Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 677–684

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

# The effects of acupuncture on pregnancy outcomes of in vitro fertilization with embryo transfer: An interdisciplinary systematic review

Ying-Er Gu[1], Xian Zhang[1], Qing Zhang[1], Min-Chen Dai, Yan Wu, Yong Zhou, Fan Qu*

*Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China*

ARTICLE INFO

*Article history:*
Received 7 March 2019
Received in revised form 25 June 2019
Accepted 1 July 2019
Available online 2 July 2019

*Keywords:*
Acupuncture
In vitro fertilization
Embryo transfer
Systematic review

ABSTRACT

The present systematic review is designed to summarize the evidence concerning the effect of acupuncture on pregnancy outcomes in vitro fertilization with embryo transfer (IVF-ET). We searched MEDLINE, the Wanfang Database, the China Academic Journal Electronic Full-text Database in the China National Knowledge Infrastructure, and the Index to Chinese Periodical Literature. Randomized controlled trials with intervention groups using acupuncture and control groups consisting of no acupuncture or sham (placebo) acupuncture in IVF-ET treatment were selected. Study characteristics were examined from these studies and an intention-to-treat approach was used to extract outcome data from each study. In total, 31 articles including 4450 women passed our selection criteria. The legitimacy, characteristics, and IVF outcomes of the included trials were summarized. Additional Traditional Chinese Medicine (TCM) theory-based, standardized, large-size, randomized, and multicenter trials are necessary prior to any conclusions being drawn on whether TCM can improve IVF outcomes.


**Contents**



## Introduction

In vitro fertilization with embryo transfer (IVF-ET) is an effective treatment for infertility worldwide, and 4,461,309 cycles were initiated between 2008 and 2010, resulting in the birth of approximately 1.15 million babies [1]. During the 3-year period of this study, the number of initiated cycles increased by almost 9.5% per annum, while the number of babies born increased by 9.1% per annum [1]. In recent years, although some new and interdisciplinary interventions have been developed, the average success rates per IVF cycle remain low, and progress in developing safe and effective therapies has been limited [2,3]. Consequently, many infertile women then asked help to complementary and alternative medical treatments [4], among which acupuncture is a frequently used adjunctive therapy.

Since the first report published in 1999 [5] suggesting that acupuncture can improve the pregnancy outcome of IVF, the application of acupuncture to IVF-ET has attracted attention from

* Corresponding author at: Women's Hospital, School of Medicine, Zhejiang University, 1 Xueshi Road, Hangzhou, Zhejiang, 310006, China.
*E-mail address:* syqufan@zju.edu.cn (F. Qu).
[1] The three authors contributed equally to the present study.

http://dx.doi.org/10.1016/j.jogoh.2019.07.008

the international community. A growing number of studies evaluating the effect of acupuncture on IVF outcomes have been performed in recent years, but they yielded inconclusive or conflicting results. Several systematic reviews and meta-analyses analyzed the effects of acupuncture among women undergoing IVF but led to contradictory conclusions [3,6–11]. Whether acupuncture improves IVF pregnancy rates is still a matter of debate. The present methodical review is designed to summarize evidence concerning the therapeutic effect of acupuncture on IVF outcomes during the administration of IVF-ET, which may provide guidance for clinical practice.

## Methods

We searched in MEDLINE (1966 to June 2019), the Wanfang Database (1982 to June 2019), China Academic Journal Electronic Full-text Database in the China National Knowledge Infrastructure (1982 to June 2019), and the Index to Chinese Periodical Literature (1978 to June 2019). The citation lists of review articles and relevant primary articles were scrutinized to reveal additional articles not highlighted by the above examination of databases. Additional information was collected by approaching the corresponding authors. No constraints of issue type or language were applied during searches. As free-text terms and Medical Subject Headings (MeSH) terms, the following keywords were sought: 'Traditional Chinese Medicine', 'acupuncture', 'auricular acupuncture', 'moxibustion', 'acupuncture therapy', 'acupressure', 'electroacupuncture' and 'auriculotherapy' as well as 'in vitro fertilization', 'embryo implantation', 'assisted reproductive techniques', 'fertilization in vitro', 'egg collection',' oocytes', and 'embryo transfer'.

Randomized controlled trials (RCTs) that evaluated the effects of acupuncture on IVF outcomes in women undergoing IVF, without intracytoplasmic sperm injection (ICSI), were selected. Women in intervention groups received acupuncture as an adjunctive of IVF-ET, while in control groups received IVF with or without no acupuncture intervention or with sham (placebo) acupuncture. Common regimens of acupuncture including traditional acupuncture (TA), electrical acupuncture (EA), auricular acupuncture (AA), transcutaneous electrical acupoint stimulation (TEAS) and laser acupuncture (LA) were considered therapeutic interventions. Trials with a crossover design were eliminated. The accepted studies needed to report at least one of the following two IVF outcomes: clinical pregnancy (detection of one or more fetal heartbeats or gestational sacs, ensured by transvaginal ultrasound), or live birth (presence of live birth after 24 weeks of pregnancy). Other IVF outcome data that could be extracted were ongoing pregnancy (more than 10 weeks gestation as defined by fetal heart activity on ultrasound), biochemical pregnancy (incidence of a definite urinary pregnancy test or human chorionic gonadotrophin test), implantation rate (number of gestational sacs per number of transferred embryos), or miscarriage (incidence of abortion prior to the 16th week of gestation).

Two reviewers examined the titles and abstracts of articles produced by the electronic searches (YG and XZ), and full manuscripts of all quotations that fit the predefined selection criteria were accepted. Any decision to include or exclude articles was made following full evaluation of the manuscript. For repeated publications, the most integrated and recent edition was chosen. Any disputes regarding inclusion were settled by a third reviewer (YZ).

