

# The Limitation of Randomized Control Trials on the Influence of Acupuncture and *In Vitro* Fertilization: A Literature Review

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## ABSTRACT

**Objective:** Acupuncture has gained popularity among patients undergoing *in vitro* fertilization (IVF). However, the beneficial effect of acupuncture for improving IVF success is controversial and debatable. Given that different meta-analyses have come to different conclusions, it is crucial to explore the clinical trials in more detail. This literature review examined the limitation of randomized controlled trials (RCTs) on the influence of acupuncture in IVF.

**Methods:** This review began with 844 studies. The inclusion criteria were studies that had acupuncture treatments in conjunction with IVF. After exclusion criteria were applied, the final number of peer-reviewed studies was 10.

**Results:** There were substantial variations in the results of the 10 RCTs. This seemed to suggest that acupuncture was not effective in conjunction with IVF treatment. However, limitations emerged that might explain these variations in results. Such limitations include timing of acupuncture and point selections; acupuncture not performed by experienced licensed acupuncturists; lack of Traditional Chinese Medicine diagnoses and fixed protocols causing biases; acupuncture dosages; and using sham acupuncture as a control.

**Conclusions:** There is an urgent need for further research into the effectiveness of acupuncture for improving IVF outcomes. This review provides insight into this complex and controversial topic, revealing limitations of the clinical trials that led to different conclusions. If future research can examine acupuncture treatment carefully to resemble real-world clinical practice—having appropriate controls and individualized acupuncture treatments—increasingly positive effects from acupuncture in IVF may be expected.

**Keywords:** infertility, IVF, embryo transfer, acupuncture, randomized trials

## INTRODUCTION

THE PREVALENCE OF INFERTILITY has increased since the past decade, with rates ranging from 9% to 18% in different parts of the world.<sup>1</sup> For patients facing infertility, *in vitro* fertilization (IVF) is perceived as the last remaining hope for being able to achieve a successful pregnancy.<sup>2</sup> Despite the advances in assisted reproductive technology

(ART), pregnancy rates remain low, at ~30%.<sup>3,4</sup> Especially in advanced maternal age, live birth rates from IVF range from 33.5% for 38–40-year-old women to 17.7% for 41–42-year-olds women.<sup>3</sup> Hence, for patients who need to undergo various cycles of IVF, it often causes great emotional stress and frustration.

Acupuncture has gained popularity around the world due to its effectiveness, lack of side-effects, and relatively low

cost, compared to biomedical treatments. After Stener-Victorin and his colleagues<sup>5</sup> suggested that acupuncture could be used as an adjunctive therapy in IVF in 1999, this attracted great interest, leading to more than 40 clinical trials in recent years. Despite Manheimer et al.<sup>6</sup> and Ng et al.<sup>7</sup> concluding that acupuncture given around the time of embryo transfer (ET) improved clinical pregnancy rates (CPRs) and live births in women undergoing IVF; 4 other meta-analyses could not confirm the same beneficial effect. Given that different meta-analyses on the effects of acupuncture on IVF outcomes have come to different conclusions, it is still a matter of debate on whether or not acupuncture improves pregnancy rates.<sup>8</sup>

The reason why meta-analyses have led to contradictory conclusions could be due to study designs, sample sizes, or methods of searching the literature. Although this is not the main focus of this review, it inspired this review to examine the details of each randomized controlled trial (RCT) and to make an attempt to achieve what would be considered the best practice in Traditional Chinese Medicine (TCM) for treating infertility. Therefore, this literature review examined the limitations of RCTs on the influence of acupuncture and IVF.

