

REVIEW

Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis

Yi Qian¹ · Xin-Ru Xia¹ · Humphrey Ochin¹ · Cun Huang¹ · Chao Gao¹ · Li Gao¹ · Yu-Gui Cui¹ · Jia-Yin Liu¹ · Yan Meng¹

Received: 9 June 2016 / Accepted: 25 November 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract

Purpose Controversial results have been reported concerning the effect of acupuncture on in vitro fertilization (IVF) outcomes. The current review was conducted to systematically review published studies of the effects of acupuncture on IVF outcomes.

Methods Women undergoing IVF in randomized controlled trials (RCTs) were evaluated for the effects of acupuncture on IVF outcomes. The treatment groups involved traditional, electrical, laser, auricular, and other acupuncture techniques. The control groups consisted of no, sham, and placebo acupuncture. The PubMed, Embase, and Web of Science databases were searched. The pregnancy outcomes data are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) based on a fixed model or random model depending on the heterogeneity determined by the Q test and I² statistic. The major outcomes were biochemical pregnancy rate (BPR), clinical pregnancy rate (CPR), live birth rate (LBR), and ongoing pregnancy rate (OPR). Heterogeneity of the therapeutic effect was evaluated by a forest plot analysis, and publication bias was assessed by a funnel plot analysis.

Results Thirty trials (a total of 6344 participants) were included in this review. CPR data showed a significant difference between the acupuncture and control groups (OR 1.26, 95% CI 1.06–1.50, $p = 0.01$), but there was significant statistical heterogeneity among the studies

($p = 0.0002$). When the studies were restricted to Asian or non-Asian area trials with a sensitivity analysis, the results significantly benefited the CPR in Asian group (OR 1.51, 95% CI 1.04–2.20, $p = 0.03$). Based on the area subgroup analysis, we found that in the Asian group, the IVF outcomes from the EA groups were all significantly higher than those from the control groups (CPR: OR 1.81, 95% CI 1.20–2.72, $p = 0.005$; BPR: OR 1.84, 95% CI 1.12–3.02, $p = 0.02$; LBR: OR 2.36, 95% CI 1.44–3.88, $p = 0.0007$; OPR: OR 1.94, 95% CI 1.03–3.64, $p = 0.04$). Meanwhile, compared with other acupuncture time, the IVF outcome results were significantly superior in the acupuncture group when acupuncture was conducted during controlled ovarian hyperstimulation (COH) (CPR: OR 1.71, 95% CI 1.27–2.29, $p = 0.0004$; LBR: OR 2.41, 95% CI 1.54–3.78, $p = 0.0001$; BPR: OR 1.50, 95% CI 1.02–2.20, $p = 0.04$; OPR: OR 1.88, 95% CI 1.06–3.34, $p = 0.03$). However, when acupuncture was conducted at the time of embryo transfer, the BPR and OPR from the acupuncture groups were significantly lower than those of the controls in the Asian group (BPR: OR 0.67, 95% CI 0.48–0.92, $p = 0.01$; OPR: OR 0.68, 95% CI 0.49–0.96, $p = 0.03$).

Conclusions Based on an analysis of the studies, acupuncture improves the CPR among women undergoing IVF. When the studies were restricted to Asian or non-Asian area patients, compared with traditional acupuncture and other methods, electrical acupuncture yielded better IVF outcomes. Optimal positive effects could be expected using acupuncture in IVF during COH, especially in Asian area. However, as a limitation of this review, most of the included studies did not mention the number of embryos transferred.

✉ Yan Meng
ctmengyan@hotmail.com

¹ The State Key Laboratory of Reproductive Medicine, Clinical Center of Reproductive Medicine, The First Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China

Keywords Acupuncture · In vitro fertilization · Clinical pregnancy rate

Introduction

Approximately 9% of women of reproductive age suffer from infertility. In vitro fertilization (IVF) may offer the best treatment success rate for most patients diagnosed with infertility. For many couples, in vitro fertilization—embryo transfer (IVF-ET) provides the last possibility for pregnancy. Nevertheless, many IVF cycles do not result in pregnancy [41], and repeated treatment cycles are needed to achieve pregnancy. The repeated cycles not only place significant economic pressure on the patients and their families but are also invasive and time-consuming [16, 55]. Therefore, new therapies that can improve reproductive outcomes are highly desirable. As an important part of traditional Chinese medicine (TCM), acupuncture has gained increased popularity worldwide, especially in Western countries, due to its convenience, lack of side effects, and unique therapeutic effects [19, 30].

Acupuncture is one of the oldest, most commonly used medical procedures in the world and can be traced back for at least 3000 years [36]. Studies have shown encouraging results regarding acupuncture treatment of nausea and vomiting [17], postoperative pain [6], addiction [26], and general pain syndromes [44]. Furthermore, acupuncture has been used for obstetrical and gynecological problems and has a long history of treating female infertility [18, 25]. The mechanisms by which acupuncture influences female fertility are believed to involve a general sympathoinhibitory effect through increased blood flow to the uterus and ovaries [48, 49], resulting in uterine conditions favoring implantation.

As a method of treating disease, the theory of acupuncture is based on the energy flow of qi and the principles of TCM meridians and acupoints. It is said that the imbalance of qi in the body causes disease, which can be treated by stimulating specific acupoints on the body surface. There are inherent relationships between acupoints and internal organs that correspond loosely to the principles of Western medical practice. Therefore, diseases of the entrails may be reflected in acupoints through meridians, and acupuncture at acupoints can affect the corresponding organs through meridians.

Traditional acupuncture (TA) involves inserting disposable sterilized needles into the skin at acupoints along the meridians. The needles can then be stimulated by hand or by a small electric current in the case of electroacupuncture (EA). In a conventional acupuncture treatment, four to ten acupoints are placed for 15–30 min. Other types of acupuncture exist, such as auricular acupuncture (AA) and laser acupuncture (LA), which are both commonly used in IVF patients to improve pregnancy rates. LA is a new form of treatment that combines both modern

science technology and traditional methods by using a low-energy laser beam to directly irradiate the acupoints.

Although many types of assisted reproductive technologies have been utilized clinically, the effect of acupuncture on IVF outcomes is still unknown. Since the first relevant clinical research was published in 1999 [50], a growing number of studies have been performed to explore the therapeutic effect of acupuncture on the outcomes of IVF. These studies had variable designs and generally yielded inconclusive or conflicting results, rendering the clinical decision of whether to recommend or omit the use of acupuncture during IVF difficult. As the most reliable tools for summarizing the existing evidence, several systematic reviews and meta-analyses have been published. However, they often show differences in results, and the conclusions have also been inconsistent and contradictory.

The largest systematic review and meta-analysis performed to date [33], published in June 2013, included 24 trials with 5807 patients and showed that although the pooled clinical pregnancy rates were higher in the acupuncture group, the live birth rates (LBRs) were not significantly different from those in the control group. A systematic review and meta-analysis published in July 2013 [5] indicated that the authors found no evidence of an overall benefit of acupuncture for improving the LBR, regardless of whether acupuncture was performed during oocyte retrieval or during embryo transfer (ET), and there was no evidence that acupuncture had any significant effect on pregnancy or miscarriage rates. However, a meta-analysis in 2012 [57] showed that acupuncture, especially during controlled ovarian hyperstimulation, can improve clinical pregnancy rates in women undergoing IVF.

Therefore, new randomized evidence is required to address the uncertainty regarding the conclusions of these reviews. Consequently, a new comprehensive systematic review and overall meta-analysis is indispensable for drawing more reliable conclusions concerning the ability of acupuncture to improve pregnancy rates when used as an adjunct in women undergoing IVF.

Methods

Literature and research strategy

We conducted a systematic review of studies reporting the therapeutic effect of acupuncture on the outcomes of IVF published up to December 2015 using PubMed, EMBASE, the Cochrane Library, and the Clinical Trials Register. We also searched Chinese databases, such as the Wanfang Database, and Chinese National Knowledge Infrastructure (CNKI) online facilities to collect articles with case-con-

trol studies related to the therapeutic effect of acupuncture on the outcomes of IVF in China. The reference lists of the relevant articles were also collected. Searches were performed through the websites <http://www.baidu.com> and <http://scholar.google.com> to identify additional eligible studies. Free words or MESH words (“acupuncture” OR “electroacupuncture” OR “auricular-acupuncture” OR “laser acupuncture” OR “moxibustion”) and (“in vitro fertilization” OR “assisted reproduction technology”) were used in PubMed. These keyword retrieval strategies were also used in other databases.

Inclusion criteria and data extraction

In this review, we selected randomized controlled trials (RCTs) in which the target areas were women undergoing IVF with or without intracytoplasmic sperm injection (ICSI) treatment. We included RCTs in any language, published as either full articles or abstracts. Different from recent reviews [5], the therapeutic intervention selected in our review was any accepted regimen of acupuncture, including TA, EA, AA, LA, and other methods, compared with no or sham (placebo) acupuncture. Moreover, the pregnancy rates were reported from a single IVF cycle per woman randomized to receive either acupuncture or the control intervention.