The checklist produced by the Cochrane menstrual disorders and subfertility group was used for the appraisal of the methodological quality of publications. Information regarding the concealment of allocation, adequacy of randomization,

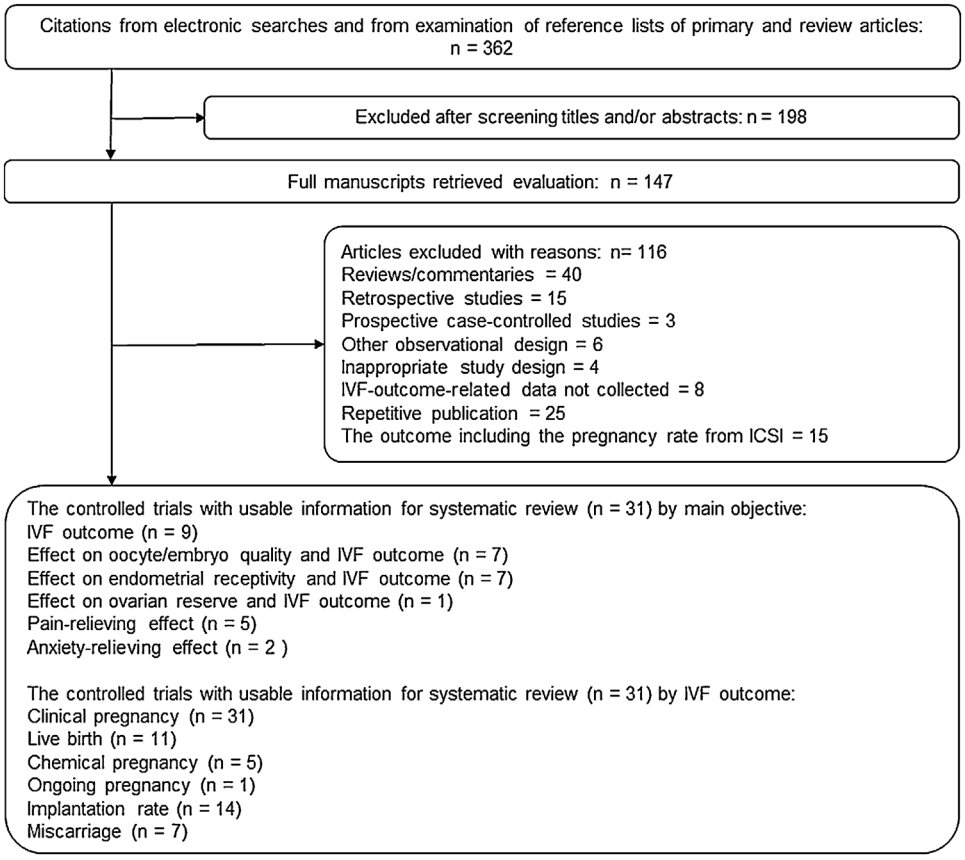


**Fig. 1.** The methods used to identify and select relevant literature.

blinding, and use of sham acupuncture, comparability at baseline, intention-to-treat (ITT) analysis, power analysis, and observance of the STRICTA (standards for reporting interventions in clinical trials of acupuncture) guidelines were searched by inspecting studies thoroughly in addition to contacting study authors if necessary. Acceptable delivery methods of pretended acupuncture included application of true acupuncture in the acupoints not formulated for the alleviation of any ailments, use of sham (placebo) needles, skin-deep needling in the true points or use of fake laser acupuncture.

Study features including population characteristics and intervening therapies were obtained from every trial report. Results data from the research articles were collected by means of an ITT approach.

**Table 1**
Quality of the 31 randomised trials involving the use of acupuncture during in vitro fertilization treatment included in the systematic review.

| Study | Single/ Multi center | Randomization method | Concealment of allocation | Comparability at baseline | Blinding | ITT | Adherence to STRICTA | Power analysis | Administered acupuncture |
|---|---|---|---|---|---|---|---|---|---|
| Stener-Victorin et al. (1999) [5] | Multicenter | Not mentioned | Adequate | Unclear | No | Yes | No | No | Trained midwives |
| Stener-Victorin et al. (2003) [12] | Multicenter | Sealed, unlabeled envelopes | Adequate | Yes | No | No | Yes | Yes | Trained nurses |
| Humaidan & Stener-Victorin (2004) [13] | Single center | Sealed, unlabeled envelopes | Adequate | Yes | No | Yes | Yes | Yes | Trained nurses |
| Gejervall et al. (2005) [14] | Single center | Computerized randomization | Unclear | Unclear | No | No | Yes | Yes | Four midwives |
| Sator-Katzenschlager et al. (2006) [15] | Single center | Computerized randomization | Unclear | Yes | Double blind | Yes | Yes | Yes | Trained gynecologist |
| Craig et al. (2007) [16] | Multicenter | Computerized randomization | Adequate | Yes | Single blind | No | No | No | Acupuncturist |
| Chen et al. (2009) [17] | Single center | Computerized randomization | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Domar et al. (2009) [18] | Single center | Computerized randomization | Adequate | Yes | Single blind | Yes | No | No | Acupuncturist |
| Cui et al.(2011) [19] | Single center | Sealed envelope way | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Sun et al.(2012) [20] | Single center | Computerized randomization | Unclear | Yes | No | Yes | No | No | Not mentioned |
| Gu et al.(2012) [21] | Single center | Random number table | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Villahermosa et al.(2013) [22] | Single center | Computerized randomization | Adequate | Yes | No | Yes | No | Yes | Not mentioned |
| Craig, et al.(2014) [23] | Multicenter | Computerized randomization | Adequate | Yes | Single blind | Yes | Yes | Yes | Acupuncturist |
| Qu et al.(2014) [24] | Single center | Computerized randomization | Adequate | Yes | Double blind | Yes | Yes | Yes | Two independent trained nurses |
| Li et al. (2015) [25] | Single center | Random number table | Unclear | Yes | No | No | No | No | Not mentioned |
| Shuai et al. (2015) [26] | Single center | Computerized randomization | Adequate | Yes | Single blind | Yes | No | No | Acupuncturist |
| Chen et al. (2015) [27] | Single center | Not mentioned | Adequate | Yes | Single blind | Unclear | No | No | Not mentioned |
| Yang et al.(2015) [28] | Single center | Random number table | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Zheng et al. (2015) [29] | Single center | Not mentioned | Unclear | Yes | Unclear | No | No | No | Not mentioned |
| Qu et al. (2017) [30] | Single-center | Computerized randomization | Adequate | Yes | Single blind | No | Yes | Yes | Two professional acupuncturists |
| Gao et al. (2017) [31] | Single-center | Random number table | Unclear | Yes | No | No | No | No | Not mentioned |
| Gao et al. (2017) [32] | Single-center | Not mentioned | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Peng et al. (2017) [33] | Single-center | Random number table | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Gillerman et al. (2018) [34] | Single-center | Computerized randomization | Adequate | Yes | Single blind | Yes | Yes | Yes | Acupuncturist with 20 years of experience |
| Jin et al. (2018) [35] | Single-center | Random number table | Unclear | Yes | No | No | No | No | Not mentioned |
| Ma et al. (2018) [36] | Single-center | Random number table | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Wang et al. (2018) [37] | Single-center | Random number table | Unclear | Yes | No | Unclear | Yes | No | Trained nurse |
| Xu et al. (2018) [38] | Single-center | Not mentioned | Unclear | No | No | Unclear | No | No | Not mentioned |
| Zhang et al. (2018) [39] | Single-center | Not mentioned | Unclear | Yes | No | Unclear | No | No | Not mentioned |
| Shuai et al. (2019) [40] | Single center | Block randomization | Adequate | Yes | Single blind | Yes | Yes | Yes | Professional acupuncturist with more than 3 years of experience |
| Gao et al. (2019) [41] | Single-center | Coin toss | Unclear | Yes | No | Unclear | No | No | Not mentioned |