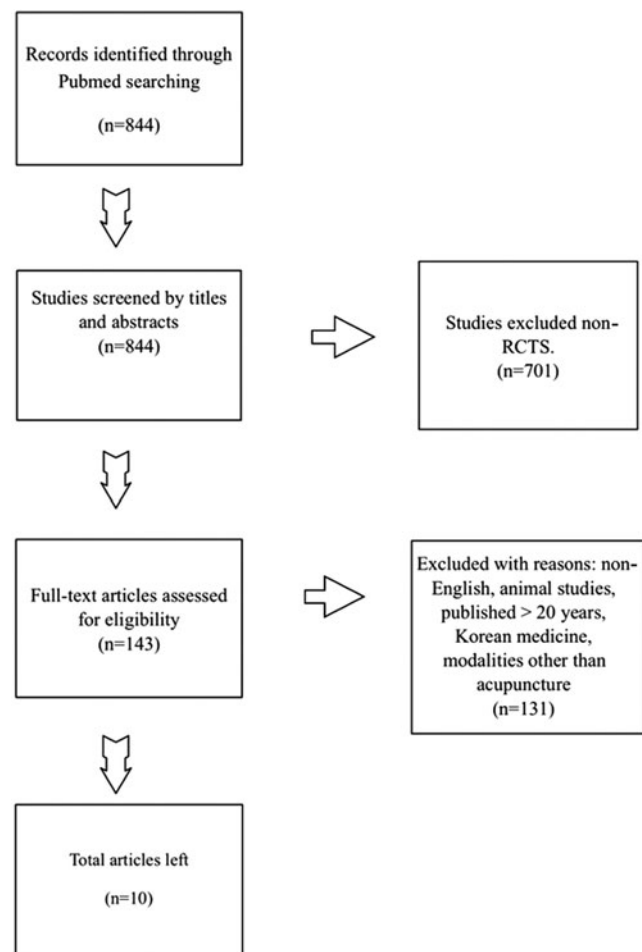
## METHODS

The literature search included PubMed, peer-reviewed scholarly articles published with no limitation on publication dates within 20 years of the current year that were full-text and sorted by best match to the following search terms: Acupuncture; acupuncture therapy; needle; dry needling; Traditional Chinese Medicine; Assisted Reproductive Technique; and Fertilization in Vitro.

The review began with 844 studies. The inclusion criteria were RCTs on acupuncture treatments with IVF. The exclusion criteria were studies that were not based on TCM; any studies published more than 20 years ago; any male-infertility-related articles; any studies published in a language other than English; any nonhuman studies; any studies with fewer than 50 subjects; or any studies using any modalities other than TCM, including acupuncture. This left the final number of peer-reviewed studies for this review at 10 studies. Figure 1 illustrates how eligibility was identified.

## RESULTS

RCTs are valued in modern medicine because they can: test for causality; determine the magnitude of an effect; assess risks and benefits of treatments; and minimize selection and measurement bias.<sup>9</sup> Therefore, to grasp the limitation of RCTs, it was necessary to examine the study design in each of the 10 RCTs (Fig. 2).



**FIG. 1.** Flow diagram for identification of eligible studies. RCT, randomized controlled trial.

## True Acupuncture Versus No-Acupuncture

In 2002, Paulus et al.<sup>9</sup> conducted the first prospective RCT on 160 infertile women (ages 21–43) undergoing IVF. There were 2 groups—an acupuncture group and a no-acupuncture group. The acupuncture treatments were performed 25 minutes before and after ET. Acupoints before ET were PC 6, SP 8, LR 3, GV 20, and ST 29; after ET, the acupoints were ST 36, SP 6, SP 10, and LI 4. Paulus et al. noted that these choices were based on “acupuncture points that relax the uterus according to the principles of TCM.” Auricular-acupuncture points for fertility were also selected. The CPRs in the acupuncture and no-acupuncture arms were 42.5% and 26.3%, respectively ( $P=0.03$ ). This study received widespread media coverage internationally, and the demand for acupuncture treatment by patients who had infertility worldwide has increased ever since.

In 2009, Domar et al.<sup>10</sup> tried to replicate the research by Paulus et al.<sup>9</sup> This newer study recruited 146 patients, and had CPRs and results of questionnaires on anxiety level and optimism as main outcome measures. Unfortunately, these