Eligible papers required data on the following outcomes [10, 23]: biochemical pregnancy rate (BPR, a positive hCG serum or urine test 11 days after ET), clinical pregnancy rate (CPR, the presence of not less than one intrauterine gestational sac or fetal heartbeat confirmed by ultrasound 4–6 weeks after ET), ongoing pregnancy rate (OPR, pregnancy beyond 12 weeks of gestation, as confirmed by fetal heart activity on ultrasound), and live birth rate (LBR, a baby born alive after 24 weeks gestation).

The studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently, and the full manuscripts of all citations that were likely to meet the pre-defined selection criteria were obtained. Second, final inclusion or exclusion decisions were made after examination of the full manuscripts. In cases of duplicate publications, the most recent and complete versions were selected. The assessment of English-language manuscripts was performed independently by three reviewers, and the assessment of manuscripts in other languages was performed by people who had command of the language. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer. The selected studies were assessed for methodological quality using the components of study design that are related to internal validity. Information on the adequacy of randomization, concealment of allocation, blinding, uses of sham (or placebo)

acupuncture, and intention-to-treat analysis was sought by examining the full-text articles and by contacting the authors when clarification was needed.

The following information was extracted from each included study: first author, publication year, quality of the methods, area of the study area, interventions, outcomes, and other information. The methodological quality of the trials was assessed using the risk of bias tool described in the Cochrane handbook for systematic reviews of interventions [27].

Data synthesis and analysis

The measure of treatment efficacy was the pooled relative risk (RR) of achieving CPR, BPR, OPR, and LBR in women in the acupuncture group compared with women in the control group. According to previous studies [33, 34], the CPR was chosen because it provided more RCTs and more data that contributed to our primary analyses. However, the BPR, OPR, and LBR were analyzed as secondary outcomes.

All of the meta-analyses were based on both the number of women randomized and the number of women who completed ET. The pregnancy rate data are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) using the Review Manager 5.1 meta-analysis software. We evaluated heterogeneity using both the I^2 statistic, which indicates the proportion of variability across trials not explained by sampling variation alone, and the p value of the χ^2 test of heterogeneity. Although interpreting the importance of inconsistency depends on other factors in addition to the I^2 values, the Cochrane Handbook suggests the following approximate guide to interpreting I^2 values: “0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; and 75–100% may represent considerable heterogeneity”. For pooled data, we used a fixed-effects model for these meta-analyses if the heterogeneity of the trial characteristics showed no significance; otherwise, we used a random-effects model. For our meta-analysis, we mostly used a random effects model because of the heterogeneity of the trial characteristics and areas studied. Location, acupuncture time, and intervention type were used as variables in the sensitivity sub-group analysis.

Results

Study characteristics

A total of 78 citations were obtained from the electronic search. The reference lists of the primary and reviewed articles were examined, and 45 were selected for retrieval.

The process of literature identification and selection is shown in Fig. 1. Of the 45 full manuscripts examined, 30 articles including a total of 6344 women met the selection criteria for our review. The quality and characteristics of these included trials are summarized in Tables 1 and 2, respectively.

Objectives and outcomes

All 30 of the included trials ($n = 6344$) provided clinical pregnancy rate data, 17 of the 30 included trials ($n = 4366$) provided biochemical pregnancy rate data, 10 of the 30 included trials ($n = 3602$) provided ongoing pregnancy rate data, and 9 of the 30 included trials ($n = 2331$) provided live-birth rate data.

Methodological quality

The randomization methods, allocation concealment, comparability at baseline, blinding method, and adherence to Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) are all key factors affecting the quality of trials. As shown in Table 2, randomization methods were used in 19 trials [1, 4, 7, 8, 12–14, 21, 28, 29, 31, 35, 39, 43, 45–47, 51, 56]. Most of the trials reported adequate concealment of allocation, with the exception of eight trials that failed to clearly describe the concealment of allocation [2–4, 9, 21, 31, 43, 52]. Comparability at baseline was clearly stated in 21 of the included studies [1, 3, 4, 8, 12–14, 20, 29, 31, 32, 35, 37, 39, 42, 43, 45–47, 54, 56]. Single blinding

was applied in seven trials [7, 14, 31, 38, 39, 45, 56], and double-blinding was applied in seven trials [1, 13, 20, 35, 43, 46, 47].

Interventions

Seventeen of the selected studies involved the administration of TA [46]. EA was used in 7 studies, and other methods, such as AA and combined acupuncture treatment, were used in 10 studies.

Area

We divided the studies into two groups depending on where the study was conducted: Asian and non-Asian groups. Twelve of the selected studies were performed in Europe: three were conducted in Germany [13, 38, 39], three in Sweden [21, 50, 51], three in Denmark [1, 29, 54], and two in Austria [43, 45]. There were two trials in Italy [2, 37], two in Brazil [12, 31], and seven trials in the United States [3, 7, 8, 14, 20, 32, 35]. These 22 studies were included in the non-Asian group, whereas 8 of the studies were performed in Asia and were included in the Asian group, namely, 7 trials in China [4, 9, 28, 46, 47, 52, 56] and one trial in Iran [42].

Centers

Five of the studies were multicenter trials [1, 7, 8, 50, 51], whereas all of the remaining studies were single-center trials.

Fig. 1 Flow diagram of the inclusion and exclusion of studies in the systematic review

