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ASSISTED REPRODUCTION TECHNOLOGIES

Effects of acupuncture-related therapies on pregnancy outcomes among women undergoing in vitro fertilization and embryo transfer: a Bayesian network meta-analysis

Chengli Bin[1] · Hanzhi Zhong[1] · Shipeng Zhang[2] · Yiping Luo[3] · Jiali Su[2] · Maoya Li[1] · Shaobin Wei[1]

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Abstract

Background This network meta-analysis aimed to assess the efficacy of different acupuncture-related therapies in improving pregnancy outcomes among women undergoing in vitro fertilization and embryo transfer (IVF-ET).

Methods Randomized controlled trials (RCTs) examining acupuncture-related therapies as adjuncts to IVF-ET were systematically searched in eight databases from inception until January 15, 2025. Dichotomous outcomes concerning efficacy were evaluated as odds risk (OR) and continuous data as mean difference (MD) and 95% credible intervals (CrI) utilizing R 4.1.2 and Stata 16.1.

Results Through a comprehensive literature search, we ultimately identified 96 RCTs that involved 14,736 participants and 15 interventions in this systematic analysis. Based on the clinical pregnancy rate outcome, warm acupuncture for three menstrual cycles before oocyte retrieval (WA-TTP, OR 3.56, 95% CrI 2.05 to 6.25, low certainty, SUCRA = 89.54%), acupuncture combined with moxibustion for three menstrual cycles before oocyte retrieval (AC + M-TTP, OR 3.31, 95% CrI 1.05 to 11.77, low certainty, SUCRA = 78.70%), and acupuncture for one menstrual cycle before oocyte retrieval (AC-OTP, OR 2.69, 95% CrI 1.76 to 4.09, moderate certainty, SUCRA = 77.98%) demonstrated potential superiority compared to false acupuncture or no treatment (F/N). Significant subgroup differences between clinical pregnancy rates were observed by subgroup analysis.

Conclusion Acupuncture-related therapies can potentially enhance clinical pregnancy rates among women undergoing IVF-ET, with WA-TTP, AC + M-TTP, and AC-OTP demonstrating potential superiority. AC-TTP demonstrated a greater efficacy in improving live birth rates, increasing endometrial thickness, and reducing pulsation index. Our findings emphasize that acupuncture-related therapies with a limited number of sessions before or after embryo transfer show minimal clinical benefit except auricular acupressure.

Keywords Acupuncture-related therapies · In vitro fertilization and embryo transfer · Network meta-analysis · Randomized controlled trial · Pregnancy outcomes

Abbreviations

CDC	Centers for Disease Control and Prevention
ART	Assisted reproductive technology
IVF-ET	In vitro fertilization and embryo transfer
RIF	Recurrent implantation failure
ERA	Endometrial receptivity array
EA	Electroacupuncture

✉ Maoya Li
lmy0321@stu.cdutcm.edu.cn

✉ Shaobin Wei
weishaobin5620@163.com

Chengli Bin
2876214643@qq.com

Hanzhi Zhong
zhonghanzhi@stu.cdutcm.edu.cn

Shipeng Zhang
1343108750@qq.com

Yiping Luo
1149508185@qq.com

Jiali Su
942418146@qq.com

[1] Department of Gynecology, Hospital of Chengdu University of Traditional Chinese Medicine, Jinniu District, No. 37, Shierqiao Road, Chengdu, Sichuan Province, China

[2] Graduate School, Chengdu University of Traditional Chinese Medicine, Jinniu District, No. 37, Shierqiao Road, Chengdu, Sichuan Province, China

[3] Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

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NMA	Network meta-analysis
PRISMA-NMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
CNKI	China National Knowledge Infrastructure
VIP	Chinese Scientific Journals Database
MeSH	Medical Subject Heading
RCTs	Randomized controlled trials
ICSI	Intracytoplasmic sperm injection
AI	Artificial insemination
F/N	False acupuncture or no treatment
PI	Pulsation index
RI	Resistance index
OR	Odds risk
MD	Mean difference
CrI	Credible intervals
SUCRA	Surface under the cumulative ranking curve
AC	Acupuncture
TEAS	Transcutaneous electrical acupoint stimulation
WA	Warm acupuncture
AA	Auricular acupressure
AC + AA	Acupuncture combined with auricular acupressure
AC + M	Acupuncture combined with moxibustion
OTP	Treatment for one menstrual cycle before oocyte retrieval
TTP	Treatment for three menstrual cycles before oocyte retrieval
ET	Several sessions before or after embryo transfer
HPOA	Hypothalamic-pituitary-ovarian axis
TCM	Traditional Chinese Medicine

