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Systematic review

A systematic review and meta-analysis of acupuncture in *in vitro* fertilisation

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Background Numerous randomised studies have reported pregnancy outcome in women who received acupuncture during their *in vitro* fertilisation (IVF) treatment cycle.

Objective The objective of this study was to conduct a systematic review with meta-analysis of the trials of acupuncture during IVF treatment on the outcomes of clinical pregnancy and live birth rates.

Search strategy Searches were conducted in MEDLINE, EMBASE, Cochrane Library, ISI Proceedings and SCISEARCH.

Selection criteria All randomised controlled trials that evaluated the effects of acupuncture compared with no treatment or sham acupuncture in women undergoing IVF–intracytoplasmic sperm injection treatment were included.

Data collection and analysis Study selection, quality appraisal and data extraction were performed independently and in duplicate. A sensitivity analysis was conducted where the meta-analysis was restricted to trials in which sham acupuncture was used in the control group. Meta-regression analysis was used to explore the association between study characteristics and pregnancy rates.

Main results Thirteen relevant trials, including a total of 2500 women randomised to either acupuncture or control group, were identified. No evidence of publication bias was found (Begg's test, $P = 0.50$). Five trials ($n = 877$) evaluated IVF outcome when acupuncture was performed around the time of transvaginal oocyte retrieval, while eight trials ($n = 1623$) reported IVF outcome when acupuncture was performed around the time of embryo transfer (ET). Meta-analysis of the five studies of acupuncture around the time of egg collection did not show a significant difference in clinical pregnancy (relative risks [RR] = 1.06, 95% CI 0.82–1.37, $P = 0.65$). Meta-analysis of the eight studies of acupuncture around the time of ET showed no difference in the clinical pregnancy rate (RR = 1.23, 95% CI 0.96–1.58, $P = 0.1$). Live birth data were available from five of the eight studies of acupuncture around the time of ET. Meta-analysis of these studies did not show a significant increase in live birth rate with acupuncture (RR = 1.34, 95% CI 0.85–2.11). Using meta-regression, no significant association between any of the studied covariates and clinical pregnancy rate was found ($P > 0.05$ for all covariates).

Conclusion Currently available literature does not provide sufficient evidence that adjuvant acupuncture improves IVF clinical pregnancy rate.

Keywords Acupuncture, IVF, oocyte retrieval, embryo transfer, clinical pregnancy, randomised trials.

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Introduction

Approximately three-quarters of all *in vitro* fertilisation (IVF) cycles fail.[1] Clinicians are constantly searching for ways to improve IVF results by methods other than replacing more embryos. Over the past decade, a number of treatment strategies have been designed to increase IVF success rate, primarily through improving the quality of embryos replaced or uterine environment or both. Many of these strategies, however, have been introduced into clinical practice and promoted to patients before a clear evidence of benefit has been established.[2,3]

One of the treatments that has gained popularity in recent years is the use of alternative therapies, and in particular acupuncture, as an adjunctive treatment to improve IVF outcome.[4,5] The scientific rationale for using acupuncture during IVF treatment has not been fully accepted but focuses mainly on its potential role in enhancement of uterine receptivity through increased blood flow[6] and quiescence.[7] In addition, a perceived reduction in anxiety and stress after

acupuncture[8–10] has often been cited as an additional justification for its use.

Numerous studies have already reported IVF outcome in women who had received acupuncture during their IVF treatment cycle. These studies had variable design and have generally yielded inconclusive or conflicting results, rendering the clinical decision whether to recommend or omit the use of acupuncture during IVF difficult to make.[11–13] A recent systematic review examined the role of acupuncture at the time of embryo transfer (ET);[14] it excluded numerous randomised studies that evaluated the role of acupuncture at the time of egg retrievals.[15–19] Furthermore, new randomised evidence[20] has emerged since the publication of this review, casting uncertainty on the conclusions of the review.

In the present study, we sought to conduct a systematic review of randomised trials involving the use of acupuncture during IVF treatment, to generate a more precise estimate of the effect of acupuncture on IVF outcome.

Materials and methods

Literature search

We searched MEDLINE (1966 to January 2008), EMBASE (1974 to January 2008), Cochrane Library (2007:4) and SCI-SEARCH (1974 to January 2008) for relevant studies. A combination of Medical Subject Headings (MeSH) and text words was used to generate two subsets of citations, one including studies of acupuncture ('acupuncture', 'acupressure', 'moxibustion', electroacupuncture', 'auricular-acupuncture' and 'acupunc*') and the other studies of IVF and intracytoplasmic sperm injection (ICSI) ('in vitro fertilization', 'Fertilization-in-vitro', 'intracytoplasmic-sperm-injection', 'sperm-injections-intracytoplasmic', 'assisted reproductive techniques', 'embryo transfer' and 'embryo implantation'). These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. We also searched ISI Proceedings for conference abstracts, and ISRCTN Register and Meta-register for RCTs (*mRCT*) for continuing and archived randomised controlled trials. The reference lists of relevant primary and review articles were examined to identify cited articles not captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations. Authors were contacted to obtain missing information. No language restrictions was placed in any of our searches.

