Systematic Review and Meta-Analysis

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Acupuncture for infertile women without undergoing assisted reproductive techniques (ART)

A systematic review and meta-analysis

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Abstract

Background: Acupuncture is widely used for infertile women without undergoing assisted reproductive techniques (ART) in China but its effect is unclear. We aim to assess whether acupuncture and its combined therapy exert a positive influence on the outcome of female fertility.

Methods: We searched 6 databases, including Medline, EMBASE, the Cochrane Central Register of Controlled Trials, the China National Knowledge Infrastructure (CNKI), the China Science and Technology Journal Database (VIP), and Wan-Fang Data, from inception to June 2018. Studies of randomized controlled trials (RCTs) on women with infertility treated by acupuncture or its combined therapy were included. A meta-analysis was performed using Revman 5.3. The methodological quality of the studies was assessed through the risk of bias assessment tool by the Cochrane Collaboration.

Results: The pregnancy rate was significantly improved with treatment (RR = 1.84, 95% CI 1.62 to 2.10, $P < .00001$), compared to that in the control group. Subgroup analysis showed that comparing with pure western medicine intervention, no matter intervention with acupuncture alone, with acupuncture plus western medicine, with acupuncture plus Chinese medicine, or acupuncture plus Chinese medicine and western medicine, all of these subgroups exhibited significant improvement. The subgroup according to different types of infertility showed a significant improvement in infertility caused by polycystic ovary syndrome, tubal infertility, ovulatory disorder, and other factors. In addition, the ovulation rate and endometrial thickness were significantly increased. The level of LH was obviously decreased. Moreover, with acupuncture, less adverse effects occurred. The funnel plot revealed that publication bias might exist. All trials included had unclear risks in the aspects of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, and other bias. Only 1 study was assessed as unclear risk in random sequence generation. In the incomplete outcome data, all studies were low risk, except 1.

Conclusions: Acupuncture and its combined therapy may be effective for treating female infertility. However, the included studies are not robust enough to draw a firm conclusion due to the not robustly sampled quality of the included studies. Future high-quality RCTs are needed to confirm our findings.

Abbreviations: ART = assisted reproductive techniques, CNKI = the China National Knowledge Infrastructure, VIP = the China Science and Technology Journal Database, RCTs = randomized controlled trials, CI = confidence interval, COS = controlled ovarian stimulation, IUI = intrauterine insemination, IVF = in vitro fertilization, CAM = complementary and alternative medicine, TCM = traditional Chinese medicine, LH = luteinizing hormone, FSH = follicle stimulating hormone, RR = relative risk, ET = embryo transfer, PCOS = polycystic ovary syndrome, OHSS = ovarian hyperstimulation syndrome, LUFS = luteinized unruptured follicle syndrome, HPRL = hyperprolactinemia, HCG = human chorionic gonadotrophin, ECG = Electrocardiograph.

Keywords: acupuncture, female infertility, meta-analysis, systematic review

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1. Introduction

Infertility is a disease of the reproductive system defined as the lack of conception after self-reported on the 1 year period without using any birth control.[1] Approximately 12% to 15% of couples at reproductive age are affected by infertility around the world.[2] It has been reported that infertility is an underobserved yet significant public health issue that results in social, psychological, and economic consequences.[3–5] Although the underlying problem lies with the male in more than 50% of all cases of global childlessness, infertility is still a social burden for women.[6] Ovulatory disorders, endometriosis, pelvic adhesion, tubal blockage and other tubal abnormalities, hyperprolactinemia, and congenital (septate uterus) and acquired (myomas and synechiae) uterine abnormalities have contributed to the main causes of female infertility.[7,8] Conventional therapies, including clomiphene citrate, human menopausal gonadotropin, follicle-stimulating hormone, human chorionic gonadotropin, gonadotropin-releasing hormone analogs, aromatase inhibitor, and metformin, are used to treat female infertility.[9,10] However, some drugs used to treat infertility may increase the risk of cancer [11–15] or have unknown pharmacological effects when used to treat infertile women aged 40 years or older.[16,17] The current method for the treatment of infertility is ART, including controlled ovarian stimulation (COS) with or without intrauterine insemination (IUI) and in vitro fertilization (IVF). Although the use of ART has improved the prospects of infertility treatment, the success rates are still approximately 30% per cycle, and failure can lead to heavy financial and psychological burdens on the family and society.[18,19]

Due to limitations of the treatment effectiveness of Western medicine, the use of complementary and alternative medicine (CAM) in reproductive endocrinology and infertility has gained increasing popularity worldwide,[20] and acupuncture and its combined therapy are particularly popular options. Acupuncture, involving the insertion of needles into the skin along the meridians, contributes to an integral part of traditional Chinese medicine (TCM). A number of systematic reviews have been performed over the years to assess the effect of acupuncture on live birth rates in IVF.[21–23]

However, comprehensive meta-analysis evidence showing the therapeutic effect and safety of acupuncture for female infertility is still lacking. The important outcomes of acupuncture, including ovulation rate, endometrial conditions, and hormonal changes, have not been well investigated in RCTs. Hence, we aim to summarize and critically evaluate the currently available evidence from RCTs of acupuncture for the treatment of infertility.

2. Methods

2.1. Identification and eligibility of studies

A comprehensive search was performed without restriction of year of publication. Medline, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from database inception through June 2018. The Chinese language database, the China National Knowledge Infrastructure, the China Science and Technology Journal Database, and Wan-Fang Data were searched up to June 2018. Appendix I, http://links.lww.com/MD/D122 provides the search strategy adjusted for each database.

2.2. Study selection

2.2.1. Types of studies. All published randomized controlled trials in English or Chinese language were scrutinized in this study. We excluded nonrandomized trials, quasi-experimental studies, and all observational studies because they are associated with a high risk of bias.

2.2.2. Types of participants. Participants were included if the following criteria were met:

1. Women aged 20–40 years.
2. A husband with semen of normal quality and shape.
3. Women who failed to conceive with unprotected sexual life for 1 year.
4. Women with a gynecological diagnosis of infertility.
5. Women not receiving treatment by assisted reproductive technology.

2.2.3. Types of interventions. The experimental group received acupuncture or its combined therapy, and the control group received other standard therapies, such as injected Western drugs and oral Western medication.

However, we did not include studies in which the intervention of the control group was not clearly recommended according to the latest NICE guidelines.

2.2.4. Types of outcome measurements. Primary outcomes included pregnancy rate, which was confirmed with a pregnancy test and ultrasound. Secondary outcomes included ovulation rate, endometrial thickness, endocrine indexes, such as luteinizing hormone (LH) and follicle stimulating hormone (FSH), and adverse events.

2.3. Risk of bias assessment

Two reviewers (L.Y. and W.L.Q.) independently performed a risk of bias assessment of the included RCTs using the Cochrane risk-of-bias tool[24] and the following criteria: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any disagreements were resolved by discussion. Every criterion was rated as 'low' (low risk of bias), 'high' (high risk of bias), or 'unclear' (uncertain risk of bias).

