Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis

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Objective: To evaluate the effect of acupuncture on in vitro fertilization (IVF) outcomes.
Design: Systematic review and meta-analysis.
Patient(s): Women undergoing IVF in randomized controlled trials (RCTs) who were evaluated for the effects of acupuncture on IVF outcomes.
Setting: Not applicable.
Intervention(s): The intervention groups used manual, electrical, and laser acupuncture techniques. The control groups consisted of no, sham, and placebo acupuncture.
Main Outcome Measure(s): The major outcomes were clinical pregnancy rate (CPR) and live birth rate (LBR). Heterogeneity of the therapeutic effect was evaluated with a forest plot analysis. Publication bias was assessed by a funnel plot analysis.
Result(s): Twenty-four trials (a total of 5,807 participants) were included in this review. There were no significant publication biases for most of the comparisons among these studies. The pooled CPR (23 studies) from all of the acupuncture groups was significantly greater than that from all of the control groups, whereas the LBR (6 studies) was not significantly different between the two groups. The results were different when the type of control was examined in a sensitivity analysis. The CPR and LBR differences between the acupuncture and control groups were more obvious when the studies using the Streitberger control were ignored. Similarly, if the underlying effects of the Streitberger control were excluded, the LBR results tended to be significant when the acupuncture was performed around the time of oocyte aspiration or controlled ovarian hyperstimulation.
Conclusion(s): Acupuncture improves CPR and LBR among women undergoing IVF based on the results of studies that do not include the Streitberger control. The Streitberger control may not be an inactive control. More positive effects from using acupuncture in IVF can be expected if an appropriate control and more reasonable acupuncture programs are used. (Fertil Steril® 2012;97:599–611. ©2012 by American Society for Reproductive Medicine.)
Key Words: Acupuncture, pregnancy rate, in vitro fertilization

With rapid economic development, lifestyle changes, and increased environmental pollution, the incidence of infertility has gained increased worldwide attention. In vitro fertilization–embryo transfer (IVF-ET) is the most successful infertility treatment, and for many people, it provides the last possibility for pregnancy. However, the average IVF delivery rate per single initiated cycle using fresh nondonor oocytes is still only 33% (1). The majority of IVF cycles do not result in pregnancy, and multiple IVF cycles are generally needed to achieve pregnancy. Owing to the relatively low IVF success rate per cycle, some patients are not successful even after several ETs, even when the appropriate techniques for controlled ovarian hyperstimulation (COH), IVF, embryo culture and transfer, etc., are correctly performed. At the same time, the latent safety problems associated with using large doses of ovulation stimulants to obtain more eggs for IVF cannot be ignored (2). Furthermore, IVF is an expensive procedure, and some couples can afford only a limited number of treatments. Repeated cycles place enormous economic pressure on the patients and their families. Therefore, it is important to maximize the efficiency of the procedure (3). Many patients have turned to complementary and alternative medical (CAM) treatments to increase the success rate of IVF. Among these CAM treatments, acupuncture is a frequently used adjunctive therapy.

Acupuncture is an important part of traditional Chinese medicine (TCM)

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that dates back at least 3,000 years. Acupuncture can cure disease because it can stimulate the body's self-regulatory ability as characterized by integrity and ambidirectional dominance. Consumer surveys (4, 5) have shown that 7%–19% of the population in Europe has used acupuncture to treat various kinds of diseases. Acupuncture has also gained increased popularity in Western countries owing to its convenience, lack of side effects, and unique therapeutic effects.

As a method of treating disease, acupuncture is based on the principles of TCM meridians and acupoints. Meridians are the main and collateral channels of a network of passages through which vital energy circulates and along which acupoints are distributed. There are 14 main meridians, on which more than 400 acupoints are located. Acupoints are not isolated; they are special points on the surface of the body where the vital energy (qi and blood) of the viscera infuses. In other words, there are inherent relationships between acupoints and internal organs that correspond loosely to the organs of Western medicine. Therefore, diseases of the entrails may be reflected in acupoints through meridians, and acupuncture at acupoints can affect the corresponding organs through meridians. Traditional acupuncture involves inserting disposable sterilized needles into the skin at acupoints along the meridians. The needles can then be stimulated by hand or by a small electric current in the case of electroacupuncture (EA). In a conventional acupuncture treatment, four to ten points are needled for 15–30 minutes. Acupuncturists emphasize a sensation called "de qi," which is characterized both by the patient feeling soreness, numbness, or heaviness at the needling point or along the meridians and by the acupuncturist sensing a sinking and compactness below the needle; it is considered to be an important factor for obtaining therapeutic efficacy (6). Laser acupuncture is a new form of this treatment; it combines modern science and technology with traditional methods by using a low-energy laser beam to directly irradiate acupoints.

Since the first report by Stener-Victorin et al. (7) in 1999 suggesting that acupuncture can increase the clinical pregnancy rate (CPR) of IVF, the application of acupuncture to IVF has attracted great interest from the international community.

More than 40 clinical trials evaluating acupuncture in IVF have been performed in recent years. However, whether acupuncture improves IVF pregnancy rates is still a matter of debate. Some studies have suggested a positive impact from adding acupuncture to IVF, but others do not confirm this effect. Seven systematic reviews and meta-analyses of randomized controlled trials (RCTs) have investigated the ability of acupuncture to increase IVF success rates. However, these meta-analyses have led to contradictory conclusions.

The first meta-analysis was performed by Manheimer et al. (seven trials with 1,366 participants) and published in *BMJ* in February 2008 (8). The main conclusions of that study were that acupuncture given around ET improved the rates of clinical pregnancy, ongoing pregnancy, and live birth in women undergoing IVF. The second analysis was conducted by Ng et al. (10 trials with 2,003 subjects) and published in *Fertility and Sterility* in July 2008 (9); it clearly demonstrated that the IVF pregnancy rate was significantly increased, especially when the acupuncture was administered on the day of ET. The third analysis, published by Cheong et al. (6) in the *Cochrane Database of Systematic Reviews* in 2009 (13 trials with 2,300 participants), concluded that acupuncture performed on the day of ET increased live birth rates (LBRs) but did not increase CPRs or show beneficial effects on pregnancy outcomes when acupuncture was performed around the time of oocyte retrieval. The other four meta-analyses, published by El-Toukhy et al. in 2008 (13 trials, 2,500 participants) (10), Cheong et al. in 2010 (14 trials, 2,670 subjects) (11), El-Toukhy et al. in 2009 (12), and Sunkara et al. in 2009 (13) (14 trials, 2,870 subjects), could not confirm a beneficial effect from using acupuncture during IVF.

Why did these meta-analyses addressing the same question produce such different answers? Systematic reviews and meta-analyses are generally regarded to be the most reliable tool for summarizing the existing evidence. However, they often show differences in their results and conclusions. The most common reasons for these discrepancies are differences in inclusion criteria and methods of searching the literature, data extraction, and data analysis (14), though all of these aspects were considered in some way in these reviews. In particular, some older and even more recent RCTs were ignored in these analyses. Therefore, it is difficult to draw a definitive conclusion based on the published meta-analyses. Consequently, a new comprehensive systematic review and overall meta-analysis is indispensable for drawing more reliable conclusions on the ability of acupuncture to improve pregnancy outcomes when used as an adjunct in women undergoing IVF.

