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REVIEW

Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis

BIOGRAPHY

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KEY MESSAGE

Acupuncture may be effective when compared to no adjunctive treatment with increasing clinical pregnancies and live births, but is not an efficacious treatment when compared with sham controls.

ABSTRACT

This was a systematic review and meta-analysis to examine the efficacy, effectiveness and safety of acupuncture as an adjunct to embryo transfer compared with controls to improve reproductive outcomes. The primary outcome was clinical pregnancy. Twenty trials and 5130 women were included in the review. The meta-analysis found increased pregnancies (risk ratio [RR] 1.32, 95% confidence interval [CI] 1.07–1.62, 12 trials, 2230 women), live births (RR 1.30, 95% CI 1.00–1.68, 9 trials, 1980 women) and reduced miscarriage (RR 1.43, 95% CI 1.03–1.98, 10 trials, 2042 women) when acupuncture was compared with no adjunctive control. There was significant heterogeneity, but no significant differences between acupuncture and sham controls. Acupuncture may have a significant effect on clinical pregnancy rates, independent of comparator group, when used in women who have had multiple previous IVF cycles, or where there was a low baseline pregnancy rate. The findings suggest acupuncture may be effective when compared with no adjunctive treatment with increased clinical pregnancies, but is not an efficacious treatment when compared with sham controls, although non-specific effects may be active in both acupuncture and sham controls. Future research examining the effects of acupuncture for women with poorer IVF outcomes is warranted.

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KEYWORDS

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INTRODUCTION

Assisted reproductive technology (ART), including IVF, has become widespread for treating infertility [*European IVF-Monitoring Consortium (EIM) et al., 2016*]. Today there are over 6 million children that have been conceived through ART (*Dyer et al., 2016*). Although a well-established treatment, each step of IVF is complex and invasive, and each step carries with it a possibility of failure. IVF is a resource-intensive and costly treatment option for both women and their families, and for public health care expenditure (*Chambers et al., 2009*). Therefore, new therapies that improve reproductive outcomes are highly desirable.

Women seek information and treatment about complementary health approaches to increase their chances of achieving a pregnancy and live birth (*de Lacey et al., 2017; Rayner et al., 2009, 2011*), and also to improve their health, quality of life and to reduce stress whilst undergoing treatment cycles (*de Lacey and Smith, 2013*). Acupuncture has become a frequently used adjunctive treatment prior to and during IVF treatment (*Domar et al., 2012*). In the USA, 30% of a patient cohort engaged in acupuncture prior to IVF treatment and 47% during IVF treatment (*Domar et al., 2012*).

Acupuncture involves needle insertion and manipulation into specifically chosen acupuncture points located in the subcutaneous tissue. Early trials indicated that a short course of acupuncture administered prior to and immediately following embryo transfer (embryo transfer) may provide benefits in improving reproductive outcomes (*Dieterle et al., 2006; Paulus et al., 2002; Smith et al., 2006*). Delivery of this short treatment became common in clinical practice (*Bovey et al., 2010; Smith et al., 2014*). The number of published randomized clinical trials (RCT) has increased over time, and evidence of the effects from acupuncture compared with controls has become less clear. Systematic reviews have found no statistically significant difference in clinical pregnancy or live birth rates when compared with a control (*Cheong et al., 2013; Manheimer et al., 2013*). This review incorporates new evidence from recently published RCT. The objective of this review was to examine the efficacy, effectiveness and safety of acupuncture as an adjunct to embryo transfer compared with controls or no adjuvant treatment to improve clinical pregnancies live births among women undergoing IVF.

MATERIALS AND METHODS

We included RCT that compared acupuncture with sham acupuncture controls or no adjuvant treatment. We considered only RCT where acupuncture was administered during an IVF cycle and included acupuncture treatment administered within 1 day of embryo transfer and with the objective of improving assisting conception and IVF success rates. Trials administered at other stages of the IVF cycle were excluded due to a different treatment rationale. We excluded non-randomized studies, and crossover trials (due to the time-limited intervention). We included women undergoing intracytoplasmic injection (ICSI) or IVF and planning to undergo a fresh or frozen embryo transfer. The intervention included acupuncture involving the needling of meridian points based on the theory of traditional Chinese medicine. We included manual or electro-acupuncture stimulation and excluded dry needling (treatment of myofascial trigger points), transcutaneous electrical nerve stimulation and laser stimulation of acupuncture points.

The primary outcome was clinical pregnancy, with secondary outcomes including live birth, ongoing pregnancy, miscarriage and adverse events. Trials needed to report on one of the following outcomes to be included: clinical pregnancy (i.e. presence of gestational sac) or a viable pregnancy (evidence of a fetal heartbeat), confirmed by transvaginal ultrasound, ongoing pregnancy (i.e. pregnancy beyond 12 weeks of gestation, as confirmed by fetal heart activity on ultrasound), or live birth.

The following databases were searched: PubMed, Embase and the Cochrane Register of Controlled Clinical Trials (CENTRAL). We also searched the proceedings of the annual conferences on ART for 2001–2018: American Society for Reproductive Medicine; European Society of Human Reproduction and Embryology; and Pacific Coast Reproductive Society. We also searched for previous systematic reviews on this topic and reviewed their reference lists. We searched using the keywords: acupuncture, acupuncture treatment, acupuncture therapy, electro-acupuncture, auricular acupuncture, acup* and reproductive techniques, assisted reproductive technology, IVF, ICSI, embryo transfer, embryo implantation, egg collection, combined with RCT (TABLE 1). The search was restricted to English language texts.

The titles and abstracts were screened by one author (ZS), and independently verified by a second author (CS). Full text versions of the papers were retrieved by ZS. Any disagreement as to which studies to include were resolved by a third author (MA). For each study two authors (CS, MA, HT, ZS) independently extracted data and independently assessed the methodological quality of the trials using the Cochrane risk of bias tool (*Higgins et al., 2011*). Data extraction included details of the study design, intervention and control, characteristics of participants, geographical setting and study outcomes. Authors who had published abstracts were contacted for an update on publication status. When no response was received, relevant data was extracted from a previously published review (*Manheimer et al., 2013*). Two trials (*Smith et al., 2006, 2018*) undertaken by three authors (CS, RN, NJ) of this review were independently assessed by authors MA, AT and ZS. The quality of the acupuncture delivered during the trial was assessed by two authors using the NICMAN scale (*Smith et al., 2017*). The NICMAN scale comprises 11 domains related to study design, rationale of the intervention, specific criteria relating to the acupuncture characteristics including needling stimulation, whether manually or using electro-stimulation, duration and frequency of treatment and practitioner training. Scores were allocated as follows: 2 points for yes, 0 for no, 1 for unclear or partial agreement. The responses to the individual items were summed to create an overall summary score representing the quality of the acupuncture administered. Data were entered into RevMan software (*The Nordic Cochrane Centre and The Cochrane Collaboration, 2014*).

Data analysis

Meta-analyses were undertaken using risk ratios (RR) with 95% confidence intervals (CI) reported. The unit of analysis was the participant randomized. In addition, for

TABLE 1 DATABASE SEARCH STRING AND NUMBER OF RECORDS FOUND

Database	Search string	Search limits	Records found
CENTRAL (Cochrane Register of Controlled Clinical Trials)	acupuncture OR "acupuncture treatment" OR "acupuncture therapy" OR electro-acupuncture OR "auricular acupuncture" OR "acup and reproductive techniques" OR "assisted reproductive technology" OR IVF OR ICSI OR "embryo transfer" OR "embryo implantation" OR "egg collection" AND "randomised controlled trial"	Title / abstract/ Keywords	4187
PubMed	((acupuncture OR "acupuncture treatment" OR "acupuncture therapy" OR electro-acupuncture OR "auricular acupuncture" OR "acup* and reproductive techniques" OR "assisted reproductive technology" OR IVF OR ICSI OR "embryo transfer" OR "embryo implantation" OR "egg collection")) AND "randomised controlled trial"	Title / abstract English	229
Embase	((acupuncture or "acupuncture treatment" or "acupuncture therapy" or electro-acupuncture or "auricular acupuncture" or "acup* and reproductive techniques" or "assisted reproductive technology" or IVF or ICSI or "embryo transfer" or "embryo implantation" or "egg collection") and "randomised controlled trial")	Abstract English	233
Total			4649
Conference proceedings and reference tracking	na	na	32
Grand total			4681

na = not available.

miscarriage outcomes we also reported as per pregnancy. We included randomized women who commenced an IVF cycle but did not complete treatment due to a cancelled cycle. We excluded data for women who withdrew consent for their data to be used, or for whom data on clinical outcomes was missing. Multiple live births were counted as one live birth event. The sham-controlled and no adjuvant treatment-controlled trials were analysed separately. A random-effects meta-analysis was applied based on the expected heterogeneity within the acupuncture treatment protocols and were conducted using Comprehensive Meta-Analysis software (Version 3). Random-effects meta-analysis was undertaken when there were a minimum of three studies per subgroup. We formally tested heterogeneity by examining the *P*-value of the I^2 statistic. If at least 10 trials were available for a meta-analysis, we assessed for the likelihood of publication bias by constructing funnel plots. Publication bias and meta-regression were carried out using Comprehensive Meta-Analysis software (version 3).