2.4. Data extraction

After an initial screening of the titles and abstracts retrieved from the electronic databases, conducted by L.Y. and W.L.Q, the whole content of all potentially eligible studies was analyzed. For each enrolled study, the following characteristics were extracted: topic, author, dateline, study design, participants, treatment regime, control intervention, outcome measures, and adverse events reported.

2.5. Statistical analysis

All statistical analyses were performed using Reviewer Manager Software, version 5.3 (Cochrane Collaboration, Oxford, UK). The relative risk (RR) and 95% confidence intervals (CIs) were calculated for the dichotomous data (pregnancy and ovulation rates). Continuous data (LH, FSH, and endometrial thickness) are presented as the mean differences with 95% CIs. The statistical heterogeneity in the RCTs was examined based on the I^2 test; $I^2 \geq 50\%$ indicated substantial heterogeneity.[25] Because a small number of component studies may limit the

Table 1

Characteristics of the included studies.

Study ID	Participants (infertility types)	Sample (Experimental/ Control)	Intervention		Outcomes
			Experimental	Control	
Chai 2017[27]	PCOS infertility	46/46	Diane-35, metformin, Guishen Pill orally and acupuncture	Diane-35, metformin and placebo orally	⑥
Chen 2018[28]	Ovulation aplastic infertility	35/35	Acupuncture	Clomiphene orally and HCG intramuscularly	②
Dai 2017[29]	PCOS infertility	50/48	Metformin and clomiphene orally combined with acupuncture and auricular point sticking	Metformin and clomiphene orally	②③④
Du 2014[30]	PCOS infertility	41/41	Traditional Chinese medicine orally and acupuncture	Clomiphene orally	②⑥
Duan 2017[31]	HPRL infertility	30/30	Traditional Chinese medicine orally and thermal moxibustion	Bromocriptine orally	①②③④⑤⑥
Fang 2017[32]	Ovulation aplastic infertility	40/40	Zhuang medicine medicated thread moxibustion and Zhuang medicine orally	Clomiphene orally	②⑤⑥
Hu 2014[33]	HPRL infertility	30/30	Bromocriptine plus with clomiphene orally, combined with acupuncture	Bromocriptine plus with clomiphene orally	⑥
Li 2016[34]	PCOS infertility	20/20	Herb-partitioned moxibustion	Clomiphene orally	②
Liang 2015[35]	PCOS infertility	30/30	Clomiphene orally and acupuncture	Clomiphene orally	②③④⑥
Lin 2018[36]	PCOS infertility	30/30	Acupuncture	Clomiphene orally	②③
Liu 2012[37]	Luteal insufficiency infertility	30/30	Traditional Chinese medicine orally and acupuncture	Progesterone capsule orally	①⑤
Liu 2016[38]	Ovulation aplastic infertility	30/30	Traditional Chinese medicine orally and moxibustion	Clomiphene orally	①⑤
Qin 2018[39]	PCOS infertility	40/40	Clomifene citrate tablets and traditional Chinese medicine orally, with acupuncture	Clomifene citrate tablets and ethinylestradioland cyproterone acetate tablets orally	②③④⑤
Wang 2017[40]	Tubal obstruction infertility	30/30	Traditional Chinese medicine orally, rectal perfusion and acupuncture	Fallopian tube injection of gentamicin, dexamethasone, chymotrypsin, sodium chlorideL	
Xu 2014[41]	PCOS infertility	128/122	Traditional Chinese medicine orally and moxibustion	Ethinylestradiol and cyproterone acetate tablets	③④
Xu 2018[42]	PCOS infertility	30/30	Diane-35 orally and acupuncture	Diane-35 orally	①②③④⑤⑥
Yang 2017[43]	LUFS infertility	32/32	Acupuncture and auricular point sticking	HCG intramuscularly	①②
Yin 2018[44]	PCOS infertility	40/40	Diane-35, letrozole and traditional Chinese medicine orally and electroacupuncture	Diane-35 and letrozole orally	②⑥
You 2018[45]	All kinds of infertility	20/20	Acupuncture, warming-needle moxibustion or electroacupuncture	Progynova orally	⑤
Yuan 2016[46]	PCOS infertility	60/58	Diane-35 and clomiphene orally and HCG intramuscularly, combined with traditional Chinese medicine orally and acupuncture	Diane-35 and clomiphene orally and HCG intramuscularly	②③④⑤⑥
Zhu 2017[47]	PCOS infertility	45/45	Clomiphene citrate orally, HCG intramuscularly and electroacupuncture	Clomiphene citrate orally and HCG intramuscularly	②⑥
Zhuo 2017[48]	Ovulation aplastic infertility	30/30	Traditional Chinese medicine orally and acupuncture	Clomiphene orally and HCG intramuscularly	②⑤

pregnancy rate ② ovalution rate ③ LH ④ FSH ⑤ endometrial thickness ⑥ adverse events PCOS = polycystic ovary syndrome, LUFS = luteinized unruptured follicle syndrome, LH = luteinizing hormone, FSH = follicle stimulating hormone.

validity of the heterogeneity tests, we used a random-effects model, even when low heterogeneity was detected. A funnel plot was used to assess publication bias in the case that there were >10 trials included in the meta-analysis.[26] Sensitivity analyses were conducted for primary outcomes.

The analyses used in this paper were based on previous published studies, no ethical approval and patient consent are required.

3. Results

3.1. Study Selection

We found a total of 4746 relevant articles by the initial searches from the relevant databases. At first, 1782 duplicate publications were excluded. Among the 2964 potential articles, 2556 articles were removed by reading the title and the abstract. A total of 514 full-text publications were evaluated for eligibility. A total of 492 articles were further removed because they did not meet the inclusion criteria. Finally, 22 trials with a total of 2591 participants were included in this systematic review.[27–48]

3.2. Description of Studies

The characteristics of the included studies in this review are shown in Table 1. The 22 included studies were all conducted in China. One article (4.5%)[45] was reported in the English database, and the remaining articles (95.5%) were reported in the Chinese database.

All subjects included in this study were diagnosed with infertility. Twelve (54.5%) of the included studies[27,29,30,34–36,39,41,42,44,46,47] investigated infertility related to polycystic ovarian syndrome. Four (18.18%) studies[28,32,38,48] investigated infertility related to ovulation with vaginal-uterine aplasia. One (4.5%) study[40] investigated infertility related to tubal obstruction. One (4.5%) study[37] investigated infertility related to luteal insufficiency. Two (9.1%) studies[31,33] investigated infertility related to HPRL. One (4.5%) study[43] investigated infertility related to luteinized unruptured follicle syndrome (LUFS). One (4.5%) study[45] investigated all kinds of infertility.