Study selection

Studies were selected if the target population was women undergoing IVF with or without ICSI treatment, the therapeutic intervention was any accepted regimen of (needle or laser) acupuncture compared with no or sham (placebo) acupuncture and pregnancy outcome was reported from a single IVF cycle per woman randomised to receive either acupuncture or control intervention. Studies with a crossover design were excluded.

The outcome measures of interest were clinical pregnancy and live birth rates per IVF cycle started. For the purpose of this review, clinical pregnancy was defined as the ultrasound identification of an intrauterine gestational sac after IVF treatment.

Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinised by two reviewers independently (T.E.-T. and S.K.S.), and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent and complete versions were selected. The assessment of English language manuscripts was performed independently by two reviewers (T.E.-T. and S.K.S.) and other language manuscripts by people who had command of the language. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.).

The selected studies were assessed for methodological quality using the components of study design that are related to internal validity.[21,22] Information on the adequacy of randomisation, concealment of allocation, blinding, the use of sham (or placebo) acupuncture and intention-to-treat analysis was sought by examining the full-text articles and by contacting the authors if clarification was needed.

For our review, we accepted any standard method of delivering sham acupuncture, including (a) superficial needling of the true acupuncture points, (b) application of true acupuncture in the wrong location or in points designed for *other* medical conditions, (c) use of blunt (placebo) needles or (s) use of sham laser acupuncture.

Data extraction and statistical analysis

Study characteristics such as population features and interventions (e.g. exact regimen of acupuncture, time of commencement and duration of treatment) were extracted from each study. Outcome data from each study were extracted in 2×2 structured tables using an intention-to-treat approach, and the results were pooled and expressed as relative risks (RR) with 95% CI. Heterogeneity of treatment effects was evaluated graphically using forest plot and statistically using chi-square test.

We proceeded to perform meta-analyses separately for the two broad groups of studies defined by the timing of delivery of acupuncture, that is around the time of transvaginal oocyte retrieval (TVOR) and around the time of ET. We also attempted to do a sensitivity analyses based on whether sham acupuncture was used in the control group. For our meta-analysis, we used a random effects model because of the encountered heterogeneity of the trials' characteristics and populations studied.[23] Meta-regression was then used to

explore the possible sources of the observed heterogeneity between studies.[24]

To assess for publication bias, we performed a funnel plot analysis using Begg's test.[25] As the meta-analysis did not involve subjecting patients to an intervention, and data were extracted from pre-existing literature, there was no need for obtaining approval by our local research ethics committee. All statistical analyses were performed using Stata 8.0 (StatCorp LP, TX, USA) and RevMan 4.2.10 (Cochrane Collaboration, Oxford, UK) softwares.

Results

The literature search yielded 83 citations, of which 43 were selected for retrieval. Figure 1 summarises the process of literature identification and selection. Of the 43 full manuscripts examined, 13 articles,[15–20,26–32] including a total of 2500 women, met the selection criteria for our review. The methodological quality of the included trials is summarised in Table 1. No evidence of publication bias or related biases was suggested from the funnel plot analysis (Begg's test, $P = 0.50$).

Five of the 13 included trials ($n = 877$) provided pregnancy outcome data when acupuncture was performed around the time of TVOR,[15–19] while the remaining eight trials ($n = 1623$) evaluated pregnancy outcome when acupuncture was performed around the time of ET.[20,26–32] Each group of trials was considered separately.

Acupuncture at the time of TVOR

Main study characteristics

Five trials ($n = 877$) reported IVF outcome when acupuncture was performed at the time of TVOR. Tables 2 and 3 show the features of the five trials and the acupuncture points used, respectively. The mean age of participants ranged from 30.5 to 34.4 years. All five studies were performed in Europe: three were conducted in Sweden,[15,16,18] one was conducted in Denmark[17] and one was conducted in Austria.[19] Three trials were performed in a single centre,[17–19] while the remaining two were multicentre trials.[15,16]

Four of the five trials[15,17–19] were designed to assess the pain-relieving effects of acupuncture used at the time of TVOR compared with conventional analgesia. Only one study used[16] the IVF pregnancy rate as the primary outcome. Three of the five trials[17–19] were powered to detect a clinically significant difference in pain intensity or wellbeing after TVOR between the study groups, and in one study, *a priori* power calculation was not described.[15] The only study[16] that was powered to detect a 10% difference in the clinical pregnancy rate between the study groups was terminated prematurely

