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Systematic review

Effects of acupuncture during in vitro fertilization or intracytoplasmic sperm injection: An updated systematic review and meta-analysis

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ABSTRACT

Introduction: Systematic reviews need constantly updating as new evidence emerges. The aim of this comprehensive systematic review/meta-analysis focused on trials that provided acupuncture during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) which were compared with routine care for a range of outcomes - implantation rate, biochemical pregnancies (presence of a positive urinary pregnancy test or a positive serum human chorionic gonadotrophin test), clinical pregnancies, ongoing pregnancies, and rates of miscarriage and live birth.

Methods: A systematic search of MEDLINE and EMBASE databases for randomized controlled trials (RCTs) on acupuncture treatment during IVF or ICSI was carried out from database inception until July 31, 2017. Study selection, data extraction, quality assessment and bias assessment were carried out by 2 researchers independently, with adjudication by the third researcher when necessary. A meta-analysis was performed to compare outcomes between women receiving acupuncture and those receiving routine care, and pooled relative risks (RR) were calculated.

Results: Statistically significant differences were observed in rates of clinical pregnancy (RR = 1.19, 95% confidence intervals (CI): 1.06–1.34 p = 0.002), live birth (RR = 1.36, 95% CI: 1.09–1.69 p = 0.006), and implantation rate (RR = 1.31, 95% CI: 1.08–1.59 p = 0.006) between the acupuncture and the control groups. No significant differences were found for biochemical pregnancies (RR = 1.12, 95% CI: 0.92–1.35 p = 0.268), ongoing pregnancies (RR = 1.21, 95% CI: 0.95–1.55 p = 0.130), or miscarriage (RR = 0.89, 95% CI: 0.67–1.20 p = 0.447) between the two groups. Adverse events were described in 4 studies.

Conclusions: Acupuncture may have an impact on the outcome rates of implantation, clinical pregnancy, and live birth; however, well-designed RCTs are warranted to further validate its effects.

1. Introduction

Worldwide, in vitro fertilization (IVF) has successfully resulted in the birth of more than 3 million children [1]. Each year, more than 300,000 IVF or intracytoplasmic sperm injection (ICSI) cycles are carried out in Europe [2]. Moreover, in the United States, the number of children that are conceived through IVF or ICSI comprises 2%–3% of the total number of babies born [3]. Acupuncture has been used by numerous infertile couples undergoing infertility treatment as an effective non-pharmacological traditional Chinese medical (TCM) therapy [4–8]. Reports suggest that fertility issues are the second leading health condition causing individuals to choose acupuncture treatment in the United Kingdoms [9]. However, given that data from clinical trials are inconsistent, physicians and infertile couples face challenges in deciding whether to choose acupuncture for improving the IVF or ICSI outcome [10].

In 2012, a systematic review and meta-analysis was conducted which included 17 randomized controlled trials (RCTs). The data indicated that acupuncture did not improve the pregnancy rate in women having IVF or ICSI [11]. Several possible assumptions on the sources of heterogeneity in the study were proposed [11] and guidance was provided for future trial design [12]. Given the release of numerous new

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studies since 2012, it was necessary to perform an updated review and meta-analysis to inform clinical practice.

2. Materials and methods

2.1. Search strategy

To investigate whether acupuncture treatment could improve IVF and/or ICSI outcomes, a systematic review and meta-analysis were performed. We searched MEDLINE (1966 to July 2017), SCISEARCH (1974 to July 2017), the Cochrane Menstrual Disorders and Subfertility Group trials register (July 2017), AMED (Allied and Complementary Medicine) (1985 to July 2017), Cumulative Index to Nursing and Allied Health Literature (1982 to July 2017), EMBASE (1974 to July 2017), and reference lists for the relevant studies. Chinese researches were also searched from the Wanfang Database (1982 to July 2017), China Academic Journal Electronic full text Database in China National Knowledge Infrastructure (1982 to July 2017), and Index to Chinese Periodical Literature (1978 to July 2017). ISI Proceedings for conference abstracts, and International Standard Randomized Controlled Trial Number (ISRCTN) Register and meta-register for randomized controlled trials (mRCT) were also searched for randomized controlled trials. To identify published articles that were not identified by electronic searches, relevant references were addressed. When needed, we contacted the authors involved in the studies, and any absent data were obtained. None of our searches involved restrictions in terms of publication type or language.

During our search, we used the following free text terms and Medical Subject Headings (MeSH) terms: ("acupuncture", "acupressure", "moxibustion", "electroacupuncture", "auricular-acupuncture", "auriculotherapy", "acupuncture therapy" and "Traditional Chinese Medicine") and ("in vitro fertilization", "fertilization in vitro", "intracytoplasmic-sperm-injection", "assisted reproductive techniques", "oocytes", "egg collection", "embryo transfer" and "embryo implantation").

2.2. Study selection

In this study, only RCTs in which acupuncture was compared with no acupuncture treatment or sham treatment during IVF/ICSI were selected. Therapeutic intervention included several accepted acupuncture procedures, such as acupuncture using lasers, traditional acupuncture using needles, electro-acupuncture, and auricular acupuncture. Any study that included a crossover design was excluded. Eligible trials required the extraction of data including at least one of the following outcomes: biochemical pregnancy (presence of a positive urinary pregnancy test or a positive serum human chorionic gonadotrophin test), clinical pregnancy (fetal heartbeat or at least one gestational sac present, confirmed by trans-vaginal ultrasound), ongoing pregnancy (pregnancy beyond 10 weeks of gestation, as confirmed by fetal heart activity on ultrasound), live birth (presence of a baby born alive after 24 weeks gestation), miscarriage (presence of miscarriage before the 16th weeks of pregnancy), and implantation rate(number of gestational sacs per number of transferred embryos).

Manuscripts identified were independently analyzed by 2 investigators (X.Z. and Y.Z.). Moreover, full manuscripts were obtained for any citation with the potential to meet the inclusion criteria. After thorough inspection of the entire manuscript, a decision was made to include or exclude the study. When duplicate manuscripts were included, only the most up-to-date version was included. Any disagreement was resolved by review and adequate discussion with a fourth reviewer (F.Q.).

2.3. Assessments Bias risk

Risk of bias was assessed independently by two authors (X.Z. and Y.W.) with the "Risk of Bias table" (Table 1) in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. Sequence generation, allocation concealment, blinding (or masking), incomplete data assessment, selective outcome reporting, and other sources of bias were assessed with three potential responses: Low risk, High risk, and unclear. Disagreements between review authors were resolved by discussion or with a third author (Q.F.).

2.4. Data extraction and quality assessment

Treatment effects were evaluated and pooled relative risks (RRs) were calculated. This was performed by comparing the rates of clinical, biochemical, ongoing pregnancy, implantation, live birth, and miscarriage among women who underwent acupuncture treatment compared with controls. From each study, the extracted features included population characteristics and interventions. An intention-to-treat approach was used to extract outcome data from each study.

Study quality was evaluated using internal validity criteria selected from a list established by the Cochrane Menstrual Disorders and Subfertility Group. Data regarding adequacy of randomization, blinding, comparability at baseline, concealment of allocation, intention-to-treat analysis, sham acupuncture, power analysis, and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines adherence were determined by investigating the entire manuscript. Moreover, the corresponding authors were contacted if additional information was needed or if clarification was required. Sham acupuncture was accepted when it used any standard method of delivery; for example, the use of acupuncture at sites that are not intended for treatment, the use of standard acupoints, and the application of sham laser acupuncture or blunt (placebo) needles.