Note : ITT, intention-to-treat analysis; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture.

## Results

### *Principle study characteristics*

Database interrogation and inspection of the citation lists of primary research papers and reviews yielded 362 references, of which 198 were utilized further. Fig. 1 outlines the methods used to identify and select relevant literature. Of the 147 full manuscripts scrutinized, 31 articles [5,12–41] including a total of 4450 females fit the inclusion criteria. Assessment of the quality and approach of the accepted studies are summarized in Table 1 and Table 2, respectively.

Seven of the selected publications were carried out in European countries: 3 in Sweden [5,12,14]; 1 in Denmark [13], 1 in Austria [15], and 2 in UK [34,42]. Three trials were completed in the USA [16,18,23]. One trial was conducted in Brazil [22]. The remaining twenty studies were conducted in China [17,19,20,24–33,35–41]. Four of these were multicenter trials [5,12,16,23], while all of the others were single center trials.

All trials included a broad selection of women undergoing in vitro fertilization, with a wide range of ages, body mass index (BMI), inclusion criteria, cause of infertility, and numbers of previous treatment cycles. In these trials women with infertility problems mainly due to tubal factors [20,21,24,27,33,35,38], poor ovarian response (POR) / decreased ovarian reserve (DOR) [17,29,31,39], polycystic ovary syndrome (PCOS) [19,25,28], or had a history of implantation failure [22,26,32,36,41].

Twenty-four trials were performed primarily to assess the effect of acupuncture on IVF outcomes [12,16–19,21–23,25–36,38–41], and among these 24 trials seven of them also evaluated the effect on the oocyte/embryo quality [17,19,25,28,30,31,39], seven on endometrial receptivity [26,27,32,33,36,38,41] and one on ovarian reserve [29]. Besides the secondary IVF outcomes, the main objective in six trials was to assess the pain-relieving effects of acupuncture [5,12–15,37], and in the remaining two trials to assess the anxiety-relieving effect of acupuncture [20,24].

Eight trials used EA [5,12,13,17,19,25,28,43], 16 trials used TA [16,18,20–23,27,31–36,38,39,41], three trials used AA [15,24,37] and two of these trials used both AA and EA [15,37], and four trials used TEAS [26,29,30,40]. Six trials [15,22,24,26,29,40] used sham or placebo intervention as the control group, while others used no acupuncture interventions as control. Three trials [22,24,29] had both sham and no acupuncture interventions as the control group.

Acupuncture time in these trials could be divided into four types: around the time of embryo transfer [16,18,22–24,30,34,35], around the time of transvaginal oocyte retrieval (TVOR) [5,12–15,22,30,37], during the course of controlled ovarian hyperstimulation (COH) [20–22,27,29,34,35,39,40], for months prior to COH [17,19,25,28,31–33,39,41] or FET (frozen-thawed embryo transfer) [26,36,38]. In eight trials [19,22,25,30,34,35,28,39], acupuncture was performed at multiple time points mentioned above.

All 31 trials were RCTs. Randomization methods, the concealment of allocation, blinding type, comparability at baseline, and adherence to STRICTA are all factors crucial to our assessment of the quality of trials. Twenty-four trials reported the use of randomization methods (summarized in Table 1). Thirteen trials adequately report the concealment of allocation, while others unclearly. Comparability at baseline was detailed in 28 of the articles. Single blinding was applied in 8 trials [16,18,23,26,27,30,34,40] and double blinding was applied in 2 trials [15,24]. STRICTA was adhered to in 9 studies [10,12–15,23,24,30,34].

### *Effects on IVF outcomes*

Clinical pregnancy outcome was available from all the 31 trials, and live birth outcome was available from 11 trials. Totally 20 trials (n = 2689) found that acupuncture can significantly improve the clinical pregnancy rate (CPR) [5,15,17,20–22,24,26,29–36,38–41], while 9 trials (n = 1541) found that acupuncture had no significant effect on CPR when comparing with the control [12–14,18,19,25,27,28,37]. Eight trials (n = 1437) found that acupuncture can significantly improve the live birth rate (LBR) [5,22,24,26,30,33,34,40], while 1 trial (n = 66) found that acupuncture had no significant effect on LBR [19]. In addition, two trials (n = 220) found that acupuncture had a negative effect on both CPR and LBR [16,23].