MATERIALS AND METHODS

Literature Search and Data Collection

We searched digital databases for relevant studies, including Pubmed (1977 to July 2011), Embase (1974 to July 2011), the Cochrane Library, and the Clinical Trials Register. We also searched Chinese databases, such as the Wanfang database (1998 to July 2011), CNKI database (1999 to July 2011), and VIP database (1989 to July 2011).

The following were used as free text terms and MeSH terms (shown in italics): acupuncture, electroacupuncture, acupuncture and moxibustion, acupoint and IVF, in vitro fertilization, and assisted reproductive (or reproduction) technology. We combined this search strategy with a filter for clinical trials.

The following terms were used in the Chinese database searches: "ZHEN JIU" (which means "acupuncture and moxibustion"); "ZHEN CI" (which means "acupuncture"); "TI WAI SHOU JING" (which means "in vitro fertilization"); "SHI GUAN YING ER" (which means "test tube baby"); and "IVF."

We also carefully scanned the references of relevant publications and added the relevant publications to the search. When questions arose related to the design or outcomes of the trials, the corresponding authors were contacted to confirm the information we extracted from their trials or to clarify any ambiguities.

Study Selection

All RCTs that evaluated the effects of acupuncture, including manual (MA), electrical (EA), and laser (LA) acupuncture techniques, on IVF outcomes in women undergoing IVF with or without intracytoplasmic sperm injection (ICSI) were considered. The control groups consisted of no, sham, and placebo acupuncture ("no acupuncture" meaning no adjunctive treatment). In principle, four styles of sham or placebo acupuncture exist: 1) superficial needling in true acupoints or in nonacupoints nearby; 2) true needling in nonacupoints or in acupoints thought not to influence fertility; 3) blunt (placebo) needling on the surface of true acupoints or nonacupoints nearby (e.g., Streitberger placebo acupuncture); and 4) sham LA in which the laser device does not emit light pulses. Neither the type, i.e., full article or abstract, nor language of the publication restricted the trials included in this study.

Retrospective studies, case series, and studies with a crossover design were excluded. RCTs without a clear description of at least one of the IVF outcomes, particularly those not describing the exact numbers of pregnancies (events) and initial setups (total), were also not considered.

The literature searching, study selection, data extraction, and statistical analysis were performed independently by two reviewers (Zheng and Zhang). Any disagreements about inclusions or analyses were resolved by consensus or arbitration by a third reviewer (Huang).

Data Extraction and Analysis

Specific characteristics were extracted from each study: method of randomization, allocation concealment, blinding, sample size, population features, intervention (e.g., acupuncture style, MA, EA, or LA), time of commencement, duration of treatment, type of control (no, sham, or placebo acupuncture), number of randomizations, and IVF outcomes.

The IVF outcomes consisted of the biochemical pregnancy rate (BPR; a positive hCG serum or urine test $\geq$11 days after ET), CPR (presence of at least one intrauterine gestational sac or fetal heartbeat confirmed by ultrasound 4–6 weeks after ET), ongoing pregnancy rate (OPR; pregnancy beyond 10 weeks of gestation, as confirmed by fetal heart activity on ultrasound), LBR (a baby born alive after 24 weeks gestation), implantation rate (IR; number of gestational sacs divided by number of transfered embryos), miscarriage rate (MR; [CP − OP]/CP), and any reported side effects from the treatment.

The pregnancy outcomes reported in these trials were pooled and expressed as odds ratios (OR) with 95% confidence intervals (CIs) in the Review Manager 5.1 meta-analysis software. Both the different control methods and the different acupuncture times were used for sensitivity subgroup analyses. We used a fixed-effects model for these meta-analyses if the heterogeneity for the trials' characteristics showed $P>.05$; otherwise, we used a random-effects model. All of the meta-analyses were based on both the number of women randomized and the number of women who completed ET. That is, we performed both an intention-to-treat analysis (ITT) and a treated-per-protocol analysis (TPP); the former would underestimate the effect of acupuncture, the latter overestimate it.

The heterogeneity of the therapeutic effects was evaluated graphically with the use of forest plot analysis and statistically by chi-square test. The publication bias was assessed by funnel plot analysis (R 2.0).

RESULTS

Thirty-one RCTs involving acupuncture and IVF were identified. Seven trials were excluded: Quintero et al 2004 (15), Udoff et al 2006 (16), Humaidan et al 2006 (17), Moy et al 2008 (18), Kong et al 2009 (19), Li et al 2009 (20), and Omodei et al 2010 (21). Although the study conducted by Quintero et al. (2004) was a randomized-control and double-blind trial, it was also a crossover pilot study using a needle-like device for the sham acupuncture control. Furthermore, data for the exact pregnancy events and totals were not available, because the trial used pregnancy rates only, which was also the reason for excluding the Udoff et al 2006, Moy et al 2008, and Omodei et al 2010 studies. Both the Humaidan et al 2006 and the Kong et al 2009 studies were RCTs, but the control was a real acupuncture group with only the stimulation parameter differing from the intervention group. The data on the number of canceled IVF cycles in Li et al 2009 was inconsistent, for which reason we excluded it.

Twenty-four trials (7, 22–44) (a total of 5,807 participants and 5,547 finished ETs; Table 1) were included in the analysis.

Publishing Form

Nineteen trials were published as full text, and five [Paulus et al 2003 (23), Benson et al 2006 (27), Craig et al 2007 (28), Fratterelli et al 2008 (30), and Arnoldi et al 2010 (39)] were published as abstracts. Twenty-two trials were published in English and two [Cui et al 2007 (29) and Chen et al 2009 (31)] in Chinese.

Country

The trials were conducted in nine different countries. Three of them were performed in fertility clinics in Germany [Paulus et al 2002 (22), Paulus et al 2003 (23), and Dieterle et al 2006 (26)], six were from the United States [Benson et al 2006 (27), Craig et al 2007 (28), Fratterelli et al 2008 (30), Domar et al 2009 (32), Magarelli et al 2009 (34), and Moy et al 2011 (40)] and one each was from Australia [Smith et al 2006 (24)], Brazil [Madaschi et al 2010 (38)], Italy [Arnoldi et al 2010 (39)], and Austria [Sator-Katzenschlager et al 2006 (44)]. Three studies were performed in Sweden [Gejervall et al 2005 (43), Stener-Victorin et al 1999 (7), and Stener-Victorin et al 2003 (41)], five were from China [Chen et al 2009 (Jinan) (31), Cui et al 2007 (Jinan) (29), Ho et al 2009 (Taiwan) (33), So et al 2009 (Hong Kong) (35), and So et al 2010 (Hong Kong) (36)], and three were from Denmark [Humaidan et al 2004 (42), Westergaard et al 2006 (25), and Andersen et al 2010 (37)].

TABLE 1

Characteristics of the studies included in this review.