2.5. Statistical analysis

Study heterogeneity was evaluated using Cochran's Q test and I^2 statistics, which defines significant heterogeneity as $P < 0.10$ and/or $I^2 > 50\%$. When no significant heterogeneity could be observed, a fixed-effects model was applied. In other cases, a random-effects model was used to specify additional conservative estimates. Forest plots of the rates of pregnancy were generated for the acupuncture-complemented treatment versus no/sham acupuncture. Subgroup analyses were performed using the following conditions: I. type of control (placebo or no acupuncture invention); II. adherence to STRICTA guidelines (yes or no); III. number of centers (single or multiple); IV. acupuncture type (electrical acupuncture or traditional acupuncture); V. administration of acupuncture (by acupuncturist or not). Subsequently, sensitivity analysis was performed to explore whether the overall findings were affected if individual studies were excluded. Publication bias was assessed by using funnel plot, Begg's test and Egger's test. STATA software version 12.0 (STATA Corp, College Station, TX, USA) was used to perform the statistical analyses.

3. Results

3.1. Results from risk of bias assessment

By the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0., of 31 randomized controlled trials (RCTs), there were 17 (54.8%) RCTs with low risk of bias arising from the random sequence generation, 20 (64.5%) RCTs with low risk of bias due to allocation concealment, 10 (32.2%) RCTs with low risk of bias due to blinding of participants and personnel, 27(87.1%) RCTs had low risk of bias in blinding of outcome assessment, 23 (74.2%) RCTs had low risk of bias in incomplete outcome data, and 28 (90.3%) RCTs had low risk of bias due to selective reporting. Table 2 shows results from the risk of bias assessment.

Table 1
The Cochrane Collaboration's tool for assessing risk of bias.

Random sequence generation	
Low risk of bias	The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator.
High risk of bias	The investigators describe a nonrandom component in the sequence generation process. Usually, the description would involve some systematic, nonrandom approach, for example, sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day)of admission.
Unclear risk of bias	Insufficient information about the sequence generation process to permit judgement of"Low risk"or"High risk."
Allocation concealment	
Low risk of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance.
High risk of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on using an open random allocation schedule(e.g., a list of random numbers); assignment envelopes were used without appropriate safe guards(e.g., if envelopes were unsealed or nonopaque or not sequentially numbered).
Blinding of participants and personnel	
Low risk of bias	Any one of the following: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
High risk of bias	no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Unclear risk of bias	Any one of the following: insufficient information to permit judgement of"Low risk"or"High risk"; the study did not address this outcome.
Blinding of outcome assessment	
Low risk of bias	Anyone of the following: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
High risk of bias	Anyone of the following: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Unclear risk of bias	Any one of the following: insufficient information to permit judgement of "Low risk" or "High risk"; the study did not address this outcome.
Incomplete outcome data	
Low risk of bias	Anyone of the following: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
High risk of bias	Anyone of the following: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention eff ;ect estimate.
Unclear risk of bias	Any one of the following: insufficient information to permit judgement of "Low risk" or "High risk" (e.g., number randomized not stated, no reasons for missing data provided); the study did not address this outcome.
Selective reporting	
Low risk of bias	Any of the following: the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
High risk of bias	Anyone of the following: not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods, or subsets of the data(e.g., subscales) that were not prespecified.
Unclear risk of bias	Insufficient information to permit judgement of "Low risk" or "High risk", it is likely that the majority of studies will fall into this category.
Other bias	
Low risk of bias	The study appears to be free of other sources of bias
High risk of bias	There is at least one important risk of bias. For example, the study had a potential source of bias related to the specific study design used, or has been claimed to have been fraudulent; or had some other problem.
Unclear risk of bias	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias.

3.2. Study characteristics

The electronic searches yielded a total of 238 publications. After evaluation of the selected articles and applying the inclusion/exclusion criteria, 86 publications were selected for further retrieval. The flow chart of the literature search and the selection process is presented in Fig. 1. Of all 86 publications examined, 31 manuscripts [13–43] which included 6098 women met our inclusion criteria. Tables 3 and 4 show the specific details of the studies included.

3.3. Adverse event

Among the included 31 papers, adverse events were described in 4 studies [21,36,38,43], among which, 2 studies [36,38] showed no adverse event and another 2 studies [21,43] reported adverse events. Sator-Katzenschlager et al. [21] reported "inadequate comfort ", while Zheng et al. [43] reported 7 cases (2.5%) with dizziness, and 3 cases (1.1%) with fatigue.

3.4. Outcomes of IVF

Regarding the clinical pregnancy outcome, data from all 31 included trials (n = 6098) were available for analysis [13–43], and significant heterogeneity was found among the studies (I^2 = 63.4%, P = 0.000). When using the random-effects model, clinical pregnancy outcome was significantly different between the acupuncture and the control groups (RR = 1.19, 95% CI: 1.06–1.34, P = 0.002; Fig. 2).

Regarding the biochemical pregnancy outcome, data from 12 out of the 31 included trials were accessible (n = 2864) [17,19,20,23,24,26–29,32,34,35]. Moreover, a significant heterogeneity was found among the studies (I^2 = 77.4%, P = 0.000). When the random-effects model was used, the biochemical pregnancy outcome was not significantly different between the two groups (RR = 1.12, 95% CI: 0.92–1.35, P = 0.268; Fig. 3).

Fig. 4 shows that for ongoing pregnancy outcome, data were obtained from 9 out of the 31 included trials (n = 2454) [14–16,20,22,23,27,28,34]. Significant heterogeneity was found among studies (I^2 = 67.1%, P = 0.002). When using the random-effects model, no significant difference was found regarding the outcome of ongoing pregnancy between groups after combining the results from all 9 trials

Table 2
Risk of bias table: review authors' judgments about each risk of bias item presented as percentages across all included studies.