Other IVF outcomes including implantation rate (IR), biochemical pregnancy rate (BPR), miscarriage rate (MR) and ongoing pregnancy rate (OPR) were available from some of these 31 trials. Ten trials (n = 1605) found that acupuncture can significantly improve IR [5,17,21,24,26,30,33,35,40,41], while four trials (n = 660) found no significant effect on IR [12,13,27,36]. One trial (n = 84) found that acupuncture can significantly improve BPR [22], two trials (n = 350) found no significant effect on BPR [13,18] and two trials (n = 220) found that acupuncture had a negative effect on BPR [16,23]. Seven trials (n = 1307) found that acupuncture had no significant effect on the miscarriage outcome [5,12,19,25,28,29,37]. Only one trial (n = 286) reported OPR and found that acupuncture had no significant effect on OPR [12].

While according to the clinical characteristics of patients, four trials including women with POR / DOR [17,29,31,39] and five trials with one or more implantation failures [22,26,32,36,41] found that acupuncture can significantly improve the CPR, even the BPR [22,26,40]. Three trials including women with PCOS found that acupuncture had no significant effect on CPR [19,25,28]. Among the six trials including women with tubal factors, five found that acupuncture can significantly improve the CPR [20,21,33,35,38] and one found no significant effect [27].

While according to different acupuncture time, acupuncture performed around ET showed significant improvement in CPR and LBR in five trials [22,24,30,34,35], while showed negative effect on CPR and LBR in two trials [16,23]. Acupuncture performed in the time of TVOR in six trials mainly showed an analgesic effect, and two of these trials also found that acupuncture can significantly improve CPR [12,15] while other four found no significant effect [5,13,14,37]. Acupuncture performed during COH showed significant improvement in CPR in seven trials [20–22,29,34,35,40] and one of these trials also suggested improvement in ovarian reactivity [29], while showed no significant effect on IVF outcomes in one trial [27]. Acupuncture performed for 1–3 months prior to COH or for 1–3 menstrual cycles before FET in eight trials found that acupuncture can significantly improve CPR with improvement in endometrial receptivity [26,32,33,36,38,41] and oocyte /embryo quality [17,31]. Acupuncture performed both before and during COH in four trials and one of them found significant effect on IVF outcomes [39] while other three trials found no significance [19,25,28].

While according to the type of acupuncture, all the four trials using TEAS found that acupuncture can significantly improve CPR and BPR [26,29,30,40]. Among 8 trials using EA, two showed significant improvement in IVF outcomes [5,15,17] while six showed no significant effect [12–14,19,25,28]. Among 16 trials using TA, 12 showed significant improvement in IVF outcomes [20–22,31–36,38,39,41] while 4 showed no positive effect [16,18,23,27]. Among three trials using AA, two showed significant improvement in IVF outcomes [15,24] while one showed no significant effect [37].

While according to the type of control, all the six trials using the sham acupuncture as control found that acupuncture can significantly improve the CPR [15,22,24,26,29,40]. The positive effect, no significant effect or negative effect of acupuncture on CPR

**Table 2**
Characteristics of the 31 randomized trials involving the use of acupuncture during in vitro fertilization treatment included in the systematic review.

| Study | Main objective | Participants | Country | Intervention | Control | Acupuncture time | IVF outcomes |
|---|---|---|---|---|---|---|---|
| Stener-Victorin et al. (2003) [12] | IVF outcome | 286 randomized—eligible women aged ≤38 years, BMI ≤ 28 kg/m2, had four or more follicles of size≥18 mm and no more than three previous IVF attempts | Sweden | EA + PCB | Alfentanil + PCB | Before oocyte aspiration | CPR, OPR, IR, MR |
| Craig et al. (2007) [16] | | 107 randomized—women undergoing IVF who have not had acupuncture within 3 months | USA. | TA | No adjuvant treatment | Before and after ET | CPR, BPR |
| Domar et al. (2009) [18] | | 150 randomized—women scheduled to have ET using non-donor eggs | USA | TA | No adjuvant treatment | Before and after ET | CPR, BPR |
| Gu et al. (2012) [21] | | 56 randomized—women 25-36 years old with infertility due to tubal-induced gamete transport barriers | UK | TA | No adjuvant treatment | During COH | CPR, IR |
| Villahermosaet al. (2013) [22] | | 84 randomized—women infertile patients who had at least two previous unsuccessful attempts of IVF, aged < 38 years | Brazil | TA + moxibustion | sham TA; No adjuvant treatment | During COH, before ovarian puncture and on the day after ET | CPR, BPR |
| Craig et al. (2014) [23] | | 113 randomized—no inclusion criteria | USA | TA | No adjuvant treatment | Before and after ET | CPR, LBR, BPR |
| Jin et al. (2018) [35] | | 193 randomized—infertile women aged 25-40 years and with tubal blockage | China | TA | No adjuvant treatment | During COH until 7 days after ET | IR, CPR |
| K. Gillerman et al. (2018) [34] | | 157 randomized—women aged < 43 years old and BMI < 30 undergoing their first or second IVF cycle (with a fresh or frozen/thawed embryo replacement) | UK | TA | No adjuvant treatment | During COH, during the pre-embryo transfer treatment, before and immediately after ET | LBR, CPR |
| Shuai et al. (2019) [40] | | 124 randomized—women with RIF | China | TEAS | sham TEAS | During COH and to the day of ET | IR, CPR, LBR |
| Chen et al. (2009) [17] | Effect on oocyte / embryo | 60 randomized—women with POR or DOR and undergoing frozen ET | China | EA | No adjuvant treatment | From 1 month before COH to the day of TVOR | CPR,IR |
| Cui et al. (2011) [19] | quality and IVF outcome | 66 randomized—infertile women aged 23–39 years with PCOS | China | EA | No adjuvant treatment | From 1 month before COH and during COH | CPR, LBR, MR |
| Li et al. (2015) [25] | | 217 randomized—PCOS women infertile due to tubal blockage | China | EA | No adjuvant treatment | For 1 month before COH and during COH | CPR, MR |
| Yang et al. (2015) [28] | | 200 randomized—women with PCOS aged 21-39 years | Chins | EA | No adjuvant treatment | Before COH until the day of egg retrieval | CPR, MR |
| Gao et al. (2017) [31] | | 120 randomized—women undergoing more than 2 IVF-ET cycles and had 2 or more cycle cancellation due to low ovarian response | China | TA + TCM decoction; TA | TCM decoction; No intervention | For 3 months before COH | CPR |
| Qu et al. (2017) [30] | | 481 randomized—infertile women with bilateral tubal blockage before | China | TEAS | No adjuvant treatment | For 2 hours before TVOR and 2 hours before ET | CPR, IR, LBR |
| Zhang et al. (2018) [39] | | 80 randomized—women with POR | China | TA + TCM Capsules | HRT | Before and during COH and to the day of TVOR | CPR |
| Shuai et al. (2015) [26] | Effect on endometrial receptivity and IVF outcome | 68 randomized—women aged 25-40 years old, with a previous unsuccessful IVF outcome and undergoing FET | China | TEAS | Sham TEAS | For 3 menstrual cycles prior to FET | CPR, LBR, IR |
| Chen et al. (2015) [27] | | 114 randomized—women aged 24-35 with infertility due to tubal-induced gamete transport barriers | China | TA + moxibustion | No adjuvant treatment | During COH to ET | CPR, IR |
| Gao et al. (2017) [32] | | 80 randomized—women aged 26-32 years with one or more unsuccessful attempts at IVF-ET | China | TA + TCM decoction | No adjuvant treatment | For 3 months before COH | CPR |
| Peng et al. (2017) [33] | | 68 randomized—women with infertility due to tubal blockage | China | TA + Moxibustion | No adjuvant treatment | For 3 months before COH | CPR, LBR, IR |
| | | | China | Warm needing | No adjuvant treatment | | CPR, IR |