Subgroup analyses

We planned a number of subgroup analyses on characteristics that may influence the effects of acupuncture on clinical pregnancy, both participant and intervention related. The relationship between continuous moderators and effect size estimates were explored with meta-regression analyses, with categorical moderators explored through subgroup analysis. Categorical moderators included: fresh or frozen IVF cycle, fresh or frozen embryo transfer, embryo stage at transfer (blastocyst, cleavage or mixed), women's age, number of acupuncture treatments, standardized Paulus protocol or modified treatment protocol, timing of treatments during IVF cycle, type of sham (invasive versus non-invasive), location of sham points (on verum points versus non-acupuncture points) and acupuncture administered on-site at the IVF clinic or off-site. Continuous moderators included acupuncture quality using the NICMAN scale score and previous number of IVF cycles.

The number of acupuncture treatments were combined into two groups (<3 and >3) to allow for subgroup analysis as meta-regression was not appropriate due to the small range of treatment numbers. Similarly, due to the small age range of women, age was combined into two categories (<38 years and >38 years). We also examined the effect of the control group as a baseline estimate of the pregnancy rate, a clinical characteristic previously found to benefit trials with lower baseline pregnancy rates (*Manheimer et al., 2008, 2013*). In these two reviews the variable was categorized as higher (32% or greater, the European pregnancy rates per embryo transfer) or lower (*European IVF-monitoring Consortium et al., 2017*). Planned comparisons of location of sham points and acupuncture treatment location (on-site versus off-site) could not be included due to fewer than three studies being present in one of the comparison groups. Separate analysis of fresh or frozen trials in the meta-regression was not possible due to an insufficient number of frozen trials to make any meaningful comparisons.

RESULTS

A total of 4681 potential references were identified. After 727 duplicates were removed, the studies were examined by title, abstract and full text for eligibility (FIGURE 1). Of the 37 studies examined by the full text, 20 trials met the inclusion criteria for this review (*Andersen et al., 2010; Arnoldi et al., 2010; Craig et al., 2014; Dieterle et al., 2006; Domar et al., 2009; Feliciani et al., 2011; Gillerman et al., 2016; Madaschi et al., 2010; Morin et al., 2017; Moy et al., 2011; Omodei et al., 2010; Paulus et al., 2002, 2003; Rashidi et al., 2013; Smith et al., 2006, 2018; So et al., 2009, 2010; Villahermosa et al., 2013; Westergaard et al., 2006*).

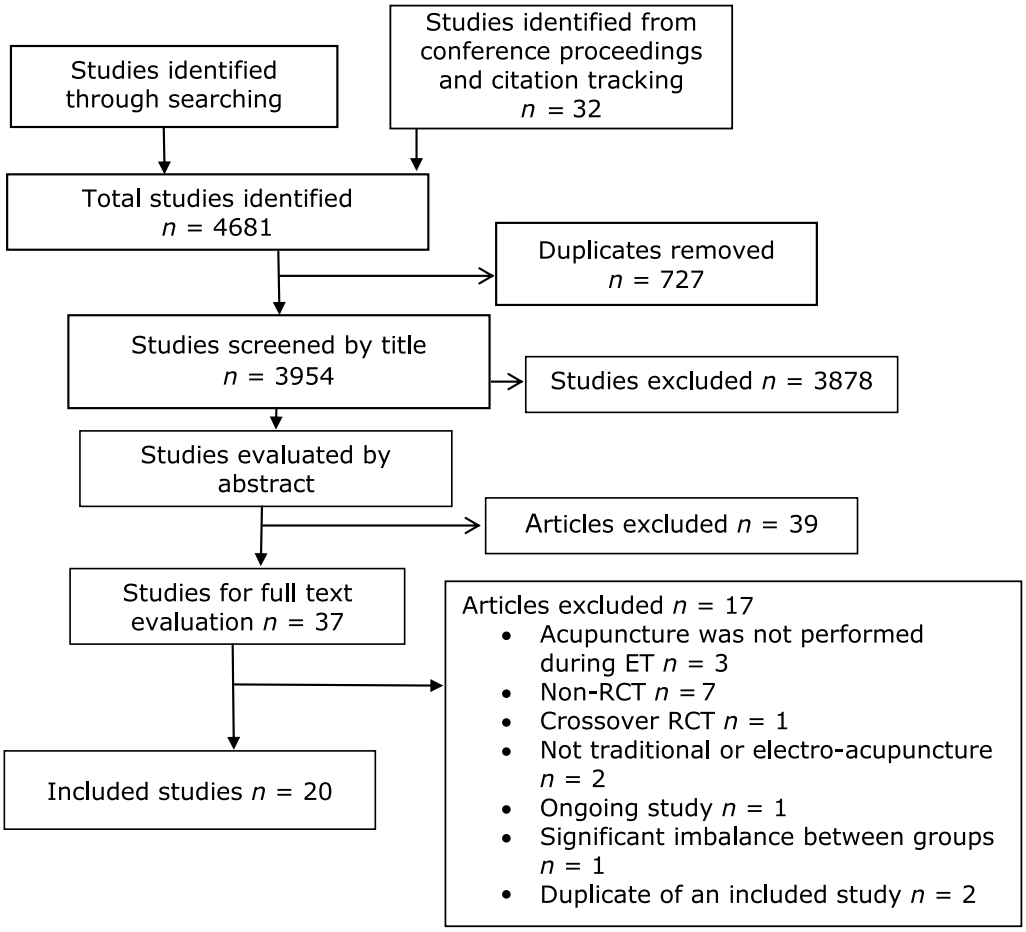

FIGURE 1 PRISMA flow chart of included studies.

Seventeen studies were excluded. Seven studies did not meet the criteria of an RCT (*Emmons and Patton, 2000; Ke et al., 2011; Porat-Katz et al., 2017; Teshima et al., 2007; Wang et al., 2007; Youran et al., 2008; Pastuszek et al., 2013*) and in three studies acupuncture was not performed within a day of embryo transfer (*Cui et al., 2011; Stener-Victorin et al., 1999, 2003*). Two studies were not based on traditional or electro-acupuncture (*Shuai et al., 2014; Zhang et al., 2011*), one study was a crossover RCT (*Quintero and Centre, 2004*), two studies were duplicate publications of an included trial (*Benson et al., 2006; Fratterelli et al., 2011*), one study was ongoing at the time of reporting interim results (*Udoff et al., 2006*) and there was a significant imbalance between the treatment and control groups in one study (*Udoff et al., 2014*).

Trial characteristics

Twenty RCT were included. Characteristics of the studies are shown in TABLE 2. Four studies were undertaken in the USA, three each in Italy and Germany. Two studies were each undertaken in Australia, Brazil, China, and Denmark. Single studies were undertaken in Iran and the UK. Twenty trials reported on clinical pregnancy rates, 13 trials reported on ongoing pregnancy rates, 14 trials reported on live birth rates. Five trials reported on adverse events (*Morin et al., 2017; Moy et al., 2011; Smith et al., 2018; So et al., 2009, 2010*). Sample sizes ranged from 46 to 848 women, and studies were reported between 2002 and 2018. Fourteen trials recruited women undergoing a fresh cycle, one trial restricted eligibility to women undergoing a frozen cycle and one trial recruited women doing a mixture of fresh or frozen cycles, and four trials did not report this characteristic. Eleven trials undertook a cleavage-day embryo transfer, five trials reported a mixture of cleavage and blastocyst embryo transfer and four trials did not report this characteristic. One trial recruited women with polycystic ovary syndrome (PCOS) only (*Rashidi et al., 2013*).