study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Stener-Victorin et al. [13]	unclear	Low risk	High risk	High risk	High risk	unclear	unclear
Paulus et al. [14]	Low risk	Low risk	unclear	Low risk	Low risk	Low risk	unclear
Stener-Victorin et al. [16]	unclear	Low risk	High risk	High risk	High risk	Low risk	unclear
Paulus et al. [15]	unclear	Low risk	High risk	Low risk	Low risk	Low risk	unclear
Humaidan and Stener-Victorin [17]	unclear	Low risk	High risk	High risk	Low risk	Low risk	unclear
Gejervall et al. [18]	Low risk	unclear	High risk	High risk	Low risk	unclear	unclear
Dieterle et al. [20]	unclear	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Westergaard et al. [23]	unclear	Low risk	High risk	Low risk	Low risk	unclear	unclear
Smith et al. [22]	High risk	Low risk	unclear	Low risk	Low risk	Low risk	unclear
Sator-Katzenschlager et al. [21]	Low risk	unclear	Low risk	Low risk	Low risk	Low risk	unclear
Benson et al. [19]	unclear	unclear	High risk	Low risk	Low risk	Low risk	unclear
Craig et al. [24]	Low risk	Low risk	unclear	Low risk	High risk	Low risk	unclear
Domar et al. [26]	Low risk	Low risk	High risk	Low risk	High risk	Low risk	unclear
Chen et al. [25]	Low risk	unclear	High risk	Low risk	Low risk	Low risk	unclear
So et al. [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Andersen et al. [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Moy et al. [29]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	unclear
Madaschi et al. [30]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	unclear
Cui et al. [31]	High risk	unclear	High risk	Low risk	Low risk	Low risk	unclear
Zhang et al. [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Sun et al. [33]	Low risk	unclear	High risk	Low risk	Low risk	Low risk	unclear
Rashidi et al. [34]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	unclear
Villahermosaet al. [35]	unclear	unclear	High risk	Low risk	Low risk	Low risk	unclear
Qu et al. [38]	unclear	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Craig et al. [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Hong et al. [37]	High risk	unclear	Low risk	Low risk	High risk	Low risk	unclear
Shuai et al. [41]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear
Li et al. [40]	Low risk	unclear	High risk	Low risk	High risk	Low risk	unclear
chen et al. [39]	High risk	Low risk	unclear	Low risk	Low risk	Low risk	unclear
Yang et al. [42]	Low risk	unclear	High risk	Low risk	Low risk	Low risk	unclear
Zheng et al. [43]	unclear	unclear	High risk	Low risk	High risk	Low risk	unclear

(RR = 1.21, 95% CI: 0.95–1.55, P = 0.130).

Regarding the implantation rate, data from 11 out of the 31 included trials were available (n = 4333) [13,16,17,20,23,25,27,32,37,38,41]. However, no significant heterogeneity was found among the studies (I^2 = 68.6%, P = 0.000). When combining the data from all 11 trials, a significant difference in the implantation rate was observed between the groups based on the random-effects model (RR = 1.31, 95% CI: 1.08–1.59, P = 0.006; Fig. 5).

Regarding the live birth outcome, information was extracted from 12 out of the 31 included trials (n = 3188) [14,15,20,23,27,28,30–32,36,38,41],and significant heterogeneity was found among the studies (I^2 = 70.1%, P = 0.000). Moreover, when using the random-

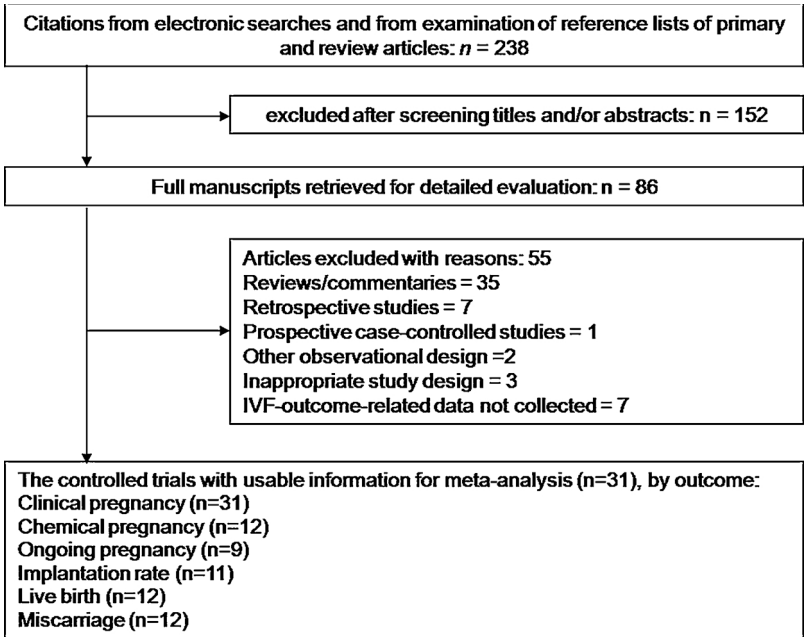

Fig. 1. Flowchart of the study selection.

Table 3
Quality of the 31 randomized trials involving the use of acupuncture during in vitro fertilization or intracytoplasmic sperm injection treatment included in the systematic review with meta-analysis.

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. [13]	Multicenter	Not mentioned	Adequate	Unclear	No	Yes	No	No	Trained midwives
Paulus et al. [14]	Single center	Computerized randomization	Adequate	Yes	Single blind	Yes	No	No	Trained examiner
Stener-Victorin et al. [16]	Multicenter	Not mentioned	Adequate	Unclear	No	No	Yes	Yes	Trained nurses
Paulus et al. [15]	Single center	Not mentioned	Adequate	Unclear	No	Yes	No	No	Not mentioned
Humaidan and Stener-Victorin [17]	Single center	Not mentioned	Adequate	Yes	No	Yes	Yes	Yes	Trained nurses
Gejervall et al. [18]	Single center	Computerized randomization	Unclear	Unclear	No	No	Yes	Yes	Four midwives
Dieterle et al. [20]	Single center	Not mentioned	Adequate	Yes	Double blind	Yes	No	Yes	Physician
Westergaard et al. [23]	Single center	Unclear	Adequate	Yes	No	No	Yes	Yes	Nurse
Smith et al. [22]	Single center	Block randomization	Adequate	Yes	Single blind	Yes	Yes	Yes	Acupuncturist
Sator-Katzenschlager et al. [21]	Single center	Computerized randomization	Unclear	Yes	Double blind	Yes	Yes	Yes	Trained gynecologist
Benson et al. [19]	Single center	Not mentioned	Unclear	Yes	No (except laser groups)	Yes	No	No	Acupuncturist
Craig et al. [24	Multicenter	Computerized randomization	Adequate	Yes	Single blind	No	No	No	Acupuncturist
Domar et al. [26]	Single center	Computerized randomization	Adequate	Yes	Single blind	Yes	No	No	Acupuncturist
Chen et al. [25]	Single center	Computerized randomization	Unclear	Yes	No	Yes	No	No	Unclear
So et al. [27]	Single center	Computerized randomization	Adequate	Yes	Double blind	Yes	Yes	Yes	Acupuncturist
Andersen et al. [28]	Multicenter	Computerized	Adequate	Yes	Double blind	Yes	Yes	Yes	Nurses who were authorized professional acupuncturists
Moy et al. [29]	Single center	Computerized randomization	Adequate	Yes	Double blind	Yes	Yes	Yes	Acupuncturist
Madaschi et al. [30]	Single center	Computerized randomization	Adequate	Yes	No	Yes	Yes	Yes	Acupuncturist
Cui et al. [31]	Single center	Sealed envelope way	Unclear	Yes	No	Yes	No	No	Not mentioned
Zhang et al. [32]	Single center	Computerized randomization	Adequate	Yes	Single blind	No	Yes	Yes	Acupuncturist
Sun et al. [33]	Single center	Computerized randomization	Unclear	Yes	No	Yes	No	No	Not mentioned
Rashidi et al. [34]	Single center	Computerized randomization	Adequate	Yes	No	Yes	Yes	Yes	Acupuncturist
Villahermosa et al. [35]	Single center	Not mentioned	Unclear	Yes	No	Yes	No	Yes	Not mentioned
Qu et al. [38]	Single center	Not mentioned	Adequate	Yes	Double blind	Yes	Yes	Yes	Two independent trained nurses
Craig et al. [36]	Multicenter	Computerized randomization	Adequate	Yes	Single blind	Yes	Yes	Yes	Acupuncturist
Hong et al. [37]	Single center	Random falling tone to date	Unclear	Yes	No	No	No	No	Not mentioned
Shuai et al. [41]	Single center	Computerized randomization	Adequate	Yes	Single blind	Yes	No	No	Not mentioned
Li et al. [40]	Single center	Random number table	Unclear	Yes	No	Yes	No	No	Acupuncturist
chen et al. [39]	Single center	Sealed envelope way	Adequate	Yes	Single blind	Yes	No	No	Acupuncturist
Yang et al. [42]	Single center	Random number table	Unclear	Yes	No	Yes	No	No	Not mentioned
Zheng et al. [43]	Single center	Not mentioned	Unclear	Yes	No	No	No	No	Not mentioned

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

Table 4
Characteristics of the 31 randomized trials Involving the use of acupuncture during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment included in the systematic review with meta-analysis.