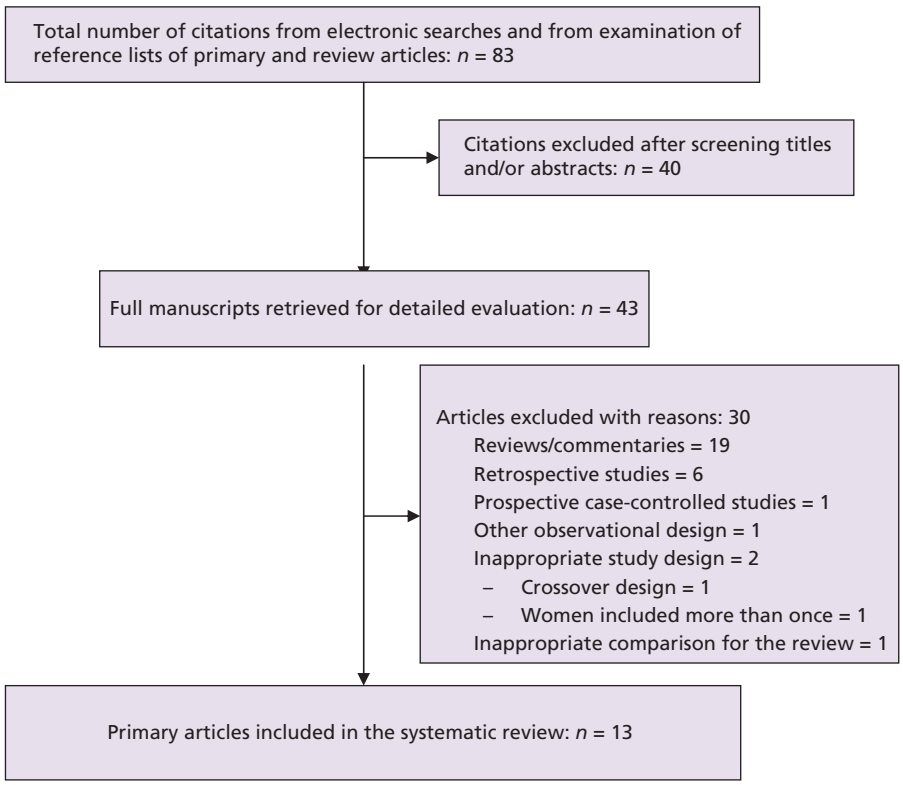

Figure 1. Study selection process for the systematic review of acupuncture in women undergoing IVF–ICSI treatment.

Table 1. Quality of studies included in the systematic review of acupuncture use during IVF

Study	Method of randomisation	Allocation concealment	Blinding	Placebo intervention	ITT	Comparability at baseline
Stener-Victorin *et al.*[15] (1999)	Not mentioned	Adequate	No	No	Yes	Unclear
Paulus *et al.*[26] (2002)	Computerised randomisation	Adequate	Single blind	No	Yes	Yes
Stener-Victorin *et al.*[16] (2003)	Not mentioned	Adequate	No	No	No	Unclear
Paulus *et al.*[27,33] (2003)	Not mentioned	Adequate	No	Yes	Yes	Unclear
Humaidan and Stener-Victorin[17] (2004)	Not mentioned	Adequate	No	No	Yes	Yes
Gejervall *et al.*[18] (2005)	Computerised randomisation	Unclear	No	No	No	Unclear
Dieterle *et al.*[30] (2006)	Not mentioned	Adequate	Double blind	Yes	Yes	Yes
Westergaard *et al.*[28] (2006)	Unclear	Adequate	No	No	No	Yes
Smith *et al.*[29] (2006)	Block randomisation	Adequate	Single blind	Yes	Yes	Yes
Sator-Katzenschlager *et al.*[19] (2006)	Computerised randomisation	Unclear	Double blind	Yes	Yes	
Benson *et al.*[32] (2006)	Not mentioned	Unclear	No (except laser groups)	No (except laser group)	Yes	Yes
Domar *et al.*[31] (2006)	Not mentioned	Adequate	Single blind	No	Yes	Yes
Craig *et al.*[20] (2007)	Computerised randomisation	Yes	Single blind	No	No	Yes

ITT, intention-to-treat analysis.

based on the results of an interim analysis, which showed no difference in the clinical pregnancy rate between the two groups. None of the five studies used a sham acupuncture technique in the control group. One study[18] described the IVF protocol used. The quality of the embryos replaced and day of ET were reported in only one of the five studies,[19] although the day of ET was not standardised among the study participants in that study.

IVF treatment outcome

For the clinical pregnancy rate, data were available from all five trials. Using the random effects model, pooling of the results from all five trials showed no significant difference in the clinical pregnancy rate between the acupuncture and the controls groups (RR = 1.06, 95% CI 0.82–1.37, $P = 0.65$; Figure 2).

Acupuncture around the time of ET

Main study characteristics

Eight trials ($n = 1623$) compared IVF outcome when acupuncture was performed around the time of ET with that in a control group. Tables 4 and 5 show features of these trials and the acupuncture points used, respectively. Four of the eight studies[20,27,31,32] were published as conference abstracts only, while the remaining four were published as full reports.

