

# Acupuncture and in vitro fertilisation research: current and future directions

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## ABSTRACT

**Background** Acupuncture is a common adjuvant treatment to support patients undergoing in vitro fertilisation (IVF). However, the impact of acupuncture and the different roles it can play in IVF remain unclear.

**Objective** In this paper, we present an overview and critique of the current evidence on acupuncture's impact on IVF-related stress, describe harms, and propose future directions for investigation.

**Conclusion** Two to three acupuncture sessions performed on or around the day of embryo transfer are insufficient interventions to improve IVF birth outcomes but provide significant IVF-related stress reduction. Research investigating acupuncture to support IVF is heterogeneous and confounded by the lack of an appropriate comparator. However, evidence suggests several acupuncture sessions improve endometrial thickness, reduce stress, and improve patient satisfaction. Observational studies suggest more sessions are associated with increases in clinical pregnancy and live birth rates. An optimised acupuncture intervention with a reasonable comparator is necessary for future studies, with evidence-based guidance on technique and number of sessions. Acupuncture should not be rejected as an adjuvant therapy for IVF, but more studies are needed to clarify acupuncture's role in supporting IVF cycles.

## INTRODUCTION

To build a family, some couples require *in vitro* fertilisation (IVF) treatment, and many will pursue adjuvant therapies like acupuncture to improve their chances of success or help them cope. Yet the role of acupuncture as an adjuvant therapy to IVF to improve pregnancy outcomes still remains unclear.<sup>1,2</sup>

RCTs assessing acupuncture's impact on IVF outcomes often use two to three acupuncture sessions on or around embryo transfer (ET), also known as ET acupuncture. In trials, ET acupuncture is compared with no acupuncture treatment, or penetrating or non-penetrating needle controls, often called sham and/or placebo needling.

The primary outcomes are either pain relief during oocyte retrieval and/or difference in pregnancy outcomes between groups. Secondary outcomes may include stress and anxiety measures. Heterogeneity is a significant issue among acupuncture IVF trials, such as differences in baseline pregnancy rates, acupuncture point selection, number of sessions, timing of when sessions are administered, type of needling control and location of treatment.<sup>1,2</sup> IVF patient response to acupuncture or related techniques may also be influenced by infertility diagnosis or patient prognosis.<sup>3,4</sup>

Preliminary estimates suggest between a quarter<sup>5</sup> to one-half<sup>6</sup> of US women undergoing IVF also use acupuncture alongside their cycles. Acupuncture is a modality within the system of East Asian medicine (EAM) and has been used to support fertility for thousands of years. Frequently, it is administered together with dietary and lifestyle modifications, and/or Chinese herbal therapy. Historically, reproduction was economically and culturally vital to the Chinese and their livelihoods. The extensive historical record of treatment strategies to ensure a couple's fecundity has been documented in cases since the beginning of the Common Era, including successes and failures, and provides the framework for modern EAM treatment.<sup>7</sup>

Acupuncture is understood to affect several mechanisms associated with reproduction. First, acupuncture is thought to induce neurotransmitter secretion, which activates the release of gonadotropin-releasing hormone, and thereby increases ovulation, promotes menstrual regularity and regulates overall fertility.<sup>8,9</sup> Acupuncture is also thought to inhibit central sympathetic nerve activity, and thereby increase blood flow to uterine and ovarian tissue.<sup>10</sup> Finally, through its effects on



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increasing endogenous opioid production, acupuncture appears to downregulate various stress responses that are known to inhibit fertility.<sup>11 12</sup>

A recent narrative review of the acupuncture IVF literature focused on acupuncture's impact on IVF birth outcomes, and methodological issues with trial design such as different acupuncture points used, control arms and outcome measures, all contributing to heterogeneity within the literature.<sup>13</sup> Nandi *et al*<sup>13</sup> also recommended that: (1) trials ensure they follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guideline, a formal CONSolidated Standards of Reporting Trials (CONSORT) extension; (2) an acupuncture protocol be developed; and (3) researchers refrain from using 'placebo needles' as a control arm. We seek to expand on those critiques and present an overview and critique of the current evidence on acupuncture's impact on IVF-related stress, describe harms and further refine recommendations for future directions for investigation.