Study	Participants	Country	Intervention	Control	Placebo intervention	IVF outcomes
Stener-Victorin et al. [13]	150 randomized—no inclusion criteria	Sweden	EA and PCB	Alfentanil + PCB	No	CPR,IR,MR
Paulus et al. [14]	160 randomized—only women with good quality embryos included	Germany	TA and AA for 25 min before and after ET	Lying still for 25 min before and after ET	No	CPR,OPR,LBR
Stener-Victorin et al. [16]	286 randomized—eligible women aged < 38 years, BMI < 28 kg/m^2, had 4 or more follicles sized > 18 mm and no more than 3 previous IVF attempts	Sweden	PCB and EA	Alfentanil + PCB	No	CPR,OPR,IR,MR
Paulus et al. [15]	200 randomized—only women with good quality embryos included	Germany	TA for 25 min before and after ET	Sham (noninvasive)	Yes	CPR,OPR,LBR
Humaidan and Stener-Victorin [17]	200 randomized—no inclusion criteria	Denmark	PCB and EA	Alfentanil + PCB	No	CPR,BCP,IR
Gejervall et al. [18]	160 randomized—no inclusion criteria	Sweden	PCB and EA	Premedication + Alfentanil + PCB	No	CPR
Dieterle et al. [20]	225 randomized—no inclusion criteria	Germany	TA for 30 min after ET and 3 days later + Chinese medical herbs	Placebo needling at acupoints designed not to influence fertility	Yes	CPR,BCPR,OPR,IR,LBR,MR
Westergaard et al. [23]	300 randomized—no inclusion criteria	Denmark	TA for 25 min before and after ET with or without a third session for 25 min 2 days after ET	Bed rest for 1 hour after ET	No	CPR,BCPR,OPR,IR,LBR
Smith et al. [22]	228 randomized—women with a planned ET were eligible	Australia	TA	Placebo needling at points close to the real acupuncture acupoints	Yes	CPR,OPR
Sator-Katzenschlager et al. [21]	94 randomized—women aged < 43 years, BMI < 28 kg/m^2, had 4 or more follicles of size > 18 mm	Austria	AA with or without electrical stimulation + PCA	PCA + placebo AA	Yes	CPR
Benson et al. [19]	258 randomized—women scheduled to have ET were eligible	USA	Traditional needle or laser acupuncture for 25 min before and after ET	Sham laser acupuncture, relaxation or no intervention	No (except laser group)	CPR,BCPR
Craig et al. [24]	107 randomized—women undergoing IVF who have not had acupuncture within 3 months	USA	TA for 25 min before and after ET	No intervention	No	CPR,BCPR
Domar et al. [26]	150 randomized—women scheduled to have ET using non-donor eggs were eligible	USA	TA for 25 min before and after ET	Lay quietly for same amounts of time	No	CPR,BCPR
Chen et al. [25]	60 randomized—women undergoing frozen ET	China	EA from the fifth day of natural menstrual cycle	No intervention	No	CPR,IR
So et al. [27]	370 randomized—women who had a normal uterine cavity shown on ultrasound scanning on the day of TVOR	China	TA for 25 min before and after ET	Placebo needling for 25 min before and after ET	Yes	CPR,BCPR,OPR,IR,LBR,MR
Andersen et al. [28]	635 randomized—women < 37 years of age, treatment with IVF/ICSI and transfer of 1 or 2 embryos in the first, second, or third stimulated cycle	Denmark	TA accompanying ET	Placebo needling accompanying ET	Yes	CPR,BCPR,OPR,LBR
Moy et al. [29]	161 randomized—women < 38 years old undergoing IVF with or without ICSI	USA	TA and AA for 25 min before and after ET	Placebo needling in non-qi lines in the predetermined locations. AA was performed at the following acupoints: knee, heel, allergic area, mouth	Yes	CPR,BCPR
Madaschi et al. [30]	516 randomized patients—aged ≤35 years and undergoing ICSI cycles for the first time	Brazil	TA for 25 min before and after ET	None	No	CPR,LBR,MR
Cui et al. [31]	66randomized women—infertile women aged 23–39 years	China	EA was administered 30 min before and during COH	None	No	CPR,LBR,MR
Zhang et al. [32]	330 randomized women—infertile women aged 21–44 years, undergoing frozen-cryopreservation embryo transplant or fresh cycle IVF with or without ICSI	China	TEAS was administered 30 min after/ before and before ET	Mock TEAS	Yes	CPR,IR,LBR,BCPR
Sun et al. [33]	97 randomized—women were candidates for IVF-ET	China	TA + Chinese material medical was performed before ET	None	No	CPR
Rashidi et al. [34]	62 randomized—women aged 18–40 years with PCOS who were candidates for IVF/ICSI	Iran	Acupuncture was performed before and after ET	None	No	CPR,OPR,BCPR,MR
Villahermosa et al. [35]	84 randomized—women infertile patients diagnosed with embryo implantation failure aged < 38 years	Brazil	TA + moxibustion before ovarian puncture and on the day after embryo transfer	Sham TA	Yes	CPR,BCP

(*continued on next page*)

Table 4 (*continued*)

Study	Participants	Country	Intervention	Control	Placebo intervention	IVF outcomes
Qu et al. [38]	305 randomized—women infertile patients with tubal blockage	China	AA 4 times with 15 min each time by themselves before and after ET	Sham AA or no AA	Yes	CPR,IR,LBR
Craig et al. [36]	113 randomized—no inclusion criteria	USA	TA performed before and after ET	None	No	CPR,LBR
Hong et al. [37]	109 randomized—women with IVF/ICSI	China	EA lasted for 30 min from the day of Gn injection to the day of embryo transfer	None	No	CPR,IR,MR
Shuai et al. [41]	68randomized—women 25–40 years old undergoing hCG-induced natural cycle FET	China	EA lasted for 30 min before the scheduled FET	Mock TEAS	Yes	CPR,LBR,IR,MR
Li et al. [40]	217 randomized—women > 40 years old with PCOS	China	EA for 30 min before and at the time of controlled ovarian hyperstimulation	None	No	CPR,MR
chen et al. [39]	114 randomized—women 24–35 years old with infertility due to tubal-induced gamete transport barriers	China	TA + moxibustion for 30 min before ET	No TA	No	CPR
Yang et al. [42]	200randomized—women who were PCOS patients aged 21–39 years	China	EA was administered 30 min before COH	None	No	CPR,MR
Zheng et al. [43]	240 randomized—women 26–47 years old with infertility due to tubal-induced gamete transport barriers	China	TEAS lasted for 30 min per day during the ovulation cycle until the day of egg retrieval	False HANS, artificial endometrial cycle treatment (AEC)	Yes	CPR,MR

Note: PCB, paracervical block; EA, electroacupuncture; CP, clinical pregnancy; IR, implantation rate; MR, miscarriage rate; TA, traditional acupuncture; AA, auricular acupuncture; ET, embryo transfer; OP, ongoing pregnancy; LB, live birth; BMI, body–mass index; CPR, clinical pregnancy rate; BCP, biochemical pregnancy; PCA, patient-controlled analgesia (remifentanil pump); TVOR, time of transvaginal oocyte retrieval; TEAS, transcutaneous electrical acupoint stimulation.

effects model, a significant difference was observed between the groups in the live birth outcome after combining the results from the 12 trials (RR = 1.36, 95% CI: 1.09–1.69, $P = 0.006$; Fig. 6).