Twelve trials used a no adjunctive treatment control (*Arnoldi et al., 2010; Craig et al., 2014; Domar et al., 2009; Feliciani et al., 2011; Gillerman et al., 2016; Madaschi et al., 2010; Morin et al., 2017; Omodei et al., 2010; Paulus et al., 2002; Rashidi et al., 2013; Villahermosa et al., 2013; Westergaard et al., 2006*). One trial included three arms: acupuncture, a sham and no adjunctive control (*Villahermosa et al., 2013*). A sham control was used in nine trials (*Andersen et al., 2010; Dieterle et al., 2006; Moy et al., 2011; Paulus et al., 2003; Smith et al., 2006, 2018; So et al., 2009, 2010; Villahermosa et al., 2013*). Three sham control trials inserted needles but into areas away from verum points or at verum points not associated with fertility (TABLE 3). Six sham controls used non-invasive (non-penetrating) sham needles. Two trials placed these sham needles on sham points, and four trials placed the sham device on verum points. Twelve trials administered two treatments immediately before and after embryo transfer, five trials administered two treatments on the day of embryo transfer, and either additional treatment during the time of ovarian stimulation (four studies) and/or in the luteal phase (three studies). Seven trials administered the standardized Paulus acupuncture protocol (*Paulus et al., 2002*).

TABLE 2 CHARACTERISTICS OF STUDIES INCLUDED IN THIS REVIEW

Study	Country	Number	Outcomes	Acupuncture	Control	Fresh or frozen cycle	Stage of embryo development
Andersen	Denmark	635	Pregnancy, ongoing, live birth	30 min pre and post ET[a]	Non-invasive sham control	Fresh	Cleavage
Arnoldi	Italy	204	Pregnancy	Three sessions: (i) day 5 of ovarian stimulation; (ii) 30 min before ET; (3) immediately after ET[a]	No adjunctive treatment	Not reported	Cleavage
Craig	USA	113	Pregnancy, live birth	Off site. First within 1–2 h before ET; second within 1–2 h after ET[a]	No adjunctive treatment	Fresh	Blastocyst and cleavage
Dieterle	Germany	225	Pregnancy, ongoing pregnancy, live birth	Two sessions: first immediately after ET; second 3 days after ET[a]	Invasive sham control[b]	Fresh	Cleavage
Domar	USA	146	Pregnancy	Two sessions: first 25 min before ET; second immediately after ET	Lying quietly for 25 min	Fresh	Not reported
Feliciani	Italy	46	Pregnancy, ongoing pregnancy, live birth	Three sessions: first 5–7 days before egg retrieval; second 2 to 3 days before oocyte retrieval; third within 1 h after ET[a]	No adjunctive treatment	Fresh	Blastocyst and cleavage
Gillerman	UK	157	Pregnancy, live birth	Three sessions: first between days 6 and 8 of ovarian stimulation; second 25 min before ET; second immediately after ET	No adjunctive treatment	Not reported	Not reported
Villahermosa	Brazil	84	Clinical pregnancy	Five sessions; on 1st and 7th day of ovarian stimulation, day before ovarian induction and the day after transfer	Invasive sham[b] control and no adjunctive treatment	Fresh	Cleavage
Madaschi	Brazil	416	Pregnancy, ongoing pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	No adjunctive treatment	Not reported	Cleavage
Morin[c]	USA	843	Pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	No adjunctive treatment	Fresh and frozen	Blastocyst and cleavage
Moy	USA	161	Pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	Invasive sham control[b]	Fresh	Cleavage
Omodei	Italy	168	Pregnancy, ongoing pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET[a]	No adjunctive treatment	Not reported	Not reported
Paulus	Germany	160	Pregnancy, ongoing pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	No adjunctive treatment	Fresh	Cleavage

(continued on next page)

Table 2 – (continued)

Study	Country	Number	Outcomes	Acupuncture	Control	Fresh or frozen cycle	Stage of embryo development
Paulus	Germany	200	Pregnancy, ongoing pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	Non-invasive sham control	Fresh	Not reported
Rashidi	Iran	62	Pregnancy	Five sessions, day 21 of previous cycle, first day of ovarian stimulation, 2 days before oocyte retrieval, two on the day of ET[a]	No adjunctive treatment	Fresh	Cleavage
Smith	Australia	228	Pregnancy, ongoing pregnancy	Three sessions: first between day 9 of ovarian stimulation; second 25 min before ET; second immediately after ET[a]	Non-invasive sham control	Fresh	Blastocyst and cleavage
Smith[d]	Australia	848	Pregnancy, live birth	Three sessions: first between days 6 and 8 of ovarian stimulation; second 25 min before ET; second immediately after ET[a]	Non-invasive sham control	Fresh	Blastocyst and cleavage
So	Hong Kong/China	370	Pregnancy, ongoing pregnancy, live birth	Two sessions: first 25 min before ET; second immediately after ET	Non-invasive sham control	Fresh	Cleavage
So	Hong Kong/China	226	Pregnancy, ongoing pregnancy, live birth	One session immediately after ET[a]	Non-invasive sham control	Frozen	Cleavage
Westergaard[e]	Denmark	300	Pregnancy, ongoing pregnancy	Two sessions: first 25 min before ET; second immediately after ET[a]	No adjunctive treatment	Fresh	Cleavage

ET = embryo transfer

[a] Modified Paulus protocol.

[b] Needles but into areas away from 'true points' or points that were not associated with fertility.

[c] 843 women randomized to four-arm study, data extracted on two groups, acupuncture vs no adjunctive control (n = 210).

[d] 39 missing or women withdrew consent for data to be used.

[e] 27 women withdrew consent or treatment cancelled.

Methodological quality of the trials

The risk of bias assessment is presented in FIGURE 2. The most frequent risk of bias was from inadequate blinding of study participants, with eight of the 20 studies at a low risk of bias. Overall the risk of any selection bias at randomization appears low.

The NICMAN scores (out of 23) ranged from 6 (*Omodei et al., 2010*) to 23 (*Smith et al., 2018*) (TABLE 2). The majority of trials scored 16. Only one trial (*Smith et al., 2018*) scored full points on each of the domains (FIGURE 3). Overall the general methodological domains related to participants, interventions, comparison group, outcomes and study design all scored high. The domains related to acupuncture were mixed. Both justification for point selection and the number of treatments used were adequate in the majority of trials. The lowest-scoring domains related to the reporting of practitioner experience, acupuncture point location and the use of differential diagnosis.

Effect of the interventions

There was no statistical difference between acupuncture and sham control for clinical pregnancy, ongoing pregnancy, live birth and miscarriage (FIGURES 4 to 7). There was evidence of statistically significant increased pregnancies when acupuncture was compared with no adjunctive treatment (RR 1.32, 95% CI 1.07–1.62, 12 trials, 2230 women). This positive effect was seen with ongoing pregnancies (RR 1.42, 95% CI 1.17–1.73, 6 trials, 1144 women), live births (RR 1.30, 95% 1.00–1.68, 9 trials, 1980 women) and reduced miscarriage (RR 1.43, 95% CI 1.03–1.98, 10 trials, 2042 women). The benefit for miscarriage was not significant when expressed as per pregnancy (RR 1.08, 95% CI 0.79–1.46). However, there was substantial heterogeneity for clinical pregnancy (I^2 = 61%) and live birth (I^2 = 63%) outcomes. The funnel plot for the outcome of clinical pregnancy suggests some asymmetry (FIGURE 8). Applying the Begg and Mazumdar test for publication bias (one-tailed), no evidence of publication bias was found in the sham control group (P = 0.038) (*Begg and Mazumdar, 1994*). The subsequent Duval and Tweedie's trim and fill analysis (*Duval and Tweedie, 2000*) for sham controls showed no significant change in the primary outcome of clinical pregnancy

