Effectiveness of acupuncture in women with polycystic ovarian syndrome undergoing in vitro fertilisation or intracytoplasmic sperm injection: a systematic review and meta-analysis

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ABSTRACT

Objectives The aim of this systematic review was to assess the evidence from randomised controlled trials (RCTs) on the efficacy, effectiveness and safety of acupuncture in women with polycystic ovarian syndrome (PCOS) undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Methods We searched a total of 15 databases through October 2015. The participants were women with PCOS (diagnosed using the Rotterdam criteria) undergoing IVF or ICSI. Eligible trials were those with intervention groups receiving manual acupuncture (MA) or electroacupuncture (EA), and control groups receiving sham acupuncture, no treatment or other treatments. Outcomes included the clinical pregnancy rate (CPR), live birth rate (LBR), ongoing pregnancy rate (OPR) and incidence of ovarian hyperstimulation syndrome (OHSS) and adverse events (AEs). For statistical pooling, the risk ratio (RR) and its 95% (confidence interval) CI was calculated using a random effects model.

Results Four RCTs including 430 participants were selected. All trials compared acupuncture (MA/EA) against no treatment. Acupuncture significantly increased the CPR (RR 1.33, 95% CI 1.03 to 1.71) and OPR (RR 2.03, 95% CI 1.08 to 3.81) and decreased the risk of OHSS (RR 0.63, 95% CI 0.42 to 0.94); however, there was no significant difference in the LBR (RR 1.61, 95% CI 0.73 to 3.58). None of the RCTs reported on AEs.

Conclusions Acupuncture may increase the CPR and OPR and decrease the risk of OHSS in women with PCOS undergoing IVF or ICSI. Further studies are needed to confirm the efficacy and safety of acupuncture as an adjunct to assisted reproductive technology in this particular population.

INTRODUCTION

The diagnosis of polycystic ovarian syndrome (PCOS) is based on the presence of two of the following three criteria: oligo-ovulation or anovulation; hyperandrogenism (clinical or biochemical); and the demonstration of polycystic ovaries on pelvic ultrasound assessment.[1] Women with PCOS may be subfertile, potentially due to the effects of obesity and/or metabolic, inflammatory and endocrine abnormalities on ovulatory function, oocyte quality and endometrial receptivity.[2]

In vitro fertilisation (IVF) is recommended as a third-line treatment for PCOS patients.[3] The most important complication of ovarian stimulation, which frequently precedes oocyte retrieval and embryo transfer, is the occurrence of ovarian hyperstimulation syndrome (OHSS), which is an exaggerated response to ovulation induction therapy.[3] OHSS has a broad spectrum of clinical manifestations, from mild illness that requires only careful observation to severe disease requiring hospitalisation and intensive care.[4] The initial presentation of OHSS typically includes abdominal distension due to enlarged ovaries; if OHSS progresses, the abdominal circumference increases as a result of intraperitoneal fluid accumulation.[5] The use of metformin during IVF or intracytoplasmic sperm injection (ICSI) increases the clinical

pregnancy rate (CPR) and decreases the risk of OHSS; however, side effects (predominantly gastrointestinal) are more common among those taking metformin.[6]

Acupuncture involves the insertion of fine needles into the body. Recent systematic reviews have reported conflicting findings as to whether or not acupuncture improves the live birth rate (LBR) in women undergoing IVF.[7] Meta-analyses of acupuncture trials are complicated by the following issues: (1) the validity of sham controls; (2) the influence of the baseline pregnancy rate; and (3) variations in treatment timing in relation to egg retrieval or embryo transfer, intervention characteristics and the overall number of treatments.[7] Furthermore, these reviews have included both patients with PCOS and those with infertility secondary to various other factors. Several clinical studies have indicated that acupuncture improves ovulatory dysfunction and insulin sensitivity, and decreases testosterone, in patients with PCOS.[8–10] Given that women with PCOS undergoing ovarian stimulation are considered to be at increased risk for OHSS, it is important to confirm the effects and safety of acupuncture as an adjunct treatment in this particular population, to maximise the success rates of IVF or ICSI.