Introduction

Infertility, defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse, constitutes a significant global public health issue [1]. A 2019 survey by the Centers for Disease Control and Prevention (CDC) reported that 2.4 million (8.5%) currently married women aged 15–49 were infertile, with primary infertility accounting for 19.4% and secondary infertility for 6.0% in the USA [2]. Nevertheless, the current global incidence of infertility is likely higher [3]. In the USA, the number of women receiving infertility services accounted for approximately 12.7% [2]. Assisted reproductive technology (ART) has offered hope to thousands of infertile couples globally, resulting in over 8 million children being conceived through ART [4]. In vitro fertilization and embryo transfer (IVF-ET) is the most prevalent ART procedure globally, featuring reported global pregnancy success rates for non-donor IVF/ICSI cycles of 26.5% in 2014 [5] and 34.1% per transfer in 2018 around European countries [6]. IVF procedures are multifaceted encompassing numerous interconnected stages and may attribute their lower success rates to factors such as endometrial receptivity, embryo quality, and embryo transfer strategies [7]. Recurrent implantation failure (RIF) after IVF can significantly increase the financial and psychological burdens on patients, in addition to the physical harm caused by repeated procedures and retrievals [8].

Improving the pregnancy success rates of IVF-ET continues to be a significant challenge faced by researchers globally. As a result, there is a high demand for adjuvant therapies to enhance fertility outcomes. Currently, techniques such as ultrasound guidance [9], pharmacological interventions to reduce uterine contractility [10, 11], preimplantation genetic screening [12], and the endometrial receptivity array (ERA) [13], among other auxiliary measures, are employed to enhance the clinical pregnancy rates in IVF-ET. These treatment approaches are not universally suitable for all patients and should be tailored to address the causes of implantation failure. Furthermore, there are many adverse reactions and high costs; many patients still face the problem of embryo implantation failure [14].

Since Stener-Victorin et al. [15]. demonstrated that electroacupuncture (EA) could improve the pregnancy rate of IVF-ET in 1999, acupuncture-related therapies have been integrated in all stages of IVF-ET as an auxiliary means, effectively enhancing the embryo implantation rate and clinical pregnancy success rate. The USA is the first country in the world to legislate on acupuncture, with acupuncture therapy gaining wide recognition and usage [16]. Based on the CDC's 2018 Fertility Clinic Success Rates Report, a survey of the official websites of 456 fertility clinics in the USA showed that 111 clinics recommended and utilized acupuncture therapy, accounting for 24.3% [17]. Studies have shown that acupuncture plays an important role in improving embryo quality (by enhancing ovarian artery blood flow, oocyte quality [18], ovarian reserve function, and promoting ovulation [19]), promoting embryo implantation (by enhancing endometrial receptivity [20] and reducing anxiety [21]), and achieving the effect of a higher clinical pregnancy rate [22].

Nowadays, some systematic reviews and meta-analysis [23–25] have been published to evaluate the effect of acupuncture as an adjunct to IVF-ET. However, there were some heterogeneity and methodological quality defects, and different conclusions have been drawn [26–28]. Moreover, research on acupuncture-assisted IVF-ET frequently utilizes varied types and sessions, making comprehensive

comparisons difficult. Acupuncture-related therapies were classified into different types according to the way of acupuncture and treatment targets, such as manual acupuncture, electroacupuncture, auricular acupuncture, and warm acupuncture. Previous reviews have overlooked different types, acupoint selection, and sessions of acupuncture interventions [29, 30]. Consequently, our study aims to provide more comprehensive and reliable evidence to evaluate the effects of acupuncture-assisted IVF-ET via a Bayesian network meta-analysis (NMA). This study systematically evaluates and compares the efficacy of distinct acupuncture types and treatment durations, establishing a robust evidence base to guide updates in clinical guidelines for optimizing reproductive outcomes.

Methods

Protocol and registration

Our paper followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-analyses (PRISMA-NMA) and the Cochrane Collaboration [31]. The completed PRISMA checklist is presented in Supplementary File 1. The detailed methods of this network meta-analysis were provided by a protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023417465). Given that the analyses were based on previously published studies, ethical approval and consent were not required.

