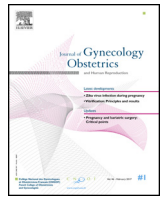




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## Review

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



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### 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.

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### 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

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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,

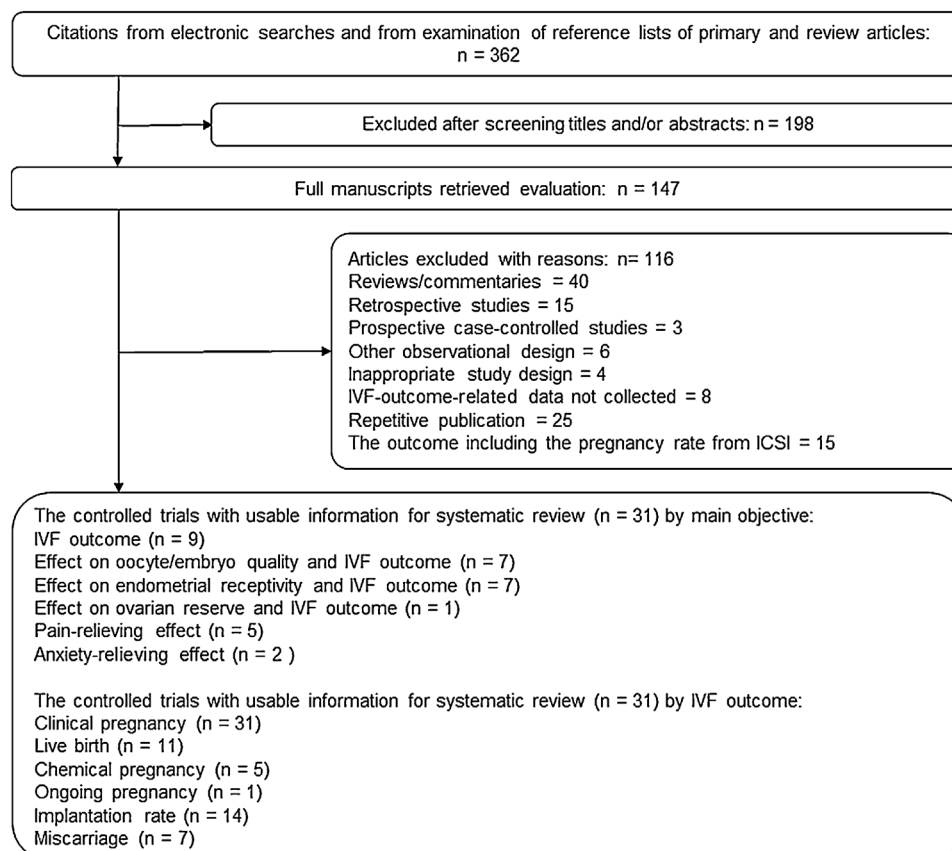


Fig. 1. The methods used to identify and select relevant literature.

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 $\leq 38$ years, BMI $\leq 28$ kg/m <sup>2</sup> , had four or more follicles of size $\geq 18$ 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
Villahermosa et 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 quality and IVF outcome	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]		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	China	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 needling	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 <sup>2</sup> , 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 <sup>2</sup> , 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.

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