Therefore, the aim of this systematic review was to summarise and evaluate the current evidence from randomised controlled trials (RCTs) regarding the efficacy/effectiveness of acupuncture provided during IVF or ICSI at achieving pregnancy in women with PCOS, and to consider its safety.

METHODS

Literature search strategy

We searched electronic databases for relevant studies published before October 2015. The search included four international, three Chinese, six Korean and two Japanese databases: Ovid-Medline (1946 to October 2015), Ovid-EMBASE (1974 to October 2015), Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED; 1985 to October 2015), China National Knowledge Infrastructure (CNKI), Wanfang DATA, Chongqing VIP, KoreaMed, Oriental Medicine Advanced Searching Integrated System (OASIS), Korean Medical Database (KMBASE), Korean Studies Information Service System (KISS), Society Database of Korea Institute of Science and Technology Information (KISTI), National Digital Science Library (NDSL), Japan Science and Technology Information Aggregator, Electronic (J-STAGE) and Medical*Online (http://www.medicalonline.jp/). The combinations of MeSH terms and keywords included 'polycystic ovary', 'polycystic ovary syndrome', 'amenorrhea', 'acupuncture', 'electroacupuncture', 'in vitro fertilization' and 'intracytoplasmic sperm injection'. The detailed search strategies are provided in online supplementary file 1. No language restrictions were imposed.

Study selection

All studies were selected and independently reviewed by two reviewers (JJ and YJL). The titles and abstracts were initially reviewed, and articles that did not fit the eligibility criteria were excluded. If the title or abstract appeared to meet the eligibility criteria or we were unable to determine its eligibility, the full texts of the articles were obtained for further evaluation. Discrepancies between the reviewers were resolved by consensus.

Types of studies

We included all RCTs that compared acupuncture treatment with placebo (ie, efficacy trials), no treatment (ie, effectiveness trials) or other active intervention (ie, comparative effectiveness trials) in women with PCOS undergoing IVF or ICSI. Non-randomised trials, quasi-experimental studies and observational studies were excluded.

Types of participants

The trials involved women who were diagnosed with PCOS based on the definition agreed by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) consensus meeting in 2003.[1] Any woman with two out of the following three criteria was considered to have PCOS: (1) oligo-ovulation or anovulation; (2) hyperandrogenaemia; or (3) polycystic ovaries. Importantly, other aetiologies of hyperandrogenism (such as androgen-secreting tumours, hyperprolactinaemia, thyroid disease, Cushing syndrome and congenital adrenal cortical hyperplasia) needed to have been excluded.

Types of interventions

We included any trial in which the acupuncture intervention involved the insertion of needles into traditional acupuncture points regardless of the type of acupuncture (ie, both manual acupuncture (MA) and electroacupuncture (EA) studies) were included, while studies that did not involve skin penetration, such as those evaluating acupressure or moxibustion, were excluded. Studies that investigated laser acupuncture or the combined effects of acupuncture and related modalities, such as herbal medicine, were also excluded.

Types of control groups

Trials that included sham acupuncture, no treatment or other treatments (eg, metformin) in the control group were considered. Trials in which the other treatments were applied to both groups (acupuncture and control) in the same manner were also included.

Types of outcome measures

Primary outcomes were CPR and LBR. Secondary outcomes included the ongoing pregnancy rate (OPR)

and the incidence of OHSS and adverse events (AEs). Clinical pregnancy was defined as the identification of an intrauterine gestational sac on an ultrasound scan. Ongoing pregnancy was defined as evidence of a gestational sac with a fetal heartbeat at 12 weeks gestation, and live birth was defined as delivery of a live infant after 20 completed weeks of gestation.