Search strategies

Two authors independently conducted searches in several databases including Medline (accessed through PubMed), Embase, Cochrane Central Register of Controlled Trials, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), Wanfang data, and China Biomedical Literature Database (SinoMed) from their inception to January 15, 2025, with no limitation on language and publication data. The search strategy incorporated a comprehensive set of Medical Subject Headings (MeSH) and keyword search terms, including acupuncture, moxibustion, electroacupuncture, auriculotherapy, acupoint, transcutaneous electrical acupoint stimulation, in vitro fertilization-embryo transfer, IVF-ET, assisted reproductive technology, ART, test-tube fertilization, fertilization in vitro, test-tube babies, embryo transfers, and blastocyst transfer, which were utilized in various combinations. All database search strategies are detailed in Supplementary File 2. Additional eligible studies were identified by manually searching the reference lists of relevant meta-analyses and review articles.

Selection criteria

Among the randomized controlled trials (RCTs) we included were those that compared acupuncture-related therapies to sham acupuncture or no adjuvant treatment. The target population comprised women undergoing IVF-ET excluded intracytoplasmic sperm injection (ICSI) and artificial insemination (AI) treatment. No restrictions were placed on the reasons for the assisted reproduction. The experiment group received either a single therapy or a combination of acupuncture-related therapies. The control group consisted of false acupuncture or no treatment (F/N). In this study, false acupuncture involved mimicking acupuncture and using a sham needle device that was non-invasive and avoided the "deqi" sensation. The primary outcome was clinical pregnancy (perform at least one gestational sac with an active fetal heart rate 5 to 6 weeks after ET confirmed by ultrasound scan). The secondary outcomes included live birth rate (successful rate of pregnancy with live birth after 24 weeks of gestation), the number of oocytes retrieved, endometrial thickness (mm), ovary blood flow pulsation index (PI), and ovary blood flow resistance index (RI).

Exclusion criteria

RCTs primarily designed to remove oocytes from women's ovaries, reduce emotional anxiety were excluded. Other exclusion criteria included the following: (a) studies were not RCT, such as case-control studies and cohort studies; (b) studies without available data; (c) did not meet inclusion criteria; (d) studies without relevant outcome; (e) studies with other reasons that not available.

Literature screening and data extraction

Literature was screened efficiently in two steps. First, two investigators (BCL and ZHZ) initially identified literature meeting the inclusion criteria and not the exclusion criteria by screening titles and abstracts. The second step involved reading the full texts to finalize which literature could be included in the network meta-analysis. Disagreements were resolved through discussion with a third researcher (WSB) until a consensus was reached. Two review authors (ZSP and LYP) independently extracted relevant data from the included trials. The following information was recorded: publication details (first author name, publication year), participant characteristics (age, country), and study design features (intervention classification, timing of intervention, frequency of intervention, sample sizes for experimental and control groups, embryo transfer strategies) and outcomes.

Quality assessment and certainty of the evidence

In this study, the Cochrane Risk of Bias Tool was utilized to assess the risk of bias within individual studies [32]. Two experienced investigators (BCL and ZHZ) independently conducted quality assessments for each RCT using the Cochrane Risk of Bias Tool. Discrepancies were resolved through discussion or by consulting a third author (WSB). The quality of each trial was rated as low, high, or unclear risk of bias, considering the following domains: selection bias (sequence generation and allocation concealment), performance bias (blinding of patients and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases.

The confidence in network meta-analysis system (CINeMA) was employed to evaluate the certainty of the evidence for each comparison and outcome. To communicate and summarize key findings, confidence was assessed as high, moderate, low, or very low across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [33].

Statistical analysis

We performed a Bayesian meta-analysis using the R package gemtc and rjags in R Studio version 2022.12.0 + 353. We used Stata 16.1 software to generate evidence networks, funnel plots. We presented the results of random effects models, due to the clinical heterogeneity between studies that contributed to an outcome. Bayesian Markov Chain Monte Carlo (MCMC) simulations were performed using JAGS (version 4.3.0) with 200,000 iterations, a burn-in of 50,000, and thinning interval of 10. Odds risk (OR) for dichotomous outcomes and mean difference (MD) for continuous data, both with 95% credible intervals (CrI), were the chosen effect sizes. Subgroup analyses were employed to assess the robustness of the results. If there were three arms connected by a loop, we used the split-node method and reported the Bayesian p-value to identify inconsistency [34]. If the p-value was > 0.05, the direct and indirect evidence was considered to be consistent.

