture session. Such sham needles may be likely to influence the pregnancy outcome because the type of stimulation these "sham" needles apply is comparable to applying acupressure to the acupuncture points, and indeed acupressure is a traditional form of treatment that has been shown in RCTs and systematic reviews to be effective for various conditions.<sup>28–30</sup> The results in these 3 sham-controlled trials showed that the sham acupuncture groups had higher clinical pregnancy rates than the true acupuncture groups, and in one of these RCTs,<sup>13</sup> the sham was statistically significantly better than the true acupuncture. Considering that these sham controls may not have been inert, one may ask the question whether it is appropriate for the meta-analysts to pool the sham controlled trials together with the no adjuvant treatment controlled trials, as many have done?

### Future research

Because a sham control may not be inert and indeed may have an effect on the pregnancy outcome being evaluated, and also because a sham control may not be necessary to control for placebo effects in IVF RCTs, which have entirely objective outcomes, future trials should not use a sham control and should instead compare IVF alone with IVF plus acupuncture. Such RCTs should use standardized study protocols and should follow the revised guidelines for standards of reporting interventions in clinical trials of acupuncture (STRICTA).<sup>31</sup> Future RCTs should also use an optimal acupuncture treatment protocol to allow these RCTs to adequately address the question of interest, which is whether IVF adjuvant acupuncture can work in a setting under optimal conditions. Only after efficacy trials have firmly established that acupuncture *can work* under ideal circumstances, should effectiveness trials be conducted to determine whether acupuncture *does work* under various other real world conditions.<sup>23</sup> Once a sufficient number of efficacy and effectiveness trials have been published, systematic reviewers will be able to determine whether or not, and under what conditions, acupuncture is an effective adjuvant for women undergoing IVF.

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