Four of the eight studies were conducted in Europe (three in Germany[26,27,30] and one in Denmark,[28] three in USA[20,31,32] and one in Australia[29]).

Seven of the eight trials were performed as single-centre trials,[26–32] while one study was a multicentre trial.[20] All studies were designed as two-arm trials, except the study of Westergaard *et al.*,[28] which included three arms (two intervention groups and one control group), and that of Benson *et al.*,[32] which included five arms (two intervention and three control groups). Unlike the studies examining the effect of acupuncture at the time of TVOR, all eight trials were designed with the objective to assess the effect of acupuncture performed at the time of ET on IVF outcome. Three studies[26,28,30] described the IVF protocol used. The quality of the embryos replaced and day of ET were reported in only three[26,28,29] and five studies,[20,26,28,30,32] respectively. One of the eight studies[27] did not mention the number of embryos replaced in the study groups.

Choice of therapeutic intervention

All eight studies used traditional needle acupuncture, and none used electroacupuncture. In addition, the study of Benson *et al.*[32] used laser acupuncture in one of the five arms of the trial (half of those randomised to the intervention group). Six of the eight studies used a needle acupuncture technique similar to that described by Paulus *et al.*,[26] in which the treatment group received the acupuncture treatment for 25 minutes before and 25 minutes after ET. In addition, women in the treatment group received a third acupuncture session on day 9 of ovarian stimulation in the study of Smith *et al.*[29] or 2 days after ET in the study Westergaard *et al.*[28] In

Table 2. Characteristics of the five studies in which acupuncture was performed at the time of TVOR

Study	Participants	Intervention	Administered acupuncture	Control
Stener-Victorin *et al.*[15] (1999)	150 randomised—no inclusion criteria	PCB and EA; EA started 30 minutes before TVOR; 17.3% of women received supplemental alfentanil	Trained midwives	Alfentanil + PCB
Stener-Victorin *et al.*[16] (2003)	286 randomised—eligible 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; EA started 30 minutes before TVOR; 14% of women received supplemental alfentanil	Trained nurses	Alfentanil + PCB
Humaidan and Stener-Victorin[17] (2004)	200 randomised—no inclusion criteria	PCB and EA; EA started few minutes before TVOR; 9% of women received supplemental alfentanil	Trained nurses	Alfentanil + PCB
Gejervall *et al.*[18] (2005)	160 randomised—no inclusion criteria	PCB and EA; EA started 30–45 minutes before TVOR; 20% of women received supplemental alfentanil	Four midwives	Premedication + alfentanil + PCB
Sator-Katzenschlager *et al.*[19] (2006)	94 randomised—women aged <43 years, BMI < 28 kg/m^2, had four or more follicles of size > 18 mm	AA with or without electrical stimulation + PCA	Trained gynaecologist	PCA + placebo AA

AA, auricular acupuncture; BMI, body mass index; EA, electroacupuncture; PCA, patient-controlled analgesia (remifentanil pump); PCB, paracervical block.

the study of Dieterle *et al.*,[30] acupuncture was applied for 30 minutes after ET and repeated 3 days later. In conjunction with acupuncture, the same study confounded the acupuncture intervention by placing a special Chinese herb (the seed of Caryophyllacea) on the patient's ear for 2 days after each acupuncture session. The study of Benson *et al.*[32] used laser acupuncture in half of the women in the intervention group.

Choice of control intervention

Three of the eight studies[27,29,30] used sham (placebo) needle acupuncture technique in the control group, while in the study of Benson *et al.*,[32] only one arm of the three control groups received sham laser acupuncture. In the remaining four studies,[20,28,31] the control group received no intervention. According to the principles of Chinese medicine, the sham acupuncture treatment used in these studies was designed not to influence fertility, although no evidence was provided that it did not induce either a favourable or a detrimental effect.

IVF treatment outcome

All studies of acupuncture around the time of ET. For the clinical pregnancy rate, data were available from all eight trials. There was significant statistical heterogeneity between the studies (test for heterogeneity, $P = 0.003$). Using the random effects model, pooling of the effect estimates from all eight trials showed no significant difference in the clinical pregnancy rate between the acupuncture and the control groups (RR = 1.23, 95% CI 0.96–1.58, $P = 0.09$; Figure 3). Exclusion of the study of Dieterle *et al.*,[30] because it used an additional intervention (application of the seed of Caryophyllacea on the patient's ear for 2 days after each acupuncture session), did not change the meta-analysis result (RR = 1.14, 95% CI 0.84–1.55, $P = 0.28$).

Live birth data were available from five of the eight studies ($n = 974$) of acupuncture around the time of ET.[20,26–28,30] Meta-analysis of these studies did not show a significant increase in live birth rate with acupuncture (RR = 1.34, 95% CI 0.85–2.11).