**Table 2** (*Continued*)

| Study | Main objective | Participants | Country | Intervention | Control | Acupuncture time | IVF outcomes |
|---|---|---|---|---|---|---|---|
| Ma et al. (2018) [36] | | 60 randomized—infertile women aged 25-40 years, BMI between 18.5-23.9, with RIF and undergoing FET | | | | For 1 menstruation cycle prior to FET | |
| Xu et al. (2018) [38] | | 72 randomized—women aged 24-45 years with RIF | China | TA + EA + moxibustion | No adjuvant treatment | For 3 months before FET | CPR |
| Gao et al. (2019) [41] | | 100 randomized—women with 2 failure IVF-ET attempts | China | TA + TCM decoction | No adjuvant treatment | For 3 months before COH | CPR, IR |
| Zheng et al. (2015) [29] | Effect on ovarian reserve and IVF outcome | 240 randomized—women aged 26-47 years old with DOR | China | TEAS | Sham TEAS; artificial endometrial cycle treatment; no intervention | During COH until the day of egg retrieval | CPR, MR |
| Stener-Victorin et al. (1999) [5] | Pain-relieving effect | 150 randomized—no inclusion criteria | Sweden | EA + PCB | Alfentanil + PCB | For 30 min before oocyte aspiration | CPR, IR, LBR, MR |
| Humaidan and Stener-Victorin. (2004) [13] | | 200 randomized—no inclusion criteria; | Denmark | EA + PCB | Alfentanil + PCB | A few minutes before ovum pickup | CPR, BCP, IR |
| Gejervall et al. (2005) [14] | | 160 randomized—no inclusion criteria | Sweden | EA + PCB | Premedication + alfentanil + PCB | For 30–45 min before oocyte aspiration and after the retrieval | CPR |
| Sator-Katzenschlager et al. (2006) [15] | | 94 randomized—women aged < 43 years, BMI < 28 kg/m$^2$, never had acupuncture before | Austria | Electrical AA; AA | placebo AA | Before the oocyte retrieval and lasted 1 h after the retrieval | CPR |
| Wang et al.(2018) [37] | | 148 randomized-women aged 20-45 years, BMI < 30 kg/m$^2$, first IVF-ET attempt | China | AA + EA | No adjuvant treatment | EA: 10 min. before TVOR; AA: For 2 days before TVOR. | CPR, MR |
| Sun et al. (2012) [20] | Anxiety-relieving effect | 97 randomized-women undergoing IVF-ET due to tubal factor | China | TA + TCM decoction | No adjuvant treatment | During COH | CPR |
| Qu et al. (2014) [24] | | 305 randomized-women infertile patients with tubal blockage | China | AA | sham AA; No adjuvant treatment | before and after ET | CPR, IR, LBR |

Note: IVF, vitro fertilization; ET, embryo transfer; FET, frozen-thawed embryo transfer; BMI, body mass index; RIF, recurrent implantation failure; POR, poor ovarian reserve; DOR, decreased ovarian reserve; PCOS, polycystic ovarian syndrome; PCB, paracervical block; TCM, Traditional Chinese Medicine; EA, electroacupuncture; TA, traditional acupuncture; AA, auricular acupuncture; HRT, hormone replacement therapy; CPR, clinical pregnancy rate; LBR, live birth rate; IR, implantation rate; MR, miscarriage rate; OP, ongoing pregnancy; BCP, biochemical pregnancy; TVOR, transvaginal oocyte retrieval; TEAS, transcutaneous electrical acupoint stimulation.

or BPR had been reported in the remaining trials using the no acupuncture intervention as the control group.

## Discussion

To standardize the clinical trials, the design of further research aimed at assessing the effect of acupuncture on IVF outcomes should consider the following points: (1) Traditional Chinese Medicine (TCM) theory may be used to determine the correct diagnosis of conditions affecting a patient; (2) standardization of acupuncture methods would enhance the compatibility of results between research studies; (3) live birth data should be considered as a primary outcome of the study; (4) hormone data and psychological index data should be collected during the treatment and study; (5) as the intercountry differences in infertile patients' experience, expectations, and knowledge of acupuncture and TCM may lead to variability in outcomes of IVF, international cooperation is urgently needed; (6) considering that differences exist in the protocols for various IVF and ICSI centers, an international multicenter study group should be established to determine the effects of acupuncture on IVF and ICSI outcomes [44]; (7) different confounders that have been shown to influence IVF outcome should be taken into account, including lifestyle factors (maternal and paternal age, weight, vitamin and iodine intake, alcohol and caffeine consumption, smoking, substance misuse, stress, environmental pollutants, etc.), gynecological factors (duration and cause of infertility, presence and characteristics of uterine fibroids etc.), number of previous IVF or ICSI cycles, presence of male factor, race, and ethnicity [43,45–47]; (8) for the trials using acupuncture, STRICTA criteria should be applied to make protocols reproducible [48]; (9) detailed fixed protocols centered on the appropriate diagnosis of the patient's syndrome as determined by TCM theory and expert opinion should be established and; (10) a sufficient dose of treatment over the most appropriate time period should be provided.