For the miscarriage outcome, data were obtained from 12 out of the 31 included trials ($n = 854$) [13,15,20,27,30,31,34,37,40–43], and no significant heterogeneity was found among the studies ($I^2 = 0.0\%$, $P = 0.895$). In addition, when using the fixed-effects model, no significant difference was found in miscarriage outcome between the groups when the results from the 12 trials were combined (RR = 0.89, 95% CI: 0.67–1.20, $P = 0.447$; Fig. 7).

3.5. Subgroup analysis

Table 5 presents the results of the subgroup analysis of outcomes regarding clinical pregnancy, implantation, and live birthrate. No differences were found between the groups after combining the results from the studies that adhered to the STRICTA guidelines. However, studies that did not adhere to the STRICTA guidelines did show significant differences. Additionally, the analysis of single center studies showed significant differences between the groups, whereas the analysis of multicenter studies showed no differences between the groups. The data from studies in which electrical acupuncture was used showed significant differences between acupuncture versus no/sham acupuncture. However, the data from studies using traditional acupuncture showed no significant differences.

3.6. Sensitivity analysis

Sensitivity analysis of the method used to combine the corresponding data was conducted by examining individual studies. Pooled results were not significantly altered even when the most powerful study was not included (not shown).

3.7. Publication bias

Publication bias analysis was conducted with funnel plot, Begg's and Egger's tests. The results showed that CP, BCP and OP had significant publication bias, however, the publication bias of IR, LBR and MR was negligible.

4. Discussion

As more clinical trials on exploring the effects of acupuncture on pregnancy outcomes in women having IVF or ICSI have been published since 2012, there existed differences in the findings between the present meta-analysis and the one published in 2012 by the same group. The current meta-analysis included a higher number of studies and the trend was highly significant. However, the subgroup analysis indicated a different result when studies adhered to the STRICTA protocol, single or multicenter, and the type of acupuncture with traditional acupuncture (TA) or electrical acupuncture (EA). There existed differences on the outcomes of biochemical pregnancy, clinical pregnancy, implantation, ongoing pregnancy, miscarriage and live birth, which might be induced by the different effects of acupuncture on the oocytes or uterus.

The subgroup analysis showed that the pooled outcome from trials that adhered to the STRICTA guidelines or were multi-center studies indicated that acupuncture treatment did not result in significantly improved pregnancy rates of IVF or ICSI. These findings indicate that relatively high-quality trials may not support the main result of the meta-analysis. Whether acupuncture plays a positive role in IVF or ICSI remains to be elucidated by increasing the number of high-quality studies. The subgroup analysis of the results pooled from the studies in which traditional acupuncture was conducted did not show a significant difference with the use of acupuncture. It has been suggested that the clinical therapeutic effect of electrical acupuncture may be very

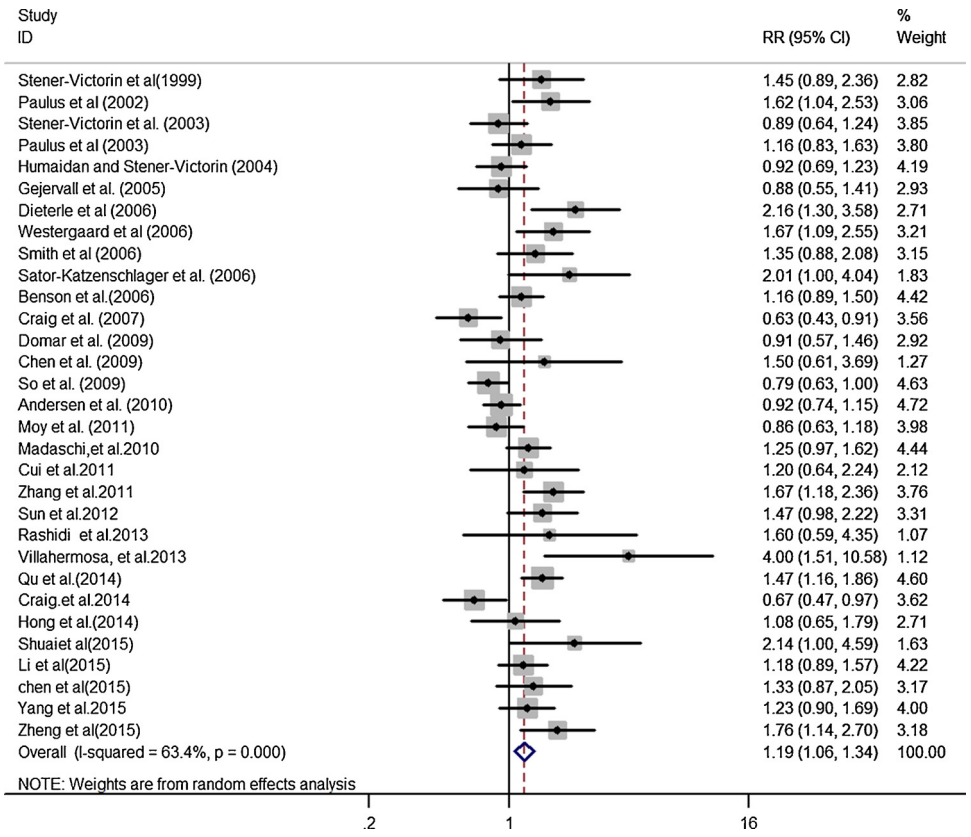

Fig. 2. Meta-analysis of the studies evaluating the effects of acupuncture on the clinical pregnancy outcome (note: RR, relative risk; CI, confidence interval).