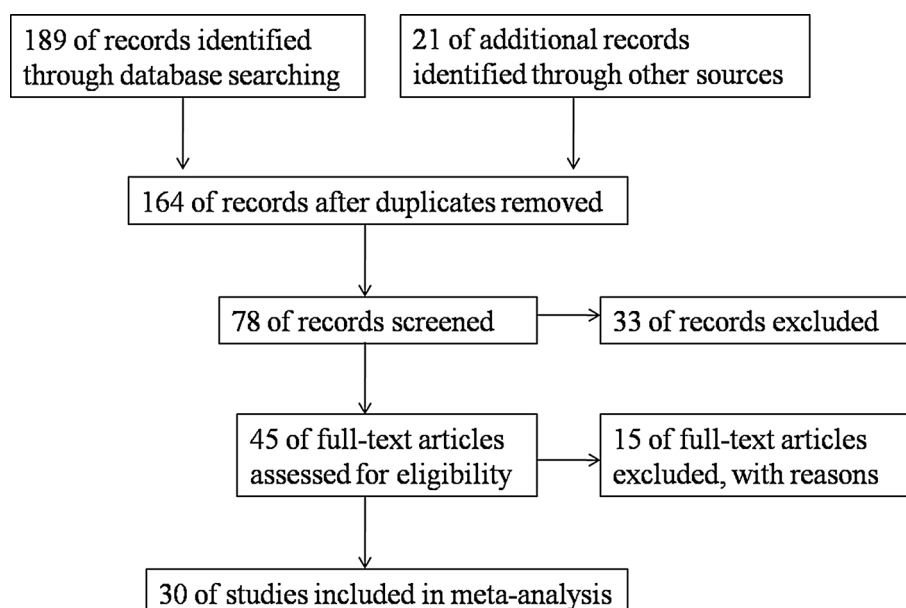


Table 1 Characteristics of the studies included in this paper

First author	Published year	Country	Single/multicenter	Participants	Intervention	Control	Time	IVF Outcomes
Stener-Victorin	1999	Sweden	Multicenter	150 randomized no inclusion criteria	PCB and EA	Alfentanil + PCB	Around the time of OA	CPR, IR, M
Paulus	2002	Germany	Single-center	160 randomized women with good-quality embryos	TA and AA	Lying still for 25 min before and after ET	25 min before and after ET	CPR
Paulus	2003	Germany	Single-center	200 randomized women with good-quality embryos	TA	Sham (non-invasive) acupuncture	25 min before and after ET	CPR
Stener-Victorin	2003	Sweden	Multicenter	286 randomized women aged <38 years, BMI <28 kg/m ² , had four or more follicles of size 18 mm or more and no more than three previous IVF attempts	PCB and EA	Alfentanil + PCB	Around the time of OA	CPR, OPR, IR, M
Humaidan	2004	Denmark	Single-center	200 randomized no inclusion criteria	PCB and EA	Alfentanil + PCB	Around the time of OA	BPR, IR
Dieterle	2005	Germany	Single-center	225 randomized no inclusion criteria	TA + Chinese medical drug	Placebo needling at points designed not to influence fertility	Luteal-phase acupuncture applied for 30 min immediately after ET and again 3 days later	CPR
Gejervall	2005	Sweden	Single-center	160 randomized no inclusion criteria	PCB and EA	Premedication+ alfentanil + PCB	Around the time of OA	CPR
Sator-Katzenschlager	2006	Austria	Single-center	94 randomized women aged <43 years, BMI <28 kg/m ² , had four or more follicles of size >18 mm	AA with or without EA + PCA	PCA + placebo AA	Around the time of OA	CPR
Smith	2006	Australia	Single-center	228 randomized women with a planned ET were eligible	TA	Placebo needling at points close to the real acupuncture points	The first undertaken on day 9 of stimulating injections, before and after ET	CPR, OPR
Benson	2006	USA	Single-center	258 randomized women scheduled to have ET were eligible	TA or LA	Sham laser acupuncture, relaxation or no intervention	25 min before and after ET	CPR, BPR, IR
Westergaard	2006	Denmark	Single-center	300 randomized no inclusion criteria	TA	Bed rest for 1 h after ET	25 min before and after embryo transfer	CPR, BPR, OPR, IR
Craig	2007	USA	Multicenter	107 randomized women undergoing IVF who have not had acupuncture within 3 months	TA	No intervention	25 min before and after ET	CPR, BPR
Fratterelli	2008	USA	Single-center	1000 randomized no inclusion criteria	TA + LA	Sham acupuncture	25 min before and after ET	BPR, CPR, OPR
Magarelli	2009	USA	Single-center	66 randomized no inclusion criteria	EA	No intervention	Before egg retrieval and 24 h before and 1 h after ET	BPR, CPR, LBR
Domar	2009	USA	Single-center	150 randomized women scheduled to have ET using non-donor eggs	TA	Lie quietly for same amounts of time	25 min before and after ET	CPR, BPR
Ho	2009	China	Single-center	44 randomized no inclusion criteria	EA	No intervention	2 times/2 weeks, day 2 of the study to the day before oocyte retrieval for 30 min	CPR
Chen	2009	China	Single-center	60 randomized women with poor ovarian response or decreased reserve	TA	No intervention	Around COH	CPR, IR, M

Table 1 continued

First author	Published year	Country	Single/multicenter	Participants	Intervention	Control	Time	IVF Outcomes
So	2009	China	Single-center	370 randomized women who had a normal uterine cavity shown on ultrasound scanning on the day of TVOR	TA	Placebo needling for 25 min before and after ET	25 min before and after ET	CPR, BPR, OPR, IR, LBR, M
Madaschi	2010	Brazil	Single-center	416 randomized women <35 years, and undergoing ICSI cycles for the first time	TA	No intervention	25 min before and after ET	CPR, LBR, M
Arnoldi	2010	Italy	Single-center	204 randomized women with a reduced ovarian reserve	TA	No intervention	Before and after ET	CPR
Andersen	2010	Denmark	Multicenter	635 randomized <37 years of age, treatment with IVF/ICSI and transfer of one or two embryos in the first, second, or third stimulated cycle	TA	Placebo needling	Before and after ET	CP, BPR OPR LBR
So	2010	China	Single-center	226 randomized FET treatment	TA	Placebo needling for 25 min after FET	25 min on site immediately after FET	BPR, CPR OPR LBR, IR, M
Omodei	2010	Italy	Single-center	168 randomized no inclusion criteria	TA	No intervention	25 min before and after ET	BPR, CPR
Moy	2011	USA	Single-center	161 randomized women <38 years old	TA and AA	Placebo needling in non-qi lines in the predetermined locations. AA was performed at the following points: knee, heel allergic area, mouth	25 min before and after ET	CPR, BPR
Zhang	2011	China	Single-center	309 randomized 21–44 years old	EA	Placebo-controlled	24 h before ET and 30 min after ET	CPR, LBR, BPR, IR, M
Cui	2011	China	Single-center	66 PCOS patients	EA	No intervention	Before COH and during COH	CPR
Sun	2012	China	Single-center	97 randomized no inclusion criteria	TA	No intervention	During COH	CPR
Daniela	2013	Brazil	Single-center	84 randomized had at least two unsuccessful attempts of IVF	TA	Sham acupuncture and no intervention	On the first and seventh day of COH, on the day before ovarian puncture and on the day after ET	CPR
Rashidi	2013	Iran	Single-center	62 women with PCOS	TA	No intervention	Around the time of OA and ET	CPR, BPR, OPR
LaTash	2014	USA	Multicenter	113 randomized no inclusion criteria	AA	No intervention	25 min before and after ET	BPR, CPR, LBR

TA traditional acupuncture, EA electroacupuncture. Other methods including LA laser acupuncture, AA auricular acupuncture, PCB paracervical block, PCA patient-controlled analgesia, CPR clinical pregnancy rate, LBR live birth rate, OPR ongoing pregnancy rate, IR implantation rate, M miscarriage, ET embryo transfer, OA oocyte aspiration, COH controlled ovarian hyperstimulation

Table 2 Methodological quality of the studies included in this paper

First author	Randomization method	Blind	Concealment of allocation	Comparability at baseline	Analysis	Adherence to STRICTA	Power analysis
Stener-Victorin	Not mentioned	No	Adequate	Unclear	ITT	No	No
Paulus	Computerized randomization	Single blind	Adequate	Yes	ITT	No	No
Paulus	Not mentioned	Single blind	Adequate	Unclear	ITT	No	No
Stener-Victorin	Sealed, unlabelled envelopes,	No	Adequate	Unclear	No	Yes	Yes
Humaidan	Sealed, unlabelled envelopes	No	Adequate	Yes	ITT	Yes	Yes
Dieterle	Sealed, unlabelled envelopes	Double-blind	Adequate	Yes	ITT	No	Yes
Gejervall	Computerized randomization	No	Unclear	Unclear	No	Yes	Yes
Sator-Katzenschlager	Computerized randomization	Double-blind	Unclear	Yes	ITT	Yes	Yes
Smith	Block randomization	Single blind	Adequate	Yes	ITT	Yes	Yes
Benson	Not mentioned	No	Unclear	Yes	ITT	No	No
Westergaard	Unclear	No	Adequate	Yes	No	Yes	Yes
Craig	Computerized randomization	Single blind	Adequate	No	ITT	No	No
Fratterelli	Not mentioned	Double-blind and	Adequate	Yes	ITT	Not clear	Not clear
Magarelli	Not mentioned	Unclear	Adequate	Yes	ITT	Yes	Yes
Domar	Computerized randomization	Single blind	Adequate	Yes	ITT	No	No
Ho	Sealed, unlabelled envelopes	No	Adequate	No	ITT	No	No
Chen	Computerized randomization	No	Unclear	Yes	ITT	No	No
So	Computerized randomization	Double-blind	Adequate	Yes	ITT	Yes	Yes
Madaschi	Computerized randomization	Single blinded	Inadequate	Yes	ITT	No	Yes
Amoldi	Not mentioned	No	Unclear	Unclear	ITT	No	No
Andersen	Computerized randomization	Double-blinded	Adequate	Yes	ITT	Yes	Yes
So	Computerized randomization	Double-blind	Adequate	Yes	ITT	No	Yes
Omodei	No mentioned	No	Adequate	Yes	Unclear	No	No
Moy	Computerized randomization	Double-blinded	Adequate	Yes	ITT	Yes	Yes
Zhang	Computerized randomization	Single blind	Adequate	Yes	ITT	Yes	Yes
Cui	Not mentioned	Unclear	No	No	ITT	No	No
Sun	Not mentioned	Unclear	Unclear	No	ITT	No	No
Daniela	Computerized randomization	Unclear	Adequate	Yes	ITT	Yes	Yes
Rashidi	No mentioned	Unclear	Adequate	Yes	ITT	Yes	Yes
LaTash	Computerized randomization	Yes	Adequate	Yes	ITT	Yes	Yes

TA traditional acupuncture, EA electroacupuncture, Other methods including LA laser acupuncture, AA auricular acupuncture, ITT intention-to-treat analysis, TPP treated-per-protocol analysis