Data extraction and risk of bias assessment

Two reviewers (JJ and YJL) extracted data using a standardised data extraction form. Discrepancies were resolved by consensus. The form included information that pertained to the first author, country where the trial was conducted, year of publication, number of participants allocated to each group, details of the acupuncture intervention, comparison group, outcome measures, and reported AEs associated with acupuncture. For cases in which the study had multiple publications, the main trial report was used as the reference and additional details were derived from the secondary papers. If the data in an article were insufficient or ambiguous, one reviewer (YJL) contacted the corresponding author by email to request additional information.

Two authors (JJ and YJL) independently evaluated the risk of bias of the included studies. Risk of bias was assessed using the Cochrane Collaboration's assessment tool.[11] The criteria consisted of seven items related to random sequence generation and allocation concealment, blinding of participants and personnel, outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. Discrepancies between the two reviewers were resolved by discussion until consensus was reached.

Statistical analyses

Statistical analyses were performed with Review Manager V.5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen; 2014). Trials were combined according to the type of intervention and type of outcome measure. For dichotomous data, we expressed the results for each study as the risk ratio (RR) using a random effects model with 95% (confidence interval) CIs. Heterogeneity between studies was assessed using the Cochrane's Q and I^2 statistics.[12] The I^2 statistic indicates the proportion of variability among trials that cannot be explained by chance alone; we considered an I^2 value >50% to indicate substantial heterogeneity.[11 12]

Level of evidence

The Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the level of evidence and summarise each outcome.[13 14] GRADE profiler software for Windows V.3.6.1 (GRADE working group) was used. The level of evidence was categorised into four levels: high, moderate, low, or very low.

RESULTS

Search results

Our initial search identified 353 articles (figure 1). After duplicate articles were removed, 281 articles were screened. We excluded 264 articles based on the title and abstract and retrieved 17 articles for more detailed evaluation. We subsequently excluded 13 publications and included four studies in our review. The characteristics of the included trials are summarised in table 1.

Study design

Three of the four RCTs originated from China and were published in Chinese;[15–17] the remaining study originated from Iran and was published in English.[18] All the RCTs involved a single centre and a two-arm design with parallel groups. One article[16] was an unpublished doctoral thesis; the remaining three studies[15 17 18] were published in peer-reviewed journals.

Participants

Four hundred and thirty participants were enrolled in these four studies. The sample size of each study ranged from 62 to 200. Calculations of sample size and statistical power were not reported in any study. All participants were subfertile women of reproductive age who met the Rotterdam diagnostic criteria for PCOS.[1] The baseline characteristics of the groups were comparable for each study.

Interventions

All the trials assessed acupuncture therapy alone in the treatment group and no treatment in the control group. One trial used MA with manual stimulation,[16] and the other trials used MA followed by electrical stimulation, that is, EA.[15 17 18] The acupuncture interventions varied between studies in terms of individual acupuncture point selection and the frequency, timing and number of acupuncture treatments. In the studies by Li *et al*[15] and Cui *et al*,[17] EA was administered during the menstrual cycle immediately before controlled ovarian hyperstimulation (COH) and during COH (not during menstruation). The needle was inserted using a rotating technique and manipulated until the patient felt *de qi*. Electrical stimulation was subsequently applied using dense-disperse waves at 16–18 Hz and endurable intensity. Treatment was administered once a day for 30 min per session. After every 5 days of EA, the patient stopped treatment for 1 or 2 days. The treatment was maintained until the day of oocyte collection. Altutunji[16] administered MA from the third day of the follicular phase until the day of human chorionic gonadotropin administration. The needles were inserted into the skin to a depth of 15–30 mm depending on the region of the body. Needle reactions were elicited during initial insertion. Every 10 min, the needles were manually stimulated by