Author	Main objective	Power calculation	Intervention			Control		Acupunc. juncture[a]	IVF outcome						Analysis
			MA	EA	LA	SC	OC		BPR	CPR	OPR	LBR	IR	MR	
1. Paulus 2002 (22)	IVF outcome	No	√				√	A		√					ITT
2. Paulus 2003 (23)	IVF outcome	No	√			√		A		√					ITT
3. Smith 2006 (24)	IVF outcome	Yes	√			√		A		√	√			√	ITT
4. Westergaard 2006 (25)	IVF outcome	Yes	√ (2)[b]				√	A	√	√	√		√	√	TPP
5. Dieterle 2006 (26)	IVF outcome	Yes	√				√	A	√	√	√		√	√	ITT
6. Benson 2006 (27)	IVF outcome	No	√		√		√ (3)[c]	A	√	√					ITT
7. Craig 2007 (28)	IVF outcome	No	√				√	A	√	√					TPP
8. Cui 2007 (29)	IVF outcome	No		√			√	C		√					ITT
9. Fratterelli 2008 (30)	IVF outcome	Unclear	√		√		√ (3)[c]	A	√	√	√				ITT
10. Chen J 2009 (31)	IVF outcome	No		√			√	C		√			√	√	ITT and TPP
11. Domar 2009 (32)	IVF outcome	No	√				√	A	√	√					ITT
12. Ho 2009 (33)	IVF outcome	No		√			√	C		√					ITT
13. Magarelli 2009 (34)	IVF outcome	Yes		√			√	C	√	√		√			ITT
14. So 2009 (35)	IVF outcome	Yes	√			√		A	√	√	√	√	√	√	ITT
15. So 2010 (36)	FET outcome	Yes	√			√		A	√	√	√	√	√	√	ITT
16. Andersen 2010 (37)	IVF outcome	Yes	√			√		A	√	√	√	√	√		ITT and TPP
17. Madaschi 2010 (38)	IVF outcome	Yes	√				√	A		√		√		√	ITT
18. Arnoldi 2010 (39)	IVF outcome	Unclear	√				√	C		√					ITT and TPP
19. Moy 2011 (40)	IVF outcome	Yes	√				√	A	√	√					TPP
20. Stener-Victorin 1999 (7)	Pain-relieving effect	No		√			√	B		√		√	√		TPP
21. Stener-Vctorin 2003 (41)	IVF outcome	Yes		√			√	B		√	√		√	√	TPP
22. Humaidan 2004 (42)	Pain-relieving effect	Yes		√			√	B		√					TPP
23. Gejervall 2005 (43)	Pain-relieving effect	Yes		√			√		√						ITT and TPP
24. Sator-Katzenschlager 2006 (44)	Pain-relieving effect	Yes	√	√			√	B		√					TPP
Total	20 IVF outcome, 4 pain-relieving effect	13 yes	16 (17)	9	2	5	19 (23)	14A 5B 5C	12	23	8	6	8	8	17 ITT, 11 TPP

Note: BPR = biochemical pregnancy rate; CPR = clinical pregnancy rate; EA = electroacupuncture; IR = implantation rate; ITT = intention-to-treat; MA = manual acupuncture; LA = laser acupuncture; LBR = live birth rate; MR = miscarriage rate; OC = other control; OPR = ongoing pregnancy rate; SC = Streitberger control; TPP = treated-per-protocol.

[a] A = acupuncture was performed around the time of embryo transfer; B = acupuncture was performed around the time of oocyte aspiration; C = acupuncture was mainly performed during the course of controlled ovarian hyperstimulation.

[b] Two MA groups.

[c] Three control groups.

Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

Centers

Four studies [Stener-Victorin et al 1999 (7) and 2003 (41), Craig et al 2007 (28), and Andersen et al 2010 (37)] were multicenter trials, but the remaining 20 studies were performed in a single center.

Objectives and Outcomes

Four of these trials [Stener-Victorin et al 1999 (7), Humaidan et al 2004 (42), Gejervall et al 2005 (43), and Sator-Katzenschlager et al 2006 (44)] were performed to evaluate the pain-relieving effects of acupuncture used around the time of oocyte aspiration (OA), and three of these four studies calculated the required sample size according to the primary objective rather than the secondary IVF outcome. The remaining 20 trials were designed to assess the effects of acupuncture on pregnancy rates from IVF, but only ten of them used a sample size sufficient to detect an effect on IVF outcomes between the study groups. Thirteen trials performed ITT analysis, seven performed TPP analysis, and four performed both ITT and TPP (Table 1).

Interventions and Controls

As presented in Table 1, 16 trials used MA as an adjunctive treatment, two of which also used LA as a second intervention group [Benson et al 2006 (27) and Fratterelli et al 2008 (30)], and Westergaard et al 2006 (25) used two MA intervention groups and one control group. Nine studies used EA.

Five studies used the Streitberger control. Smith et al 2006 (24) used sham acupuncture at points close to the real points, and Paulus et al 2003 (23), So et al 2009 (35) and 2010 (36), and Andersen et al 2010 (37) used sham acupuncture in a manner identical to the acupuncture used in the study group. Five studies used other forms of sham acupuncture. Dieterle et al 2006 (26) used an actual needling procedure on acupoints that were designed not to affect fertility, Benson et al 2006 (27) and Fratterelli et al 2008 (30) used sham LA, Sator-Katzenschlager et al 2006 (44) used adhesive tape instead of needles and no electrical stimulation, and Moy et al 2011 (40) used needles on non-qi lines. Sixteen studies used no intervention as the control group: Paulus et al 2002 (23), Westergaard et al 2006 (25), Benson et al 2006 (27), Craig et al 2007 (28), Cui et al 2007 (29), Fratterelli et al 2008 (30), Chen et al 2009 (31), Domar et al 2009 (32), Ho et al 2009 (33), Magarelli et al 2009 (34), Madaschi et al 2010 (38), Arnoldi et al 2010 (39), Stener-Victorin et al 1999 (7), Stener-Victorin et al 2003 (41), Humaidan et al 2004 (42), and Gejervall et al 2005 (43). Benson et al 2006 (27) and Fratterelli et al 2008 (30) had two intervention groups (MA and LA) and three control groups (sham LA, relaxation, and no intervention).

To simplify the statistical analyses, we combined all of the control groups that did not use the Streitberger approach into a single "other control" group, and Streitberger placebo acupuncture was considered to be a single control group.

Acupuncture Time

We divided the trials into three types according to their acupuncture times (Table 1). In type A, the acupuncture was performed around the time of ET. An example of type A is the study by Paulus et al 2002 (22), which performed two 25-minute sessions immediately before and after ET. In type B, the acupuncture was performed around the time of OA. An example of type B is the study by Stener-Victorin et al 1999 (7), which began $\geq$30 minutes before OA and terminated immediately after OA. In type C, the acupuncture was mainly performed during the course of COH, and four or more sessions were administered. An example of type C is the study by Ho et al 2009 (33), which administered treatments four times, twice a week for 2 weeks, from day 2 of the study to the day before OA. Another example is the study by Magarelli et al 2009 (34), who used nine electrostimulation acupuncture treatments before egg retrieval and one pre- and one post-ET treatment. There were a total of 14 type A trials, five type B trials, and five type C trials.