Although the majority of trials included in this review reported a positive effect of acupuncture on CPR, most of them showed poor methodological quality. Only 11 among 31 trials reported both CPR and LBR, and only one trials [34] considered LBR as a primary outcome and found that acupuncture consensus protocol in women undergoing IVF had a positive effect on IVF outcome. However, one recently published, high-quality RCTs by *Smith et al.* [49] used LBR as the primary outcome and found that acupuncture vs sham acupuncture at the time of ovarian stimulation and embryo transfer resulted in no significant difference in LBR. The variations in IVF outcomes among either the studies included in the review or other acupuncture RCTs, could due to the heterogeneity in the study quality and study design-related varieties. As we know, many factors may have impacts on the effects of acupuncture and its influence on IVF outcomes, including the use of TCM theory in the diagnosis of an individual's medical conditions, the characteristics of population, the phrase of acupuncture treatment, selection of acupoints, practitioner competency, and form of acupuncture (traditional needling, laser, auricular, or electroacupuncture).

Acupuncture is expected to complement in vitro fertilization in cases of unexplained infertility, amenorrhea, PCOS and early ovarian failure, or a prolonged menstrual cycle caused by ovarian dysfunction and when the patient has active demand to conceive. The present review showed that women with poor or decreased ovarian reserve and women with repeated implantation failures seemed to be benefit from the adjunctive acupuncture treatment when undergoing IVF. Similarly, two recent systematic review and meta-analysis [10,11] also found a benefit of acupuncture for IVF outcomes in women who have had multiple previous IVF cycles. This benefit may due to the effects of acupuncture on strengthening the natural menstrual cycle [50], improving ovarian function [51,52] and embryo quality [53], enhancing endometrial receptivity [54], and reducing infertility-related anxiety and depression [55,56]. However, the exact mechanism of those effects needs to be further investigated.

In the systematic review, 4 RCTs used TEAS in an attempt to improve outcomes for females experiencing IVF treatment and all of them showed improvement in IVF outcomes. In traditional acupuncture treatment, skin of the patients is pierced with needles, which usually leads to discomfort, bleeding, or pain. The shortcoming of the traditional acupuncture can be avoided by TEAS, a new and non-invasive acupuncture treatment [57,58]. TEAS is a new electroacupuncture method brought about by the innovation of recently developed science techniques [57,58]. Patients are mostly likely to receive non-invasive acupuncture, such as TEAS, which can also enhance the reproducibility of the acupuncture-like stimulation [57,58].

The choice of acupuncture time is usually associated to the effect of treatment and the objective of research. Although the majority of trials focus on pregnancy outcomes, in some studies reviewed here, acupuncture was administered around the time of TVOR in order to determine any effect on pain relief [5,13–15]. In other trials, acupuncture was administered around ET mainly to observe the effect on IVF outcomes. Acupuncture performed before and during COH was aimed at increasing the reactivity of the ovary to COH [29], improving uterine endometrial receptivity [40] and the oocyte or embryo quality [19,25,28]. Nonpharmaceutical treatments are often used around TVOR and ET to relieve the anxiety levels of the patients, which improves IVF outcomes [24]. Different timing in the provision of acupuncture intervention during IVF may account for variations in outcomes, thus standardized research about the timing of acupuncture during IVF is needed to define the appropriate time to provide acupuncture to maximize its effects. However, two recent meta-analyses similarly examined the effect of acupuncture performed around the time of ET on clinical pregnancy and showed contradictory in results and conclusions [9,10]. The number of trials included and different levels of methodological quality of these trials may account for the discrepancy between the two meta-analyses.

## Conclusion

This system review indicated that acupuncture appears to be beneficial to women with poor ovarian reserve or with previous unsuccessful attempts of IVF-ET. The great heterogeneity and different levels of methodological quality among RCTs may account for variations in outcomes reported by them. Large-size, standardized, TCM theory-based, randomized, and multicenter trials should be conducted in order to gather sufficient evidence to allow relevant governing bodies to make an informed choice on whether or not acupuncture can improve IVF outcomes.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