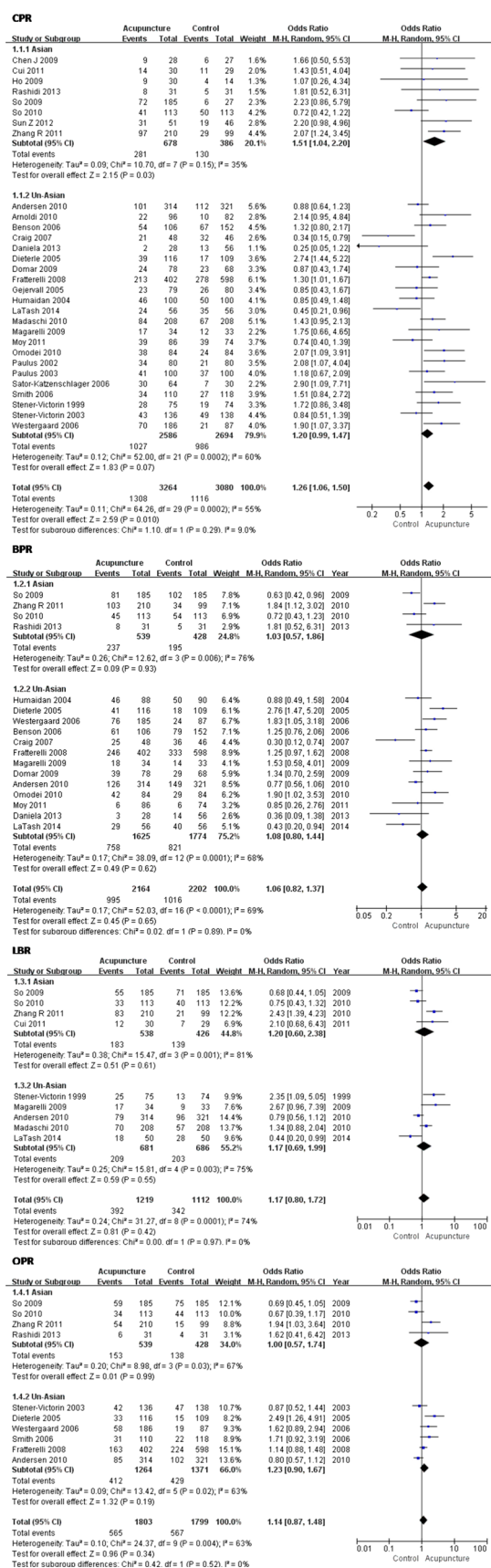


Fig. 2 Forest plots of IVF outcomes compared by area. *TA* traditional acupuncture, *EA* electroacupuncture, *Other* methods including *LA* laser acupuncture, *AA* auricular acupuncture, *ET* embryo transfer, *OA* oocyte aspiration, *COH* controlled ovarian hyperstimulation, *CPR* clinical pregnancy rate, *LBR* live birth rate, *OPR* ongoing pregnancy rate, *OR* odds ratio, *CI* confidence interval

Time of acupuncture

We divided the studies into three types (type A, B, and C) according to the time at which acupuncture was performed. In type A studies, acupuncture was performed at approximately the time of oocyte aspiration (OA). In type B studies, acupuncture was mainly performed during the course of controlled ovarian hyperstimulation (COH), and four or more sessions were administered. The remaining trials were type C studies, in which acupuncture was applied at approximately the time of ET. There were a total of five type A trials [21, 29, 43, 50, 51], nine type B trials [2, 4, 9, 12, 28, 31, 42, 52, 56], and 14 type C trials.

IVF outcomes

Comparisons of IVF pregnancy rate by area

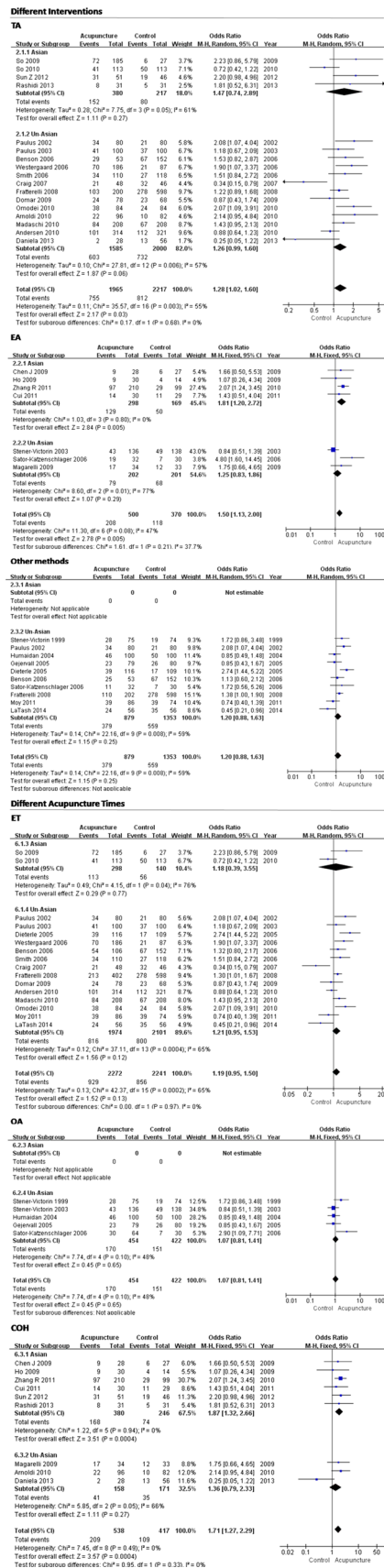
Comparisons in all areas

CPR data were available from all 30 trials ($n = 6344$), but there was significant heterogeneity among the studies ($p = 0.0002$). Using the random-effects model, pooling of the effect estimated from the 30 trials showed a significant difference in the clinical pregnancy rate between the acupuncture and control groups (OR 1.26, 95% CI 1.06–1.50, $p = 0.01$; Fig. 2).

BPR data were available from 17 trials ($n = 4366$) and also showed significant heterogeneity among these trials ($p < 0.0001$). Using the random-effects model, the pooled results showed no significant difference between the acupuncture and control groups (OR 1.06, 95% CI 0.82–1.37, $p = 0.65$; Fig. 2). LBR data were available from nine trials ($n = 2331$), and the results of the meta-analysis did not show a significant difference between the acupuncture and control groups (OR 1.17, 95% CI 0.80–1.72, $p = 0.42$; Fig. 2). There were also no significant differences in the OPR between the acupuncture and control groups (10 trials; $n = 3602$; OR 1.14, 95% CI 0.87–1.48, $p = 0.34$; Fig. 2).

Comparisons among Asians

CPR data of the studies performed in Asians were available from all eight trials ($n = 1064$), and there was no



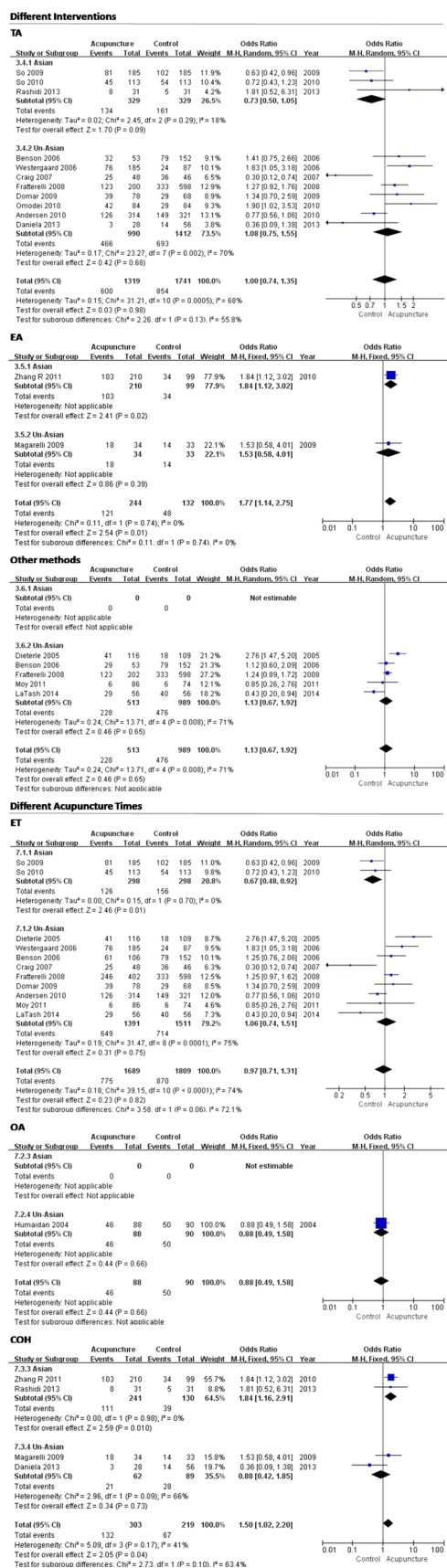


Fig. 4 Meta-analysis of the studies evaluating the effects of different types of acupuncture and different acupuncture times on the biochemical pregnancy rate. *TA* traditional acupuncture, *EA* electroacupuncture, Other methods including *LA* laser acupuncture, *AA* auricular acupuncture, *ET* embryo transfer, *OA* oocyte aspiration, *COH* controlled ovarian hyperstimulation, *OR* odds ratio, *CI* confidence interval

$p = 0.09$, Fig. 4; LBR: 2 trials; $n = 596$; OR 0.71, 95% CI 0.5–0.99, $p = 0.05$, Table 3; OPR: 3 trials; $n = 658$; OR 0.72, 95% CI 0.52–1.00, $p = 0.05$, Table 4).