As for intervention, 5 studies (22.7%)[29,33,35,42,47] examined acupuncture plus therapies of the control groups, 4 studies (18.2%)[27,39,44,46] examined acupuncture combined with TCM based on therapies in the control groups, five studies (22.7%)[28,34,36,43,45]examined acupuncture therapy alone in the intervention group, and eight studies (36.4%)[30–32,37,38,40,41,48] examined acupuncture plus TCM in the intervention group. Altogether, the control groups varied and included placebo, Chinese herbal medicine, Western medicine, physiotherapy, and laparoscopic surgery.

Of the included studies, 20 trials (90.9%)[27–33,35–38,39,40–44,46–48]reported the impact on pregnancy rate, 15 trials (68.2%)[28–32,34–36,39,42–44,46–48] reported the impact on ovulation rate, 8 trials (36.4%)[29,31,35,36,39–42,46] reported the changes in LH, 7 trials (31.8%)[29,31,35,39,41,42,46]reported the changes in FSH, 9 trials (40.9%)[31,32,37–39,42,45,46,48]reported the changes in endometrial thickness, and 10 trials (50%)[27,30–33,35,42,44,46,47] reported adverse effects.

3.3. Assessment for risk of bias

The risk of bias evaluation for each included RCT is summarized in Figure 1. Randomization was shown in all studies, apart from 1 RCT,[45] which did not report the method of randomization, rated as unclear risk of bias. The remaining 21 trials[27–44,46–48] adopted computerized randomization or a random number table to produce random sequence, rated as low risk of bias. None of the trials reported allocation concealment, so we cannot assess whether this step was included, and this domain was classified as an unclear risk of bias. Participants, personnel and outcome assessments were not mentioned as blinded in any trial and were therefore recognized as having an unclear risk of bias. Selective reporting of all included RCTs was assessed as low risk of bias, except for one trial,[46] which reported dropouts but did not state the reasons and thus was rated as an unclear risk of bias. Furthermore, the other types of biases (e.g., drug company sponsorship of the study) were rated as unclear risks of bias due to a lack of available evidence.

3.4. Pregnancy rate

The results of the meta-analysis of the primary outcome measure, pregnancy rate, are shown in Figures 2 and 3. All 20 trials, [27–33,35–38,39,40–44,46–48] including 1644 patients with infertility, were evaluated for pregnancy rate. There was a total of 827 patients in the experimental groups and 817 patients in the control groups. A heterogeneity test ($\chi^2 = 12.18$, $P = .88$, $I^2 = 0\%$) indicated moderate statistical heterogeneity between studies. Thus, a fixed-effect model was used to calculate the combined RR and 95% CI (RR = 1.84, 95% CI 1.62 to 2.10, $P < .00001$). The results of the meta-analysis showed a statistically significant increase in the pregnancy rate between the experimental and control groups, indicating that with acupuncture, the pregnancy rate can be significantly increased. According to different types of intervention and different types of infertility, the studies were divided into subgroups.

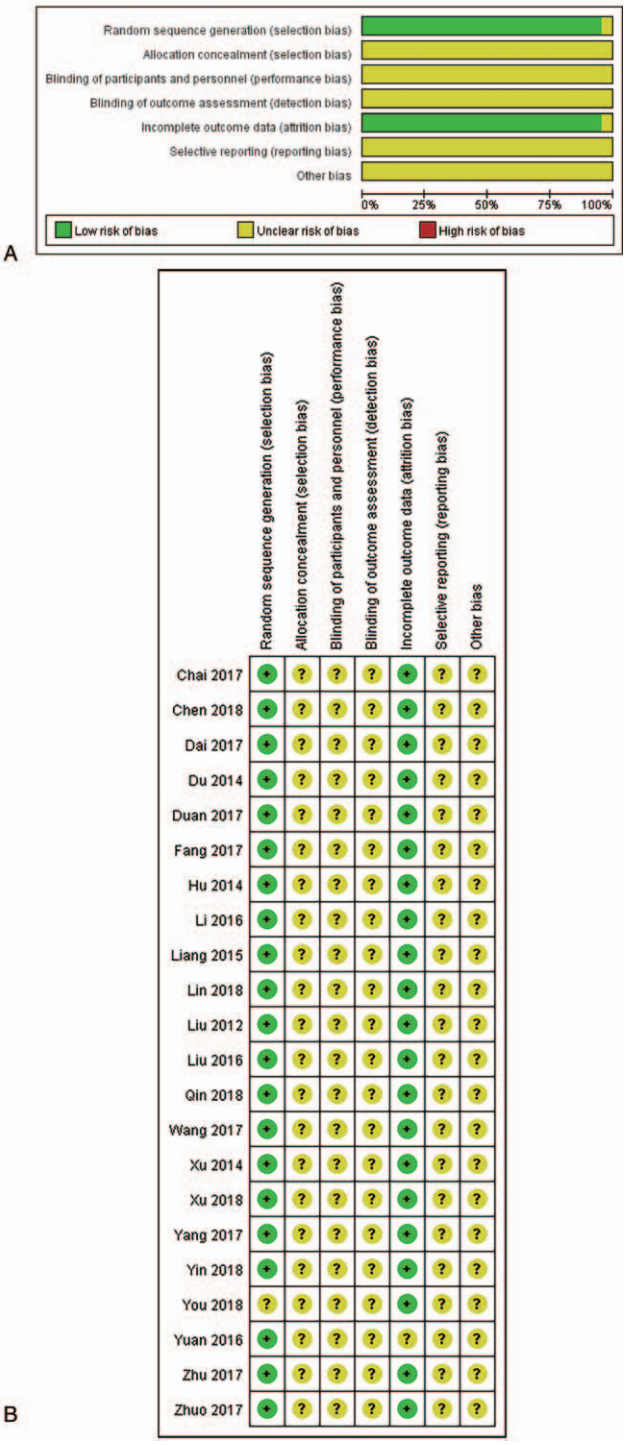

Figure 1. Assessment of risk of bias: (A) Risk of bias graph and (B) risk of bias summary.