TABLE 3 CHARACTERISTICS OF ACUPUNCTURE AND SHAM CONTROL INTERVENTIONS

Study	NICMAN score (0–23)	Number of treatments	Number of stimulation phase treatments	Pre- and post-ET intervention only	On-site ET treatment	Paulus protocol or modified protocol	Post-ET treatment	Invasive sham control	Sham points
Andersen	17	2	0	Yes	Yes	Modified	No	No	No
Arnold	12	3	1	No	Yes	Modified	No	na	na
Craig	21	2	0	Yes	No	Modified	No	na	na
Dieterle	13	2	0	No	Yes	Modified	Yes	Yes	Non-fertility points
Domar	13	2	0	Yes	Yes	Paulus	No	na	na
Feliciani	12	3	2	No	Yes	Modified	No	na	na
Gillerman	22	99	1	No	Yes	Modified	No	na	na
Madashi	19	2	0	Yes	Yes	Paulus	No	na	na
Morin	16	2	0	Yes	Yes	Paulus	No	na	na
Moy	16	2	0	Yes	Yes	Paulus	No	Yes	No
Paulus	15	2	0	Yes	Yes	Paulus	No	na	na
Paulus	15	2	0	Yes	Yes	Paulus	No	No	No
Omoedi	6	2	0	Yes	Yes	Modified	No	na	na
Rashidi	15	5	2	No	Yes	Modified	No	na	na
So	20	2	0	Yes	Yes	Paulus	No	No	No
So	20	1		No	Yes	Modified	Yes	No	No
Smith	22	3	1	No	Yes	Modified	No	No	Yes
Smith	23	3	1	No	Yes	Modified	No	No	Yes
Villahermosa	15	4	2	No	Yes	Modified	No	Yes	No
Westergaarde	16	2	0	Yes	Yes	Modified	Yes	na	na

ET = embryo transfer; na = not applicable.

when adjusting for potential effects of publication bias (RR 1.04, 95% CI 0.86–1.28).

Six trials reported on adverse effects. Trials reported nausea, dizziness, tiredness, drowsiness, headache, chest pain, pain/itching at needle site, feeling relaxed, calm and energized. There was a significant increase in pain/itching at the needle site from acupuncture compared with the non-invasive sham control (RR 1.51, 95% CI 1.24–2.00, 3 trials, 1204 women) (FIGURE 9). One trial found increased bruising for the acupuncture group compared with the non-invasive sham control (RR 3.82, 95% CI 1.28–11.39, 608 women) (*Smith et al., 2018*), and one trial found increased relaxation in the non-invasive sham control (RR 0.76, 95% CI 0.61–0.95, 228 women). One study found women receiving acupuncture reported their sessions to be more tiring ($P < 0.05$), and that they felt more fearful ($P < 0.001$) and experienced greater achiness ($P < .018$) (*Moy et al., 2011*). No side effects were reported by women in one trial (*Morin et al., 2017*).

Subgroup analysis

In studies where more than three treatments were performed, the clinical pregnancy rate significantly improved ($N = 8$ / $n = 1595$, RR 1.50, 95% CI 1.18–1.90, $P = 0.001$) while in studies where fewer than three treatments were performed, clinical pregnancy rate did not improve ($N = 13$ / $n = 3535$, RR 1.09, 95% CI 0.93–1.29, $P > 0.05$) (TABLE 4). Studies that used a modified Paulus treatment protocol significantly improved clinical pregnancy rate ($N = 14$ / $n = 3254$, RR 1.34, 95% CI 1.07–1.67, $P = 0.009$), while those using the standard Paulus protocol did not ($N = 7$ / $n = 1876$, RR 1.05, 95% CI 0.88–1.24, $P > 0.05$). The timing of the treatment delivery was a significant factor in clinical pregnancy rate. Studies that delivered treatments post the day of embryo transfer showed no benefit to clinical pregnancy rates ($N = 3$ / $n = 743$, RR 1.36, 95% CI 0.76–2.45, $P > 0.05$) while those that did not deliver any treatments post the day of embryo transfer did ($N = 18$ / $n = 4387$, RR 1.17, 95% CI 1.007–1.36, $P = 0.04$). The baseline pregnancy rate was a significant modifier of the outcome. Studies where the baseline pregnancy rate was below 32% had a significantly greater chance of clinical pregnancy, regardless of the control group ($N = 11$ / $n = 2394$, RR 1.60, 95% CI 1.36–1.88, $P < 0.001$) compared with those studies with a baseline pregnancy rate of 32% or greater ($N = 10$ / $n = 2736$, RR 0.95, 95% CI 0.84–1.07, $P > 0.05$). The type of sham used, type of cycle (fresh, frozen or mixed), maternal age or stage of embryo transfer were not significant modifiers of clinical pregnancy rate.

The meta-regression analysis found that a higher NICMAN score was related to less chance of showing a difference between active and comparator groups for clinical pregnancy rate ($N = 21$ / $n = 5130$, $B = -0.042$, SE = 0.0213, $Z = -1.98$, $P = 0.047$). The type of comparison

TABLE 4 SUBGROUP ANALYSIS ON CLINICAL PREGNANCY RATE

	Meta-analysis					Heterogeneity	
	Comparisons	**Risk ratio**	**95% CI**		***P*-value**	I^2	***P*-value**
Number of acupuncture treatments (<3 or >3)	21	1.21	1.06	1.38	**0.006**	65.9	>0.001
Fresh cycle vs frozen cycle	16	1.11	0.94	1.31	0.22	64.1	>0.001
Embryo stage at transfer	14	1.16	0.95	1.41	0.15	69.2	>0.001
Women's age at time of transfer (<38 or >38)	17	1.15	0.97	1.37	0.102	67.8	>0.001
Type of sham (invasive vs non-invasive)	9	1.01	0.86	1.19	0.91	65.4	0.003
Type of protocol (Paulus vs modified)	21	1.15	1.0	1.32	**0.041**	65.9	>0.001
Timing of treatment (post day of ET vs no further treatment)	21	1.18	1.02	1.36	**0.024**	65.9	>0.001
Baseline pregnancy rate in control group (under 32% or 32% and over)	21	1.14	1.04	1.26	**0.007**	65.9	>0.001

group was expected to be a major factor as studies with higher NICMAN scores were more likely to use sham controls. The addition of the type of comparator as a factor in the meta-regression meant the NICMAN score no longer had a significant association with clinical pregnancy rate (N = 21 / n = 5130, B = –0.031, SE = 0.0251, Z = –1.25, P > 0.05). The number of previous IVF cycles was associated with a greater clinical pregnancy rate, with studies having a greater proportion of women undergoing their second or greater IVF cycle having a significant association with clinical pregnancy rate (N = 6 / n = 2498, B = 0.0150, SE = 0.007, Z = 2.19, P = 0.029).

DISCUSSION

The search strategy identified 20 trials and 5130 women for inclusion in this review. A benefit from trials of acupuncture when administered within 1 day of embryo transfer increased clinical pregnancy, ongoing pregnancy and live births when compared with no adjunctive treatment. This was a clinically significant 30% increased chance of an improved reproductive outcome, however there was substantial heterogeneity. There was no evidence of an effect when acupuncture was compared with a sham control. There was evidence of fewer miscarriages when acupuncture was compared with no adjunctive treatment, but not when expressed as per pregnancy. Acupuncture-related side effects were reported in a small number of trials and are similar to those reported in trials in the general population (*Witt et al., 2009*), and during pregnancy (*Park et al., 2014*). Factors were explored that may influence the effect of acupuncture on reproductive outcomes using *post hoc* subgroup analysis. Three or more treatments and the use of a modified treatment protocol were significant effect modifiers on clinical pregnancy. The timing of treatment was also a significant modifier, with treatments post the day of embryo transfer showing no benefit on clinical pregnancy. Acupuncture appears to have a significant effect on clinical pregnancy rate, independent of comparator group, when used in women who have had multiple previous IVF cycles, or where there was a low baseline pregnancy rate.