Quality of the Studies

Although all twenty-four of the studies were RCTs, few provided detailed information on the randomization procedure, allocation concealment, blinding of assessors, etc., which made assessing all of the potential sources of bias in these studies difficult. There was also significant clinical heterogeneity among the studies, which may have been attributable to variations in the acupuncture techniques (MA, EA, or LA), time of commencement, total dose of the intervention, method of control, acupoints, and patient populations across these studies.

Owing to the nature of acupuncture studies, absolute double blinding was often not possible. Some studies that used sham acupuncture for the control group came near to double blinding, whereas others that used no intervention as the control were completely nonblinded trials.

Funnel plot analysis showed that there were no significant publication biases for most of the comparisons (number of trials $\geq$3), except for "Acupuncture versus all controls: LBR, IR" and "Around OA: acupuncture versus all controls: CPR".

Comparisons of IVF Pregnancy Outcomes by Type of Controls

Comparisons with all control groups. BPR data were available from 12 trials (n = 3,640), but the statistical heterogeneity between the studies was found to be significant (P=.0001). Pooling the results of these 12 trials into the random-effects model showed no distinct BPR differences between all acupuncture groups and all control groups (P=.77; OR 1.04, 95% CI 0.79–1.38]).

CPR data [Fig. 1(i)] were available from 23 trials (n = 5,599). Again, there was significant heterogeneity between these trials (P=.0002). Using the random-effects model, the pooled results showed a clear difference between all acupuncture groups and all control groups (P=.04; OR 1.22, 95% CI 1.01–1.47).

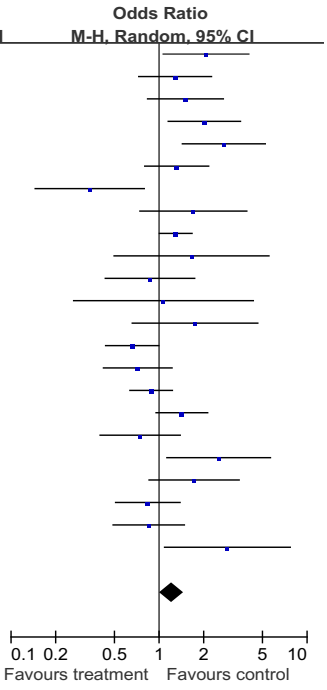
FIGURE 1

(i) Acupuncture vs. all controls

CPR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Paulus WE, 2002	34	80	21	80	4.1%	2.08 [1.07, 4.04]
Paulus WE,2003	43	100	37	100	4.8%	1.28 [0.73, 2.26]
Smith C, 2006	34	110	27	118	4.6%	1.51 [0.84, 2.72]
Westergaard LG, 2006	70	200	21	100	4.8%	2.03 [1.15, 3.55]
Dieterle S,2006	39	116	17	109	4.3%	2.74 [1.44, 5.22]
Benson MR,2006	54	106	67	152	5.3%	1.32 [0.80, 2.17]
Craig LB,2007	21	48	32	46	3.1%	0.34 [0.15, 0.79]
Cuiwei, 2007	22	47	16	47	3.2%	1.71 [0.74, 3.92]
Fratterelli JL,2008	213	402	278	598	7.4%	1.30 [1.01, 1.67]
Chen J,2009	9	28	6	27	1.9%	1.66 [0.50, 5.53]
Domar AD,2009	24	78	23	68	3.9%	0.87 [0.43, 1.74]
Ho Ming,2009	9	30	4	14	1.5%	1.07 [0.26, 4.34]
Magarelli PC,2009	17	34	12	33	2.6%	1.75 [0.66, 4.65]
So EW,2009	72	185	91	185	6.0%	0.66 [0.44, 0.99]
So EW,2010	41	113	50	113	5.1%	0.72 [0.42, 1.22]
Andersen D,2010	101	314	112	321	6.7%	0.88 [0.64, 1.23]
Madaschi C,2010	84	208	67	208	6.1%	1.43 [0.95, 2.13]
Moy I,2011	39	86	39	74	4.4%	0.74 [0.40, 1.39]
Arnoldi M,2010	22	102	10	102	3.3%	2.53 [1.13, 5.66]
Stener victorin E,99	28	75	19	74	3.9%	1.72 [0.86, 3.48]
Stener victorin E,03	43	136	49	138	5.3%	0.84 [0.51, 1.39]
Humaidan P,2004	46	100	50	100	4.9%	0.85 [0.49, 1.48]
Sator-K SM,2006	30	64	7	30	2.6%	2.90 [1.09, 7.71]
Total (95% CI)		**2762**		**2837**	**100.0%**	**1.22 [1.01, 1.47]**
Total events	1095		1055			

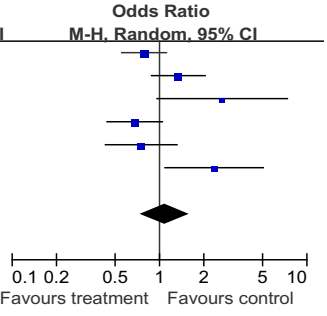
Heterogeneity: Tau² = 0.11; Chi² = 52.82, df = 22 (P = 0.0002); I² = 58%
Test for overall effect: Z = 2.04 (P = 0.04)



LBR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Andersen D,2010	79	314	96	321	21.5%	0.79 [0.56, 1.12]
Madaschi C,2010	70	208	57	208	20.0%	1.34 [0.88, 2.04]
Magarelli PC,2009	17	34	9	33	9.2%	2.67 [0.96, 7.39]
So EW,2009	55	185	71	185	19.7%	0.68 [0.44, 1.05]
So EW,2010	33	113	40	113	16.8%	0.75 [0.43, 1.32]
Stener victorin E,99	25	75	13	74	12.8%	2.35 [1.09, 5.05]
Total (95% CI)		**929**		**934**	**100.0%**	**1.09 [0.74, 1.60]**
Total events	279		286			

Heterogeneity: Tau² = 0.15; Chi² = 15.95, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 0.43 (P = 0.67)