## References

[1] Dyer S, Chambers GM, de Mouzon J, Nygren KG, Zegers-Hochschild F, Mansour R, et al. International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology 2008, 2009 and 2010. Hum Reprod 2016;31(7):1588–609.
[2] Harper J, Magli MC, Lundin K, Barratt CL, Brison D. When and how should new technology be introduced into the IVF laboratory? Hum Reprod 2012;27(2):303–13.
[3] Manheimer E, van der Windt D, Cheng K, Stafford K, Liu J, Tierney J, et al. The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update 2013;19(6):696–713.
[4] Zhang Y, Fu Y, Han F, Kuang H, Hu M, Wu X. The effect of complementary and alternative medicine on subfertile women with in vitro fertilization. eCAM 2014;2014:419425.
[5] Stener-Victorin E, Waldenstrom U, Nilsson L, Wikland M, Janson PO. A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization. Hum Reprod 1999;14(10):2480–4.
[6] Shen C, Wu M, Shu D, Zhao X, Gao Y. The role of acupuncture in in vitro fertilization: a systematic review and meta-analysis. Gynecol Obstet Invest 2015;79(1):1–12.
[7] Jo J, Lee YJ. Effectiveness of acupuncture in women with polycystic ovarian syndrome undergoing in vitro fertilisation or intracytoplasmic sperm injection: a systematic review and meta-analysis. Acupunct Med 2017;35(3):162–70.
[8] Qian Y, Xia XR, Ochin H, Huang C, Gao C, Gao L, et al. Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis. Arch Gynecol Obstet 2017;295(3):543–58.
[9] Schwarze JE, Ceroni JP, Ortega-Hrepich C, Villa S, Crosby J, Pommer R. Does acupuncture the day of embryo transfer affect the clinical pregnancy rate? Systematic review and meta-analysis. JBRA Assist Reprod 2018;22(4):363–8.
[10] Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis. Reprod Biomed Online 2019;38(3):364–79.
[11] Xie ZY, Peng ZH, Yao B, Chen L, Mu YY, Cheng J, et al. The effects of acupuncture on pregnancy outcomes of in vitro fertilization: a systematic review and meta-analysis. BMC Complement Altern Med 2019;19(1):131.
[12] Stener-Victorin E, Waldenstrom U, Wikland M, Nilsson L, Hagglund L, Lundeberg T. Electro-acupuncture as a peroperative analgesic method and its effects on implantation rate and neuropeptide Y concentrations in follicular fluid. Hum Reprod 2003;18(7):1454–60.
[13] Humaidan P, Stener-Victorin E. Pain relief during oocyte retrieval with a new short duration electro-acupuncture technique–an alternative to conventional analgesic methods. Hum Reprod 2004;19(6):1367–72.
[14] Gejervall AL, Stener-Victorin E, Moller A, Janson PO, Werner C, Bergh C. Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. Hum Reprod 2005;20(3):728–35.
[15] Sator-Katzenschlager SM, Wolfler MM, Kozek-Langenecker SA, Sator K, Sator PG, Li B, et al. Auricular electro-acupuncture as an additional perioperative analgesic method during oocyte aspiration in IVF treatment. Hum Reprod 2006;21(8):2114–20.
[16] Craig LB, Criniti AR, Hansen KR, Marshall LA, Soules MR. Acupuncture lowers pregnancy rates when performed before and after embryo transfer. Fertil Steril 2007;88:S40.
[17] Chen J, Liu LL, Cui W, Sun W. Effects of electroacupuncture on in vitro fertilization-embryo transfer (IVF-ET) of patients with poor ovarian response. Chinese acupuncture moxibustion 2009;29(10):775–9.
[18] Domar AD, Meshay I, Kelliher J, Alper M, Powers RD. The impact of acupuncture on in vitro fertilization outcome. Fertil Steril 2009;91(3):723–6.
[19] Cui W, Li J, Sun W, Wen J. Effect of electroacupuncture on oocyte quality and pregnancy for patients with PCOS undergoing in vitro fertilization and embryo transfervitro fertilization and embryo transfer. Chinese acupuncture moxibustion 2011;31(8):687–91.
[20] Sun ZG, Lian F, Zhang JW. Effects of acupuncture combined Chinese materia medica for tonifying shen and soothing gan on the anxiety and depression of patients with in vitro fertilization and embryo transplantation and on the treatment outcomes. Chinese J integrated traditional Western Med 2012;32(8):1023–7.