#### Acupuncture and stress reduction during IVF

Stress is a known mediator of infertility in couples struggling to conceive and is associated with a twofold increase in infertility.<sup>14</sup> Turner *et al*<sup>15</sup> found an association between increased pregnancy rates and women with lower stress and anxiety levels on the day before oocyte retrieval during IVF. Acupuncture treatment may improve quality of life and reduce stress and anxiety in women undergoing IVF.

Smith *et al*<sup>16</sup> investigated the use of three acupuncture treatments during an IVF cycle, and also assessed changes in functional health status via the 36-item short form survey (SF-36). Verum acupuncture was compared with a non-penetrating needle control. While there were no differences between groups in functional health status, reductions were observed in the domains of physical function, bodily pain, and mental health and vitality between enrolment and the end of the trial.<sup>16</sup>

IVF patients with comorbid anxiety may benefit from adjuvant IVF acupuncture to reduce anxiety and stress. Domar *et al*<sup>17</sup> compared ET acupuncture with no treatment, and assessed anxiety through the Spielberger Trait Anxiety Inventory. They found that acupuncture patients reported significantly less anxiety compared with the control patients (28.22 vs 31.69,  $P=0.015$ ), although acupuncture was not associated with significantly greater IVF pregnancy rates.<sup>17</sup>

So *et al*<sup>18</sup> (2009) performed two separate RCTs investigating ET acupuncture. Their objective was to assess the impact of verum acupuncture compared with a non-penetrating needle control. In their first study ( $n=370$ ) with women undergoing a fresh IVF ET, there was no difference between groups on pregnancy outcomes; however, serum cortisol and anxiety levels were reduced after the interventions in both

groups.<sup>18</sup> In a second trial of the same design, women ( $n=226$ ) undergoing frozen ET were randomised.<sup>19</sup> No differences were detected in pregnancy outcomes, but anxiety levels and serum cortisol were again significantly less after the acupuncture session in both groups.<sup>19</sup>

In a randomised trial of 43 IVF patients, Isoyama *et al*<sup>20</sup> assessed the effect of acupuncture on anxiety using the Hamilton Anxiety Rating Scale (HAM-A). They found four sessions of verum acupuncture significantly reduced the HAM-A scores compared with those receiving penetrating needle acupuncture ( $19\pm 3.2$  vs  $24.4\pm 4.2$ ,  $P=0.0008$ ).<sup>20</sup>

Acupuncture was associated with significant stress reduction (measured using the Perceived Stress Scale) in IVF patients in a prospective cohort trial of women who received ET acupuncture compared with no acupuncture.<sup>21</sup> Lower stress, measured in women receiving acupuncture, was associated with higher, but not statistically significant, pregnancy rates (64.7%), compared with the control group (42.5%) that did not receive acupuncture.<sup>21</sup>

Patients undergoing adjuvant IVF acupuncture reported that acupuncture contributed to their emotional well-being, feelings of empowerment and increased ability to cope with the IVF process.<sup>22</sup> This small study suggests that acupuncture treatment may be associated with increased emotional resilience throughout the IVF process.<sup>22</sup>

In our clinical experience, the infertility-related or IVF treatment-related stress and/or anxiety may be the primary reason a physician refers a patient for acupuncture. The psychological burden associated with infertility can be a barrier to continuing treatment.<sup>23</sup> Acupuncture may provide clinically relevant relief for stress and/or anxiety.

#### The impact of acupuncture on IVF pregnancy outcomes

Assessing the pooled effects in trials investigating acupuncture as an adjuvant to IVF outcomes is differentiated in three ways: acupuncture used for pain relief; acupuncture used for improvement of IVF outcomes; and type of comparator. For this paper, the outcomes of interest are clinical pregnancy (CPR), ongoing pregnancy (OG/PR) and live birth rates (LBR). With regard to controls, trials have used several different comparators. Verum acupuncture has been administered at or around the time of ET and compared with no treatment and/or usual care, or with a penetrating or non-penetrating (sham/placebo) needle control.

#### Acupuncture versus needle control (sham/placebo)

Cheong *et al*<sup>1</sup> found no difference between acupuncture on or around ET when compared with a 'sham' acupuncture control in the outcomes of CPR (7 trials, OR=1.04, 95% CI 0.74 to 1.46), OG/PR (6 trials, OR=1.10, 95% CI 0.74 to 1.65) and LBR (5 studies, OR=1.03, 95% CI 0.67 to 1.58).