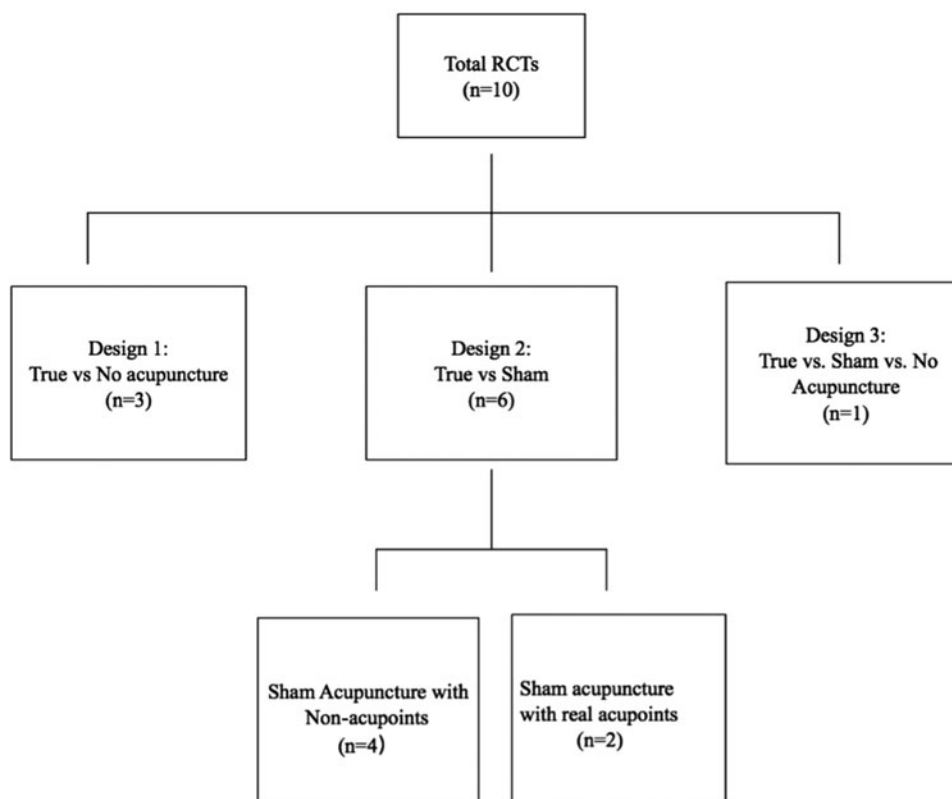


FIG. 2. Grouping methods. RCTs, randomized controlled trials.

researchers did not find significant differences in CPRs between both groups (acupuncture = 50.0% versus control group = 42.6%). However, patients in the acupuncture group reported significantly lower anxiety after ET than the control group, while also feeling significantly more optimistic about their chances of conception. The only difference between this study and previous ones is that the entire medical team was blinded to the patients' assignments.

In Brazil, Madaschi et al.<sup>11</sup> recruited a total of 416 patients and randomized the patients to either a control group or an acupuncture group. The acupuncture group's protocol was based on Paulus et al.'s study<sup>9</sup> as well. The results suggested that acupuncture treatment had no influence on clinical outcomes when performed before and after ET. To minimize the embryo quality affected by a maternal effect or paternal effect, the cycles in which the causes of infertility were due to idiopathic or tubal-uterine factors were evaluated separately. When the researchers analyzed this particular subgroup, they found a positive influence of acupuncture on pregnancy. This finding was significant because it is now arguable that an effect of acupuncture on endometrium implantation might exist.

### True Acupuncture Versus Sham Acupuncture

Many studies have shown consistently that placebo acupuncture is not inert and does have a beneficial effect.

Creating a control group has always been a problem that acupuncture research has to face. Physiologic acupuncture effects are implied if non-acupoint needling is administered in the control group. Therefore, the effects shown in this type of control group are often close to those shown in the acupuncture group.<sup>12</sup>

### Sham Acupuncture Using Non-Acupoints

Noninvasive placebo acupuncture appears to be the best control in acupuncture studies according to Stener-Victorin et al.<sup>13</sup> There were 4 studies that used non-acupoints as their sham-acupuncture groups.

Among the studies that used sham acupuncture as control groups, Dieterle et al.<sup>14</sup> was the only study concluding that its true-acupuncture group had a significantly higher pregnancy rate than its sham-acupuncture group. Dieterle et al.<sup>14</sup> had 225 infertile patients undergoing IVF/intracytoplasmic sperm injection (ICSI). Of the patients, 116 were randomized into Group 1 (study group) in which they received luteal-phase acupuncture according to the principles of TCM. Group 2 (control group) had 109 patients who received placebo acupuncture. In both groups, acupuncture was applied on the day of ET, 30 minutes immediately after the ET procedure, and again 3 days later. Group 1 had RN 4, RN 6, ST 29, PC 6, SP 10, and SP 8 needled. At the same time, a *Caryophyllaceae*, seed of *Vaccaria segetalis* was

placed on each patient's ear on stress-relief and fertility-related points. The second treatment for Group 1 used LI 4, SP 6, ST 36, KI 3, and LV 3. Group 2 was designed not to influence fertility, so the researchers chose points on the *San Jiao* meridian and Gallbladder meridian, which traditionally are not considered as meridians for fertility treatment. Non-fertility-related ear points were also used for Group 2. In Group 1, the pregnancy rate was significantly higher than in Group 2 (33.6% and 15.6%, respectively).