Studies of acupuncture versus no intervention. For the clinical pregnancy rate, data were available from five trials ($n = 815$), which compared acupuncture with no intervention. Using the random effects model, pooling of the results from these five trials showed no significant difference in the clinical pregnancy rate between the acupuncture and the controls groups (RR = 1.14, 95% CI 0.79–1.65, $P = 0.49$; Figure 4).

Studies of acupuncture versus sham acupuncture. For the clinical pregnancy rate, data were available from four trials ($n = 758$), which compared either needle or laser acupuncture with a sham acupuncture technique. Pooling of the results from these four trials showed that there was a nonsignificant trend in favour of increased clinical pregnancy rate after acupuncture compared with sham acupuncture (RR = 1.32, 95%

Table 3. The acupuncture points used in the studies of acupuncture performed at the time of TVOR

Author	Acupuncture points								
	LI 4	TE 5	ST 29	GV 20	ST 36	SP 6	KI 11	LI 10	AA
Stener-Victorin *et al.*[15] (1999)	Yes	Yes	Yes	Yes	Yes	—	—	—	—
Stener-Victorin *et al.*[16] (2003)	Yes	Yes	Yes	Yes	Yes	—	—	—	—
Humaidan and Stener-Victorin[17] (2004)	Yes	—	—	Yes	—	Yes	—	—	—
Gejervall *et al.*[18] (2005)	Yes	—	Yes	Yes	Yes	—	Yes	Yes	—
Sator-Katzenschlager *et al.*[19] (2006)	—	—	—	—	—	—	—	—	Yes

AA, auricular acupuncture; GV, governor vessel; KI, kidney; LI, large intestine; SP, spleen; ST, stomach; TE, triple energiser.

CI 0.99–1.76, $P = 0.06$; Figure 5). Exclusion of the study of Dieterle *et al.*[30] did not change the meta-analysis result (RR = 1.18, 95% CI 0.88–1.59, $P = 0.15$).

Exploration of sources of heterogeneity between studies of acupuncture around the time of ET. We attempted to explore effect of the potential sources of observed heterogeneity between the studies on pregnancy outcome using meta-regression analysis. We included in the meta-regression model study characteristics that were considered potentially significant, namely allocation concealment, nature of acupuncture technique used, who administered the acupuncture treatment, number of acupuncture sessions delivered to each woman in the intervention groups and use of sham acupuncture in the control groups. No significant association between any of these covariates and clinical pregnancy rate was found ($P > 0.05$), although the analysis was limited by the small number of studies included.

Discussion

Complimentary and alternative therapies are widely used, with acupuncture ranking among the most popular therapies being used.[5,34,35] As a result, a link between acupuncture and IVF outcome is likely to be of considerable interest to clinicians and patients alike.

Advocates of acupuncture have suggested that it could improve IVF outcome through a number of possible mechanisms, including a central sympathoinhibitory effect, resulting in increased uterine blood flow, which in turn might improve endometrial receptivity;[6] stimulation of beta-endorphins release, which could influence steroid hormone secretion;[36–39] and a direct, or endocrine-mediated, inhibitory effect on uterine activity.[41]

This systematic review and meta-analysis used the clinical pregnancy and live birth rates as indicators of the effect of acupuncture performed during IVF treatment on cycle outcome. The findings of our review fail to show a significant improvement in the clinical pregnancy or live birth rates associated with the use of acupuncture whether performed at the time of TVOR or around the time of ET. According to our results, the true effect of acupuncture performed at the time of TVOR on IVF outcome ranges from up to 13% relative reduction to a 24% relative increase in the chance of a clinical pregnancy and that of acupuncture performed around the time of ET ranges from up to 4% relative reduction to a 58% relative increase in the chance of a clinical pregnancy per IVF cycle started compared with no acupuncture.

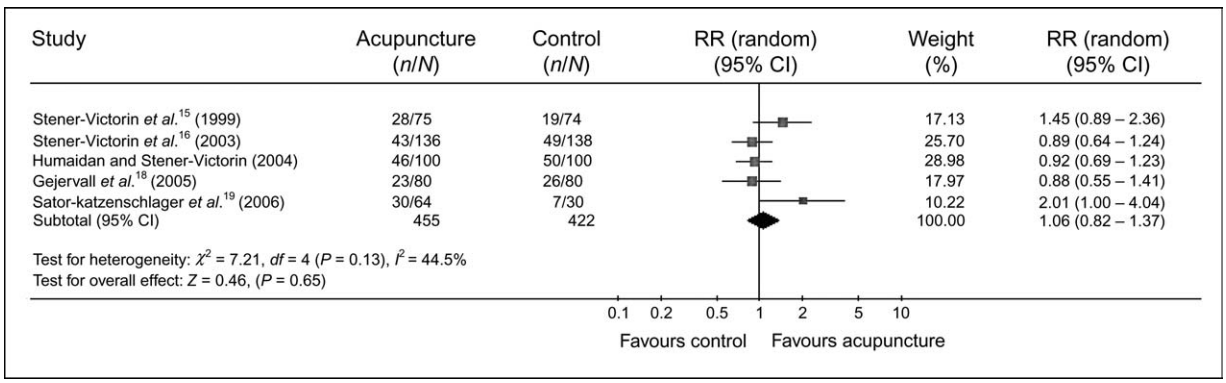

Figure 2. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of TVOR on the clinical pregnancy rate in women undergoing IVF.