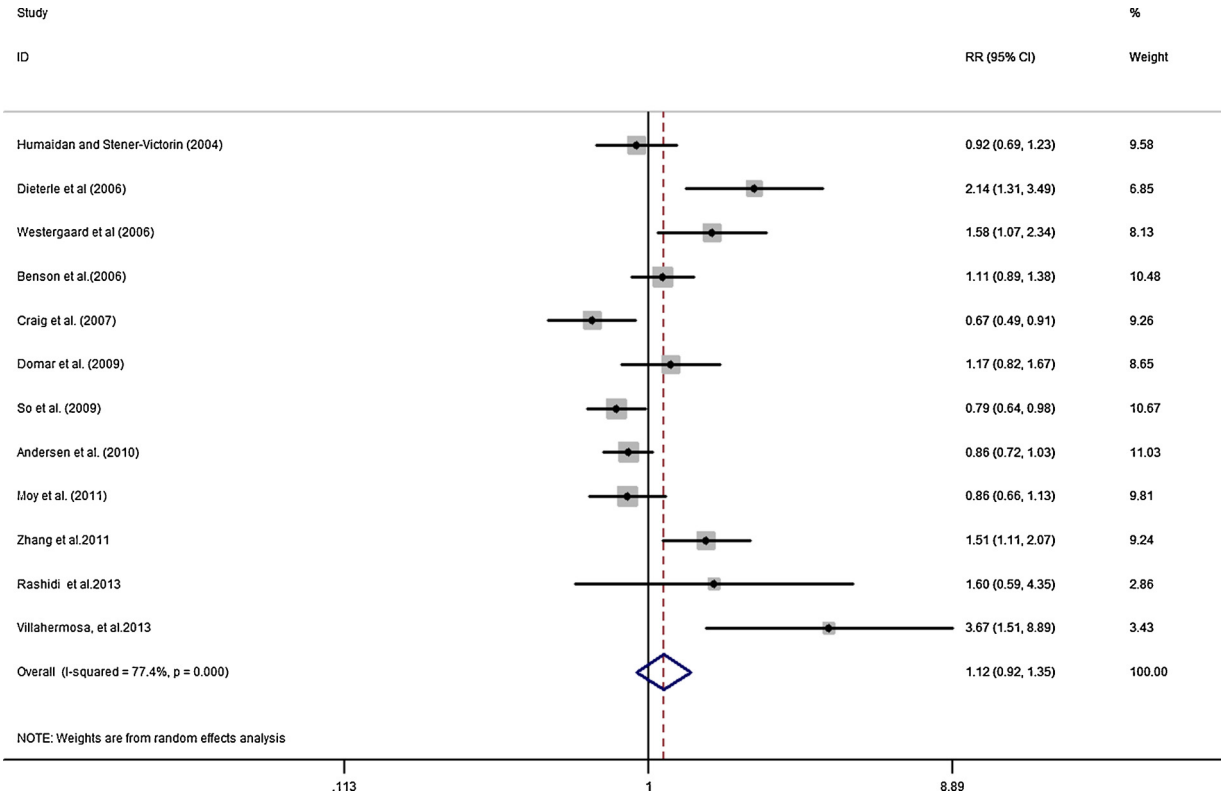

Fig. 3. Meta-analysis of the studies evaluating the effects of acupuncture on the biochemical pregnancy outcome (note: RR, relative risk; CI, confidence interval).

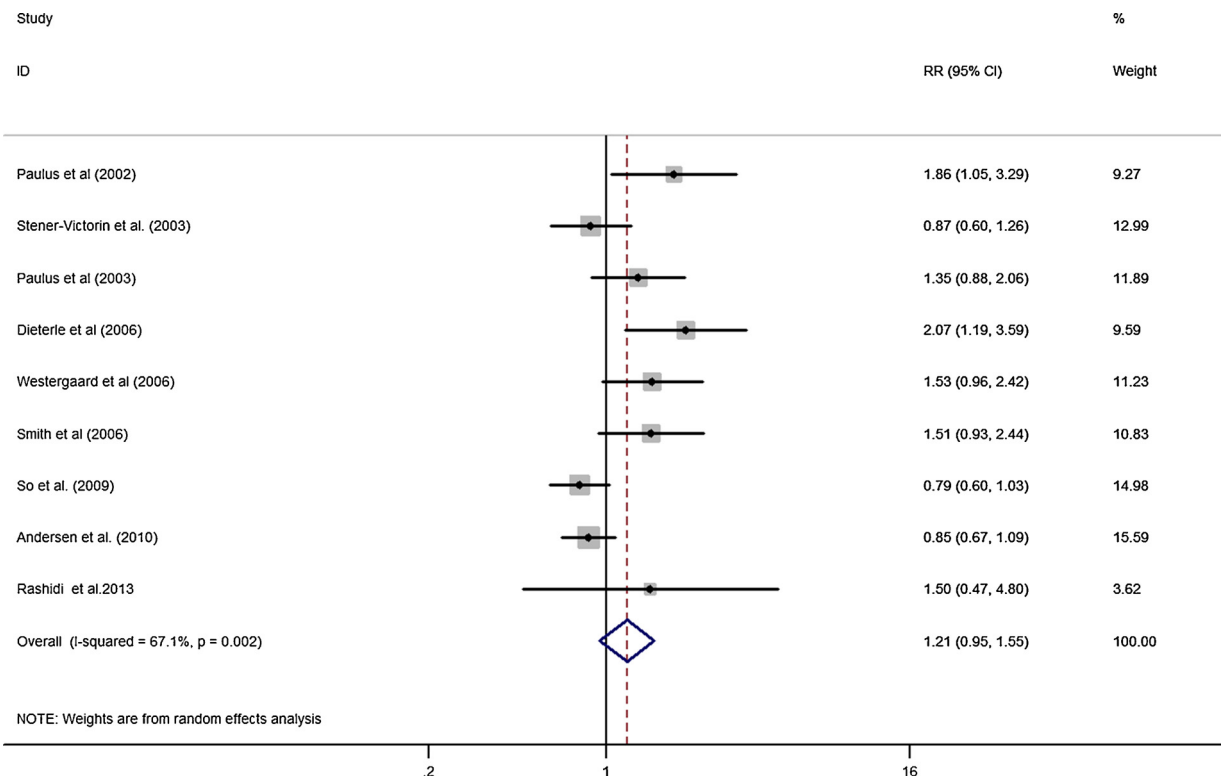

Fig. 4. Meta-analysis of the studies evaluating the effects of acupuncture on the ongoing pregnancy outcome (note: RR, relative risk; CI, confidence interval).