Smith et al.<sup>15</sup> allocated 228 patients randomly to acupuncture or sham acupuncture (with a placebo needle). Compared with other clinical trials of acupuncture, this study included a larger sample size. The researchers also used Paulus et al.'s protocol<sup>9</sup> with two modifications: (1) 2 acupoints were excluded (LV 4 and GV 20) from the initial acupuncture treatment administered before ET. (2) acupuncture was administered with point selections based on each patient's TCM diagnosis. All patients received 3 sessions, the first was on day 9 of stimulating injections, before and immediately after ET. For women in the control group, the points used were located close to but not on the verum points. The Streitberger placebo needle (a needle tip that is blunted) was used; thus, the needles did not penetrate the patient's skin. The acupuncture group's pregnancy rate was 31%, while the sham-acupuncture group had 23% but the difference did not reach statistical significance. Apart from the primary outcome, the researchers did find that there was an increase in relaxation reported in the control group, suggesting physiologic changes occurred but not on blood flow to the uterus, which had contributed to successful implantation.

Moy et al.<sup>16</sup> conducted the first RCT, published in the United States, comparing fertility outcomes of sham and true acupuncture completed on day 3 of ET. The study included 168 patients under age 38 undergoing IVF with or without ICSI. Apart from the CPR as the primary outcome, the researchers also used the McGill Pain Questionnaire. The study explored the question of whether or not true acupuncture in classical meridians was superior to sham needling of points not located on meridians. These researchers followed Paulus et al.'s basic protocol<sup>9</sup>—2 25-minute acupuncture sessions, with 1 before and 1 after ET. The only difference was that the researchers replaced PC 6 with RN 6 (Sea of Qi). In the sham group, the researchers used penetrating needles as Dieterle et al. had done.<sup>14</sup> Unlike Dieterle et al., Smith et al. placed needles in the sham group in non-acupuncture points rather than in non-infertility-related points. These researchers concluded that there was no significant difference between the 2 groups in the study (true = 45.3% versus sham = 52.7%).

Smith et al.<sup>17</sup> conducted an RCT on live births to determine the efficacy of acupuncture, compared with sham acupuncture (control), during IVF. This single-blinded, parallel-group RCT started with 848 women undergoing a fresh IVF cycle in Australia and New Zealand. Of these women, 824 received either acupuncture or sham acupuncture. The first treatment was given between days 6–8 of

follicle stimulation, and 2 treatments were given before and after ET. The acupuncture protocol was developed using a Delphi method, with a treatment strategy based on TCM. The first treatment points were ST 29, Ren 4, Ren 6, SP 6, and SP 10. In addition, up to 5 additional points based on TCM diagnoses, were selected from a standardized protocol. On the day of ET, an initial treatment was administered within 1 hour prior to ET, using ST 29, SP 8, SP 10, LR 3, Ren 4; 1 point from HT 7, PC 6, or *Yin Tang*; and auricular point *Zigong*. The second acupuncture treatment included DU 20, KD 3, ST 36, SP 6, PC 6, and the auricular point *Shen Men*. Control group patients were needled at sham points at locations away from known points to minimize physiologic effects. A Park device was also used to minimize any physiologic effects. Live births occurred in 18.3% of the patients who received true acupuncture, compared with 17.8% in the sham control group. Thus, there was no significant difference in live birth rates.

### Sham Acupuncture Using True Acupoints

Acupressure over acupoints has been shown to be an effective intervention for a number of clinical conditions. Therefore, using a noninvasive placebo needle may elicit physiologic effects. So et al.<sup>18</sup> put forward this point of view after concluding that the overall pregnancy rate was significantly higher in their study's sham acupuncture group than in its real acupuncture group. It is worth noting that this was the only study that came reached this conclusion among the studies in this review.

So et al.<sup>18</sup> compared real acupuncture with placebo acupuncture in patients undergoing IVF. The study used a randomized double-blinded method and was conducted in Hong Kong, where 370 patients were randomly allocated to either group. A registered TCM practitioner categorized these patients' conditions by four diagnostic methods according to TCM principles. The patients received 25 minutes of real or placebo acupuncture before and after ET. The acupoints used before ET were PC 6, SP 8, LR 3, GV 20, and ST 29. After ET, the needles were inserted at ST 36, SP 6, SP 10, and L 14. The placebo group underwent the same protocol performed by the same certified acupuncturists but with Streitberger's placebo needles instead. So et al. concluded that the overall pregnancy rate was significantly higher in the placebo acupuncture group than in the real acupuncture group (55.1% versus 43.8%, respectively;  $P=0.038$ ). However, the researchers could not draw a firm conclusion from the study because a control arm without any acupuncture was not included for comparison. Reduction in endometrial and subendometrial vascularity, serum cortisol concentration, and the patients' anxiety levels were both noted in the real and placebo acupuncture groups.