Table 4. Characteristics of the eight studies in which acupuncture was performed around the time of ET

Study	Participants	Intervention	Administered acupuncture	Control
Paulus *et al.*[26] (2002)	160 randomised—only women with good quality embryos included	Traditional needle acupuncture and auricular acupuncture for 25 minutes before and after ET	Trained examiner	Lying still for 25 minutes before and after ET
Paulus *et al.*[27,33] (2003)	200 randomised—only women with good quality embryos included	Traditional needle acupuncture for 25 minutes before and after ET	Not mentioned	Sham (noninvasive) acupuncture
Smith *et al.*[29] (2006)	228 randomised—women with a planned ET were eligible	3 acupuncture sessions: 1 on day 9 of stimulation and 2 sessions 25 minutes before and after ET	Acupuncturist	Placebo needling at points close to the real acupuncture points
Dieterle *et al.*[30] (2006)	225 randomised—no inclusion criteria	Traditional needle acupuncture for 30 minutes after ET and 3 days later + Chinese medical drug*	Physician	Placebo needling at points designed not to influence fertility
Westergaard *et al.*[28] (2006)	300 randomised—no inclusion criteria	Traditional needle acupuncture for 25 minutes before and after ET ± a third session for 25 minutes 2 days after ET	Nurse	Bed rest for 1 hour after ET
Domar *et al.*[31] (2006)	144 randomised—women scheduled to have ET were eligible	Traditional needle acupuncture for 25 minutes before and after ET	Not mentioned	Lay quietly for same amounts of time
Benson *et al.*[32] (2006)	258 randomised—women scheduled to have ET were eligible	Traditional needle or Laser acupuncture for 25 minutes before and after ET	Acupuncturist	Sham laser acupuncture, relaxation or no intervention
Craig *et al.*[20] (2007)	117 randomised—women undergoing IVF who have not had acupuncture within 3 months	Traditional needle acupuncture for 25 minutes before and after ET	Acupuncturist	No intervention

*The seed of Caryophyllaceae placed on the patient's ear for 2 days and pressed twice daily for 10 minutes.

The results of our systematic review and meta-analysis differ from those of the recently published systematic review examining the effects of acupuncture performed around the time of ET on pregnancy rates among women undergoing IVF.[14] There are two reasons for such difference. First, our search identified an additional study,[20] which was not included in the earlier review. Second, we included all five arms of the study of Benson *et al.*,[32] whereas the review of Manheimer *et al.*[14] excluded three arms of that study, partly because they restricted their analysis to needle acupuncture only. Even if we exclude the laser acupuncture arms of the study of Benson *et al.*,[32] the results of our meta-analysis would remain unchanged (RR = 1.25, 95% CI 0.97–1.62, $P = 0.09$).

Importantly, our review highlights the uneven methodological quality of all the randomised studies published on the use of acupuncture during IVF treatment. Although all studies had a randomised design, very few described the randomisation procedure. In addition, lack of information on allocation concealment and blinding of assessors meant that important sources of bias in these studies could not be excluded.[41] The review also illustrates the significant heterogeneity present among the studies examining the value of acupuncture performed around the time of ET. This heterogeneity could be attributed to the inconsistency in the definition of the intervention used, time of commencement of the intervention, whether sham acupuncture was used, variations in patient populations studied and IVF treatment protocols employed and differences in the quality features between the studies and their relatively small sample sizes.[12,13] Another feature that has been postulated to be important to IVF outcomes is whether the acupuncture was 'on-site' (i.e. acupuncture being performed at the same location as ET) or 'off-site'

Table 5. Acupuncture points used in the studies of acupuncture performed around the time of ET

Author	Acupuncture points														
	PC 6	SP 8	LR 3	GV 20	ST 29	ST 36	SP 6	SP 10	LI 4	CV 3	CV 4	CV 6	LI 14	KI 3	AA
Paulus *et al.*[26] (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	—	—	—	Yes
Paulus *et al.*[27,33] (2003)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	—	—	—	Yes
Westergaard *et al.*[28] (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	—	—	No
Smith *et al.*[29] (2006)	Yes	Yes	Yes	—	Yes	Yes	Yes	Yes	—	—	—	—	—	—	Yes
Dieterle *et al.*[30] (2006)	Yes	Yes	Yes	—	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes	Yes	Yes
Domar *et al.*[31] (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	—	—	—	Yes
Benson *et al.*[32] (2006)															Yes
Craig *et al.*[20] (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	—	Yes	Yes

AA, auricular acupuncture; CV, conception vessel; GV, governor vessel; KI, kidney; LI, large intestine; LR, liver; PC, pericardium; SP, spleen; ST, stomach.