3.4.1. Different types of intervention. According to Figure 2, 5 RCTs reported the pregnancy rate intervened by acupunc-

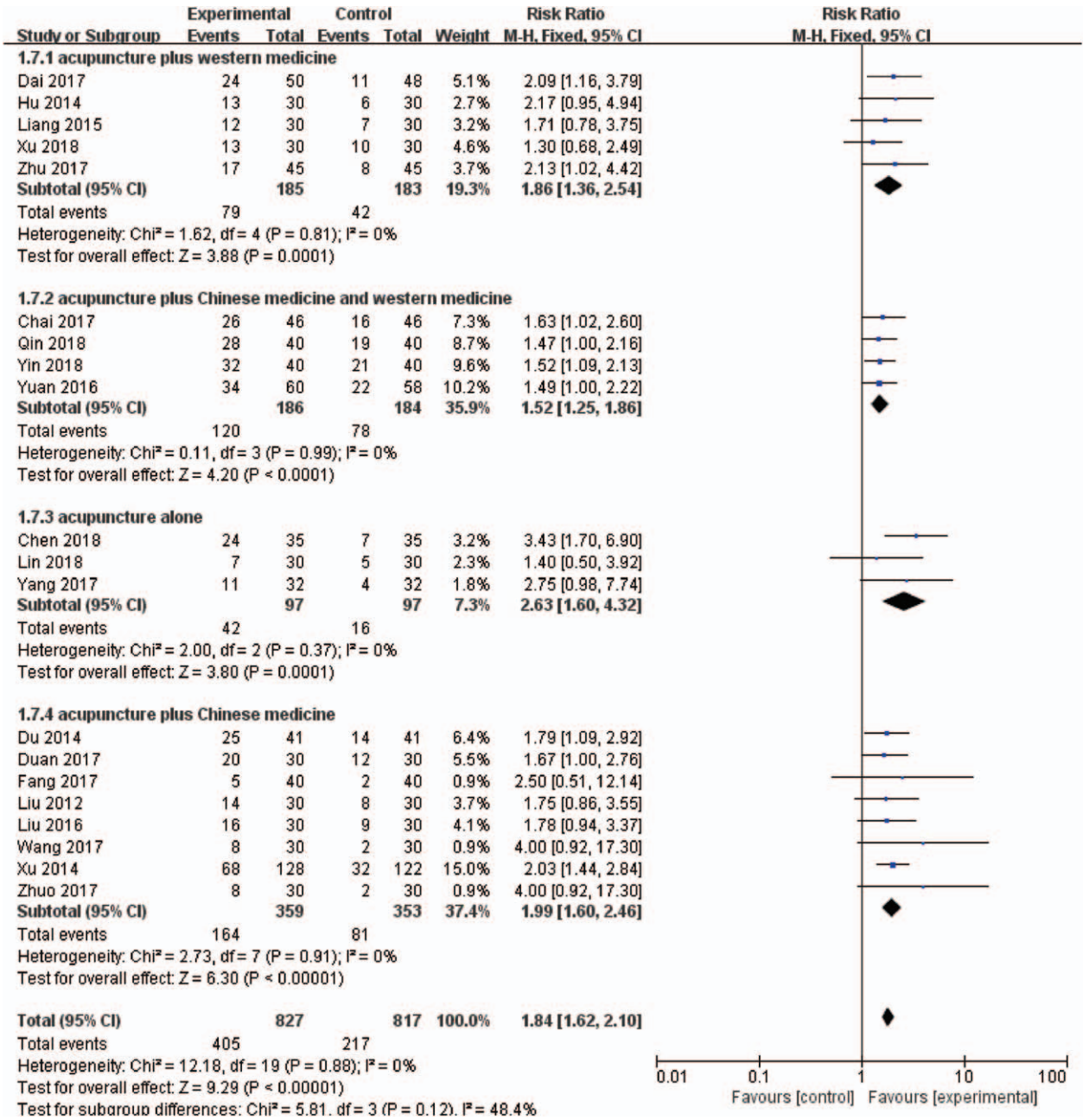

Figure 2. Forest plot of pregnancy rate (different types of intervention).

ture based on Western medicine vs Western medicine. The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.86, 95% CI 1.36–2.54, $P = .0001$). Four RCTs reported the pregnancy rate intervened by acupuncture combined with TCM based on Western medicine vs Western medicine. The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.52, 95% CI 1.25–1.86, $P < .0001$). Three RCTs reported the pregnancy rate intervened by acupuncture vs Western medicine. The meta-analysis seemed to show significant differences between the 2 groups (RR = 2.63, 95% CI 1.60–4.32, $P = 0.0001$). Eight RCTs reported the pregnancy rate intervened by acupuncture combined with TCM vs western medicine. The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.99, 95% CI 1.60–2.46, $P < .00001$).

3.4.2. Different types of infertility. According to Figure 3, eleven RCTs reported the pregnancy rate based on infertility caused by polycystic ovary syndrome (PCOS). The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.70, 95% CI 1.47–1.97, $P < .00001$). Four RCTs reported the pregnancy rate based on infertility caused by ovulatory disorder. The meta-analysis seemed to show significant differences between the 2 groups (RR = 2.65, 95% CI 1.72–4.09, $P < .0001$). Five RCTs reported the pregnancy rate based on infertility caused by other factors. The meta-analysis seemed to show significant