Non-Asians of traditional acupuncture The pooled IVF pregnancy rates from the TA groups were not significantly different from those of the control groups (CPR: 13 trials; $n = 3585$; OR 1.26, 95% CI 0.99–1.60, $p = 0.06$, Fig. 3; BPR: 8 trials; $n = 2402$; OR 1.08, 95% CI 0.75–1.55, $p = 0.68$, Fig. 4; LBR: 2 trials; $n = 1051$; OR 0.98, 95% CI 0.75–1.28, $p = 0.89$, Table 3; OPR: 4 trials; $n = 1934$; OR 1.07, 95% CI 0.87–1.31, $p = 0.54$, Table 4).

Electroacupuncture

The pooled CPR, LBR, and BPR from the EA groups were significantly higher than those of the controls (CPR: 7 trials; $n = 870$; OR 1.50, 95% CI 1.13–2.0, $p = 0.005$, Fig. 3; BPR: 2 trials; $n = 376$; OR 1.77, 95% CI 1.14–2.75, $p = 0.01$, Fig. 4; LBR: 4 trials; $n = 584$; OR 2.40, 95% CI 1.63–3.53, $p < 0.00001$, Table 3). However, the pooled OPR was not significantly different between the acupuncture and control groups (2 trials; $n = 583$; OR 1.27, 95% CI 0.57–2.79, $p = 0.56$, Table 4).

Asians of electroacupuncture The pooled IVF pregnancy rates from the EA groups were all significantly higher than those of the controls (CPR: 4 trials; $n = 467$; OR 1.81, 95% CI 1.20–2.72, $p = 0.005$, Fig. 3; BPR: 1 trial; $n = 309$; OR 1.84, 95% CI 1.12–3.02, $p = 0.02$, Fig. 4; LBR: 2 trials; $n = 368$; OR 2.36, 95% CI 1.44–3.88, $p = 0.0007$, Table 3; OPR: 1 trial; $n = 309$; OR 1.94, 95% CI 1.03–3.64, $p = 0.04$, Table 4).

Non-Asians of electroacupuncture The pooled LBR from the EA groups of the non-Asian studies was significantly higher than that of the controls (2 trials; $n = 216$; OR 2.46, 95% CI 1.33–4.53, $p = 0.004$, Table 3). However, the other pooled rates were not significantly different between the acupuncture and control groups (CPR: 3 trials; $n = 403$; OR 1.25, 95% CI 0.83–1.86, $p = 0.29$, Fig. 3; BPR: 1 trial; $n = 77$; OR 1.53, 95% CI 0.58–4.01, $p = 0.39$, Fig. 4; OPR: 1 trial; $n = 274$; OR 0.87, 95% CI 0.52–1.44, $p = 0.57$, Table 4).

Table 3 Meta-analysis of the studies evaluating the effects of different types of acupuncture and different acupuncture times on the live birth rate

Group or subgroup			Study	Model	OR, 95% CI	<i>p</i> value for heterogeneity	OR, 95% CI	<i>p</i> value for heterogeneity
Intervention	TA	Asians	2	Fixed	0.71 [0.55, 0.99]	0.78	0.87 [0.70, 1.07]	0.11
		Non-Asians	2	Fixed	0.98 [0.75, 1.28]	0.05		
	EA	Asians	2	Fixed	2.36 [1.44, 3.88]	0.82	2.40 [1.63, 3.53]	0.99
		Non-Asians	2	Fixed	2.46 [1.33, 4.53]	0.84		
	Other methods	Asians	0	–	–	–	–	–
		Non-Asians	2	Random	1.02 [0.20, 5.25]	0.003		
Acupuncture time	Around the time of ET	Asians	2	Fixed	0.71 [0.50, 0.99]	0.78	0.83 [0.68, 1.02]	0.08
		Non-Asians	3	Fixed	0.90 [0.70, 1.16]	0.03		
	Around the time of OA	Asians	0	–	–	–	–	–
		Non-Asians	1	Fixed	2.35 [1.09, 5.05]	–		
	During the time of COH	Asians	2	Fixed	2.36 [1.44, 3.88]	0.82	2.41 [1.54, 3.78]	0.95
		Non-Asians	1	Fixed	2.67 [0.96, 7.39]	–		

TA traditional acupuncture, EA electroacupuncture, Other methods including LA laser acupuncture, AA auricular acupuncture, ET embryo transfer, OA oocyte aspiration, COH controlled ovarian hyperstimulation, OR odds ratio, CI confidence interval

Other methods

The pooled CPR, BPR, and LBR results from the studies in which other methods, such as LA, AA, and combined acupuncture treatment, were performed showed no significant differences between the acupuncture and control groups (CPR: 10 trials; $n = 2232$; OR 1.20, 95% CI 0.88–1.63, $p = 0.25$, Fig. 3; BPR: 5 trials; $n = 1502$; OR 1.13, 95% CI 0.67–1.92, $p = 0.65$, Fig. 4; LBR: 2 trials; $n = 249$; OR 1.02, 95% CI 0.20–5.25, $p = 0.98$, Table 3). However, the pooled OPR showed significant differences (OPR: 2 trials; $n = 1025$; OR 1.40, 95% CI 1.05–1.87, $p = 0.02$, Table 4).

Asians of other methods No studies.

Non-Asians of other methods The results were the same as those presented in “Other methods”.

Comparisons of IVF pregnancy rate according to acupuncture time

At approximately the time of embryo transfer

The pooled IVF pregnancy rates from studies in which acupuncture treatment was performed at approximately the

time of ET showed no significant differences between the acupuncture and control groups (CPR: 16 trials; $n = 4513$; OR 1.19, 95% CI 0.95–1.50, $p = 0.13$, Fig. 3; BPR: 11 trials; $n = 3498$; OR 0.97, 95% CI 0.71–1.31, $p = 0.82$, Fig. 4; LBR: 5 trials; $n = 1747$; OR 0.83, 95% CI 0.68–1.02, $p = 0.07$, Table 3; OPR: 7 trials; $n = 2957$; OR 1.10, 95% CI 0.81–1.51, $p = 0.55$, Table 4).

Asians of the time of embryo transfer Surprisingly, the pooled BPR and OPR from the acupuncture groups were significantly lower than those of the controls (BPR: 2 trials; $n = 596$; OR 0.67, 95% CI 0.48–0.92, $p = 0.01$, Fig. 4; OPR: 2 trials; $n = 596$; OR 0.68, 95% CI 0.49–0.96, $p = 0.03$, Table 4). And the other rates showed no differences (CPR: 2 trials; $n = 438$; OR 1.18, 95% CI 0.39–3.55, $p = 0.77$, Fig. 3; LBR: 2 trials; $n = 596$; OR 0.71, 95% CI 0.50–0.99, $p = 0.05$, Table 3).

Non-Asians of the time of embryo transfer The pooled IVF pregnancy rates were not significantly different between the acupuncture and control groups (CPR: 14 trials; $n = 4075$; OR 1.21, 95% CI 0.95–1.53, $p = 0.12$, Fig. 3; BPR: 9 trials; $n = 2902$; OR 1.06, 95% CI 0.74–1.51, $p = 0.75$, Fig. 4; LBR: 3 trials; $n = 1151$; OR 0.90, 95% CI 0.70–1.16, $p = 0.44$, Table 3; OPR: 5 trials;

Table 4 Meta-analysis of the studies evaluating the effects of different types of acupuncture and different acupuncture times on the ongoing birth rate

Group or subgroup			Study	Model	OR, 95% CI	<i>p</i> value for heterogeneity	OR, 95% CI	<i>p</i> value for heterogeneity
Intervention	TA	Asians	2	Fixed	0.72 [0.52, 1.00]	0.49	0.95 [0.80, 1.13]	0.06
		Non-Asians	2	Fixed	1.07 [0.87, 1.31]	0.07		
	EA	Asians	1	Random	1.94 [1.03, 3.64]	–	1.27 [0.57, 2.79]	0.05
		Non-Asians	1	Random	0.87 [0.52, 1.44]	–		
	Other methods	Asians	0	–	–	–	–	–
		Non-Asians	2	Fixed	1.40 [1.05, 1.87]	0.06		
Acupuncture time	Around the time of ET	Asians	2	Random	0.64 [0.49, 0.96]	0.96	1.10 [0.81, 1.51]	0.003
		Non-Asians	5	Random	1.33 [0.93, 1.89]	0.02		
	Around the time of OA	Asians	0	–	–	–	–	–
		Non-Asians	1	Fixed	0.87 [0.52, 1.44]	–		
	During the time of COH	Asians	2	Fixed	1.88 [1.06, 3.34]	0.82	–	–
		Non-Asians	0	–	–	–		

TA traditional acupuncture, EA electroacupuncture, Other methods including LA laser acupuncture, AA auricular acupuncture, ET embryo transfer, OA oocyte aspiration, COH controlled ovarian hyperstimulation, OR odds ratio, CI confidence interval

$n = 2361$; OR 1.33, 95% CI 0.93–1.89, $p = 0.12$, Table 4).