These findings differ from the other systematic reviews published in 2013 and 2014, which found no difference in clinical outcome when pooling data from all trials of acupuncture around the time of embryo transfer (*Cheong et al., 2013; Manheimer et al., 2013*). The 2014 review, however, found a benefit from acupuncture when performed during ovarian stimulation plus on the day of transfer, and when performed after embryo transfer and during the implantation phase (*Shen et al., 2015*). The most recent systematic review found an improved pregnancy outcome from acupuncture when all trials were pooled, however there was substantial heterogeneity. Previous subgroup analyses have found higher pregnancy rates from acupuncture trials administered during ovarian stimulation (*Qian et al., 2017*), and an increased number of treatment sessions performed prior to and including the day of embryo transfer (*Hullender Rubin et al., 2015; Magarelli et al., 2009*). The finding that acupuncture has a stronger effect on clinical pregnancy rates where there was a low baseline pregnancy rate has been reported in earlier systematic reviews (*Manheimer et al., 2008, 2013*). The reasons for this finding are proposed to relate to differing country-specific regulations regarding the number of embryos transferred, differences in the inclusion criteria between trials, including the characteristics of women who may have a poor prognosis of IVF success (*Manheimer et al., 2013*).

To date, techniques intended to ensure optimal embryos for transfer (most notably preimplantation genetic screening [PGS], designed to select chromosomally normal embryos) and to ensure optimal endometrial receptivity (such as the endometrial receptivity array, ERA) have not featured within RCT assessing the effectiveness of acupuncture for boosting the success of

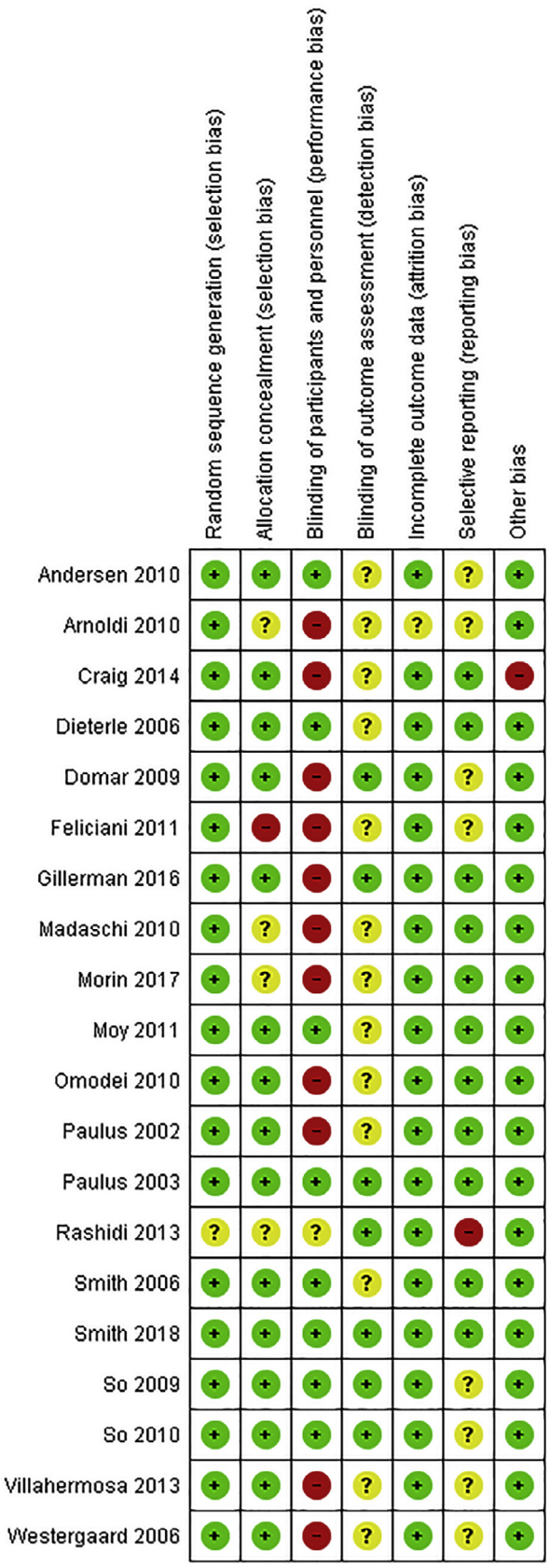

FIGURE 2 Risk of bias.

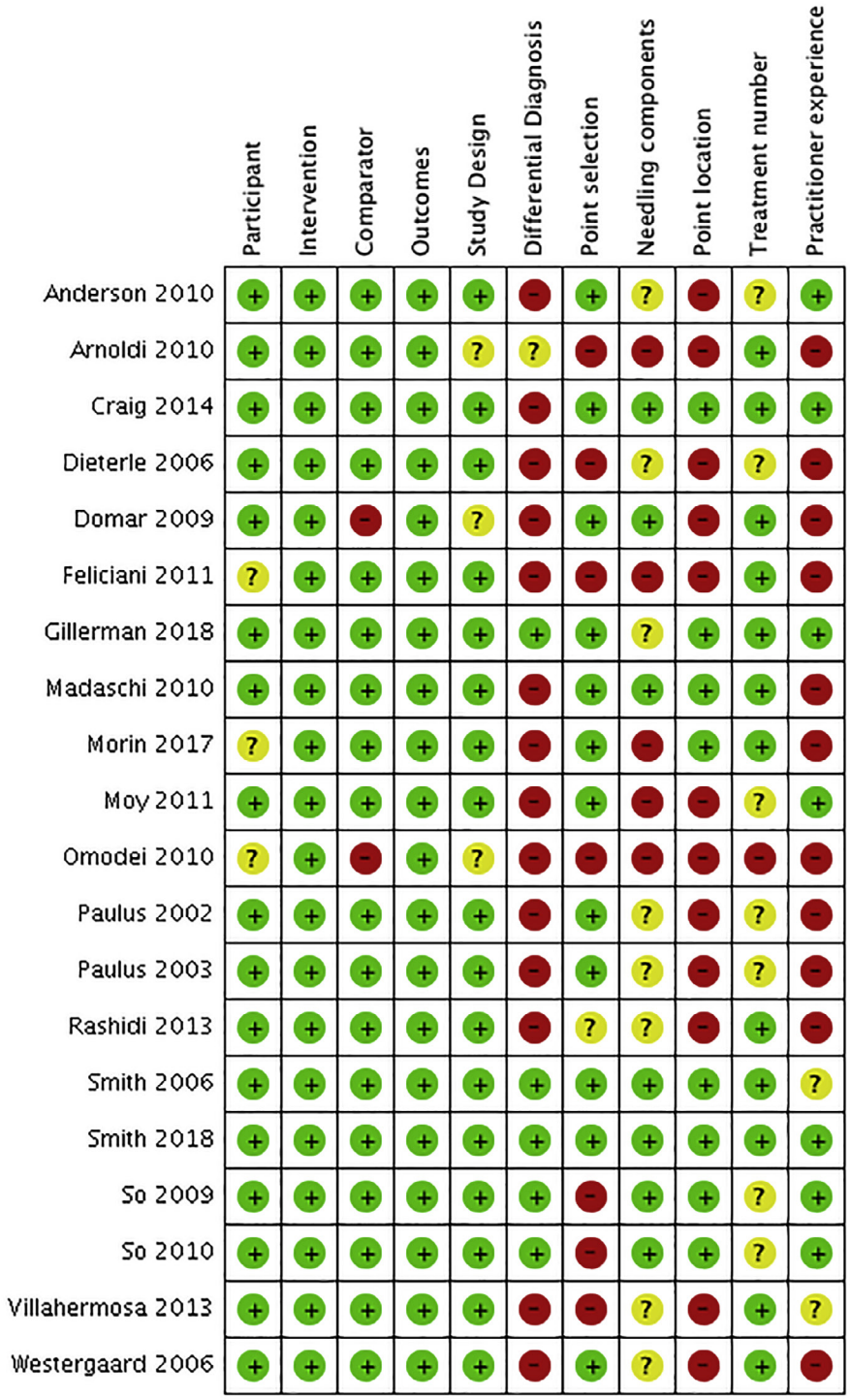

FIGURE 3 NICMAN domain by study.