[21] Gu SY, Tian Q, Hu YJ, Zhang ZL. Clinical observation of acupuncture for Nourishing Shen-Gan and Chong-Ren channels on patients being in vitro fertilization-embryo transfer. Tianjin J Traditional Chinese Med 2012;29 (05):440–2.
[22] Villahermosa DI, Santos LG, Nogueira MB, Vilarino FL, Barbosa CP. Influence of acupuncture on the outcomes of in vitro fertilisation when embryo implantation has failed: a prospective randomised controlled clinical trial. Acupunct Med 2013;31(2):157–61.
[23] Craig LB, Rubin LE, Peck JD, Anderson M, Marshall LA, Soules MR. Acupuncture performed before and after embryo transfer: a randomized controlled trial. J Reprod Med 2014;59(5-6):313–20.
[24] Qu F, Zhang D, Chen LT, Wang FF, Pan JX, Zhu YM, et al. Auricular acupressure reduces anxiety levels and improves outcomes of in vitro fertilization: a prospective, randomized and controlled study. Sci Rep 2014;4:5028.
[25] Li J, Cui W, Sun W, Zhang QY, Guan Q. Effect of electro-acupuncture on the spindle and oocytes quality in patients with PCOS. Chinese J. Integrated traditional Western Med 2015;35(3):304–9.
[26] Shuai Z, Lian F, Li P, Yang W. Effect of transcutaneous electrical acupuncture point stimulation on endometrial receptivity in women undergoing frozen-thawed embryo transfer: a single-blind prospective randomised controlled trial. Acupunct Med 2015;33(1):9–15.
[27] Chen Q, Hau C. Impacts on pregnancy outcome treated with acupuncture and moxibustion in IVF-ET patients. Chinese acupuncture moxibustion 2015;35 (4):313–7.
[28] Yang BZ, Cui W, Li J. Effects of electroacupuncture intervention on changes of quality of ovum and pregnancy out- come in patients with polycystic ovarian syndrome. Acupuncture research 2015;40(2):151–6.
[29] Zheng Y, Feng X, Mi H, Yao Y, Zhao Y, Li J, et al. Effects of transcutaneous electrical acupoint stimulation on ovarian reserve of patients with diminished ovarian reserve in in vitro fertilization and embryo transfer cycles. J Obstet Gynaecol Res 2015;41(12):1905–11.
[30] Qu F, Wang FF, Wu Y, Zhou J, Robinson N, Hardiman PJ, et al. Transcutaneous electrical acupoint stimulation improves the outcomes of in vitro fertilization: a prospective, randomized and controlled study. Explore (NY) 2017;13(5):306–12.
[31] Gao XA, Chen MZ, Ma WM, Luo GQ, Pan JL. Clinical effect of acupuncture combined with Chinese medical artificial cycle therapy on patients with low ovarian response in in vitro fertilization. J Foshan University (Natural Sciences Edition) 2017;35(06):57–61.
[32] Gao ZY, Gao XA, Luo GQ, Su WW, Wei DS, Chen MZ, et al. Study on the effect of acupuncture combined with Chinese medicine cycle therapy on IVF-EI bad endometrium. Chinese community dotctors 2017;33(34):103–4.
[33] Peng DH, Ling HC. Effect of acupuncture combined with Chinese Medicine therapy on endometrium and pregnancy outcome in patients with IVF-ET. Med Innov China 2017;14(17):121–5.
[34] Gillerman K, Kulkarni A, Shah A, Gudi A, Homburg R. The impact of acupuncture on IVF success rates: a randomised controlled trial. Fertil Sci Res 2018;5(2).
[35] Jin ZC, Zheng J, Xia M, Sun H, Liu J, Yang Q, et al. Study of acupuncture improving clinical pregnancy outcome and its mechanisms in IVF-ET patients. Chinese J Integrated Traditional Western Med 2018;38(10):1174–9.
[36] Ma JJ, Zhang QH, Weng XC, Dai MC. Effect of warm needling on endometrial receptivity and pregnancy outcome in Kidney-yang deficient patients with repeated implantation failure in IVF-ET Shanghai. J Acu-mox 2018;37 (12):1339–44.
[37] Wang MX, Teng YL. Clinical observation of auricular point combined therapy in patients with transvaginal oocyte retrieval for in vitro fertilization-embryo transfer. Chinese J Gen Prac 2018;16(11):1864–7.
[38] Xu JL, Yang ZR, Qian J, Zhuang HN, Yang ZG, Huang K, et al. Effect of stage-based acupuncture-moxibustion on endometrial thickness after repeated implantation failure in IVF-ET. Shanghai J Acu-mox 2018;37(02):200–4.
[39] Zhang XY, Zhang XX, Wang L, Wang J, Wang KK, Zhao SQ. Effect of acupuncture combined with Kuntai Capsuleson the pregnancy outcome of infertile patients with hyporesponsive ovarian failure in IVF-ET. Chinese J Human Sexuality 2018;27(11):68–71.
[40] Shuai Z, Li X, Tang X, Lian F, Sun Z. Transcutaneous electrical acupuncture point stimulation improves pregnancy outcomes in patients with recurrent implantation failure undergoing in vitro fertilisation and embryo transfer: a prospective, randomised trial. Acupunct Med 2019;37(1):33–9.
[41] Gao ZY, Luo GQ, Gao XA. Effect of acupuncture combined with TCM cycle therapy on adverse endometrial receptivity, embryo implantation rate and pregnancy rate in patients with IVE-ET Failure. J Clin Acupuncture Moxibustion 2019;35(03):31–4.
[42] Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2014;20(5):748–58.
[43] Elizur SE, Lerner-Geva L, Levron J, Shulman A, Bider D, Dor J. Factors predicting IVF treatment outcome: a multivariate analysis of 5310 cycles. Reprod Biomed Online 2005;10(5):645–9.
[44] Dieterle S. Invitation to an international multicenter study of the effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril 2006;85(5):1370.
[45] Younglai EV, Holloway AC, Foster WG. Environmental and occupational factors affecting fertility and IVF success. Hum Reprod Update 2005;11(1):43–57.
[46] Lintsen AM, Eijkemans MJ, Hunault CC, Bouwmans CA, Hakkaart L, Habbema JD, et al. Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. Hum Reprod 2007;22(9):2455–62.
[47] Cai QF, Wan F, Huang R, Zhang HW. Factors predicting the cumulative outcome of IVF/ICSI treatment: a multivariable analysis of 2450 patients. Hum Reprod 2011;26(9):2532–40.
[48] MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, et al. Revised STandards for reporting interventions in clinical trials of acupuncture (STRICTA): extending the CONSORT statement. PLoS Med 2010;7 (6)e1000261.
[49] Smith CA, de Lacey S, Chapman M, Ratcliffe J, Norman RJ, Johnson NP, et al. Effect of acupuncture vs sham acupuncture on live births among women undergoing in vitro fertilization: a randomized clinical trial. Jama 2018;319 (19):1990–8.
[50] Chang R, Chung PH, Rosenwaks Z. Role of acupuncture in the treatment of female infertility. Fertil Steril 2002;78(6):1149–53.
[51] Wang Y, Li Y, Chen R, Cui X, Yu J, Liu Z. Electroacupuncture for reproductive hormone levels in patients with diminished ovarian reserve: a prospective observational study. Acupunct Med 2016;34(5):386–91.
[52] Chen BY. Acupuncture normalizes dysfunction of hypothalamic-pituitary-ovarian axis. Acupunct Electrother Res 1997;22(2):97–108.
[53] Rashidi BH, Tehrani ES, Hamedani NA, Pirzadeh L. Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome. Acupunct Med 2013;31(2):151–6.
[54] Fu H, He Y, Gao Y, Man Y, Liu W, Hao H. Acupuncture on the endometrial morphology, the serum estradiol and progesterone levels, and the expression of endometrial leukaemia-inhibitor factor and osteopontin in rats. Evid Based Complement Alternat Med 2011;2011:606514.
[55] Sutton C, Pentland S, Roberts J. A comparison of stress levels in women undergoing single versus multiple acupuncture session prior to embryo transfer. Fertil Steril 2015;103(2, Supplement):e36–7.
[56] Sniezek DP, Siddiqui IJ. Acupuncture for treating anxiety and depression in women: a clinical systematic review. Med Acupunct 2013;25(3):164–72.
[57] Zhang R, Feng X-J, Guan Q, Cui W, Zheng Y, Sun W, et al. Increase of success rate for women undergoing embryo transfer by transcutaneous electrical acupoint stimulation: a prospective randomized placebo-controlled study. Fertil Steril 2011;96(4):912–6.
[58] Zhang Q, Gao Z, Wang H, Ma L, Guo F, Zhong H, et al. The effect of pre-treatment with transcutaneous electrical acupoint stimulation on the quality of recovery after ambulatory breast surgery: a prospective, randomised controlled trial. Anaesthesia 2014;69(8):832–9.