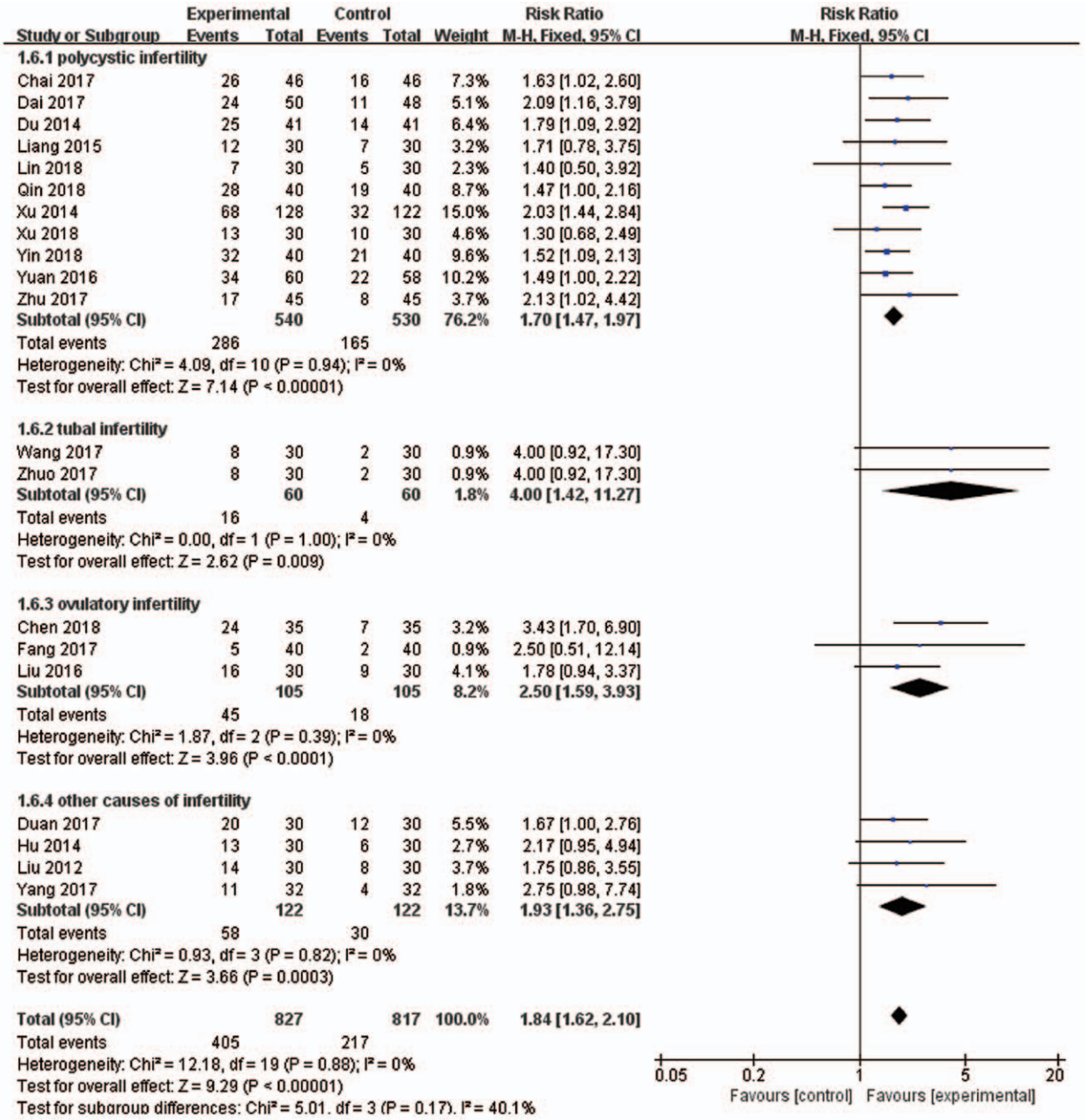

Figure 3. Forest plot of pregnancy rate (different types of infertility).

differences between the 2 groups (RR = 2.06, 95% CI 1.46 to 2.91, $P < .0001$).

3.5. Ovulation rate

The results of the meta-analysis of the secondary outcome measure, ovulation rate, are shown in Figure 4. All 15 trials,[28–32,34–36,39,42–44,46–48] including 1702 patients with infertility, were evaluated for ovulation rate. There was a total of 839 patients in the experimental groups and 863 patients in the control groups. A heterogeneity test ($\chi^2 = 13.18$, $P = .51$, $I^2 = 0\%$) indicated moderate statistical heterogeneity between studies. Thus, a fixed-effect model was used to calculate the combined RR and 95% CI (RR = 1.29, 95% CI 1.21–1.37, $P < .00001$). The results of the meta-analysis showed a statistically significant increase in the ovulation rate between the experimental and control groups, indicating that with acupuncture, the ovulation rate can be significantly increased. A subgroup analysis was performed based on different calculation methods for ovulation rate. Ten RCTs reported the ovulation rate calculated by the ovulated sample divided by the total sample. The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.31, 95% CI 1.19–1.45, $P < .00001$). Five RCTs reported the ovulation rate calculated by the ovulation cycle divided by the

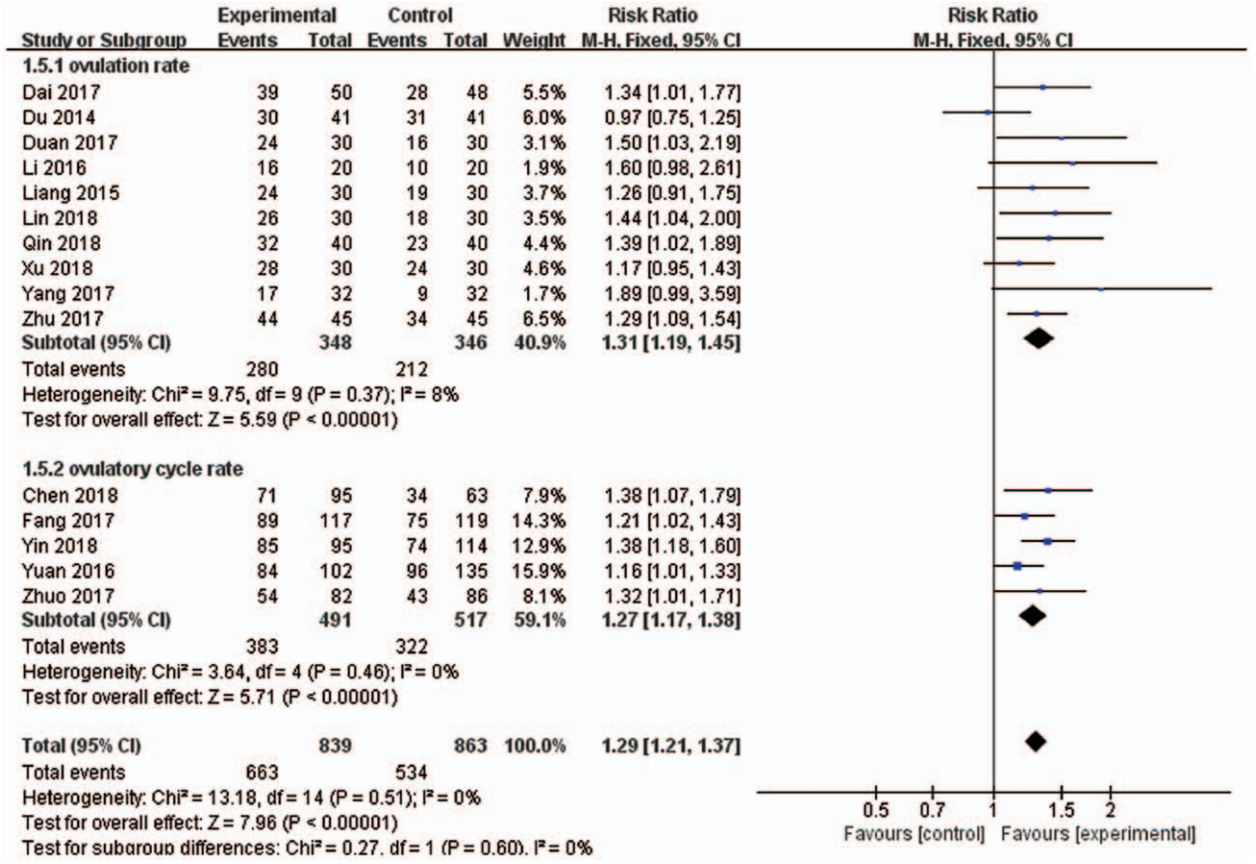

Figure 4. Forest plot of ovulation rate.

total cycle being observed. The meta-analysis seemed to show significant differences between the 2 groups (RR = 1.27, 95% CI 1.17–1.38, $P < .00001$).

3.6. LH

The results of the meta-analysis of LH are shown in Figure 5. Eight trials,[29,31,35,36,39–42,46] including 786 patients with infertility, evaluated the LH. The meta-analysis showed statistical heterogeneity between studies ($\chi 2 = 23.88$, $P = .001$, $I2 = 71\%$). Thus, a random-effects model was used for statistical analysis to calculate the combined MD and 95% CI for this parameter. There was a statistically significant difference between the experimental and control groups in LH (MD = −1.93, 95% CI −2.43 to −1.44, $P < .00001$), indicating that with acupuncture, the level of LH can be significantly improved.