Manheimer *et al*<sup>2</sup> found similar outcomes when acupuncture was compared with a ‘sham’ control in the outcomes of CPR (7 trials, relative risk (RR)=1.02, 95% CI 0.83 to 1.26), OG/PR (6 trials, RR=1.07, 95% CI 0.81 to 1.42) and LBR (5 trials, RR=1.02, 95% CI 0.76 to 1.37).

#### Acupuncture versus no treatment control

When acupuncture was compared with no treatment, acupuncture on or around the day of ET did not improve CPR (7 trials, OR=1.21, 95% CI 0.84 to 1.73) or OG/PR (4 trials, OR=1.08, 95% CI 0.57 to 2.07), but did improve LBR (3 trials, OR=1.15, 95% CI 1.14 to 2.12) in the Cochrane analysis.<sup>1</sup> The positive outcomes related to LBR may be due to the small pool of patients among only three trials and should be interpreted with caution. In the Manheimer *et al*<sup>2</sup> meta-analysis, acupuncture improved ongoing pregnancy compared with no treatment (5 trials, RR=1.43, 95% CI 1.15 to 1.79), but on the outcomes of CPR (9 trials, RR=1.22, 95% CI 0.97 to 1.52) and LBR (7 studies, RR=1.26, 95% CI 0.93 to 1.71), there was a statistical trend towards significantly improved outcomes following acupuncture.

#### Acupuncture versus any control

In the Cochrane meta-analysis of acupuncture compared with any control, there was no difference between groups in the outcomes of CPR (14 trials, OR=1.11, 95% CI 0.87 to 1.46), OG/PR (10 trials, OR=1.10, 95% CI 0.80 to 1.52) or LBR (8 trials, OR=1.22, 95% CI 0.87 to 1.70).<sup>1</sup> Manheimer *et al*<sup>2</sup> found a trend towards improved CPR (16 trials, RR=1.12, 95% CI 0.96 to 1.31), OG/PR (11 trials, RR=1.22, 95% CI 0.98 to 1.52) and LBR (12 trials, RR=1.14, 95% CI 0.92 to 1.42) following acupuncture.

#### Adverse events associated with acupuncture during IVF

Acupuncture is largely safe when performed by trained acupuncturists.<sup>24</sup> Nearly all the acupuncture IVF RCTs reported acupuncture was well tolerated. To learn more about the patient experience after ET, one trial asked participants to complete the McGill Pain Scale.<sup>25</sup> One hundred and sixty women were randomised into two groups who received either ET acupuncture at traditional acupuncture points or at non-traditional acupuncture points.<sup>25</sup> Those who received verum acupuncture reported sensing more pain on the Sensory Pain Rating Index, most specifically on the domain of ‘aching’, than the control group. However, they did not report more throbbing, shooting, stabbing, sharp, cramping, gnawing, hot burning, heavy, tender or splitting pain. On the Affective Pain Rating Index, verum acupuncture participants reported overall more affective pain than the control group, and specifically more on the domains of tiredness and fearfulness. However, they did not report more sickening or punishing pain.<sup>25</sup>

The experiences reported in the Moy *et al*<sup>25</sup> trial may not convey a clear picture of an acupuncture intervention. Within the context of acupuncture treatment, mild aching is a common intended patient response and is described as *de qi*,<sup>26 27</sup> which might include sensations such as heaviness, achiness, fullness, numbness or tingling.<sup>28</sup> The *de qi* response is thought to influence clinical effectiveness, as it may be one of the specific treatment mechanisms provoking the release of endogenous opioids,<sup>29 30</sup> changes in haemodynamics<sup>10</sup> and changes in cytoskeletal tissue modelling.<sup>31 32</sup>

Another possible adverse event is reflected in the Craig *et al*<sup>33</sup> study. In that study, acupuncture was performed offsite from the IVF clinics at an acupuncture clinic at a location unknown to the study participants. The outcomes showed that women who did not receive acupuncture had significantly more clinical pregnancies (72.9%) and live births (65.0%) than those who travelled offsite to the acupuncture clinic to receive their acupuncture treatments (46.0% and 39.1%, respectively).<sup>33</sup> It should be noted that clinical and live birth rates in the control group were much higher than the national average in the USA during these same years. In a follow-up retrospective cohort study, the Craig *et al*<sup>33</sup> protocol was administered onsite at a separate fertility clinic. When compared with no treatment, the Craig *et al* protocol was not associated with fewer live birth outcomes.<sup>34</sup> The location where patients receive acupuncture treatments, and the possible stress of travelling to offsite acupuncture clinics on ET day, and/or receiving acupuncture for the first time, could all be important mediators of acupuncture’s effect on IVF outcomes.<sup>2</sup>