Evidence networks were developed to demonstrate direct and indirect comparative relationships among different interventions [35]. We analyzed interventions based on the surface under the cumulative ranking curve (SUCRA) values in each outcome measure [36]. It quantifies the likelihood that an intervention is among the most effective options, with values ranging from 0 to 100%. A higher SUCRA value indicates a higher probability of the intervention being ranked as superior. The SUCRA value [37] for each intervention i was calculated as follows: Using Bayesian MCMC simulations, we estimated the probability of intervention i being ranked at each position r (1 st, 2nd, …, K-th), where K is the total number of interventions.

$$P(\text{rank} \le r) = \sum_{k=1}^{r} P(\text{rank} = k)$$

The SUCRA value is derived by normalizing the area under the cumulative ranking curve:

$$\text{SUCRA}i = \frac{\sum_{r=1}^{K-1} P(\text{rank} \le r)}{K-1}$$

Additionally, we mapped bubble diagrams in two dimensions to demonstrate the relative effectiveness of acupuncture-related therapies using Microsoft Excel 2019. Finally, to assess the presence of small effect sizes or publication biases for each outcome, comparison-adjusted funnel plots were generated [38].

Acupoint analysis

To conduct an in-depth analysis of acupuncture-related protocols, we extracted and analyzed acupoints from 96 literatures and used R 4.1.2 and Microsoft Excel 2019 for visualization. For frequency of acupoints more than 2, heatmap was plotted to exhibit the selection and frequency of acupoints.

Results

Study selection and characteristics

In our electronic and manual search for articles, we identified 4939 titles and abstracts, from which 421 were fully screened against our inclusion criteria. The literature of network meta-analysis ultimately included 96 RCTs involving 14,736 participants (see Fig. 1). The characteristics of the included studies and their participants are detailed in Table 1. The details of 96 randomized controlled trials included are presented in Supplementary File 3.Supplementary Table 1 presents additional study characteristics and outcome data for each study. There are 15 treatments including F/N, acupuncture for one menstrual cycle before oocyte retrieval (AC-OTP), AC for three menstrual cycles before oocyte retrieval (AC-TTP), AC for several sessions before or after embryo transfer (AC-ET), transcutaneous electrical acupoint stimulation for one menstrual cycle before oocyte retrieval (TEAS-OTP), TEAS for three menstrual cycles before oocyte retrieval (TEAS-TTP), TEAS for several sessions before or after embryo transfer (TEAS-ET), electroacupuncture for one menstrual cycle before oocyte retrieval (EA-OTP), EA for three menstrual cycles before oocyte retrieval (EA-TTP), warm acupuncture for one menstrual cycle before oocyte retrieval (WA-OTP), WA for three