3.7. FSH

The results of the meta-analysis of FSH are shown in Figure 6. Seven trials,[29,31,35,39,41,42,46] including 726 patients with infertility, evaluated FSH. The meta-analysis showed statistical

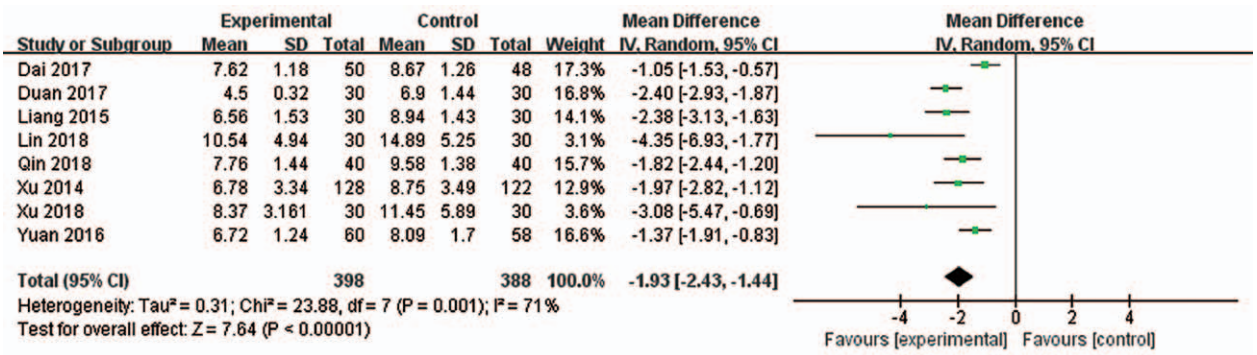

Figure 5. Forest plot of luteinizing hormone (LH).

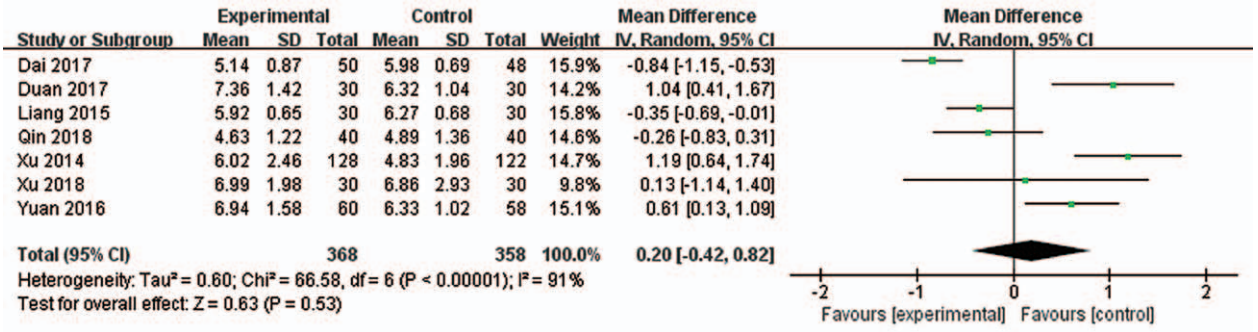

Figure 6. Forest plot of follicle stimulating hormone (FSH).

heterogeneity between studies ($\chi^2 = 66.58$, $P < .00001$, $I^2 = 91\%$). Thus, a random-effects model was used for statistical analysis to calculate the combined MD and 95% CI for this parameter. There was no statistically significant difference between the experimental and control groups in FSH (MD = 0.20, 95% CI −0.42 to 0.82, $P = 0.53$), indicating that with acupuncture, the level of FSH cannot be significantly improved.

3.8. Endometrial thickness

The results of the meta-analysis of LH are shown in Figure 7. Nine trials,[31,32,37–39,42,45,46,48] including 786 patients with infertility, evaluated the endometrial thickness. The meta-analysis showed statistical heterogeneity between studies ($\chi^2 = 278.94$, $P < .00001$, $I^2 = 97\%$). Thus, a random-effects model was used for statistical analysis to calculate the combined MD and 95% CI for this parameter. There was a statistically significant difference between the experimental and control groups in endometrial thickness (MD=1.39, 95% CI 0.51–2.27, $P = .002$), indicating that with acupuncture, the level of endometrial thickness can be significantly improved.

3.9. Adverse events

Information about reported adverse events during the treatment is presented in Table 2. Of the conducted trials, 6 studies reported adverse events in treatment during pregnancy, including abortion, heterotopic pregnancy, ovarian hyperstimulation syndrome (OHSS) occurrence rate and LUFS occurrence rate. Five studies reported adverse events of other types of uncomfortableness, including diarrhea, stomachache, nausea and vomiting, headache, burning, adnexal pain, and needle sickness. Five studies reported that no adverse events occurred. Specifically, Du 2014[30] reported 1 case of OHSS, 2 cases of LUFS and 1 case of nausea and vomiting in the control group but none in the experimental group. Xu 2018[42] reported 1 case of abortion, 2 cases of OHSS, 1 case of diarrhea and two cases of stomachache in the experimental group and two cases of abortion, 4 cases of OHSS, 2 cases of diarrhea and 4 cases of stomachache in the control group. Yin 2018[44] reported 5 cases of LUFS in the control group but none in the experimental group. Yuan 2016[46] reported five cases of abortion in the experimental group and 10 cases of abortion in the control group. Zhu 2017[48] reported two cases of abortion and 2 cases of OHSS in the experimental group and 4 cases of abortion and 3 cases of OHSS in the control group. Chai 2017[27] reported three cases of diarrhea, 1 case of stomachache and 2 cases of needle sickness in the experimental group, and 2 cases of diarrhea, three cases of stomachache and no needle sickness in the control group. Du 2014[29] reported 1 case of nausea and vomiting and 2 cases of adnexal pain in the control group but none in the experimental group. Xu 2018[42] reported 1 case of diarrhea and 2 cases of stomachache in the experimental group and 2 cases of diarrhea and 4 cases of stomachache in the control group. Above all, with acupuncture, fewer adverse effects occurred.

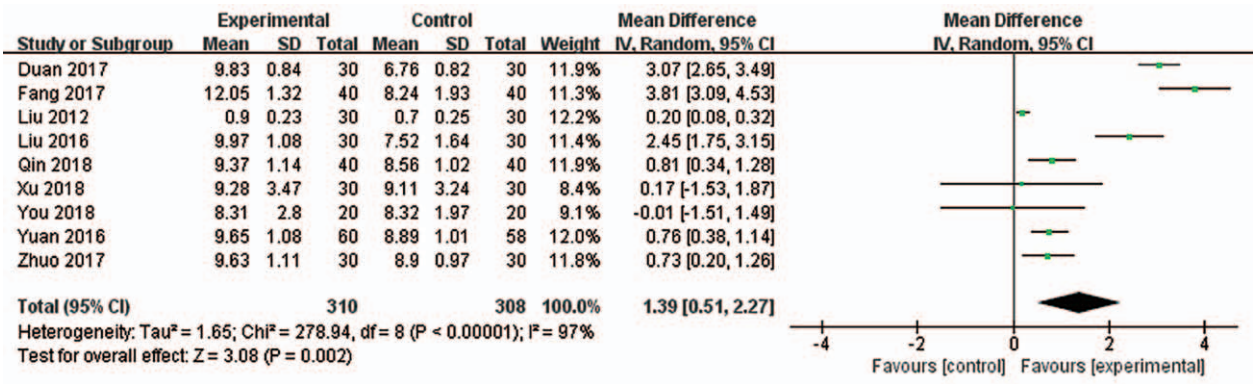

Figure 7. Forest plot of endometrial thickness.