Anderson et al.<sup>19</sup> conducted a large RCT with a total of 635 women <37 years old. The researchers excluded patients treated with frozen and thawed embryos and patients

who, in the actual cycle, already had received any kind of complementary treatments. The study examined whether or not acupuncture in relation to ET could increase ongoing pregnancy rates and live birth rates in women undergoing ART. The patients were randomized to either acupuncture or placebo acupuncture on the morning of ET. Both groups had the protocols performed by nurses who were authorized acupuncturists or nurses who received training by the four acupuncturists in the study. The acupuncture points used were identical to Paulus et al.'s<sup>9</sup> and Westergaard et al.'s.<sup>20</sup> Both groups had the same acupoints, and the patients rested with the needles in for 30 minutes before and after ET. The control group had validated Streitberger placebo-needle, in which the tip is blunt and a pricking sensation is felt by the patient, simulating puncturing of the skin. The researchers noted that in the acupuncture and placebo groups, the ongoing pregnancy rates were 27% and 32%, respectively. Live birth rates were 25% in the acupuncture group and 30% in the placebo group. These differences were not statistically significant. The results suggested that acupuncture had no effect on the outcomes of IVF and ICSI in relation to ET.

### True Acupuncture Versus Sham Acupuncture Versus No-Acupuncture

Westergaard et al.<sup>20</sup> randomized 300 patients undergoing IVF or ICSI into 3 groups. The control group received no acupuncture treatment. The ACU 1 and 2 groups received acupuncture immediately before and after ET. Additionally, another acupuncture session was performed again 2 days later in the ACU 2 group. The acupuncture points were basically the same as Paulus' protocol.<sup>9</sup> The ACU 2 group's additional session 2 days after ET had the following acupoints: DU 20; RN 3; ST 29; SP 10; SP 6; ST 36; and LI 4. The CPR was significantly higher in the ACU 1 group, compared with the control group (39% versus 26%), and the ACU 2 group CPR was also higher than the control group, but the difference did not reach statistical significance. The researchers concluded that acupuncture on the day of ET improves the reproductive outcome of IVF significantly and that adding acupuncture closer to the day of implantation did not improve the reproductive outcome further.

Another interesting conclusion revealed in this study<sup>20</sup> is that women older than age 38 did not have outcomes significantly different (control versus ACU1: 25% and 26%, respectively), compared to women younger than 38 (control versus ACU1: 23% and 49%, respectively). These age-related differences are difficult to explain, but show that acupuncture might be limited in its ability to improve CPRs for women who are 38 years or older.

In Westergaard's<sup>20</sup> study, placebo acupuncture was not used, so it could be argued that the outcomes of the 2 acupuncture groups could be placebo effects. However, these researchers argued that, if there were placebo effects associated with the acupuncture treatment environment, then the

ACU 2 group receiving more sessions on different days would have improved the outcome further, but this was not the case. This is important because the researchers raised a very solid question to answer critics who tend to argue that acupuncture is just a placebo effect.

### NOTE

The summary of the RCTs covered in this review are in Table 1.

### Limitations of the Research

After reviewing all the RCTs, it was not hard to find substantial variations in the results. While this often suggests that acupuncture is not effective in conjunction with IVF treatment, close inspection of the individual study designs illustrate significant limitations that may explain the variations in these results. Such limitations included: timing of acupuncture and point selections; acupuncture not performed by an experienced licensed acupuncturist; lack of TCM diagnoses and fixed protocol biases; acupuncture dosages; and sham acupuncture used as control groups. Similar views have been supported by Anderson and Rosenthal,<sup>21</sup> who found that these limitations are often overlooked by journal reviewers that publish these clinical studies, and by biomedical readers—because they are largely unaware of how acupuncture is practiced in real world settings.

### Timing of Acupuncture and Point Selections

According to Anderson and Rosenthal,<sup>21</sup> if acupuncture is applied at different timepoints, it will produce different results in women, because the effect of acupuncture changes with the menstrual cycle. Dieterle et al.<sup>14</sup> had a session that was 3 days after ET. This is usually when the blastocyst attaches more deeply into the uterine lining; it is the beginning of implantation. It is known that after ET, women should try to avoid strenuous workouts; it is best to take it easy and opt for mild exercise. The majority of the studies<sup>9,10,14,16,17,18,20</sup> in this review used points such as LI 4, LV 3, or SP 6 either immediately or days after ET. According to TCM classic theory, LI 4 and SP 6 are considered Forbidden points during pregnancy as they might cause miscarriages. This raises the following question: If these points are forbidden during pregnancy, would it be a good idea to include them immediately after ET or even 3 days after? Zheng et al.'s<sup>22</sup> meta-analysis review also support this viewpoint. These researchers found large heterogeneities among these clinical trials, especially in acupuncture treatments and acupoint selections. All TCM textbooks—from ancient to modern—emphasize clearly that needling at some acupoints is not appropriate for pregnant women, because a miscarriage may result.