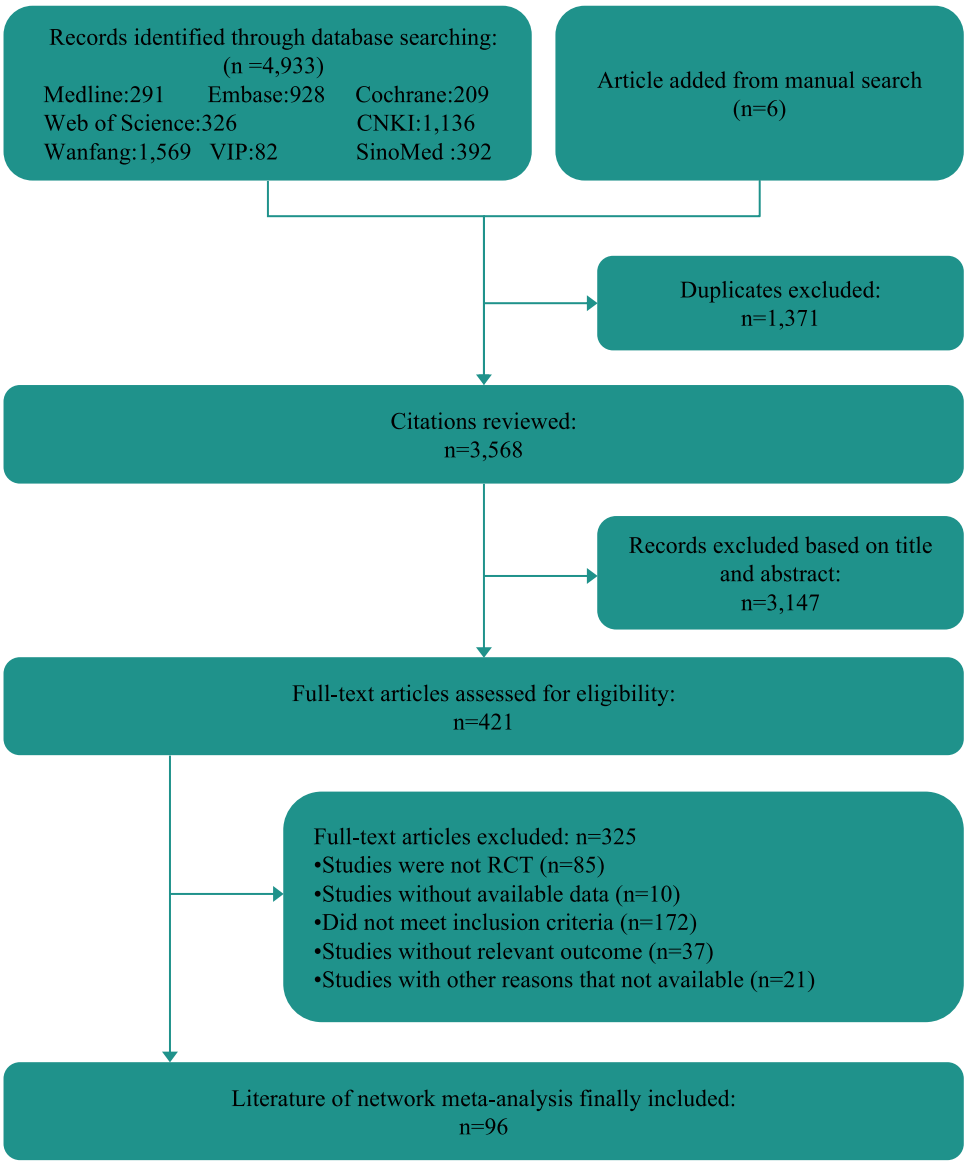

Fig. 1 Literature review flowchart. CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journals Database; SinoMed, Chinese Biomedical Literature Database; RCT, randomized controlled trial

menstrual cycles before oocyte retrieval (WA-TTP), auricular acupressure for several sessions before or after embryo transfer (AA-ET), acupuncture combined with auricular acupressure for several sessions before or after embryo transfer (AC + AA-ET), acupuncture combined with moxibustion for one menstrual cycle before oocyte retrieval (AC + M-OTP), and AC + M for three menstrual cycles before oocyte retrieval (AC + M-TTP). The parameters included were publication year, participant characteristics (age, region), study design features (total sample size, choice of control groups), and clinical features (embryo transfer strategies). Abbreviation, definition, and instruments of acupuncture-related therapies are detailed in Supplementary Table 2. Among these studies, 63.54% (61/96) were published after 2017, and 36.46% (35/96) were published before 2017. In terms of age, 30 (31.25%) studies of the participants were aged ≥ 35, 63 (65.62%) studies were aged < 35, and the remaining studies were unclear. Regarding regional distribution, 79 (82.29%) studies were conducted in China, while 17 (17.71%) were conducted elsewhere. Sixty-three RCTs (65.63%) employed comfort needling as a control, while 32 (33.33%) used no intervention as control groups. Forty-four (45.83%) RCTs involved fresh transfers; 26 (27.08%) involved frozen embryo transfers; 9 included both modalities, and 17 did not specify the embryo transfer strategy.