IVF. Future trials should specify to what extent these interventions have been used within the population under study and future meta-analyses may benefit from the use of sensitivity analyses where these interventions have (or have not) been used in included RCT.

Sham controls are used to control for acupuncture needling components such as acupuncture point location, needle insertion and stimulation, and the number of needles. The review found no effect when acupuncture was compared with a sham control. These findings may be partially explained by data from a meta-analysis that suggests that these devices may not be inert (*Zhang et al., 2015*), and that some activity may arise when applied, including sensory and psycho-social cues. The overall effects from acupuncture are

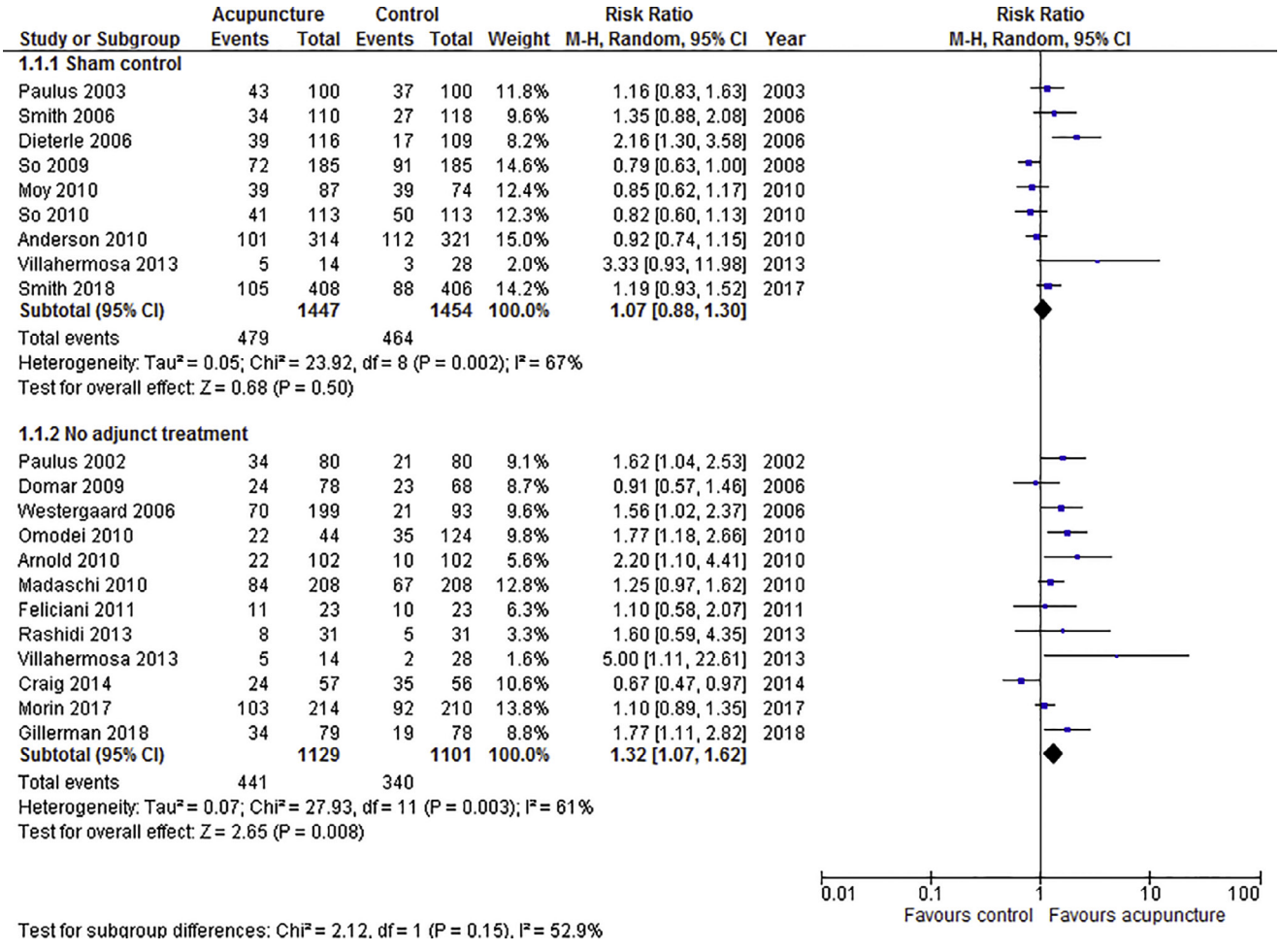

FIGURE 4 Effect of acupuncture versus control on clinical pregnancy.

described as needling, specific non-needling components (palpation, education, self-care and diagnosis), and non-specific components including time, attention, credibility and expectation (*Langevin et al., 2011*). IVF is a stressful experience (*Lemmens et al., 2004*) and the effects of acupuncture on psycho-social outcomes have been examined and found to have some benefits (*de Lacey et al., 2009; Domar et al., 2009*). In an RCT of acupuncture performed on the day of embryo transfer, no difference in reproductive outcomes was found for both acupuncture and sham acupuncture groups, however reduced anxiety levels were reported in both acupuncture and sham acupuncture groups (*So et al., 2010*). The characteristic non-needling components and non-specific effects may therefore explain why acupuncture treatments, whether verum or sham acupuncture, exert a significant anxiolytic effect during IVF (*Cummings, 2018*). The beneficial effects found when acupuncture was compared with no adjunctive treatment may be explained by previous studies suggesting an improved uterine blood flow (*Stener-Victorin et al., 1996*), modulation of endogenous opioid beta-endorphin (*Chang et al., 2002*) and various cytokines (*Zijlstra et al., 2003*).

A limitation of this review is the significant heterogeneity found across studies. Although a random-effects model was applied, these differences remained. A further limitation was that non-English language databases were not searched and so studies may have been missed. A number of early studies remain as published abstracts. This impacted on the scoring of studies using the NICMAN scale and a quality assessment. However, we followed up with primary authors, and authors of the *Manheimer et al. (2013)* review to clarify details and outcomes of this study. This enabled us to ensure we did not double count participants arising from the same trial in our review, unlike one published review (*Shen et al., 2015*).

With increased use of acupuncture by women undertaking IVF it is important that women remain informed, with up-to-date evidence about the risks and benefits from acupuncture when used as an adjunct to IVF. Women should understand that acupuncture has not been shown to be superior to a sham control, however there are potentially significant benefits when compared with no adjunctive treatment, and that acupuncture remains a low-risk intervention (*Witt et al., 2009*).

Evidence suggests acupuncture may be effective when compared with no adjunctive treatment, with increased clinical pregnancies and live births, but is not an efficacious treatment when compared with sham controls. Future research should focus on different dosing acupuncture regimens, and exploration of the components of acupuncture that are contributing to improved reproductive outcomes. Increased understanding of these components may