#### Trial methodology in acupuncture IVF RCTs

Heterogeneity in acupuncture IVF trial methodology is a significant issue.<sup>12</sup> Nearly every trial has a different methodological design with respect to interventions, timing of treatments, controls and outcome measures. Acupuncture protocols are generally standardised in trials, and mostly follow the original protocol of Paulus *et al*<sup>35</sup> involving two ET acupuncture treatments. The most commonly used traditional acupuncture points are GV20 (*Baihui*), ST29 (*Guilai*), PC6 (*Neiguan*), SP8 (*Diji*) and LR3 (*Taichong*) within the 24-hour period prior to ET, and LI4 (*Hegu*), SP10 (*Xuehai*), ST36 (*Zusanli*) and SP6 (*Sanyinjiao*) within the 1-hour period post-ET. Auricular acupuncture or acupressure is sometimes also incorporated and includes the following traditional ear points: *Shenmen*, Brain, Uterus and Endocrine.<sup>35</sup>

#### Controls in acupuncture IVF RCTs

The best comparator for acupuncture IVF RCTs is also unclear.<sup>36</sup> Given the objective nature of the outcome measure (pregnancy) in these trials, expectation as a determinant of the outcome is unlikely.<sup>36</sup>

The therapeutic benefit associated with acupuncture is thought to be due to many factors and is common to both verum and penetrating or non-penetrating needle control procedures. Associated factors include practitioner–patient interactions, the rest period when the needles are inserted, and the patient lying quietly for 20–30 min. The use of a penetrating or non-penetrating needle control confounds the ability to assess acupuncture's true impact<sup>2 36</sup> and may contribute to falsely rejecting a therapy that may provide meaningful benefit to patients in both stress reduction and pregnancy outcomes. Further, inadequate acupuncture controls obscure the evidence and hinder evidence-based clinical decision-making.

#### Future directions

The current literature seemingly points to acupuncture's lack of efficacy to improve IVF outcomes. We caution against rejecting acupuncture as a therapy alongside IVF based on the current evidence. It would be prudent if acupuncture were compared with a true placebo or sham control. But given that most acupuncture IVF RCTs have compared verum with a needling control, the validity of these trial outcomes is uncertain. Concluding that acupuncture does not improve IVF outcomes based on the current evidence base may ultimately represent a type II error. More robust evidence is clearly needed to clarify acupuncture's impact on IVF outcomes.

#### Identifying the issues: controls

Thus far, acupuncture IVF trials have used penetrating or non-penetrating needles, both on and off traditional acupuncture points as a control.<sup>1 2</sup> Penetrating or non-penetrating needles in the control arm provoke physiological effects and are not inert. A large meta-analysis demonstrated verum acupuncture was therapeutically superior to placebo acupuncture and provided modest improvements for chronic pain,<sup>37</sup> but many studies are inadequately powered to detect a significant difference. The literature thus far suggests it is more difficult to show significance over sham acupuncture for conditions in which central/general effects of acupuncture are likely to be important (eg, IVF), as opposed to local/segmental effects (eg, osteoarthritis of the knee). Large sample sizes are needed to detect a difference between verum and sham acupuncture, approximately 400 per arm.<sup>38</sup> An optimal comparator is needed to reduce patient bias and account for time spent and attention received during the acupuncture session. We strongly advise against attempts to assess efficacy by using a penetrating or non-penetrating needle control for future trials. Time and attention should be accounted for with a comparable therapy and effectiveness assessed via a pragmatic or comparative effectiveness trial design.

#### Individualised acupuncture therapy treatments

In past trials, participants were recruited according to their biomedical diagnoses, and all received standardised acupuncture treatment protocols. This differs from real-world traditional acupuncture practice settings where patients are diagnosed within the context of EAM theory, and receive individualised treatments consisting of needles and adjunctive modalities such as moxibustion, external heat, *tui na*, *gua sha* and cupping.<sup>36 37</sup> This lack of similarity between the treatments performed in the IVF clinical trials and those performed in many real-world clinical settings brings the external validity of such trial outcomes into question.