(acupuncture being delivered in a setting some distance away from the IVF unit). For example, it has been hypothesised that the negative results from the study of Craig *et al.* may have been due to the added stresses of travelling to and fro between the acupuncture and the IVF centres.[20]

In addition to methodological limitations, the included studies varied considerably in the way acupuncture was delivered, the specific points used, the total dose of acupuncture given and the treatment provider (Tables 2–5). It has been suggested that the dosage of acupuncture used in some of the randomised trials included in this systematic review was very low and that higher dosages could have improved the efficacy of acupuncture.[42] However, when the dose of acupuncture was increased in the study of Westergaard *et al.*,[28] the statistically significant improvement in clinical pregnancy rate among the acupuncture group compared with the control group was lost and the early pregnancy loss rate increased. Likewise, the study of Smith *et al.*[29] included an additional session of acupuncture on day 9 of stimulation but failed to show a significant improvement in IVF outcome after acupuncture. In a recent matched controlled study, Wang *et al.*[43] found that acupuncture performed twice weekly during the follicular and luteal phases of an IVF cycle did not improve the clinical and continuing pregnancy rates. This inconsistency in the results indicates that any beneficial effect attributed to acupuncture is unlikely to be strictly dose related.

Further difficulty in interpreting the results of the published randomised studies relates to the mechanism whereby acupuncture could improve IVF outcome. Proponents of acupuncture use suggested that it could improve uterine blood flow and hence uterine receptivity.[44] This assumption is based mainly on the results of one study, which included only ten subfertile women undergoing pituitary suppression.[6] However, the only randomised study, which assessed blood flow impedance in the uterine arteries before and after ET, failed to show any difference in the pulsatility index between the acupuncture and the control groups.[26] The same research group[33] performed a prospective cohort study on 164 women

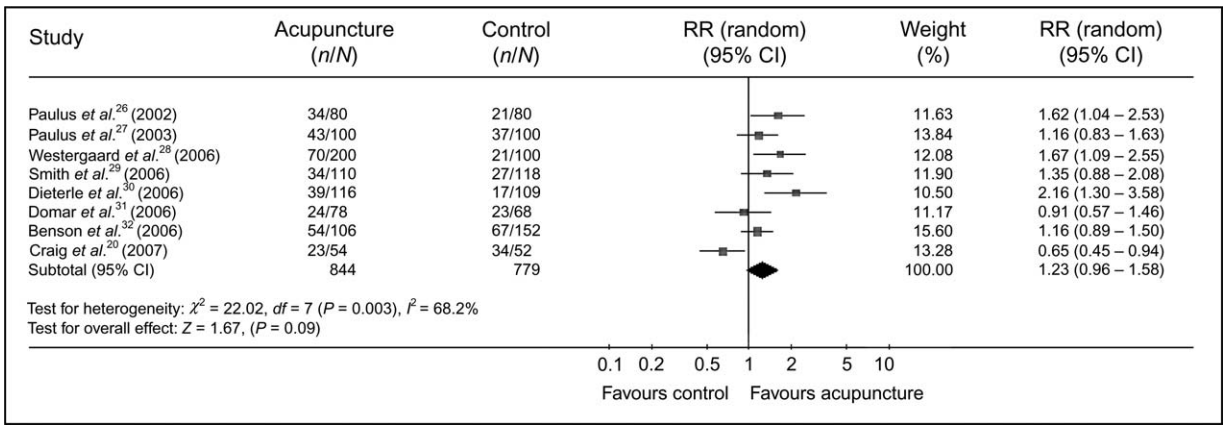

Figure 3. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of ET on the clinical pregnancy rate in women undergoing IVF.

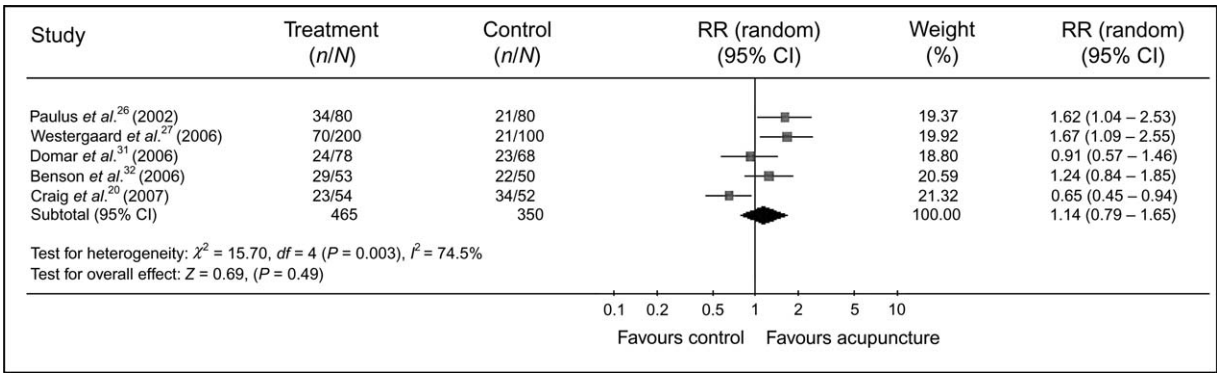

Figure 4. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of ET on the clinical pregnancy rate in women undergoing IVF when no sham acupuncture technique was used in the control groups.