At approximately the time of oocyte aspiration

The pooled IVF pregnancy rates from the studies in which acupuncture was performed at approximately the time of OA showed no significant differences between the acupuncture and control groups (CPR: 5 trials; $n = 876$; OR 1.07, 95% CI 0.81–1.41, $p = 0.65$, Fig. 3; BPR: 1 trial; $n = 178$; OR 0.88, 95% CI 0.49–1.58, $p = 0.66$, Fig. 4; LBR: 1 trial; $n = 149$; OR 2.35, 95% CI 1.09–5.05, $p = 0.03$, Table 3; OPR: 1 trial; $n = 274$; OR 0.87, 95% CI 0.52–1.44, $p = 0.57$, Table 4).

Asians of the time of oocyte aspiration No studies.

Non-Asians of the time of oocyte aspiration The results were the same as those presented in “*At approximately the time of oocyte aspiration*”.

During the time of controlled ovarian hyperstimulation

The pooled IVF pregnancy rates were significantly higher in the acupuncture group than the control group (CPR: 9

trials; $n = 955$; OR 1.71, 95% CI 1.27–2.29, $p = 0.0004$, Fig. 3; BPR: 4 trials; $n = 522$; OR 1.50, 95% CI 1.02–2.20, $p = 0.04$, Fig. 4; LBR: 3 trials; $n = 435$; OR 2.41, 95% CI 1.54–3.78, $p = 0.0001$, Table 3; OPR: 2 trials; $n = 371$; OR 1.88, 95% CI 1.06–3.34, $p = 0.03$, Table 4).

Asians of the time of controlled ovarian hyperstimulation The pooled IVF pregnancy rates of the Asians from studies in which acupuncture was performed during COH were significantly different from those in the control groups (CPR: 6 trials; $n = 626$; OR 1.87, 95% CI 1.32–2.66, $p = 0.0004$, Fig. 3; LBR: 2 trials; $n = 368$; OR 2.36, 95% CI 1.44–3.88, $p = 0.0007$, Table 3; BPR: 2 trials; $n = 371$; OR 1.84, 95% CI 1.16–2.91, $p = 0.01$, Fig. 4; OPR: the same as “*During the time of controlled ovarian hyperstimulation*”).

Non-Asians of the time of controlled ovarian hyperstimulation The pooled CPR, LBR, and BPR results from the acupuncture groups showed no significant differences compared with the control groups (CPR: 3 trials; $n = 329$; OR 1.36, 95% CI 0.79–2.33, $p = 0.27$, Fig. 3; BPR: 2 trials; $n = 151$; OR 0.88, 95% CI 0.42–1.85, $p = 0.73$,

Fig. 4). Although the LBR results tended to be higher, this difference did not reach statistical significance (1 trial; $n = 77$; OR 2.67, 95% CI 0.96–7.39, $p = 0.06$, Table 3).

Discussion

Quality of studies and outcomes

All 30 of the studies ($n = 6344$) were RCTs, and most of them provided detailed information on the randomization procedure, allocation concealment, and blinding of assessors. Due to the nature of the acupuncture studied, absolute double-blinding was not possible. Some of the studies that used sham acupuncture for the control group approximated double-blinding, whereas others that used non-intervention as the control were completely non-blinded trials.

Main results

Compared with previous reviews [33, 41], we added 6 new studies; 5 had positive results [9, 12, 52, 56], and one had a negative result [42]. However, according to the suggestion of the Cochrane Handbook concerning I^2 values, there was moderate statistical heterogeneity between the studies ($I^2 = 51\%$). There was also significant clinical heterogeneity among the studies, which may be attributed to variations in the acupuncture techniques (TA, EA, or LA), time of commencement, total dose of the intervention, method of control, acupoints, and patient areas across these studies. The ORs were pooled with a random effects model. Recent reviews [5, 33] indicated that there was no pooled benefit of adjuvant acupuncture with respect to IVF outcomes. However, in our review, all interventions were included, and we found a significant pooled benefit in the 30 trials of acupuncture over control interventions in the clinical pregnancy rate (OR 1.26, 95% CI 1.06–1.50, $p = 0.01$; Fig. 2), whereas the other IVF outcomes showed no significant differences between interventions.

Considering the distinct body reactions and capabilities of different areas, there have been studies on the different effects of acupuncture on different areas. Studies have indicated that in some diseases, the effects of traditional medications are often ethnically based [22]. Furthermore, some Chinese studies have indicated that the same acupuncture treatment may induce different reactions in different areas [53]. Based on previous studies [11, 24], it has been speculated that acupuncture treatment outcomes may differ according to area and place of residence. Therefore, in the present study, we divided the studies into two groups according to the areas in which the original RCTs were conducted. Twenty-two studies were included in the non-Asian group, and the remaining eight studies

were included in the Asian group. When the studies were restricted to trials with Asian or non-Asian areas, the results of the sensitivity analysis showed a significant benefit in the CPR outcome in the Asian group. The pooled CPR result from the acupuncture groups was significantly higher than that from the control groups (OR 1.51, 95% CI 1.04–2.20, $p = 0.03$; Fig. 2), and although it tended to be higher in the non-Asian group, the differences were not significant (CPR: 22 trials; $n = 5280$; OR 1.20, 95% CI 0.99–1.47, $p = 0.07$, Fig. 2). However, the differences in the pooled LBR, BPR, and OPR results between the acupuncture and control groups were not significant.

In the present study, the results of different methods of acupuncture showed that EA may be associated with better IVF outcomes than TA and other methods. In the subgroup analysis, we found that in the Asian groups, the pooled CPR, LBR, BPR, and OPR from the EA groups were significantly higher than those of the controls (CPR: 4 trials; $n = 467$; OR 1.81, 95% CI 1.20–2.72, $p = 0.005$, Fig. 3; BPR: 1 trials; $n = 309$; OR 1.84, 95% CI 1.12–3.02, $p = 0.02$, Fig. 4; LBR: 2 trials; $n = 368$; OR 2.36, 95% CI 1.44–3.88, $p = 0.0007$, Table 3; OPR: 1 trial; $n = 309$; OR 1.94, 95% CI 1.03–3.64, $p = 0.04$, respectively, Table 4). EA as a traditional acupuncture technique has been studied as a pain-relieving method that activates endogenous pain-inhibiting systems such as the spinal/segmental gate mechanism and the endogenous opioid system [15]. It has been found to induce pain relief similar to that of fast-acting opiates during oocyte aspiration, but with fewer side effects [51]. Studies have proved that the mechanism of EA may be due to the electrical stimulation pulses on some points; this could result in brain activation. While the specific points were not conclusively demonstrated, our present study indicates that EA, a traditional and convenient acupuncture method, still plays an important role in IVF treatment, especially in Asian areas. This may be due to a different acupoint stimulated reaction in different area residents.

A recently conducted review indicated no significant improvement in clinical pregnancy when acupuncture was performed at approximately the time of ET, which differed from our results. We found that the pooled CPR, LBR, BPR, and OPR results were significantly higher in the acupuncture groups compared with the control groups when acupuncture was conducted during the time of COH (CPR: 9 trials; $n = 955$; OR 1.71, 95% CI 1.27–2.29, $p = 0.0004$, Fig. 3; LBR: 3 trials; $n = 435$; OR 2.41, 95% CI 1.54–3.78, $p = 0.0001$, Table 3; BPR: 4 trials; $n = 522$; OR 1.50, 95% CI 1.02–2.20, $p = 0.04$, Fig. 4; OPR: 2 trials; $n = 371$; OR 1.88, 95% CI 1.06–3.34, $p = 0.03$, Table 4), and the benefit was more obvious in the Asian group. This result could be due to the potential impact of acupuncture for the treatment of female

infertility on the hypothalamic–pituitary–ovarian axis and on the uterus, but the specific mechanism is still unknown. However, if more individualized acupuncture programs are used, more positive effects from acupuncture in IVF can be achieved [57]. The effects of acupuncture change according to a patient's endocrine system; therefore, acupuncture could be used successfully at different time points during the COH procedure according to individual characteristics.

Oocyte retrieval is an important step in the IVF-ET process. In recent years, the analgesic effect of acupuncture has been clinically reported in transvaginal oocyte retrieval. There are many reports on acupuncture at some acupoints enhancing the pain threshold and having an analgesic and anesthetic effect in clinical operations. The associated mechanism may be related to the promotion of the circulation of Qi, removal of stagnancy, clearance of channels, and activation of collaterals by acupoints. Subsequently, in the present study, no significant differences were found between the acupuncture and control groups with respect to OA, which may be due to the limited RCT study numbers.