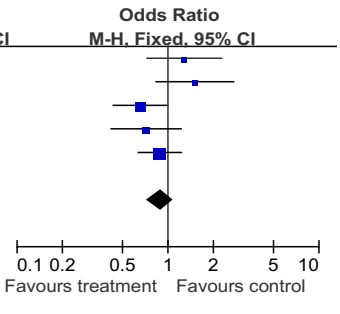


(ii) Acupuncture vs. Streitberger control

CPR

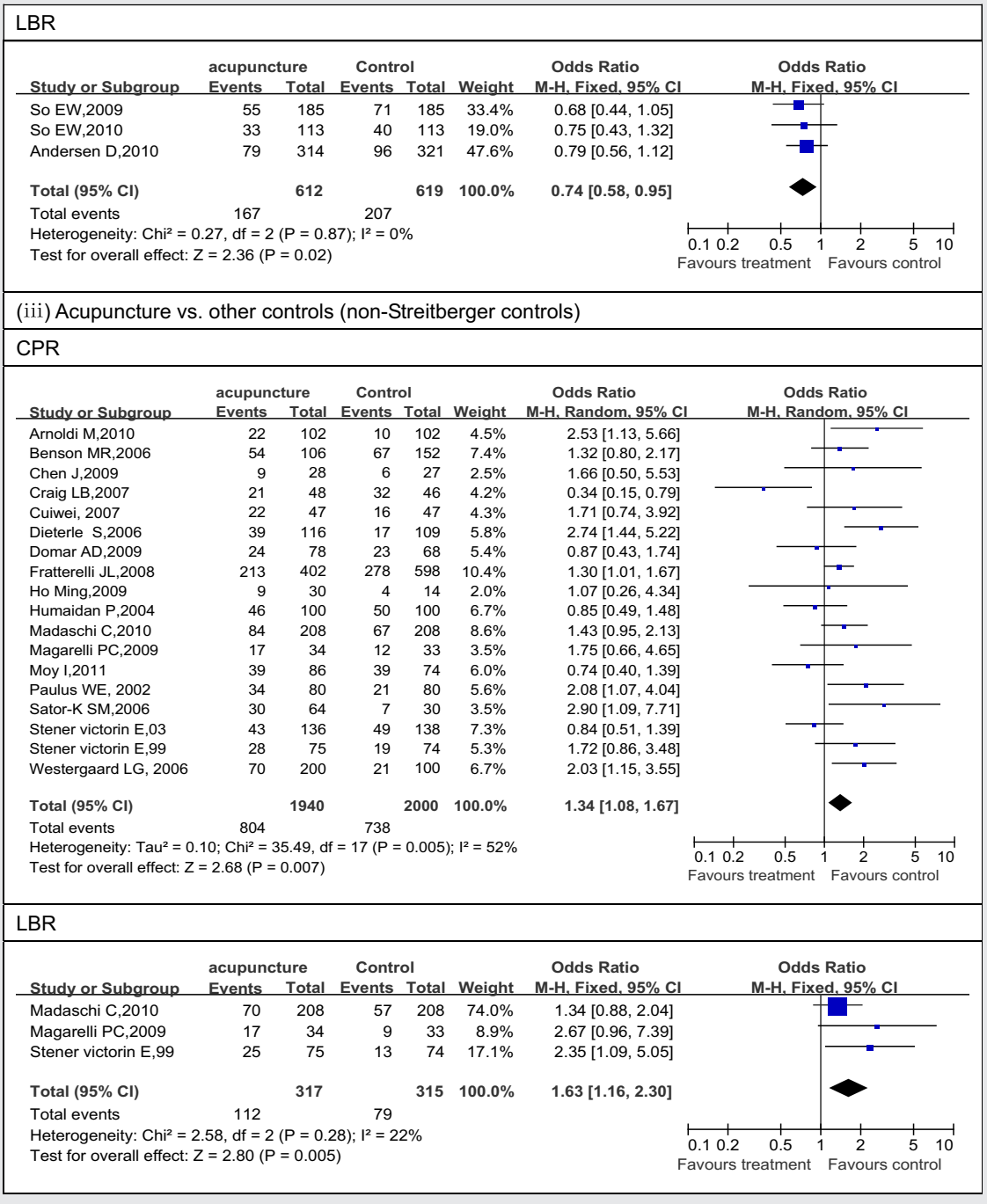
Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Paulus WE,2003	43	100	37	100	10.5%	1.28 [0.73, 2.26]
Smith C, 2006	34	110	27	118	8.9%	1.51 [0.84, 2.72]
So EW,2009	72	185	91	185	27.6%	0.66 [0.44, 0.99]
So EW,2010	41	113	50	113	15.8%	0.72 [0.42, 1.22]
Andersen D,2010	101	314	112	321	37.3%	0.88 [0.64, 1.23]
Total (95% CI)		**822**		**837**	**100.0%**	**0.89 [0.73, 1.09]**
Total events	291		317			

Heterogeneity: Chi² = 7.35, df = 4 (P = 0.12); I² = 46%
Test for overall effect: Z = 1.10 (P = 0.27)



Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

FIGURE 1 Continued



Forest plots of IVF outcomes compared by types of control. CPR = clinical pregnancy rate; LBR = live birth rate.

Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

OPR data were available from 8 trials (n = 3,258), and the results of the meta-analysis did not show a significant difference between all acupuncture groups and all control groups (*P*=.64; OR 1.07, 95% CI 0.81–1.42).

There were also no significant LBR [Fig. 1(i)], IR, and MR differences between all acupuncture groups and all control groups (LBR: 6 trials; n = 1,863; *P*=.67; OR 1.09, 95% CI 0.74–1.60; IR: 8 trials; n = 4,000; *P*=.37, OR 1.15, 95% CI 0.85–1.55; MR: 8 trials; n = 720; *P*=.70; OR 1.09, 95% CI 0.71–1.66).

Comparisons with Streitberger control. The pooled BPR, LBR, and IR results from only those studies that used the Streitberger control showed consistently significant comparisons with the respective intervention groups (BPR: 3 trials; n = 1,231; *P*=.004; OR 0.72, 95% CI 0.57–0.90;

LBR: 3 trials; n = 1,231; *P*=.02; OR 0.74, 95% CI 0.58–0.95; IR: 3 trials; n = 2,015; *P*=.04; OR 0.82, 95% CI 0.67–0.99).

The remaining IVF outcomes (CPR, OPR, and MR) showed no significant differences between the acupuncture groups and the Streitberger controls (CPR: 5 trials; n = 1,659; *P*=.27; OR 0.89, 95% CI 0.73–1.09; OPR: 4 trials; n = 1,459; *P*=.09; OR 0.82, 95% CI 0.66–1.03; MR: 3 trials; n = 315; *P*=.97; OR 0.99, 95% CI 0.54–1.81). The CPR and LBR results are shown in Figure 1(ii).

Comparisons with other controls. The pooled CPR, OPR, LBR, and IR results from the other (non-Streitberger) control groups were significantly lower than those from the respective intervention groups [CPR: 18 studies; n = 3.940; *P*=.007; OR 1.34, 95% CI 1.08–1.67; OPR: 4 studies; n = 1,799; *P*=.04; OR 1.23, 95% CI 1.01–1.51; LBR: 3 studies; n = 632; *P*=.005; OR 1.63, 95% CI 1.16–2.30; IR: 5 studies; n = 1,985; *P*=.04; OR 1.57, 95% CI 1.01–2.44; Fig. 1(iii)]. The pooled BPR and MR results showed no significant differences between the respective acupuncture groups and the other control groups (BPR: 9 trials; n = 2,409; *P*=.18; OR 1.25, 95% CI 0.90–1.72; MR: 5 trials; n = 405; *P*=.57; OR 1.19, 95% CI 0.65–2.17).

Owing to the controversy over whether LA should be included in the acupuncture group, we performed the analysis with the exclusion of the LA and the sham LA groups from Benson et al 2006 (27) and Fratterelli et al 2008 (30); the statistical significance did not change, however. Similarly, the results changed only slightly when we excluded the two studies that were not published in English [Cui et al 2007 (29) and Chen et al 2009 (31)].