Table 2

Adverse events.

Adverse events about pregnancy											
	Abotion		Heterotopic pregnancy		OHSS occurrence rate		LUFS occurrence rate		Sample		
Studies	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Total
Chen 2017	6	5	6	11	–	–	–	–	91	89	180
Cui 2018	2	3	–	–	–	–	–	–	43	45	88
Du 2014	–	–	–	–	0	1	0	2	41	41	82
Fang 2017	–	–	–	–	0	0	–	–	40	40	80
Hu 2018	–	–	0	0	–	–	–	–	25	25	50
Ke 2013	–	–	1	3	–	–	–	–	40	42	82
Pan 2017	5	3	2	2	–	–	–	–	65	66	131
Xu 2015	1	2	–	–	–	–	–	–	30	32	62
Xu 2018	1	2	–	–	2	4	–	–	30	30	60
Yin 2018	–	–	–	–	0	0	0	5	40	40	80
Yuan 2016	5	10	–	–	–	–	–	–	58	60	118
Zhu 2017	2	4	0	0	2	3	–	–	45	45	90

Adverse events about intervention											
	Diarrhea		Stomachache		Nausea and vomiting		Headache		Sample		
Studies	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Total
Chai 2017	3	2	1	3	–	–	–	–	46	46	92
Chen 2017	1	5	–	–	–	–	–	–	91	89	180
Du 2014	–	–	–	–	0	1	–	–	41	41	82
Hu 2014	–	–	–	–	6	15	1	4	30	30	60
Huang 2014	–	–	–	–	0	8	–	–	32	28	60
Liang 2015	–	–	–	–	–	–	–	–	30	30	60
Xu 2015	1	2	–	–	–	–	–	–	30	32	62
Xu 2018	1	2	2	4	–	–	–	–	30	30	60

	Burning		Adnexal pain		Needlesickness		Other descriptions				
Studies	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Total
Chai 2017	–	–	–	–	2	0	–	–	46	46	92
Chen 2017	1	0	–	–	–	–	–	–	91	89	180
Du 2014	–	–	0	2	–	–	–	–	41	41	82
Duan 2017	no adversed events, no obvious abnormalities in blood routine examination, hepatic and renal function								30	30	60
Fang 2017	no adversed events were observed								40	40	80
Liang 2015	no adversed events, no obvious abnormalities in renal function, ECG and allergic reaction								30	30	60
Xu 2015	no adversed events, the safety rating were both I								32	30	62
Xu 2018	no adversed events were observed								30	30	60

OHSS = ovarian hyperstimulation syndrome, LUFS = luteinized unruptured follicle syndrome, ECG = Electrocardiograph.

3.10. Sensitivity Analysis

We performed a sensitivity analysis by removing the trials reporting pregnancy and obtained a similar result with no heterogeneity, implying that a small sample effect did not influence the pooled effect estimate (Fig. 8). Thus, the results of the meta-analyses above were robust.

3.11. Publication Bias

Publication bias was reported via funnel plot, where the asymmetry of the funnel plots may have arisen through heterogeneity. The funnel plot (Fig. 9) showed an asymmetrical distribution of the pregnancy rate of the studies, which revealed that publication bias might exist.

4. Discussion

4.1. Summary of the main findings

The present review comprised 22 RCTs with 2591 patients from 6 databases published in either Chinese or English. Our findings provide the first clear evidence that acupuncture might be an effective intervention for infertile women without undergoing ART. Evidence of significant effectiveness in the acupuncture group was observed in pregnancy rate, ovulation rate, LH, and endometrial thickness compared to that in the control group. In addition, subgroup analyses of different types of intervention suggested that acupuncture alone or combined with other therapies is more beneficial in terms of pregnancy rate compared to the benefits of standard therapies. The other subgroup analysis also showed significant benefits of acupuncture treatment for different types of infertility. However, due to the overall unclear risk of bias of the included studies, this effect was not robust enough to draw a firm conclusion regarding the efficacy of acupuncture and moxibustion for female infertility. Acupuncture seems to be associated with few adverse events that were mild and transient; there were no withdrawals from studies due to serious adverse events.

4.2. Applicability of the current evidence

The included studies in this review addressed the effectiveness of acupuncture on pregnancy rates and primary outcomes. The