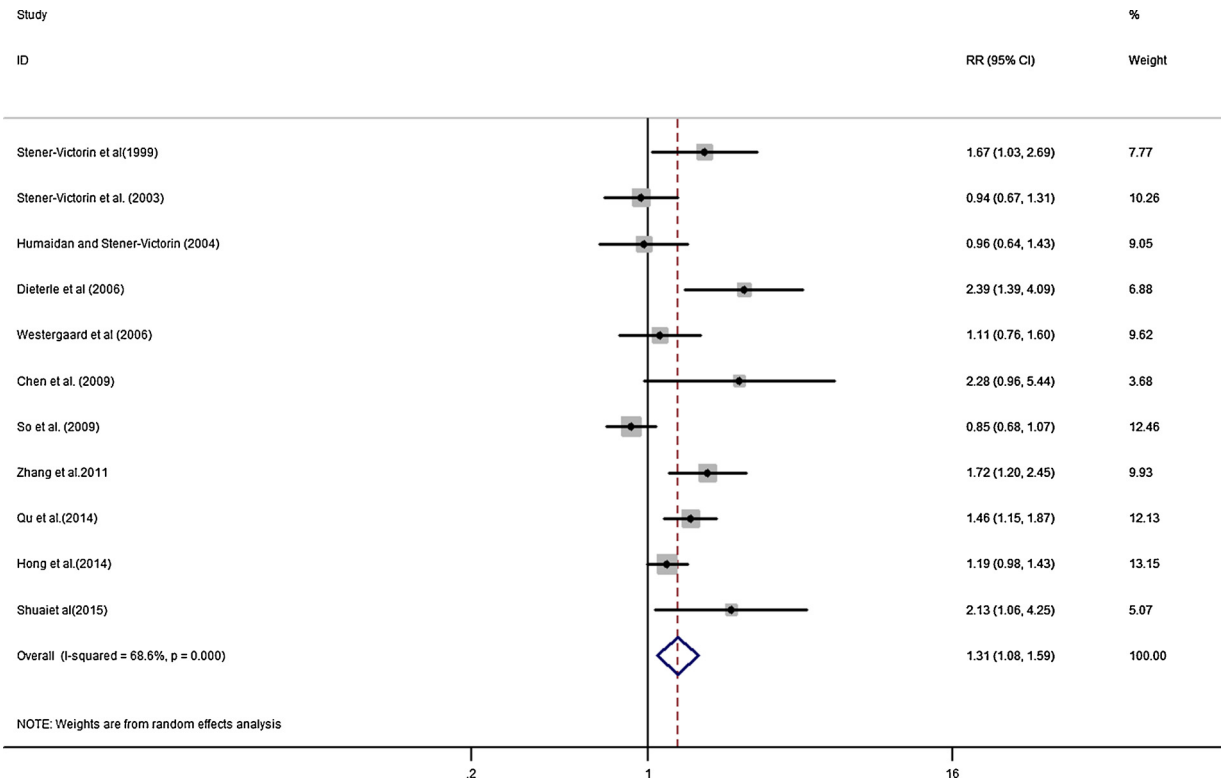

Fig. 5. Meta-analysis of the studies evaluating the effects of acupuncture on the implantation rate (note: RR, relative risk; CI, confidence interval).

different from that of traditional acupuncture. As such, whether the effect of acupuncture depends on electrical stimulation or the manipulation of an acupuncturist still needs further exploration.

Several systematic reviews and meta-analysis investigating the efficacy of acupuncture treatment on the outcomes of IVF were published between 2012 and 2016. Chen et al. [44] showed that various clinical RCTs indicated that acupuncture treatment was beneficial in increasing the pregnancy rate. The finding that acupuncture treatment could improve fertilization was not supported by other studies. Although the results are promising, additional well-designed RCTs are needed to

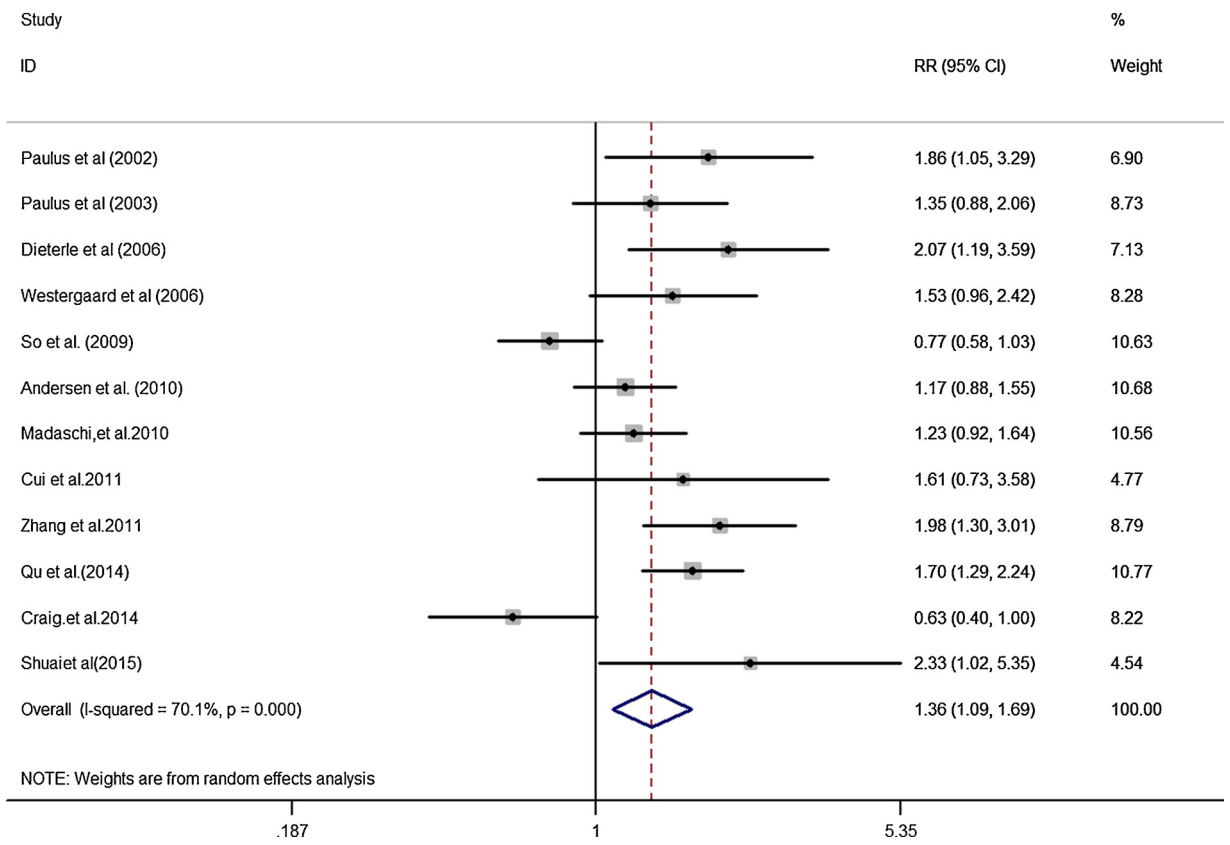

Fig. 6. Meta-analysis of the studies evaluating the effects of acupuncture on the live birth outcome (note: RR, relative risk; CI, confidence interval).