Comparisons of IVF Pregnancy Outcomes by Different Acupuncture Times and Controls

Around the time of ET. The pooled BPR, CPR, OPR, LBR, IR, and MR results from the studies in which acupuncture was performed around the time of ET showed no significant differences between all acupuncture groups and all control groups [BPR: 10 studies; n = 3,414; *P*=.82; CPR: 14 studies; n = 4,418, *P*=.32; OPR: 7 studies; n = 2,984; *P*=.51; LBR: 4 studies; n = 1,647, *P*=.18; IR: 5 studies; n = 3,176; *P*=.88; MR: 6 studies; n = 613; *P*=.64; Fig. 2(i)].

The BPR, LBR [Fig. 2 (ii)], and IR were significantly lower in the acupuncture groups than in the Streitberger controls (BPR: 3 studies; n = 1,231; *P*=.004; OR 0.72, 95% CI 0.57–0.90; LBR: 3 studies; n = 1,231; *P*=.02; OR 0.74, 95% CI 0.58–0.95; IR: 3 studies; n = 2,015; *P*=.04; OR 0.82, 95% CI 0.67–0.99). The pooled CPR [Fig. 2(ii)], OPR, and MR results showed no differences between the acupuncture groups and the Streitberger controls (CPR: 5 studies; n = 1,659; *P*=.27; OPR: 4 studies; n = 1,459; *P*=.09; MR: 3 studies; n = 315; *P*=.97).

The pooled OPR results from the acupuncture groups were significantly higher than those from the other (non-Streitberger) control groups (3 studies; n = 1,525; *P*=.01; OR = 1.33, 95% CI 1.06–1.66). The other outcomes did not differ significantly between the acupuncture groups and the other controls [BPR: 7 studies; n = 2,183; *P*=.2; CPR: 9 studies; n = 2,759; *P*=.1; LBR: 1 studies; n = 416; *P*=.17; IR: 2 studies; n = 1161; *P*=.21; MR: 3 studies; n = 298; *P*=.45; Fig. 2(iii)].

Around the time of OA. The pooled BPR, CPR, OPR, LBR, IR, and MR results from the studies in which acupuncture was performed around the time of OA showed no significant differences between all acupuncture groups and all control groups (all controls = other controls, because there was no Streitberger control around the time of OA): BPR: 1 study; n = 159; *P*=.64; CPR: 4 studies; n = 717; *P*=.48; OPR: 1 study; n = 274; *P*=.47; LBR: 1 study; n = 142, *P*=.06; IR: 2 studies; n = 729; *P*=.34; MR: 1 study; n = 92; *P*=.81; Fig. 2(iv).

During the time of COH. The pooled BPR results were significantly higher in the acupuncture group than in the controls (2 studies; n = 271; *P*=.02; OR 2.07, 95% CI 1.12–3.82). The CPR, LBR, and IR results tended to be higher, although the differences did not reach statistical significance [CPR: 4 studies; n = 260; *P*=.08; LBR: 1 study; n = 67; *P*=.06; IR: 1 study; n = 95; *P*=.06; MR: 1 study; n = 15; *P*=.52; Fig. 2(v)].

All of the results presented above are based on the ITT analyses; the results of TPP analyses were similar to those of the ITT analyses.

Side Effects

There were no significant differences between the acupuncture and control groups in the various MR comparisons. None of the 24 trials reported evidence of ovarian hyperstimulation or of any treatment side effects.

DISCUSSION

Summary of Results

The quantity of trials included in this review was substantially higher than the quantity included in earlier reviews. Compared with earlier reviews, we added ten studies; one had positive results [Magarelli et al 2009 (34)], and nine had negative results [Cui et al 2007 (29), Fratterelli et al 2008 (30), Chen et al 2009 (31), Ho et al 2009 (33), So et al 2010 (36), Andersen et al 2010 (37), Madaschi et al 2010 (38), Arnoldi et al 2010 (39), and Moy et al 2011 (40)]. Therefore, the results of the present meta-analyses differ from the earlier meta-analyses.

In general, the results showed that the pooled CPR from all of the acupuncture groups was significantly higher than that from all of the control groups (*P*=.04). The difference was more obvious when the studies that used the Streitberger control were not considered (*P*=.007). The difference in LBR between the acupuncture and the other control groups was also obvious when the studies using the Streitberger control were excluded. Similarly, the LBR results were close to significant when the acupuncture was performed around the time of OA or COH and the underlying effect of the Streitberger control was excluded. However, this result needs further confirmation, because the number of trials in which the acupuncture was administered around the time of OA or COH was comparatively small, which limited the statistical significance.

The Streitberger needle is not fixed inside the copper handle. Its tip is blunt, and a pricking sensation, simulating the

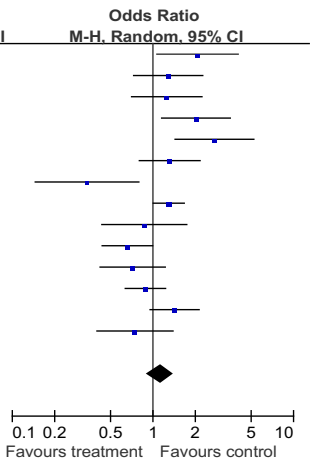
FIGURE 2

(i) Around ET: acupuncture vs. all controls

CPR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Paulus WE, 2002	34	80	21	80	5.9%	2.08 [1.07, 4.04]
Paulus WE,2003	43	100	37	100	6.8%	1.28 [0.73, 2.26]
Smith C, 2006	34	110	31	118	6.7%	1.26 [0.71, 2.23]
Westergaard LG, 2006	70	200	21	100	6.9%	2.03 [1.15, 3.55]
Dieterle S,2006	39	116	17	109	6.1%	2.74 [1.44, 5.22]
Benson MR,2006	54	106	67	152	7.5%	1.32 [0.80, 2.17]
Craig LB,2007	21	48	32	46	4.5%	0.34 [0.15, 0.79]
Fratterelli JL,2008	213	402	278	598	10.2%	1.30 [1.01, 1.67]
Domar AD,2009	24	78	23	68	5.6%	0.87 [0.43, 1.74]
So EW,2009	72	185	91	185	8.4%	0.66 [0.44, 0.99]
So EW,2010	41	113	50	113	7.1%	0.72 [0.42, 1.22]
Andersen D,2010	101	314	112	321	9.4%	0.88 [0.64, 1.23]
Madaschi C,2010	84	208	67	208	8.6%	1.43 [0.95, 2.13]
Moy I,2011	39	86	39	74	6.3%	0.74 [0.40, 1.39]
Total (95% CI)		**2146**		**2272**	**100.0%**	**1.12 [0.89, 1.42]**
Total events	869		886			