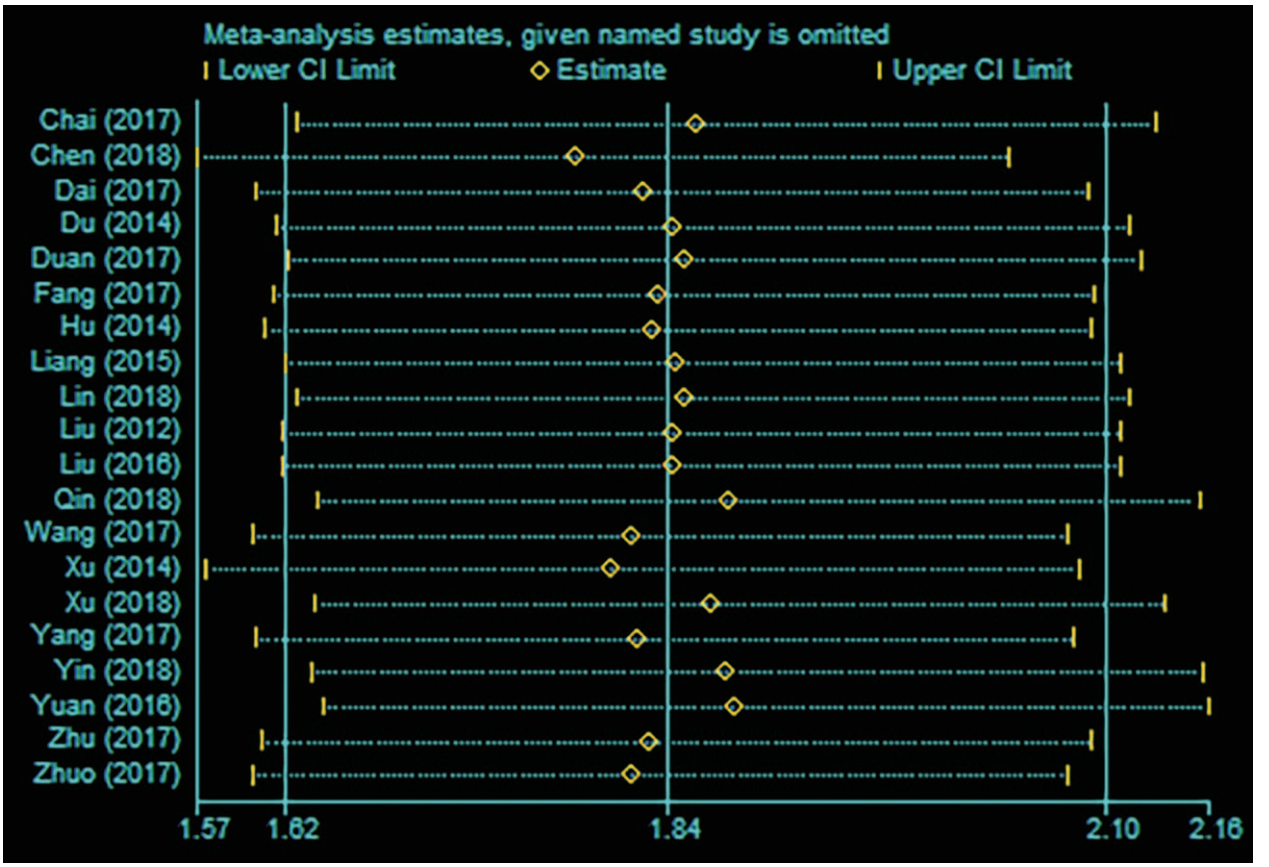

Figure 8. Sensitive analysis.

meta-analysis of a subgroup of trials showed that acupuncture is the most effective in ovulatory infertility compared to the effectiveness of the other two treatment types. Ovulation disorders account for more than 25% of infertile female partners.[49] Clomiphene citrate, a selective estrogen-receptor modulator that can increase ovarian stimulation by endogenous gonadotropin, has been used as a first-line treatment for ovulation induction for decades.[50] However, clomiphene citrate has drawbacks,

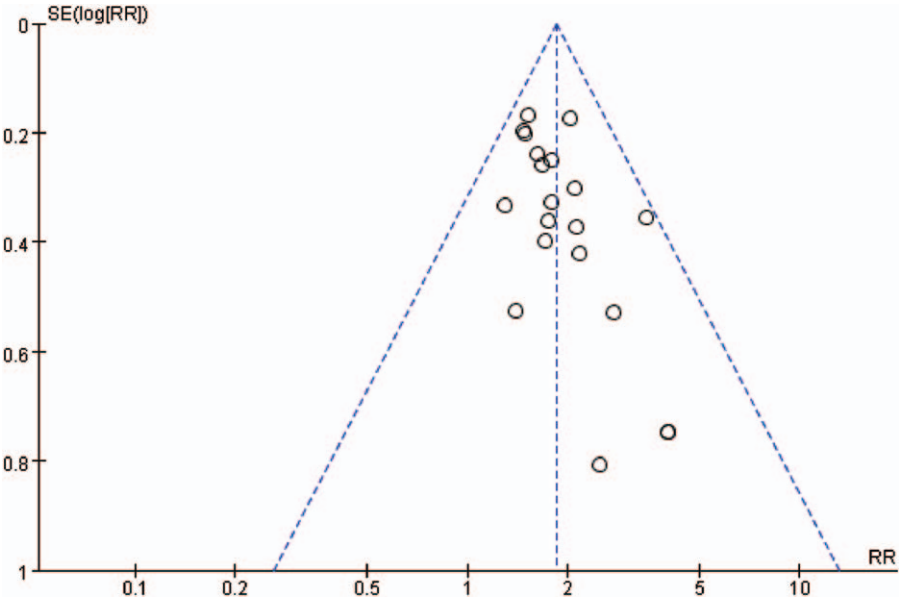

Figure 9. The funnel plot of pregnancy.

such as overall not robustly sampled efficacy, a relatively high multiple-pregnancy rate, and an undesirable side-effect profile, including mood disorders and hot flushes.[50] Our results showed that acupuncture or its combined therapy is more effective than clomiphene citrate, indicating that acupuncture can provide an alternative choice with fewer side effects for ovulation induction. We found that acupuncture alone or combined with other positive therapies could be beneficial for ovulation rates and hormone levels. Neuroendocrinological mechanisms of acupuncture have been studied in reproductive medicine.[51] Acupuncture can modulate the hypothalamic-pituitary-ovarian axis.[52] Our findings were consistent with the finding that acupuncture impacts pituitary beta-endorphin production, which in turn affects GnRH and LH secretion. Adequate endometrial thickness is generally believed to be a requisition to optimize pregnancy rate. The meta-analysis showed that the level of endometrial thickness could be significantly improved with acupuncture treatment. Because endometrial thickness is a function of uterine artery blood flow, the mechanism underlying the improvement of endometrial thickness in acupuncture treatment might be the central sympathoinhibitory effect of acupuncture in reducing uterine artery impedance, resulting in increased blood flow to the uterus. Thus, it is logical to hypothesize that acupuncture may provide a physiological environment to facilitate ovulation and fertility.

Regarding safety, 10 of the 22 included studies reported adverse events related to pregnancy and other types of uncomfortableness. However, a conclusion for the safety of acupuncture for infertility could not be drawn because of the low quality of the included trials.

4.3. Strengths and limitations of this review

To our knowledge, several studies have evaluated the effectiveness of acupuncture in improving the pregnancy rate of IVF/embryo transfer (ET) treatment. [21–23] However, in these studies, acupuncture was regarded as an adjunct in assisted reproduction, and the effectiveness of acupuncture not combined with ART for infertility was not reported. Although there are published systematic reviews and meta-analyses regarding acupuncture for PCOS, [53–55] which to some extent indicate the effectiveness of acupuncture on reproductive outcomes, it remains unknown whether acupuncture or its combined therapy are beneficial for other types of infertility, except PCOS. We tried to include key reproductive outcomes related to female infertility and important clinical outcomes, including pregnancy rate, ovulation rate, hormone changes and endometrial thickness.

There are some limitations in this review. First, there were some methodological shortcomings of the 22 included studies. None of the RCTs described attempts to blind participants or assessors or include allocation concealment measures. There was also an unclear risk of bias in the terms of selective reporting and other biases. Second, there was no study showing the effectiveness of acupuncture when compared with sham acupuncture. It is premature to determine whether acupuncture works mainly via a placebo effect. Third, all of the included trials were conducted in China. Our research lacks the representativeness of studies performed in different countries.

5. Conclusions

Current evidence identified from this review suggested that acupuncture may be effective in the treatment of female infertility. The conclusion of this present review is limited by the low quality of the included studies. Future multicenter RCTs with rigorous methodological quality are needed to clarify the role of acupuncture in female infertility.

Author contributions

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