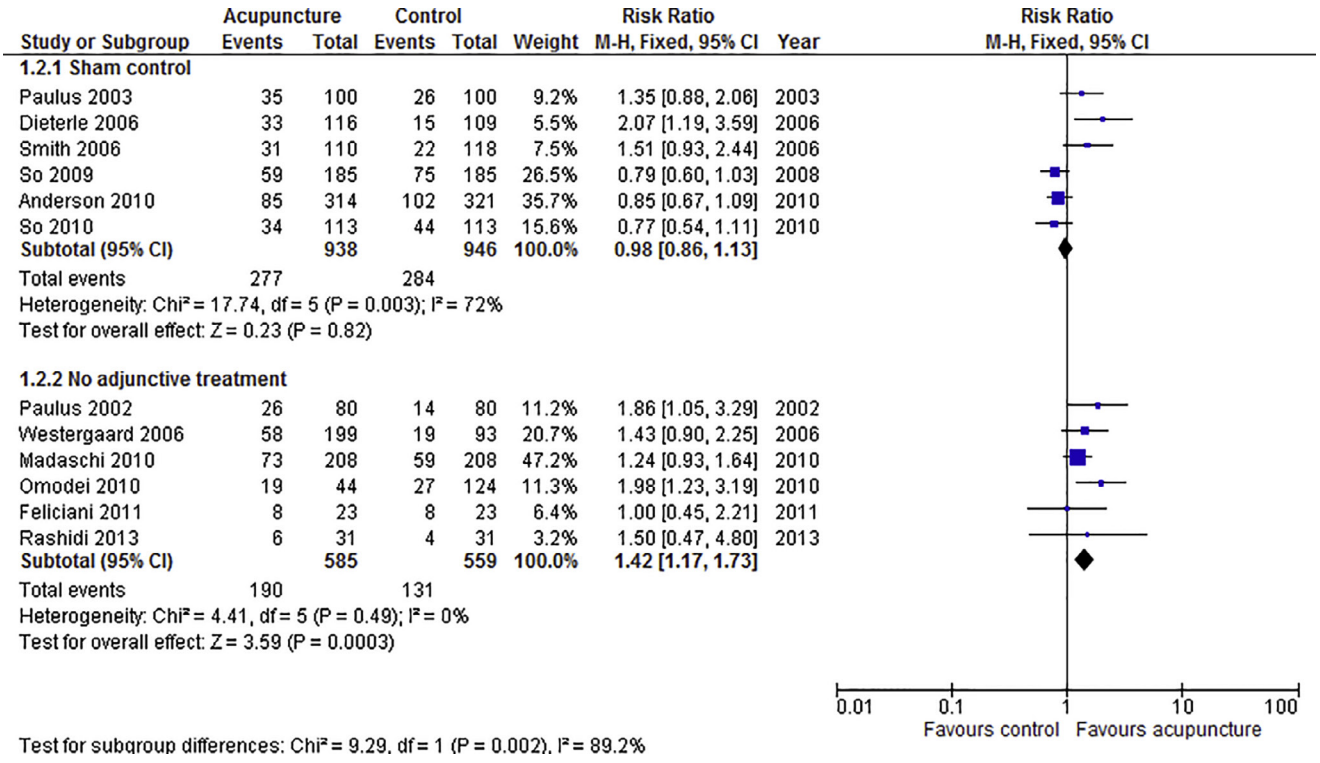

FIGURE 5 Effect of acupuncture versus control on ongoing pregnancy.

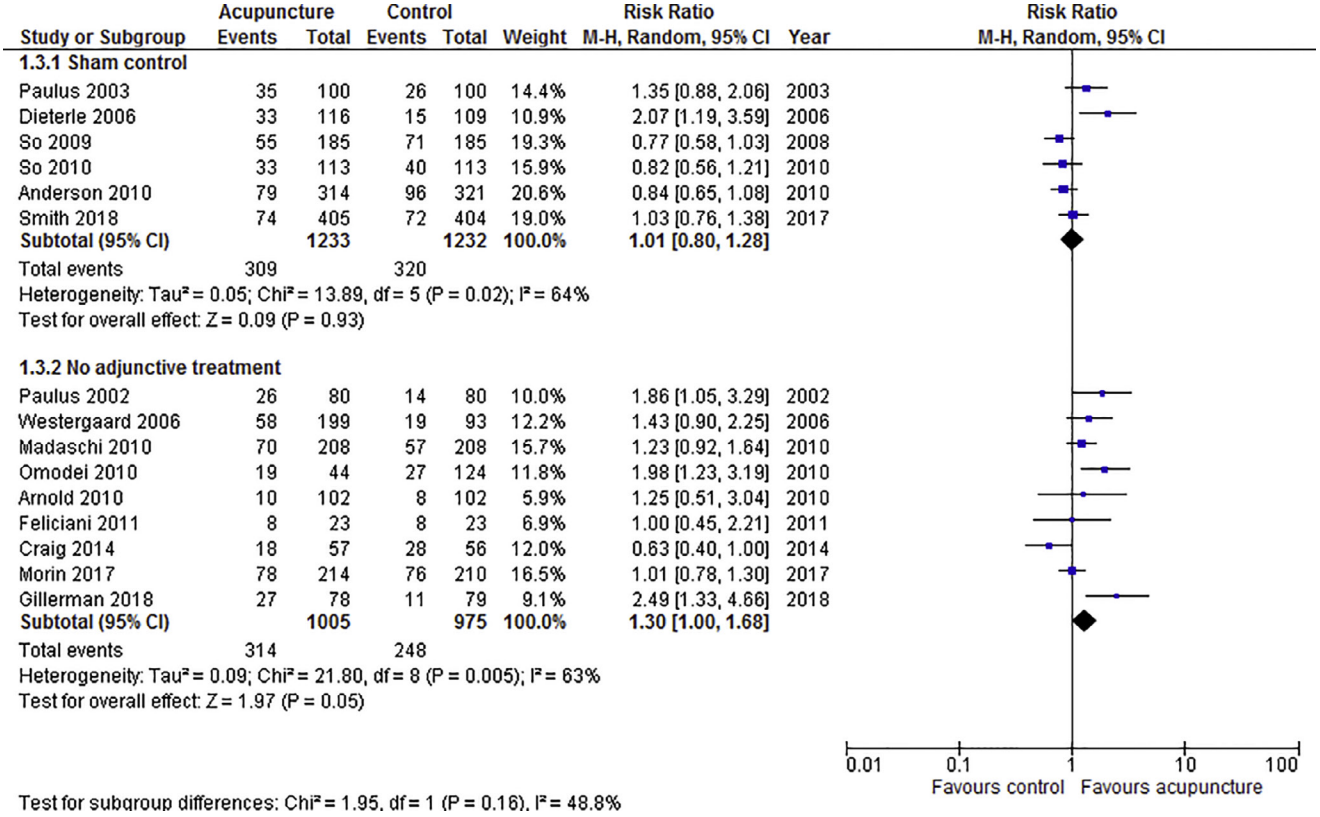

FIGURE 6 Effect of acupuncture versus control on live birth.