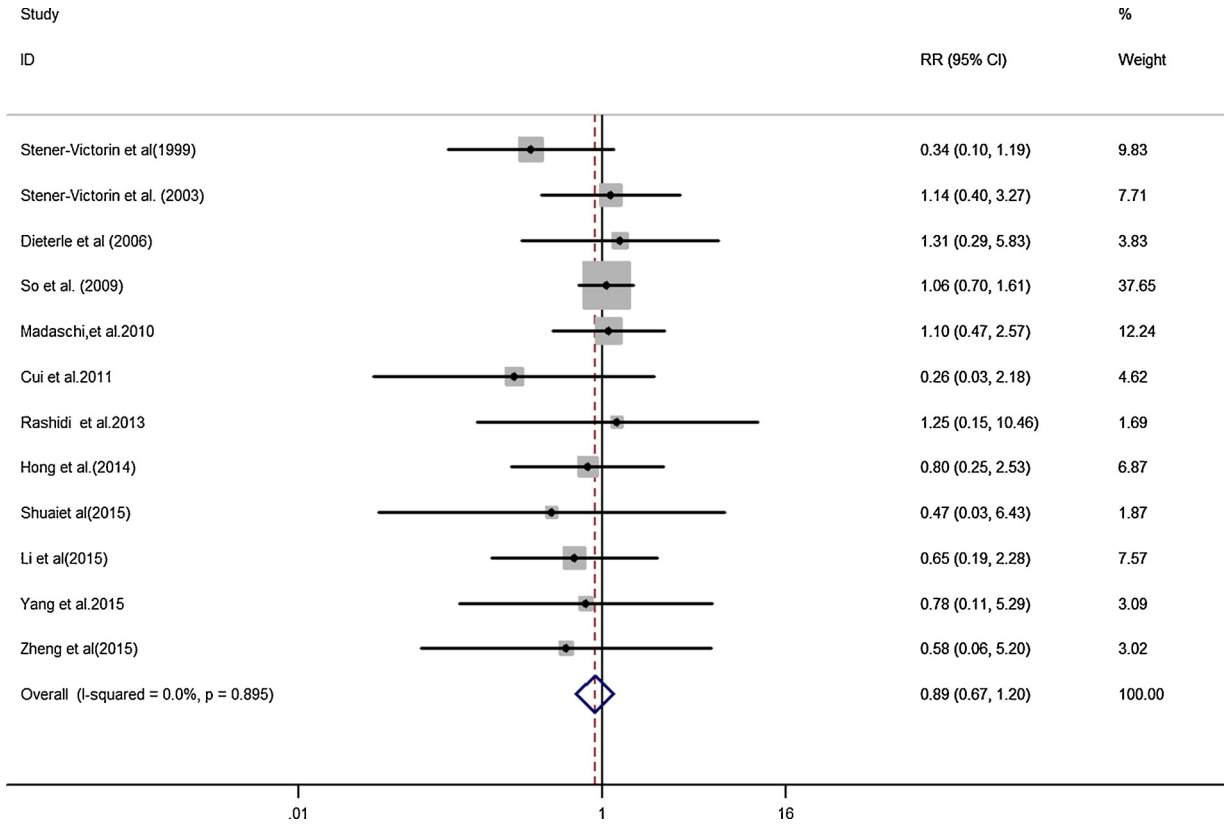

Fig. 7. Meta-analysis of the studies evaluating the effects of acupuncture on the miscarriage rate (note: RR, relative risk; CI, confidence interval).

Table 5
The results of subgroup analysis.

			No. of study	RR(95%CI)	Heterogeneity		Significance
					I^2	P	P
CP	Adherence To STRICTA	Yes	14 [16,17,18,21,22,23,27,28,29,30,32,34,36,38]	1.09(0.93 1.29)	69.9%	0.000	0.288
		No	17 [13,14,15,19,20,24,25,26,31,33,35,37,39,40,41,42,43]	1.30(1.11 1.51)	51.5%	0.007	0.001
	Center	Single	26[14,15,17–23,25–27,29–35,37–43]	1.28(1.14 1.43)	53.9%	0.001	0.000
		Multi	5 [13,15,24,28,36]	0.86(0.68 1.08)	57.7%	0.050	0.193
	Acupuncture type	EA	12 [13,16,17,18,25,31,32,37,40,41,42,43]	1.21(1.04 1.42)	38.3%	0.085	0.014
		TA	17 [14,15,20,22,23,24,26,27,28,29,30,33,34,35,36,38,39]	1.17(0.98 1.39)	73.4%	0.000	0.076
IR	Adherence To STRICTA	Yes	6 [16,17,23,27,32,38]	1.13(0.81 1.44)	71.5%	0.004	0.302
		No	5 [13,20,25,37,41]	1.77(1.15 2.74)	74.7%	0.003	0.010
	Center	Single	9[17,20,23,25,27,32,37,38,41]	1.34(1.08 1.67)	71.4%	0.000	0.008
		Multi	2 [13,16]	1.22(0.69 2.14)	73.3%	0.053	0.492
	Acupuncture type	EA	7 [13,16,17,25,32,37,41]	1.33(1.06 1.68)	57.1%	0.030	0.015
		TA	4 [20,23,27,38]	1.29(0.88 1.89)	83.1%	0.001	0.191
LB	Adherence To STRICTA	Yes	7 [23,27,28,30,32,36,38]	1.20(0.91 1.59)	79.2%	0.000	0.197
		No	5 [14,15,20,31,41]	1.70(1.31 2.20)	0.0%	0.677	0.000
	Center	Single	10 [14,15,20,23,27,30,31,32,38,41]	1.49(1.18 1.88)	65.6%	0.002	0.001
		Multi	2 [13,16]	0.88(0.48 1.62)	80.0%	0.025	0.690
	Acupuncture type	EA	3 [31,32,41]	1.96(1.39 2.75)	0.0%	0.819	0.000
		TA	9 [14,15,20,23,27,28,30,36,38]	1.25(0.99 1.59)	73.0%	0.000	0.053

Note: TA, traditional acupuncture; EA, electrical acupuncture; CP, clinical pregnancy; IR, implantation rate; LB, live birth.

verify these results. Nandi et al. [45] found that acupuncture is a safe therapeutic approach that is beneficial for patients. However, whether acupuncture is beneficial for improving the rate of live birth in IVF remains subject to further investigation. Shen et al. [4] demonstrated that acupuncture treatment performed only at the time of embryo transfer did not increase the clinical pregnancy rate of IVF. However, a combined benefit was found for acupuncture treatment in IVF when it was carried out during the follicular phase as well as at 25 min prior, after embryo transfer (RR = 1.56, 95% CI: 1.04–2.33), 30 min after embryo transfer, and during the implantation phase (RR = 1.76, 95% CI: 1.22–2.55).

The strengths and the potential limitations of this meta-analysis need to be mentioned. In the present study, the effect of acupuncture on IVF or ICSI has been comprehensively evaluated and stratified by many potential modifying factors. Furthermore, robust results were obtained from sensitivity analyses. However, we found significant heterogeneity among studies that may be attributed to differences in study design and quality. By performing the random-effects model, the heterogeneity was already considered among studies. In addition, the body–mass index of patients, the reason for infertility, and the number of times for IVF/ICSI cycles were not studied in this meta-analysis as this information was only available from a small proportion of the original studies. STRICTA guideline, which set the reporting guidelines for the acupuncture rationale, the details of needling, the treatment regimen, other components of treatment, the practitioner background and the control or comparator intervention [46], is an important key factor affecting the quality of trials. However, As shown in Table 3, only fourteen studies [16–18,21–23,27–30,32,34,36,38] adhered to STRICTA. Among the included 31 papers, adverse events were described only in 4 studies [21,36,38,43], among which, 2 studies [36,38] showed no adverse event and another 2 studies [21,43] reported adverse events. As traditional acupuncture is an invasive and aching therapy, the adverse events during the treatment should be considered in the future researches.

Taken together, although the present meta-analysis indicates that acupuncture treatment is beneficial in IVF/ICSI for improving the clinical pregnancy, implantation, and live birth outcomes, further well-designed RCTs with high-quality and increased samples sizes are still required to verify the data obtained in this study.

5. Conclusions

Acupuncture may have an impact on the outcome rates of implantation, clinical pregnancy, and live birth; however, well-designed RCTs are warranted to further validate its effects.

Conflict of interest

None.

Author contributions

Q.F. conceived and designed the study. Q.F., X.Z., and Y. Y. M. developed the search strategy for the identification of articles and identified the articles. Q.F., X.Z., and Y. Y. M. acquired and analyzed the data. Q.F., X.Z., and Y.W. drafted the manuscript. All authors have revised and approved the final version of the manuscript.

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