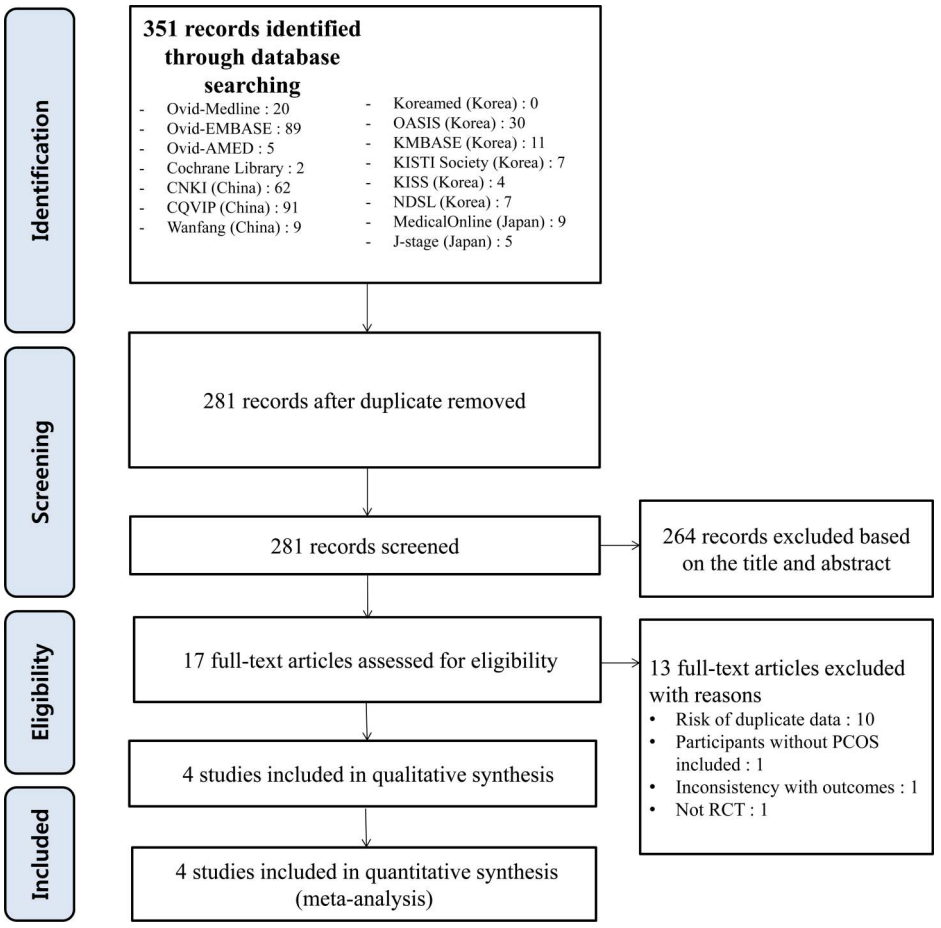

Figure 1 PRISMA flow diagram of literature search. PCOS, polycystic ovarian syndrome; PRISMA, Preferred Reporting Items for Systemic Reviews and Meta-Analyses; RCT, randomized controlled trial.

rotating, lifting and thrusting the handle to maintain the *de qi* sensation. The needles were retained in position for 30–40 min and subsequently removed. In the RCT by Rashidi *et al*,[18] EA was performed on the 21st day of the previous cycle (start of downregulation), the first day of stimulation, 2 days before oocyte retrieval, and immediately before and after embryo transfer. Insertion of the acupuncture needle into the point typically generated *de qi*. Acupuncture points were needled bilaterally to a depth of 25 mm and stimulated electrically for 30 min.

Risk of bias in included studies

Among the four included RCTs, one study utilised an inadequate randomisation procedure of selecting odd or paired numbers,[16] whereas another study[15] described adequate methods of random sequence generation using a randomisation table. We rated the other two studies[17 18] as having an unclear risk of selection bias because they failed to describe an adequate method of random number generation. With respect to allocation concealment, we rated all four studies[15–18] as having an unclear risk of selection bias because they did not describe an acceptable method. Blinding of patients was not applicable as all trials