Compounding this issue is the use, in many of these clinical trials, of acupuncture points after ET that are considered contraindicated during pregnancy according to traditional acupuncture theory.<sup>39</sup> Although it has been suggested that contraindicated points cannot cause miscarriage,<sup>38</sup> studies thus far have not assessed the use of such points during embryonic implantation. In the trial undertaken by Westergaard *et al*,<sup>40</sup> the group that received acupuncture 2 days post-ET had a higher incidence of early pregnancy loss.<sup>40</sup> The treatment performed at 2 days post-ET consisted of seven points, of which four may be considered contraindicated during pregnancy.

While currently there is no substantial evidence supporting superiority of individualised acupuncture as performed in real-world settings, over standardised acupuncture protocols, external validity appears to be an important issue. This is especially true when considered in conjunction with acupuncture point selection, safety and dosage issues. For these reasons, future trials should include individualised acupuncture treatments undertaken in the same way as those delivered in real-world settings by experienced acupuncturists.

#### Optimal acupuncture dosage

The optimal acupuncture dosage needed to improve IVF outcomes remains undiscovered. The number of sessions needed will depend on many factors and will likely vary widely between patients. Incorporating EAM diagnosis may arguably contribute to a better understanding of how much acupuncture is needed. The current literature concludes that two to three acupuncture sessions on or around the day of ET are an insufficient acupuncture dose to significantly impact birth outcomes. Patient demographics and embryology lab performance may vary significantly between clinics and countries, and therefore baseline pregnancy rates in the studies vary and affect the ability to detect differences between acupuncture and no acupuncture in IVF treatment.<sup>38</sup>

A greater number of sessions may be needed to improve outcomes. Eleven acupuncture treatments during an IVF cycle were associated with significantly improved IVF birth outcomes and fewer miscarriages



compared with no treatment.<sup>41</sup> An average of 13–14 sessions were associated with significantly more live births compared with no treatment or ET acupuncture.<sup>42</sup> Optimal acupuncture protocols, with increased numbers of acupuncture sessions, should include ET acupuncture. This comprehensive approach may reduce anxiety and stress, and improve quality of life, during the transfer phase of an IVF cycle. However, the adequate number of sessions needed, or acupuncture dosage, to improve IVF outcomes needs to be determined.

#### Characterisation of acupuncture treatment responders

More research is needed to identify and characterise treatment responders to acupuncture. Thus far, the majority of trials investigating acupuncture and IVF have focused on women under 40 undergoing fresh non-donor egg cycles. Patient demographics and treatment according to IVF cycle types may all be important variables to consider in acupuncture IVF RCT methodology. A recent multicentre RCT found women with Follicle Stimulating Hormone (FSH) levels above 7 appear to receive greater benefit from acupuncture administered on ET day.<sup>43</sup> Acupuncture during IVF was associated with the greatest benefit in women over 40.<sup>44</sup> IVF cycle type may also be a predictor of response, as ET acupuncture for donor egg cycles was associated with more live births, while the effect of same acupuncture protocol was equivocal on non-donor egg cycles.<sup>34</sup>

#### Alternative trial designs

Alternative trial designs to examine the effectiveness of acupuncture and a move away from the placebo-controlled RCT should be considered. Pragmatic acupuncture trial design permits the acupuncture intervention to be delivered similar to real-world clinical settings, as discussed above. Meaningful IVF patient-centred information could be gained from comparing acupuncture with interventions like a mind/body programme, relaxation massage or mindfulness-based stress reduction. The limitation of performing such trials is the inability to determine if the outcomes were due to specific, non-specific and/or placebo effects. But pragmatic trials would control for the time and attention aspect of receiving acupuncture.

#### CONCLUSION

Despite widespread use of acupuncture by women undergoing IVF, and thousands of years of anecdotal evidence, scientific evidence to validate the use of acupuncture to improve IVF outcomes is inconclusive. Mechanistic studies show acupuncture benefits many physiological aspects of the female reproductive system, but methodological flaws confound acupuncture IVF RCTs and limit the ability to interpret clinically meaningful outcomes. The most important issues are fixed protocol bias, inappropriate controls and inadequate

acupuncture dosage. Pragmatic acupuncture trial models, especially comparative effectiveness, represent potentially more optimal approaches to assessing the effectiveness of acupuncture on IVF patient outcomes and their quality of life. Better approaches to determine the value of acupuncture to IVF patients are urgently needed due to prevalence of IVF use, the inability of specialists to make referral decisions based on current evidence and the ongoing pursuit of acupuncture by IVF patients, who will largely pay out-of-pocket.

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