To date, an increasing number of studies have been conducted to evaluate the effect of acupuncture on IVF outcomes, but the underlying mechanism remains unclear. An important component of TCM, acupuncture is based on the classic theory of TCM. The effects of acupuncture on IVF or ICSI outcomes depend on various factors, such as diagnosis of the patient's condition according to TCM theory, selection of acupoints, skills of the acupuncturist, and efficacy of the type of acupuncture administered (traditional needling acupuncture, EA, LA, or AA). Adding to TCM theory, Pinborg et al. [40] considered that the effects of acupuncture are most likely to be involved with uterine contractility instead of uterine receptivity. Acupuncture may act by reducing the contractility of the uterus, thereby preventing expulsion of embryos after transfer. However, more basic studies are needed to further explore the mechanism.

Study limitations

There were heterogeneities among these clinical trials, especially in the acupuncture treatment method and acupoint selection. Currently, there is no generally accepted standard of reference for treatment. Both ancient and modern acupuncture books clearly emphasize that needling at some acupoints, such as Sanyinjiao, Jianjin, and Zhiyin, is not appropriate for pregnant women because an abortion can result. Therefore, using acupuncture in IVF to improve and increase the pregnancy rate expands traditional acupuncture beyond its original application range. However, different acupuncture techniques may result in

different clinical effects, and slight changes have led to quite different clinical effects in some trials. In the study by Craig et al. [8], for example, the acupuncture scheme was based on that reported by Paulus et al. [39], and only two acupoints were added; however, the results of the two studies were different. The different acupuncture sites may be another influencing factor.

The number of embryos transferred is also an important factor affecting IVF pregnancy rate. Clearly, the more embryos that are transferred, the higher the chance that a patient will become pregnant. However, in the present review, most of the included RCTs did not mention the number of embryos transferred.

Conclusion

In our study, we found that there is a benefit of acupuncture, particularly EA, on IVF outcomes, especially in Asian area. Therefore, we suggest that a future study should be conducted to identify a standard dosage of acupuncture and develop an effective protocol.

Acknowledgements The present work was supported by grants from the Science Foundation of Jiangsu Province (BK20161067) and Department of Health of China (201302013, 201402004).

Compliance with ethical standards

Conflict of interest We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: systematic review and meta-analysis".

References

- Andersen D, Lossl K, Andersen AN, Furbringer J, Bach H, Simonsen J, Larsen EC (2010) Acupuncture on the day of embryo transfer: a randomized controlled trial of 635 patients. *Reprod Biomed Online* 21:366–372. doi:[10.1016/j.rbmo.2010.03.029](https://doi.org/10.1016/j.rbmo.2010.03.029)
- Arnoldi M, Diaferia D, Corbucci MG, De Lauretis L (2010) The role of acupuncture in patients at unfavourable reproductive prognosis in IVF: a prospective randomised study. *Hum Reprod* 25:I257–I257
- Benson MR, Elkind-Hirsch KE, Theall A, Fong K, Hogan RB, Scott RT (2006) Impact of acupuncture before and after embryo transfer on the outcome of in vitro fertilization cycles: a prospective single blind randomized study. *Fertil Steril* 86:S135–S135. doi:[10.1016/j.fertnstert.2006.07.362](https://doi.org/10.1016/j.fertnstert.2006.07.362)
- Chen J, Liu LL, Cui W, Sun W (2009) Effects of electroacupuncture on in vitro fertilization-embryo transfer (IVF-ET) of patients with poor ovarian response. *Zhongguo Zhen Jiu* 29:775–779
- Cheong YC, Dix S, E Hung Yu Ng, Ledger WL, Farquhar C (2013) Acupuncture and assisted reproductive technology.

- Cochrane Database Syst Rev 7:CD006920. doi:[10.1002/14651858.CD006920.pub3](https://doi.org/10.1002/14651858.CD006920.pub3)
6. Christensen PA, Noreng M, Andersen PE, Nielsen JW (1989) Electroacupuncture and postoperative pain. *Br J Anaesth* 62:258–262
 7. Craig LB, Criniti AR, Hansen KR, Marshall LA, Soules MR (2007) Acupuncture lowers pregnancy rates when performed before and after embryo transfer. *Fertil Steril* 88:S40–S40. doi:[10.1016/j.fertnstert.2007.07.143](https://doi.org/10.1016/j.fertnstert.2007.07.143)
 8. Craig LB, Rubin LEH, Peck JD, Anderson M, Marshall LA, Soules MR (2014) Acupuncture performed before and after embryo transfer a randomized controlled trial. *J Reprod Med* 59:313–320
 9. Cui W, Li J, Sun W, Wen J (2011) Effect of electroacupuncture on oocyte quality and pregnancy for patients with PCOS undergoing in vitro fertilization and embryo transfer. *Zhongguo Zhen Jiu* 31:687–691
 10. Daya S (2003) Pitfalls in the design and analysis of efficacy trials in subfertility. *Hum Reprod* 18:1005–1009
 11. Deurenberg P, Deurenberg-Yap M, Schouten FJ (2002) Validity of total and segmental impedance measurements for prediction of body composition across ethnic population groups. *Eur J Clin Nutr* 56:214–220. doi:[10.1038/sj.ejcn.1601303](https://doi.org/10.1038/sj.ejcn.1601303)
 12. di Villahermosa DI, dos Santos LG, Nogueira MB, Vilarino FL, Barbosa CP (2013) Influence of acupuncture on the outcomes of in vitro fertilisation when embryo implantation has failed: a prospective randomised controlled clinical trial. *Acupunct Med* 31:157–161. doi:[10.1136/acupmed-2012-010269](https://doi.org/10.1136/acupmed-2012-010269)
 13. Dieterle S, Ying G, Hatzmann W, Neuer A (2006) Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. *Fertil Steril* 85:1347–1351. doi:[10.1016/j.fertnstert.2005.09.062](https://doi.org/10.1016/j.fertnstert.2005.09.062)
 14. Domar AD, Meshay I, Kelliher J, Alper M, Powers RD (2009) The impact of acupuncture on in vitro fertilization outcome. *Fertil Steril* 91:723–726. doi:[10.1016/j.fertnstert.2008.01.018](https://doi.org/10.1016/j.fertnstert.2008.01.018)
 15. Dong C, Hu L, Liang F, Zhang S (2015) Effects of electroacupuncture on labor pain management. *Arch Gynecol Obstet* 291:531–536. doi:[10.1007/s00404-014-3427-x](https://doi.org/10.1007/s00404-014-3427-x)
 16. Du XF, Yang XH, Li J, Hao M, Guo YH (2016) Growth hormone co-treatment within a GnRH agonist long protocol improves implantation and pregnancy rates in patients undergoing IVF-ET. *Arch Gynecol Obstet*. doi:[10.1007/s00404-016-4163-1](https://doi.org/10.1007/s00404-016-4163-1)
 17. Dundee JW, Ghaly RG, Fitzpatrick KT, Abram WP, Lynch GA (1989) Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *J R Soc Med* 82:268–271
 18. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC (1998) Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 280:1569–1575
 19. El-Toukhy T, Khalaf Y (2010) A new study of acupuncture in IVF: pointing in the right direction. *Reprod Biomed Online* 21:278–279. doi:[10.1016/j.rbmo.2010.06.024](https://doi.org/10.1016/j.rbmo.2010.06.024)
 20. Fratterelli J, Leondires M, Fong K, Theall A, Locatelli S, Scott R (2008) Laser acupuncture before and after embryo transfer improves art delivery rates: results of a prospective randomized double-blinded placebo controlled five-armed trial involving 1000 patients. *Fertil Steril* 90:S105
 21. Gejvall AL, Stener-Victorin E, Moller A, Janson PO, Werner C, Bergh C (2005) Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. *Hum Reprod* 20:728–735. doi:[10.1093/humrep/deh665](https://doi.org/10.1093/humrep/deh665)
 22. Goh KL (2011) Clinical and epidemiological perspectives of dyspepsia in a multiracial Malaysian population. *J Gastroenterol Hepatol* 26(Suppl 3):35–38. doi:[10.1111/j.1440-1746.2011.06648.x](https://doi.org/10.1111/j.1440-1746.2011.06648.x)
 23. Griesinger G, Dafopoulos K, Schultze-Mosgau A, Felberbaum R, Diedrich K (2004) What is the most relevant standard of success in assisted reproduction? Is BESST (birth emphasizing a successful singleton at term) truly the best? *Hum Reprod* 19:1239–1241. doi:[10.1093/humrep/deh237](https://doi.org/10.1093/humrep/deh237)
 24. Guricci S, Hartiyanti Y, Hautvast JG, Deurenberg P (1999) Prediction of extracellular water and total body water by multi-frequency bio-electrical impedance in a Southeast Asian population. *Asia Pac J Clin Nutr* 8:155–159
 25. Harris P, Rees R (2000) The prevalence of complementary and alternative medicine use among the general population: a systematic review of the literature. *Complement Ther Med* 8:88–96. doi:[10.1054/ctim.2000.0353](https://doi.org/10.1054/ctim.2000.0353)
 26. He D, Berg JE, Hostmark AT (1997) Effects of acupuncture on smoking cessation or reduction for motivated smokers. *Prev Med* 26:208–214. doi:[10.1006/pmed.1996.0125](https://doi.org/10.1006/pmed.1996.0125)
 27. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928. doi:[10.1136/bmj.d5928](https://doi.org/10.1136/bmj.d5928)
 28. Ho M, Huang LC, Chang YY, Chen HY, Chang WC, Yang TC, Tsai HD (2009) Electroacupuncture reduces uterine artery blood flow impedance in infertile women. *Taiwan J Obstet Gynecol* 48:148–151. doi:[10.1016/S1028-4559\(09\)60276-X](https://doi.org/10.1016/S1028-4559(09)60276-X)
 29. Humaidan P, Stener-Victorin E (2004) Pain relief during oocyte retrieval with a new short duration electro-acupuncture technique—an alternative to conventional analgesic methods. *Hum Reprod* 19:1367–1372. doi:[10.1093/humrep/deh229](https://doi.org/10.1093/humrep/deh229)
 30. Hunt KJ, Coelho HF, Wider B, Perry R, Hung SK, Terry R, Ernst E (2010) Complementary and alternative medicine use in England: results from a national survey. *Int J Clin Pract* 64:1496–1502. doi:[10.1111/j.1742-1241.2010.02484.x](https://doi.org/10.1111/j.1742-1241.2010.02484.x)
 31. Madaschi C, Braga DP, Figueira Rde C, Iaconelli A Jr, Borges E Jr (2010) Effect of acupuncture on assisted reproduction treatment outcomes. *Acupunct Med* 28:180–184. doi:[10.1136/aim.2009.002022](https://doi.org/10.1136/aim.2009.002022)
 32. Magarelli PC, Cridennda DK, Cohen M (2009) Changes in serum cortisol and prolactin associated with acupuncture during controlled ovarian hyperstimulation in women undergoing in vitro fertilization—embryo transfer treatment. *Fertil Steril* 92:1870–1879. doi:[10.1016/j.fertnstert.2008.10.067](https://doi.org/10.1016/j.fertnstert.2008.10.067)
 33. Manheimer E, van der Windt D, Cheng K, Stafford K, Liu JP, Tierney J, Lao LX, Berman BM, Langenberg P, Bouter LM (2013) The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update* 19:696–713. doi:[10.1093/humupd/dmt026](https://doi.org/10.1093/humupd/dmt026)
 34. Manheimer E, Zhang G, Udoff L, Haramati A, Langenberg P, Berman BM, Bouter LM (2008) Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis. *BMJ* 336:545–549. doi:[10.1136/bmj.39471.430451.BE](https://doi.org/10.1136/bmj.39471.430451.BE)
 35. Moy I, Milad MP, Barnes R, Confino E, Kazer RR, Zhang X (2011) Randomized controlled trial: effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization. *Fertil Steril* 95:583–587. doi:[10.1016/j.fertnstert.2010.05.024](https://doi.org/10.1016/j.fertnstert.2010.05.024)
 36. Ng EH, So WS, Gao J, Wong YY, Ho PC (2008) The role of acupuncture in the management of subfertility. *Fertil Steril* 90:1–13. doi:[10.1016/j.fertnstert.2008.02.094](https://doi.org/10.1016/j.fertnstert.2008.02.094)
 37. Omodei U, Piccioni G, Tombesi S, Dordoni D, Fallo L, Ghilardi F (2010) Effect of acupuncture on rates of pregnancy among women undergoing in vitro fertilization. *Fertil Steril* 94:S170–S170