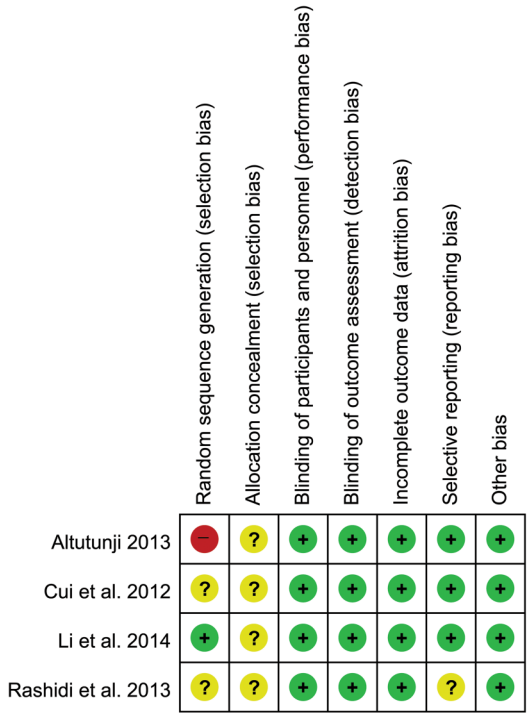

Figure 2 Risk of bias for included studies, as assessed using the Cochrane Collaboration's risk of bias tool. + high risk of bias; ? unclear risk of bias; – low risk of bias.

Table 1 Characteristics of the included trials

Study	Country (Period)	Number of participants	Age (years)	BMI (baseline)	Duration of infertility (years)	Acupuncture (type)	Comparison	Acupuncture points	Number of sessions	Relevant outcomes	Adverse events
Li *et al*[15]	China (Jan 2009–Dec 2012)	Acu: 102 Control: 98	Acu: 31±5 Control: 31±5	Acu: 23.36±6.40 Control: 23.33±3.58	Acu: 4.36±3.16 Control: 4.69±3.41	EA	No intervention	BL23, CV6, ST36, SP6, PC6 and *Zigong*	>20	CPR, OHSS	NR
Altutunji[16]	China (Mar 2011–Jul 2012)	Acu: 33 Control: 69	Acu: 28.03±3.70 Control: 27.97 ±4.03,	Acu: 22.57±3.02 Control: 22.68±2.75	Acu: 4.12±2.32 Control: 3.62±1.66	MA	No intervention	CV3 + bilateral LR3, SP6, SP8, ST36, SP10, ST29 and LI4	8–12	CPR, OPR, OHSS	NR
Cui *et al*[17]	China (Jan 2007–Dec 2008)	Acu: 34 Control: 32	Acu: 29.3±3.7 Control: 29.3±3.45	Acu: 24.24±4.13 Control: 23.96±3.14	Acu: 4.00±2.62 Control: 4.25±3.01	EA	No intervention	CV4, CV3, SP6, KI3 and *Zigong*	>20	LBR, CPR, OPR, OHSS	NR
Rashidi *et al*[18]	Iran (Jun 2009–Sep 2010)	Acu: 31 Control: 31	Acu: 31.03±4.82 Control: 32.10±4.68	Acu: 27.83±4.61 Control: 26.10±4.15	Acu: 9.09±4.65 Control: 9.41±4.93	EA	No intervention	First three sessions: LI4, SP6, LR3, CV4, GV20, ST36 and auricular points (ovary and uterus). Next two sessions: LR3, SP10, PC6, ST29 and auricular points (*Shenmen*)	5	CPR, OPR	NR

Data are presented as mean±SD.
Acu, acupuncture; BMI, body mass index; CPR, clinical pregnancy rate; EA, electroacupuncture; LBR, live birth rate; MA, manual acupuncture, NR, not reported; OHSS, ovarian hyperstimulation syndrome; OPR, ongoing pregnancy rate.

compared acupuncture with no active intervention. Blinding of the outcome assessor was only explicitly reported in one trial.[16] While the other three trials[15 17 18] failed to report whether outcome assessors were blinded or not, it was judged that the results were not likely to have been influenced by any potential lack of blinding because the outcomes of pregnancy rate were objective in nature. Thus, we rated these studies as being at low risk for performance and detection bias. All trials[15–18] were at low risk of attrition bias without any significant incomplete outcome data. One trial[18] that did not report LBR had an unclear risk of bias for selective reporting. The other three trials[15–17] had a low risk of bias because they reported all expected outcomes. Other sources of bias were deemed to be low risk in all trials. A graphical summary of the overall risk of bias assessment is presented in figure 2.