TABLE 1. SUMMARY OF RANDOMIZED CONTROLLED TRIALS

<i>Study (1<sup>st</sup> author, yr, &amp; ref. #)</i>	<i>Participants</i>	<i>Intervention</i>	<i>Control</i>	<i>IVF outcomes</i>
Paulus et al., 2002 <sup>9</sup>	160 randomized—only women with good quality embryos included	25 min before & after ET	Bed rest for 25 min	CPR
Domar, et al., 2009 <sup>10</sup>	150 randomized—women scheduled to have ET with non-donor eggs were eligible	2 sessions—25 min before & after ET	Bed rest for 25 min	CPR, anxiety, optimism on surveys
Madaschi et al., 2010 <sup>11</sup>	416 randomized—women undergoing ICSI cycles for the first time	2 sessions—25 min before & after ET	No intervention	CPR, IR, LBR, MR
Dieterle et al., 2006 <sup>14</sup>	225 randomized—no inclusion criteria	30 min after ET & again 3 days later	Placebo needling at acupoints indicated not to influence fertility	CPR, OPR
Smith et al., 2006 <sup>15</sup>	228 randomized—women with a planned ET were eligible	3 sessions—day 9 & before & after ET	Placebo needling at points close to the real acupuncture	CPR, OPR, IR
Moy et al., 2011 <sup>16</sup>	161 randomized—women < age 38 old undergoing IVF, with or without ICSI	2 sessions—25 min before & after ET	Placebo needling on non-acupoints	CPR, CPR*
Smith et al., 1998 <sup>17</sup>	848 randomized—women undergoing fresh IVF cycles	3 sessions—follicle stimulation day & before after ET	Placebo needling on non-acupoints	CPR, LBR
So et al., 2009, <sup>18</sup>	370 randomized—women who had normal uterine cavities shown on US scanning on the day of TVOR	2 sessions—25 min before & after ET	Placebo needling on the same acupoints	CPR, OPR, IR, LBR, MR
Andersen et al., 2010 <sup>19</sup>	635 randomized—< age 37, treatment with IVF/ICSI & transfer of 1 or 2 embryos in the 1st, 2nd, or 3rd stimulated cycle	2 sessions—30 min before & after ET	Placebo needling on the same acupoints	CPR, OPR, LBR
Westergaard et al., 2006 <sup>20</sup>	300 randomized—no inclusion criteria	2 or 3 sessions 25 min before & after ET, with or without a 3rd session for 25 min 2 days after ET	Bed rest for 1 hr after ET	CPR, OPR

yr, year; min, minutes; ET, embryo transfer; CPR, clinical pregnancy rate; OPR, ongoing pregnancy rate; IR, implantation rate; hr, hour; US, ultrasound; TVOR, transvaginal oocyte retrieval; LBR, live birth rate; MR, miscarriage rate; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; CPR\*, chemical pregnancy rate.

However, 1 review showed that using Forbidden points was not associated with increased rates of adverse pregnancy outcomes in controlled clinical trials.<sup>23</sup> This is still a scientifically unknown area that awaits exploration. It is not fully understood how Qi works in meridians throughout the body and what role Qi plays according to the biomedical perspective. Therefore, it is still questionable whether or not using contraindicated points after ET would lower the pregnancy rate. Hence, any uses of “the Four Gates” (LI 4 and LV 3), with the hope of redistributing Qi, or any of the Forbidden points contraindicated in pregnancy should be carefully reconsidered in any clinical trials that attempts to increase pregnancy rates.

### Acupuncture Administered by Non-Acupuncturists

Several studies<sup>14,19,20</sup> showed that the acupuncture procedures were not administered by licensed acupuncturists but rather by nurses or technicians who had very limited training in acupuncture before treating the patients. In reality, it takes years of training and practicing before one can be experienced in acupuncture. For instance, De Qi (an excitation of Qi or life force inside meridians induced by stimulation of acupuncture needles) is considered an essential part of the process to achieve therapeutic effectiveness in acupuncture treatment.<sup>24</sup> Although most of the individuals performing the acupuncture in these studies believed that they achieved De Qi sensations, without experience, the so called “sensations” could just have been the pain when the needle penetrates the skin or a nervous response caused by the needle hitting a nerve. When acupuncture treatments were not done by licensed acupuncturists, it added another avoidable bias in the outcome of those studies.