38. Paulus WE, Zhang M, Strehler E, Seybold B, Sterzik K (2003) Placebo-controlled trial of acupuncture effects in assisted reproduction therapy. *Hum Reprod* 18:18–19
39. Paulus WE, Zhang MM, Strehler E, El-Danasouri I, Sterzik K (2002) Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 77:721–724. doi:[10.1016/S0015-0282\(01\)03273-3](https://doi.org/10.1016/S0015-0282(01)03273-3)
40. Pinborg A, Loft A, Andersen AN (2008) Acupuncture with in vitro fertilisation. *BMJ* 336:517–518. doi:[10.1136/bmj.39503.643727.80](https://doi.org/10.1136/bmj.39503.643727.80)
41. Qu F, Zhou J, Ren RX (2012) Effects of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis. *J Altern Complement Med* 18:429–439. doi:[10.1089/acm.2011.0158](https://doi.org/10.1089/acm.2011.0158)
42. Rashidi BH, Tehrani ES, Hamedani NA, Pirzadeh L (2013) Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome. *Acupunct Med* 31:151–156. doi:[10.1136/acupmed-2012-010198](https://doi.org/10.1136/acupmed-2012-010198)
43. Sator-Katzenschlager SM, Wolfler MM, Kozek-Langenecker SA, Sator K, Sator PG, Li B, Heinze G, Sator MO (2006) Auricular electro-acupuncture as an additional perioperative analgesic method during oocyte aspiration in IVF treatment. *Hum Reprod* 21:2114–2120. doi:[10.1093/humrep/del110](https://doi.org/10.1093/humrep/del110)
44. Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, Hillman S, Brizz B, Cohn DL (1998) Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. *Terry Bein Community Programs for Clinical Research on AIDS. JAMA* 280:1590–1595
45. Smith C, Coyle M, Norman RJ (2006) Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer. *Fertil Steril* 85:1352–1358. doi:[10.1016/j.fertnstert.2005.12.015](https://doi.org/10.1016/j.fertnstert.2005.12.015)
46. So EW, Ng EH, Wong YY, Lau EY, Yeung WS, Ho PC (2009) A randomized double blind comparison of real and placebo acupuncture in IVF treatment. *Hum Reprod* 24:341–348. doi:[10.1093/humrep/den380](https://doi.org/10.1093/humrep/den380)
47. So EW, Ng EH, Wong YY, Yeung WS, Ho PC (2010) Acupuncture for frozen-thawed embryo transfer cycles: a double-blind randomized controlled trial. *Reprod Biomed Online* 20:814–821. doi:[10.1016/j.rbmo.2010.02.024](https://doi.org/10.1016/j.rbmo.2010.02.024)
48. Stener-Victorin E, Kobayashi R, Kurosawa M (2003) Ovarian blood flow responses to electro-acupuncture stimulation at different frequencies and intensities in anaesthetized rats. *Auton Neurosci* 108:50–56. doi:[10.1016/j.autneu.2003.08.006](https://doi.org/10.1016/j.autneu.2003.08.006)
49. Stener-Victorin E, Kobayashi R, Watanabe O, Lundberg T, Kurosawa M (2004) Effect of electro-acupuncture stimulation of different frequencies and intensities on ovarian blood flow in anaesthetized rats with steroid-induced polycystic ovaries. *Reprod Biol Endocrinol* 2:16. doi:[10.1186/1477-7827-2-16](https://doi.org/10.1186/1477-7827-2-16)
50. Stener-Victorin E, Waldenstrom U, Nilsson L, Wikland M, Jansson PO (1999) A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization. *Hum Reprod* 14:2480–2484
51. Stener-Victorin E, Waldenstrom U, Wikland M, Nilsson L, Hagglund L, Lundberg T (2003) Electro-acupuncture as a per-operative analgesic method and its effects on implantation rate and neuropeptide Y concentrations in follicular fluid. *Hum Reprod* 18:1454–1460
52. Sun ZG, Lian F, Zhang JW (2012) 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. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 32:1023–1027
53. Wang XY (2008) Influence of different constitution of races on application of acupuncture therapy. *Zhongguo Zhen Jiu* 28:819–821
54. Westergaard LG, Mao Q, Kroglund M, Sandrini S, Lenz S, Grinstead J (2006) Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial. *Fertil Steril* 85:1341–1346. doi:[10.1016/j.fertnstert.2005.08.070](https://doi.org/10.1016/j.fertnstert.2005.08.070)
55. Yang R, Yang S, Li R, Chen X, Wang H, Ma C, Liu P, Qiao J (2015) Biochemical pregnancy and spontaneous abortion in first IVF cycles are negative predictors for subsequent cycles: an over 10,000 cases cohort study. *Arch Gynecol Obstet* 292:453–458. doi:[10.1007/s00404-015-3639-8](https://doi.org/10.1007/s00404-015-3639-8)
56. Zhang R, Feng XJ, Guan Q, Cui W, Zheng Y, Sun W, Han JS (2011) Increase of success rate for women undergoing embryo transfer by transcutaneous electrical acupoint stimulation: a prospective randomized placebo-controlled study. *Fertil Steril* 96:912–916. doi:[10.1016/j.fertnstert.2011.07.1093](https://doi.org/10.1016/j.fertnstert.2011.07.1093)
57. Zheng CH, Zhang MM, Huang GY, Wang W (2012) The role of acupuncture in assisted reproductive technology. *Evid Based Complement Alternat Med* 2012:543924. doi:[10.1155/2012/543924](https://doi.org/10.1155/2012/543924)