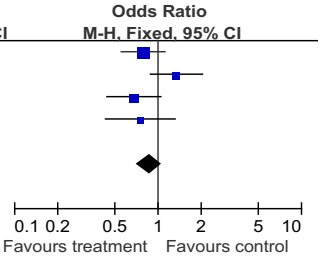
Heterogeneity: Tau² = 0.12; Chi² = 39.14, df = 13 (P = 0.0002); I² = 67%
Test for overall effect: Z = 1.00 (P = 0.32)



LBR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andersen D,2010	79	314	96	321	38.0%	0.79 [0.56, 1.12]
Madaschi C,2010	70	208	57	208	20.2%	1.34 [0.88, 2.04]
So EW,2009	55	185	71	185	26.7%	0.68 [0.44, 1.05]
So EW,2010	33	113	40	113	15.1%	0.75 [0.43, 1.32]
Total (95% CI)		**820**		**827**	**100.0%**	**0.87 [0.70, 1.07]**
Total events	237		264			

Heterogeneity: Chi² = 5.96, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 1.34 (P = 0.18)

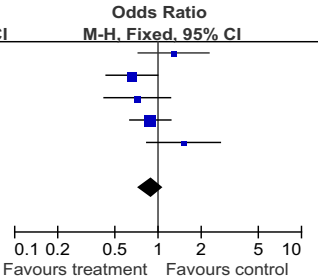


(ii) Around ET: acupuncture vs. Streitberger control

CPR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Paulus WE,2003	43	100	37	100	10.5%	1.28 [0.73, 2.26]
So EW,2009	72	185	91	185	27.6%	0.66 [0.44, 0.99]
So EW,2010	41	113	50	113	15.8%	0.72 [0.42, 1.22]
Andersen D,2010	101	314	112	321	37.3%	0.88 [0.64, 1.23]
Smith C, 2006	34	110	27	118	8.9%	1.51 [0.84, 2.72]
Total (95% CI)		**822**		**837**	**100.0%**	**0.89 [0.73, 1.09]**
Total events	291		317			

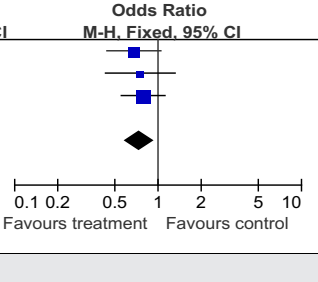
Heterogeneity: Chi² = 7.35, df = 4 (P = 0.12); I² = 46%
Test for overall effect: Z = 1.10 (P = 0.27)



LBR

Study or Subgroup	acupuncture Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
So EW,2009	55	185	71	185	33.4%	0.68 [0.44, 1.05]
So EW,2010	33	113	40	113	19.0%	0.75 [0.43, 1.32]
Andersen D,2010	79	314	96	321	47.6%	0.79 [0.56, 1.12]
Total (95% CI)		**612**		**619**	**100.0%**	**0.74 [0.58, 0.95]**
Total events	167		207			

Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

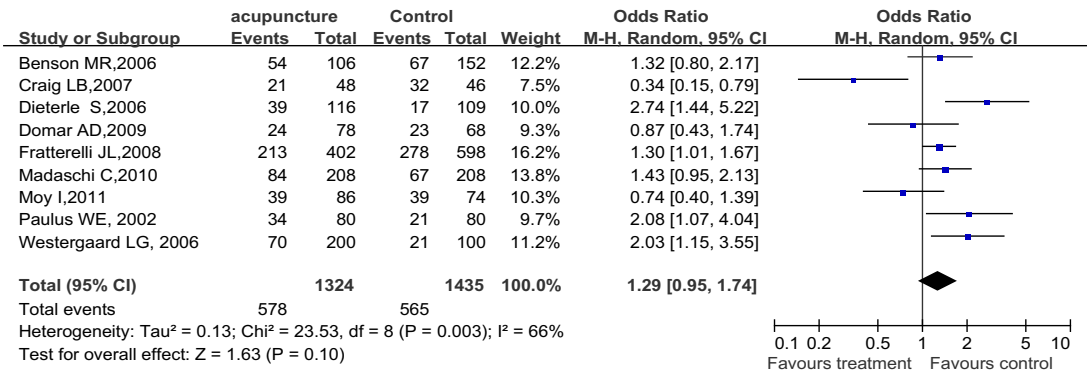


Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

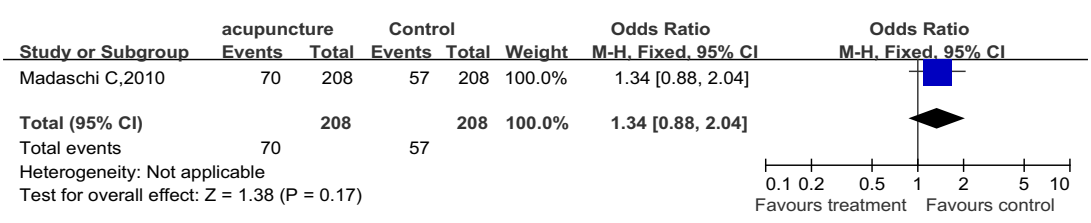
FIGURE 2 Continued

(iii) Around ET: acupuncture vs. other controls (non-Streitberger controls)

CPR

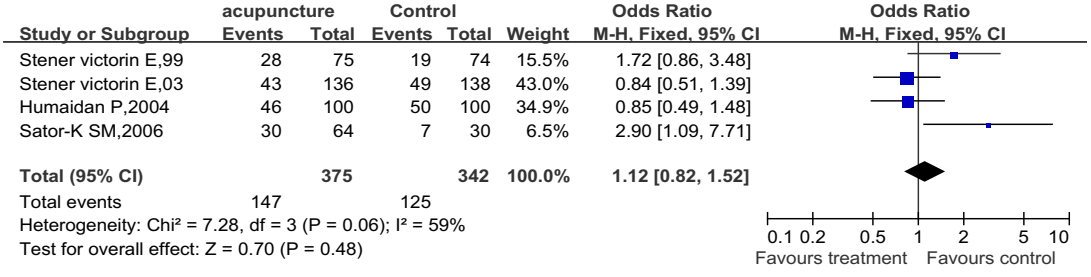


LBR

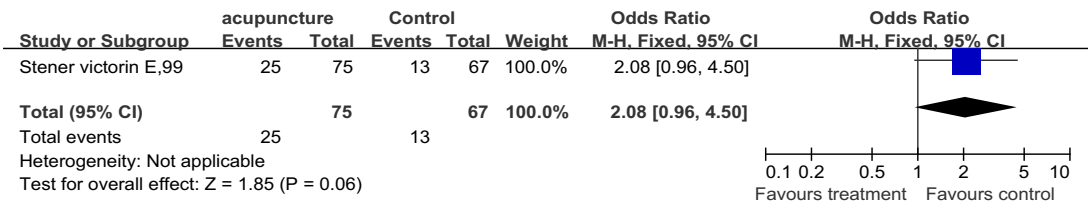


(iv) Around OA: acupuncture vs. all controls (here, all controls=other controls)