Effectiveness of acupuncture

Primary outcomes

Only one study[17] documented the LBR for acupuncture versus no treatment: there was no significant difference in LBR between the acupuncture and control groups (RR 1.61, 95% CI 0.73 to 3.58, p=0.24; n=66). Four studies[15–18] assessed the CPR. The pooled data indicated that acupuncture significantly increased the CPR compared with no treatment (RR 1.30, 95% CI 1.01 to 1.65, I^2=0%, p=0.02; n=404), as shown in figure 3.

Secondary outcomes

OPR results were extracted from two studies.[16 18] OPR was significantly increased in the acupuncture group compared with the no treatment group (RR 1.99, 95% CI 1.06 to 3.74, I^2=0%, p=0.03; n=164). Furthermore, the pooled results from three trials[15–17] indicated that the incidence of OHSS was significantly lower in the acupuncture group compared with the no treatment group (RR 0.63, 95% CI 0.42 to 0.94, I^2=0%, p=0.03; n=368).

Adverse events and level of evidence

None of the RCTs reported data regarding AEs. The levels of evidence of all outcomes as determined by GRADE were low because of the risk of bias within the trials and the small sample sizes (table 2).

DISCUSSION

This systematic review and meta-analysis found no conclusive evidence that acupuncture treatment during IVF or ICSI improves LBR in women with PCOS, which is likely a reflection of the limited number of studies. However, our pooled results indicated that acupuncture treatment increases CPR and OPR and decreases the risk of OHSS. These seemingly positive results should be interpreted cautiously, mainly because of the limited number of participants and the unclear risk of bias regarding allocation