Given that every country or area may have different qualifications for licensed acupuncturists, it would be better to have experienced acupuncturists administer acupuncture in clinical trials.

### Lack of TCM Diagnoses and Fixed Protocol Bias

The Delphi method used in Smith et al.<sup>17</sup> is a relatively new approach, compared to the protocol used based on TCM principles. The Delphi method is based on the results of multiple rounds of questionnaires interspersed with controlled opinion feedback collected from a panel of experts.<sup>25</sup> Either method has fallen into a fixed protocol bias. Although some acupuncture points are recommended for each TCM pattern according to TCM classics, it is still important to modify the acupuncture points based on individual symptoms and patients' constitutions. In other words, there is no such thing as “a fixed protocol” that is supposed to suit every single patient. It is incompatible with the individualized nature of TCM.

### Acupuncture Dosages

According to Anderson and Rosenthal,<sup>21</sup> acupuncture dosage includes the number of points needed in a single treatment and the total number of treatments that the patient receives. Most of the studies in this review adopted the so-called “Paulus protocol,”<sup>9</sup> the same regimen often recommended by fertility clinics to women undergoing IVF. This protocol of acupuncture 25 minutes before and after ET somehow became the role model, and many RCTs have adopted it. In terms of needle points, it consists of 4–5 body acupoints and an additional 4 ear acupoints for each treatment. This is considered a very low dosage of acupuncture, on both the number of needles in a single treatment and the total of number of treatments. The clinically *recommended* dosage of acupuncture usually includes 6–10 (or often more) acupuncture points given in each of at least 6 (or often more) acupuncture treatments.<sup>21</sup> Therefore, Anderson and Rosenthal<sup>21</sup> suggested that it is most advisable to start acupuncture and Chinese herbal medicine 3–6 months before undergoing ART, if circumstances allow.

### Sham Acupuncture as a Control

Several placebo-controlled randomized trials have been published addressing acupuncture in relation to ET in the last decade. This type of trial is still considered the gold standard for demonstrating that a treatment has a specific effect over placebo.<sup>19</sup> Dieterle et al.<sup>14</sup> were using points on *San Jiao* and Gallbladder meridians and assumed they would not influence fertility. Other studies<sup>15,16,17</sup> used non-acupuncture points to achieve the same effect. However, there have been arguments against placebo (sham) acupuncture. Birkeflet et al.<sup>26</sup> argued that it was not rational to choose non-acupuncture points or superficial puncturing on acupoints for sham acupuncture, because, according to Chinese medicine's meridian theory, the human body is like a network covered with meridians—divergent meridians and Extraordinary meridians; and muscle tendons and skin areas. These meridians and areas either have direct contact with viscera or work as connections that bridges the paths between them. Therefore, it is very difficult to choose a point and prove that it has no effect on the body. So et al.<sup>18</sup> also suggested that placebo acupuncture may not be an inert control; these researchers found significant changes in physiology and psychology following the placebo and real acupuncture treatments.

## DISCUSSION

Since Paulus and his colleagues<sup>9</sup> published the results of the first RCT investigating the effects of acupuncture on pregnancy rates of patients undergoing IVF, many RCTs were conducted and have led to contradictory conclusions. The aim of this literature review was to examine the

limitations of RCTs on the influence of acupuncture and IVF. After reviewing all the RCTs and the individual study designs, it is not hard to find that there were significant limitations that have led to the variations in results. Anderson and Rosenthal stated: “Consequently, it becomes very difficult to demonstrate a statistically significant difference between a suboptimal verum intervention and a therapeutically beneficial placebo intervention.”<sup>21</sup>

The majority of the studies<sup>9,10,14,16–18,20</sup> in this review used points contraindicated during pregnancy and then administering acupuncture immediately or in the days after ET. Although Carr<sup>23</sup> showed that there was no adverse effect induced by these points, it is still unclear what the effect would be of these points administered at this timing on implantation rates. Hence, any uses of controversial points after ET should be reconsidered carefully.

In addition, several studies<sup>14,19,20</sup> showed that the acupuncture procedures were not administered by licensed acupuncturists but by nurses or medical doctors who had very limited training in acupuncture, potentially adding bias and error to the administration of the studies. While different countries have different qualifications for licensed acupuncturists, it would be best to have experienced acupuncturists to eliminate bias in future clinical trials.