undergoing IVF and found that acupuncture treatment did not inhibit uterine activity as previously suggested.

Another suggested benefit from acupuncture, which might potentially lead to improvement in IVF success rate, was reduction of stress levels and improvement in psychological wellbeing in women undergoing IVF.[28,30,45] Interestingly, the only two randomised trials that attempted to test this hypothesis failed to provide supportive evidence. The study of Smith *et al.*[29] found more women in the control group reporting sense of 'relaxation' and feeling 'calm and peaceful' after ET (67 and 64%, respectively) compared with the acupuncture group (51 and 55%, respectively). Furthermore, Domar *et al.*[31] reported no significant differences between the study and the control groups in optimism levels after ET.

The choice of the control intervention also varied between the studies that examined the effect of acupuncture performed around the time of ET and could have contributed to the conflicting results reported in these studies. Paulus *et al.*[27] and Myers[12] raised the possibility that acupuncture might exaggerate pregnancy rates after IVF through a placebo effect. Contrary to this suggestion, pooling the results of the four studies in which no placebo intervention was employed in the control group yielded an effect size closer to the line of unity than the studies that employed a sham acupuncture technique. Furthermore, different forms of sham acupuncture were employed in the four studies that examined the effect of acupuncture at the time of ET on IVF outcome. The lack of a reproducible and reliable sham acupuncture technique that does not affect the acupoints (e.g. by acupressure or *shiatsu*) and is devoid of any negative effect[12] undermines the reliability of the results of these studies, may explain to a certain extent the significant degree of heterogeneity present among these studies and underlines one of the many difficulties faced in conducting such trials.[42,46,47]

Given the cost, relative invasiveness of acupuncture, potential for harm and the significant variation in the inherent features of the published studies, women embarking on IVF should be advised that based on current knowledge, there is insufficient evidence that receiving acupuncture during IVF treatment (whether at time of oocyte collection or ET) improves cycle outcome. Our review shows clearly that despite the publication of 13 trials of acupuncture during IVF, well-designed and conducted research into the efficacy and cost-effectiveness of acupuncture carried out as an adjunct to IVF treatment is still needed before clinicians could recommend its use.

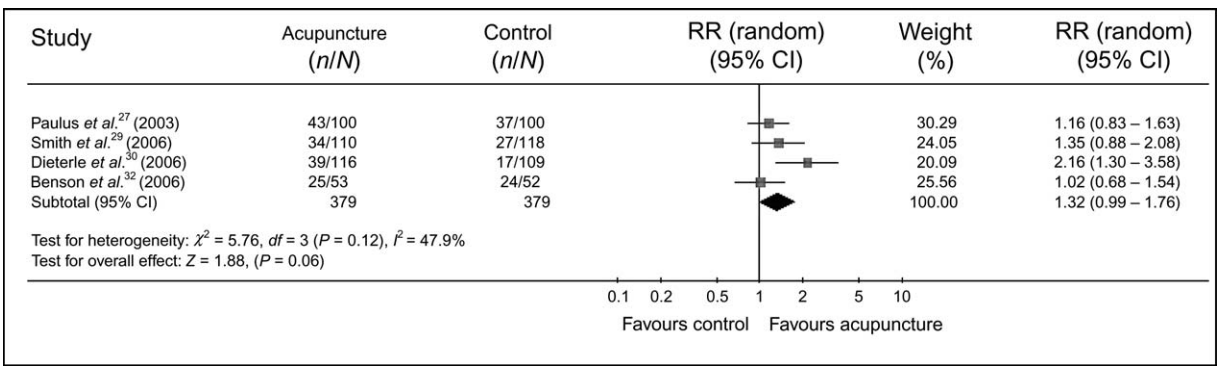

Figure 5. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of ET on the clinical pregnancy rate in women undergoing IVF when sham acupuncture technique was used in the control groups.

Disclosure of interests

The authors state that they have no conflict of interest relating to any pharmaceutical, clinical, consumer or other groups.

Contribution to authorship

A.C. conceived the review; T.E.-T., S.K.S. and M.K. performed literature searches, study selection and data extraction. T.E.-T. and A.C. performed the analysis and wrote the initial draft. M.K., S.K.S., R.D. and Y.K. critically revised the manuscript.

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