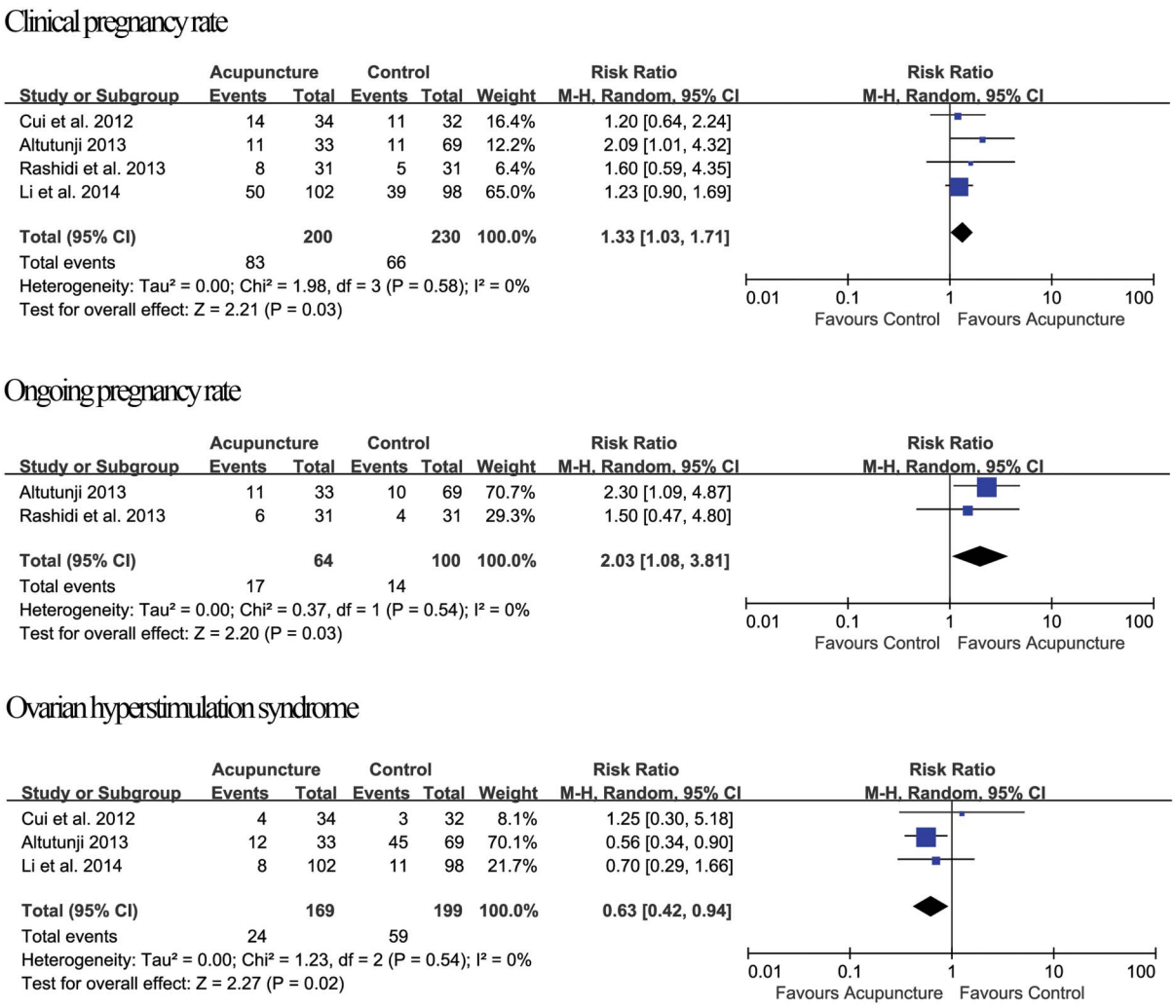

Figure 3 Forest plots demonstrating the effects of acupuncture on clinical pregnancy and ongoing pregnancy rates and the incidence of ovarian hyperstimulation syndrome, relative to no treatment.

concealment in the included studies. The level of evidence of all outcomes was assessed as 'low' using GRADE, and AEs were not reported by any trials.

Acupuncture treatment at or around the time of IVF may increase uterine blood flow, inhibit uterine motility, modulate immune function and/or relieve depression, anxiety and stress.[19] Collectively, these mechanisms of action of acupuncture are considered to result in improved embryo implantation. Although the exact underlying mechanism of action by which acupuncture reduces the risk of OHSS remains unknown, it may involve decreased production of vascular endothelial growth factor, which is one of the most important factors in the pathophysiology of OHSS.[20] Acupuncture also reduces serum anti-Mullerian hormone levels and ovarian volume in women with PCOS.[21] Meanwhile, there is emerging evidence for the effects of acupuncture in patients with diminished ovarian reserve who appear to be at the end of the reproductive dysfunction spectrum.[22] However, further research is required to elucidate the precise effects and mechanisms of action of acupuncture in these two patient populations with reproductive dysfunction.

Acupuncture has been shown to have similar effects to metformin in terms of increased CPR during IVF or ICSI.[6] Metformin is potentially better at decreasing the risk of OHSS when compared with acupuncture; however, metformin treatment is also associated with (predominantly gastrointestinal) side effects.[6]

In the present study, the overall quality of evidence for all outcomes was rated as low using GRADE methods. Only one trial had a low risk of selection bias in view of adequate randomisation. Furthermore, all trials had an unclear risk of bias due to uncertain allocation concealment. Therefore, the included studies are not entirely free from selection bias, which could result in an overestimation of the benefits of acupuncture in the included trials.