Whether or not it is the Delphi method used in Smith et al.<sup>17</sup> or Paulus et al.’s<sup>9</sup> protocol based on TCM principles, either method has a fixed protocol bias. Such biased results occur when the same acupuncture treatment protocol is administered to all patients regardless of their TCM diagnoses. TCM diagnosis is important because it determines acupuncture-point selections.<sup>27</sup> Most RCTs in this review did not include TCM diagnoses at all, or as So et al.’s<sup>18</sup> study, the studies used TCM diagnoses in patients before treatments but decided to proceed with standardized protocols anyway. Although the acupuncture points chosen were recommended by TCM classics, it is still essential to modify the acupuncture points based on individual symptoms and patients’ constitutions. In reality, TCM treatments are largely focused on individualizations; therefore, no fixed protocol will suit every patient.<sup>28</sup>

Most of the studies in this review only had 2–3 sessions of acupuncture, 25 minutes before and after ET, with or without that third session. This is considered a very low dosage of acupuncture. This refers to the so called “Paulus protocols”: acupuncture 25 minutes before and after ET.<sup>9</sup> The same regimen is often recommended by fertility clinics to women undergoing IVF. It only consists of 4–5 body acupoints and an additional 4 ear acupoints and a total of 2 treatment sessions. This is far from the clinically required dosage of acupuncture.

Finally, placebo-controlled randomized trials are considered the gold standard for demonstrating that a treatment has a specific effect over placebo<sup>14,19</sup> and other studies<sup>15–17</sup> have tried to use either non-fertility-related acupoints or non-acupuncture points to minimize the effect of the pla-

cebo. Birkeflet et al.<sup>26</sup> argued that it is not rational to choose non-acupuncture points or perform superficial puncturing on acupoints for sham acupuncture because, based on Chinese medicine’s meridian theory, the human body is a network and the meridians are all connected. It is very difficult to choose a point and prove that it has zero effect on the body. So et al.<sup>18</sup> also supported this theory based on their findings. Westergaard et al.<sup>20</sup> did not use placebo acupuncture in their study, and it could be argued that the improvement of the reproductive outcomes found in the acupuncture group could have been a placebo effect. If a placebo effect existed in that study, then the other acupuncture group who had an extra session would have further improved reproductive outcomes, but this was not the case. This is significant because it shows that acupuncture is not just a placebo.

## Research Implications

Subfertility has been a growing problem for various reasons. IVF is perceived as the last remaining hope of being able to achieve a successful pregnancy. However, the success rate still remains low. Although many clinical trials were conducted in the past decades the effectiveness of acupuncture in IVF still remains debatable. This review provided an insight regarding this complex and controversial topic. The review revealed the limitations of the clinical trials that led to different and conflicting conclusions. It will make a big difference if a well-constructed RCT was designed and conducted in the future.

## Limitations

The results of this review showed clearly that there were many existing limitations in the current RCTs that may have influence their study outcomes. What is less clear is if all of the extant RCTs in acupuncture and IVF have the same limitations. Furthermore, the quality and quantity of the trials included in this article were considered low. There are far too many RCTs conducted in the past decades, and the total of 10 articles reviewed in herein merely have small differences in outcomes and their study designs, which is unlikely to make too much of a difference.

## Recommendations for Future Research

This review only began to reveal the limitations of RCTs that current researchers are facing. In the future, studies should let experienced acupuncturists diagnose each patient based on TCM principles and use individualized acupuncture points rather than a “one-size-fits-all” fixed protocol. TCM emphasizes individualized treatment based on a syndrome-differentiation system, which is similar to tailored medical, personalized, and precision medicine.<sup>29</sup> The frequency of acupuncture treatments should also vary



depending on an individual's situation—and merely 2 sessions is definitely far from enough dosage for many patients.

Placebo controls are commonly used to exclude psychologic factors. The studies have shown that it is difficult to establish reasonable controls in clinical acupuncture research and that acupuncture's effects have been questioned because of that. If sham acupuncture may not be an inert control and may affect the pregnancy outcome, and the aim is only to evaluate the effectiveness of acupuncture, a nonintervention control or relaxation control would probably suffice.<sup>22</sup>

## CONCLUSIONS

Given that more women are undergoing IVF now, there is an urgent need for further research on the effectiveness of acupuncture for improving IVF outcomes. Although there are many limitations in current RCTs, if future research can examine acupuncture treatment to resemble real-world clinical practice, such as an appropriate control and individualized acupuncture treatments, a more-objective understanding of the clinical outcomes as well as a potential for more-positive effects of acupuncture with IVF can be expected. Additionally, use of placebo acupuncture may affect the outcomes; therefore, replacing placebo acupuncture with a nonintervention control or relaxation control is needed. Whether acupuncture is beneficial in terms of improving pregnancy rates in IVF still remains subject to further well-designed RCTs.

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