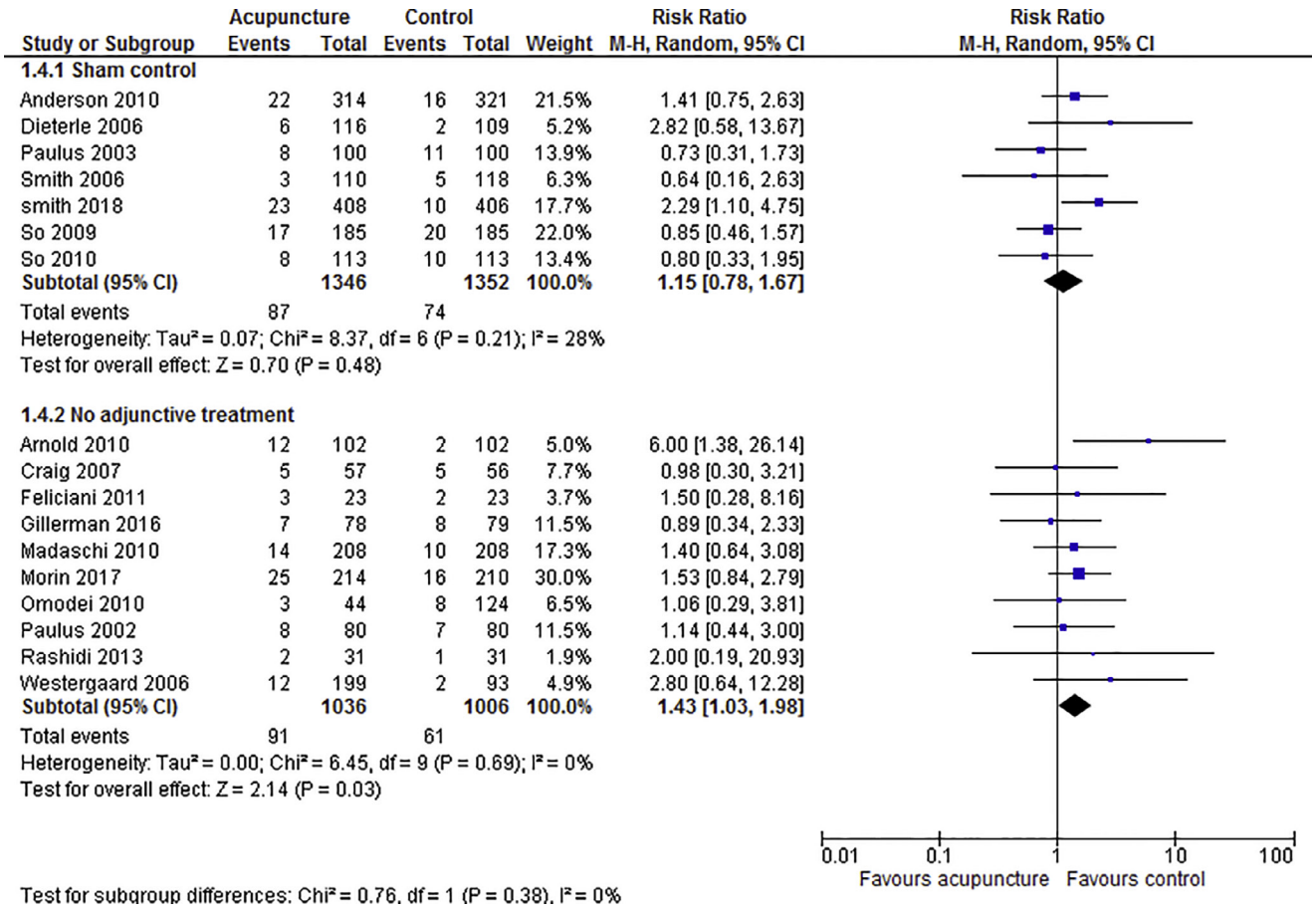

FIGURE 7 Effect of acupuncture versus control on miscarriage.

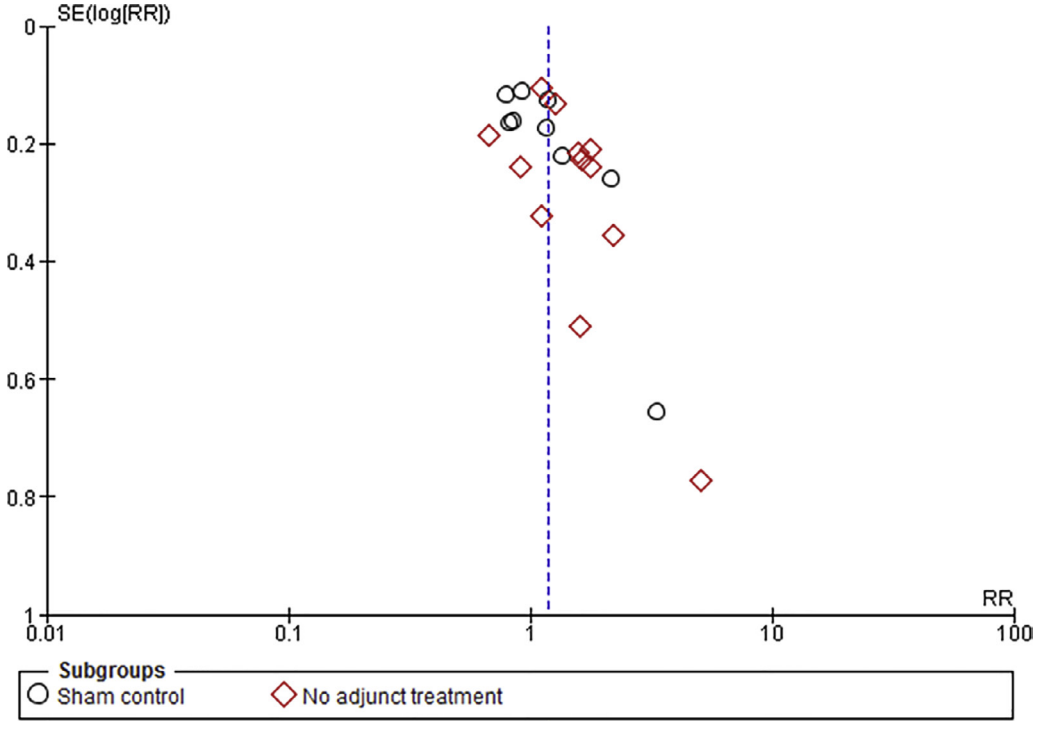

FIGURE 8 Funnel plot for clinical pregnancy.

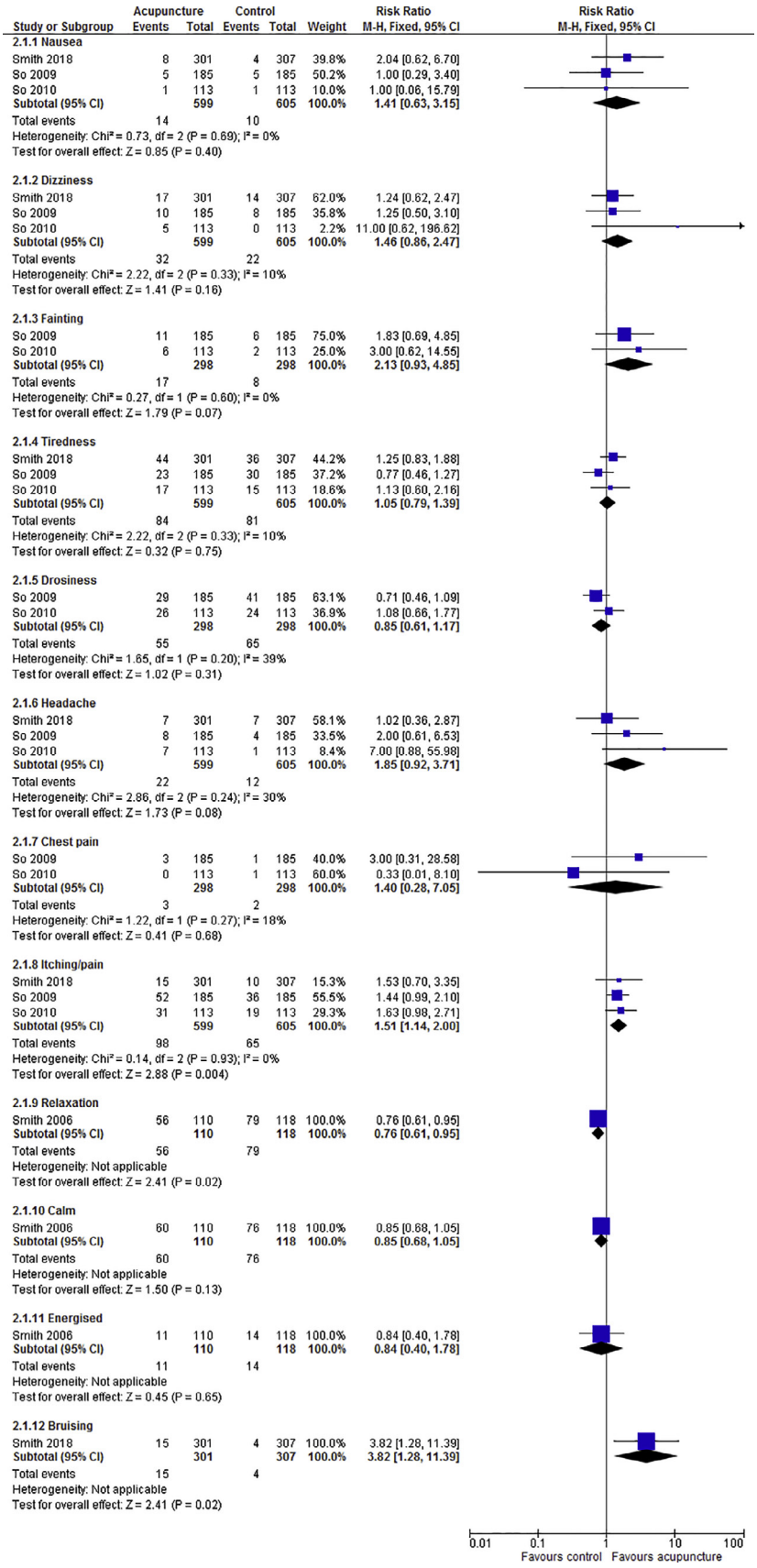

FIGURE 9 Effect of acupuncture versus control on side effects/adverse effects.

have broader application to the care and treatment modalities provided to women undergoing IVF. Further exploration of the effects of acupuncture for women with poorer IVF outcomes is warranted.

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