One limitation of this review is the lack of complete data from some studies, despite our attempts to obtain missing information from the study authors. We conducted a thorough search and made every effort to

Table 2 Summary of findings

Acupuncture vs no treatment during IVF or ICSI in women with PCOS

Patient or population: patients with PCOS undergoing IVF
Setting: RCT
Intervention: acupuncture
Comparison: control (no acupuncture)

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Level of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Outcomes	Comparison	Acupuncture				
Live birth rate	219 per 1000	352 per 1000 (153 to 619)	RR 1.61 (0.73 to 3.58)	66 (1 study)	⊕⊕⊖⊖ low†‡	
Clinical pregnancy rate	287 per 1000	387 per 1000 (301 to 499)	RR 1.35 (1.05 to 1.74)	430 (4 studies)	⊕⊕⊖⊖ low†‡	
Ongoing pregnancy rate	140 per 1000	279 per 1000 (148 to 524)	RR 1.99 (1.06 to 3.74)	164 (2 studies)	⊕⊕⊖⊖ low†‡	
OHSS	296 per 1000	190 per 1000 (127 to 288)	RR 0.64 (0.43 to 0.97)	368 (3 studies)	⊕⊕⊖⊖ low†‡	

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Serious risk of bias as a result of randomisation and allocation concealment.
‡Low number of participants.
GRADE, Grades of Recommendations, Assessment, Development and Evaluation; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovarian syndrome; RCT, randomized controlled trial; RR, risk ratio.

identify all existing RCTs that assessed acupuncture treatment in women with PCOS who were undergoing assisted reproductive technology cycles; however, it remains possible that there are unpublished studies that were consequently not retrieved.

Implications for practice

The current evidence suggests that acupuncture increases CPR and OPR and decreases the risk of OHSS in patients with PCOS undergoing IVF or ICSI. Thus, acupuncture could be used as an OHSS prevention strategy. It was not possible to compare the effects of acupuncture on the IVF or ICSI outcomes of women with PCOS compared with those of women with other types of infertility due to discordance of previous systematic reviews. Interestingly, GV20, LI4, SP6, ST29 and ST36 appear to be the most frequently needled acupuncture points among women with variable causes of infertility undergoing IVF,[23] whereas CV3, CV4 and *Zigong* were also included for women with PCOS undergoing IVF in this review.

Implications for research

Only one trial[17] reported the LBR, and none of the trials reported the rate of healthy 'take-home' babies, which is considered to be the most important long-term outcome of interest for patients.[6] The primary endpoints of the four trials were not clearly reported. In addition, no trial reported a formal sample size calculation, which is an essential prerequisite to ensure adequate statistical power.[24]

None of the four studies used a sham intervention or included a conventional control group. However, the need to blind participants is arguably less critical when the outcome is entirely objective (ie, pregnancy and birth).[25] Moreover, if sham acupuncture is not an inert placebo but rather an active treatment that may affect pregnancy outcome, then its use as a control may further confuse, rather than clarify, the interpretation of the effects of acupuncture on IVF outcomes.[26] Thus, a comparative study to determine the effectiveness of acupuncture relative to a conventional control treatment, such as metformin, would be informative.

One[18] of the four trials used only five acupuncture sessions. This approach may be considered 'low dose'; a clinically valid dosage of acupuncture typically involves needle insertion at 4–10 (or more) acupuncture points and more than six sessions.[27] Furthermore, most of the trials used relatively fixed protocols for all individuals in the trial, without considering individual characteristics. It has been argued that treatment should be individually tailored to obtain optimal outcomes.[28]

In this review, no studies reported information regarding AEs. Although existing studies regarding acupuncture for various conditions have supported the assertion that it is a relatively safe treatment modality,[29] acupuncture treatment varies considerably and is not without risk.[30] Future clinical trials must identify potential AEs more thoroughly.[31]

Most of the included studies improperly reported or failed to report items such as allocation

concealment and blinding. Thus, there is an ongoing need for future high quality trials, which should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (including prospective ethical approval and trial registration[32–34]) and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[35]

CONCLUSION

This review indicated that acupuncture may increase the CPR and OPR and decrease the risk of OHSS during IVF or ICSI. Further rigorously designed studies are needed to confirm the efficacy and safety of acupuncture in patients with PCOS using IVF or ICSI.

Contributors JJ and YJL were responsible for the study concept, design, and literature search; they participated in the data analysis and interpretation and approved the final manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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