CPR



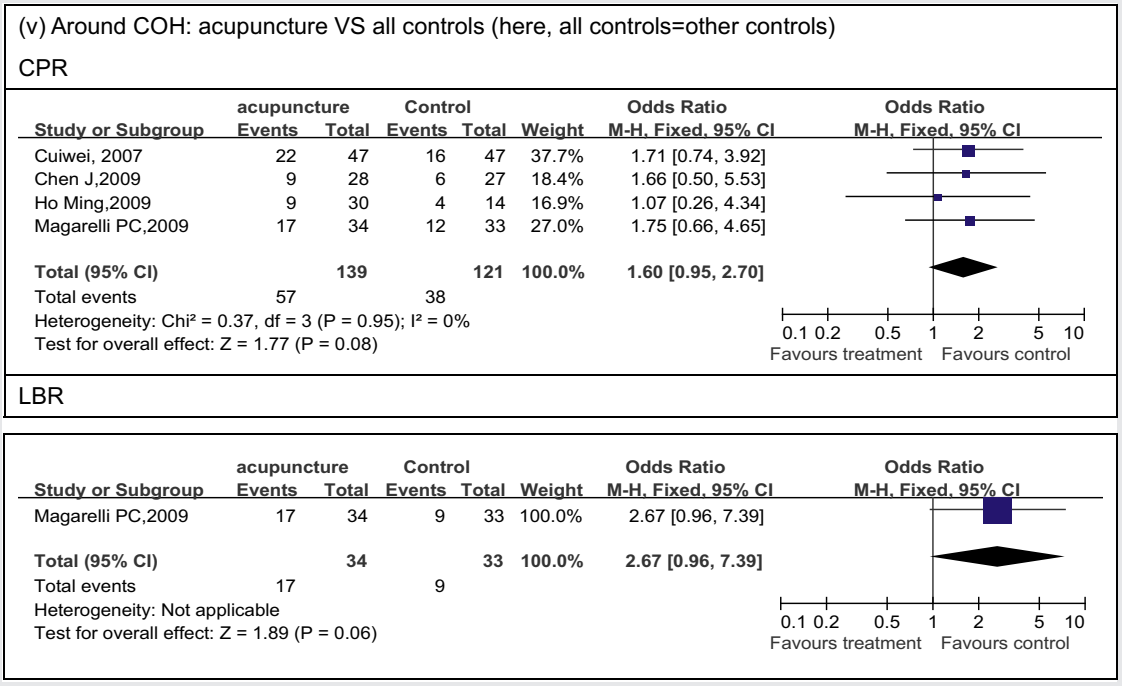
LBR



Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

puncturing of the skin, is felt by the patient when it touches the skin. The needle moves inside the handle and appears to be shortened. This noninvasive placebo acupuncture has been thought to be the best control for acupuncture studies. Based on the results of this review, however, there are strong indications that this placebo approach may not be an inert control. Just as the patient cannot feel the pricking sensation if the placebo technique is too mild, the acupressure effect (35) cannot be eliminated when the pressure is too heavy. Therefore, the noninvasive placebo needle used in some studies

FIGURE 2 Continued



Forest plots of IVF outcomes compared by different acupuncture times and controls. CPR = clinical pregnancy rate; LBR = live birth rate; ET = embryo transfer; OA = oocyte aspiration; COH = controlled ovarian hyperstimulation.

Zheng. Effects of acupuncture on IVF pregnancy rates. Fertil Steril 2012.

may have elicited physiologic effects similar to those of acupressure. Why did the acupuncture group have lower LBR odds than the Streitberger control group? On the one hand, it may have been due to the acupressure effect. On the other hand, the minimally invasive stimulation of acupuncture is often accompanied by some degree of discomfort or pain, which may have induced a harmful response. Therefore, the harmful reaction produced by real acupuncture can be avoided by this noninvasive stimulation, and patients may find this treatment more physiologically and psychologically acceptable. Therefore, the Streitberger control group may have had a higher LBR. From this result we can infer that increasing the intensity of the stimulation at acupoints (as occurs in the Streitberger group) in the adjunctive treatment, such as occurs in acupressure and transcutaneous electrostimulation, should be considered. It is likely that better therapeutic effects can be achieved in this manner.

Study Limitations

There were large heterogeneities among these clinical trials, especially in acupuncture treatment and acupoint selection. Both ancient and modern acupuncture books clearly emphasize that needling at some acupoints, such as Sanyinjiao, Jianjin, and Zhiyin, is not appropriate for pregnant women, because an abortion may result. Therefore, using acupuncture in IVF to improve and increase the pregnancy rate expands traditional acupuncture beyond its original application range. However, the acupuncture times and acupoints in these clinical trials were determined by the acupuncturists based on their experience, and they were not certain of the curative effect. Different acupuncture schemes may result in different clinical effects. Even slight changes may lead to quite different clinical effects in some trials. In Craig et al 2007 (28), for example, the acupuncture scheme was based on one reported by Paulus et al 2002 (22), and only two acupoints were added; however, the results of the two studies were contradictory, although the acupuncture sites were different. Of course, the different acupuncture sites may be another influencing factor.

In addition, most of the courses of acupuncture treatment were too short to completely correct infertility states caused by long-term insufficiency or imbalance. Furthermore, the acupuncture programs lacked syndrome differentiation and treatment according to individual characteristics. The mechanisms of acupuncture in infertility treatment have been reported to possibly relate to hormone regulation, increased ovarian and uterine blood flow, inhibited uterine motility, increases in endometrial thickness, and stress reduction (45). Therefore, the discrepancies observed in various studies may be due to the specific indications for acupuncture treatment within the study populations not being specified. Some experts have proposed that better therapeutic efficacy can be achieved by performing a more individualized acupuncture program (46).

Placebo control is commonly used in clinical trials to exclude psychologic factors. However, it is difficult to establish a reasonable and suitable control in clinical acupuncture research; therefore, various acupuncture effects have been questioned. The Streitberger technique is widely accepted as the most reasonable control method; however, several trials

have suggested that this control is not completely inert. If the sham is not an inert placebo but rather an active treatment that may affect the pregnancy outcome, using sham acupuncture as the control may confuse rather than clarify the interpretation of the effects of acupuncture on IVF outcomes (47).

Given these peculiarities of acupuncture therapy, there is a controversy concerning the correct acupuncture placebo control group for use in studies of acupuncture in IVF. However, we strongly encourage active exploration of a reasonable and reliable acupuncture control method. Superficial needling in irrelevant acupoints or nonacupoints, which should not influence fertility according to TCM theory, is one of the possibilities.

CONCLUSION

This review indicates that acupuncture improves CPR and LBR among women undergoing IVF based on the results of the studies that do not include the Streitberger control, and that the Streitberger control may not be an inactive control. More positive effects from acupuncture in IVF can be expected if an appropriate control and more individualized acupuncture programs are used. Superficial needling in irrelevant acupoints or nonacupoints is one of the possibilities for control. Appropriate acupuncture times (around the time of COH or OA or through the time of COH to the time of OA), enough treatment courses (at least four sessions) and syndrome differentiation and treatment according to individual characteristics should be strongly considered in the acupuncture programs. We could design several different acupuncture groups in parallel for further observation to optimize the best program.

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