Quality assessment

In the systematic review, 25 trials (26.04%) exhibited a low overall risk of bias, 21 RCTs (21.88%) displayed a high risk of bias, and the remaining trials (52.08%) had an unclear risk. The majority of trials (71.88%) demonstrated a low

Table 1 Characteristics of studies included and their participants

Study characteristics and participants	No (%) of studies
Publication year	
≥ 2017	61 (63.54%)
< 2017	35 (36.46%)
Population features	
Age	
≥ 35	30 (31.25%)
< 35	63 (65.62%)
NR	3 (3.13%)
Region	
China	79 (82.29%)
No-China	17 (17.71%)
Study design features	
Total sample size	
≥ 110	33 (34.38%)
< 110	63 (65.62%)
Choice of control groups	
False or placebo acupuncture control	63 (65.63%)
No acupuncture invention control	32 (33.33%)
Other control	1 (1.04%)
Clinical features	
Embryo transfer strategies	
Fresh	44 (45.83%)
Frozen	26 (27.08%)
Fresh and frozen	9 (9.38%)
NR	17 (17.71%)

NR, not reported

risk of bias, as detailed through the study's stochastic methods. Twenty-nine articles demonstrated a low risk of bias by mentioning the specific allocation concealment method; however, the remaining articles lacked explicit details. Given the nature of acupuncture-related therapies, implementing a double-blind design is challenging. Eighteen RCTs demonstrated a low risk of bias concerning blinding. Forty-one trials (42.71%) reflected a low risk of bias in incomplete outcome data with sufficient original data. The selection and reporting biases of most studies (87.5%) presented an unclear risk. Supplementary Table 3 provides a detailed assessment of the risk of bias for each RCT.

Network meta-analysis

The network plot of clinical pregnancy rate and live birth rate was presented in Fig. 2. According to the clinical pregnancy outcomes, there are five closed loops in the network evidence of the included trials (Fig. 2A). The size of the nodes represented the total sample size of the intervention, which indicated that AC-ET had the largest sample size (1830, 25.98%), and WA-OTP had the smallest sample size (30, 0.43%). In addition, the direct evidence between AC-ET and F/N (14 RCTs) was greater than for other comparisons based on the thickness of the lines between interventions. The network evidence of the included trials based on the live birth rate is presented in Fig. 2B. As a result, AC-ET had the most participants (N = 2597, 44.75%), and TEAS-OTP had the fewest (N = 122, 2.10%). The network plots for the number of oocytes retrieved, endometrial thickness, PI, and RI are detailed in Supplementary File 4.

Primary outcome

Clinical pregnancy rate

Based on the outcome of clinical pregnancy rate, we included 14 interventions: AC-OTP (6 RCTs, 316 participants), AC-TTP (7 RCTs, 325 participants), AC-ET (14 RCTs, 1830 participants), TEAS-OTP (11 RCTs, 483 participants), TEAS-TTP (8 RCTs, 1064 participants), TEAS-ET (5 RCTs, 937 participants), EA-OTP (13 RCTs, 738 participants), EA-TTP (11 RCTs, 590 participants), WA-OTP (1 RCT, 30 participants), WA-TTP (4 RCTs, 127 participants), AA-ET (1 RCT, 45 participants), AC + AA-ET (4 RCTs, 483 participants), AC + M-OTP (1 RCT, 57 participants), and AC + M-TTP (1 RCT, 37 participants). The network plot for the primary outcome appears in Fig. 2A. The network meta-analysis results are presented in Table 2. The confidence ratings by CINeMA are shown in Supplementary Table 4. The results indicated that WA-TTP (OR 3.56, 95% CrI 2.05 to 6.25, low certainty), AC + M-TTP (OR 3.31, 95% CrI 1.05 to 11.77, low certainty), AC-OTP (OR 2.69, 95% CrI 1.76 to 4.09, moderate certainty), TEAS-TTP (OR 1.92, 95% CrI 1.44 to 2.63, low certainty), EA-TTP (OR 1.73, 95% CrI 1.31 to 2.30, moderate certainty), EA-OTP (OR 1.71, 95% CrI 1.32 to 2.20, moderate certainty), TEAS-ET (OR 1.48, 95% CrI 1.15 to 1.93, high certainty), and AC-ET (OR 1.21, 95% CrI 1.02 to 1.47, very low certainty) compared with the control treatment (F/N). Moreover, WA-TTP (OR 2.93, 95% CrI 1.64 to 5.30, moderate certainty), AC-OTP (OR 2.21, 95% CrI 1.41 to 3.43, moderate certainty), AC-TTP (OR 1.90, 95% CrI 1.25 to 2.89, moderate certainty), TEAS-TTP (OR 1.58, 95% CrI 1.13 to 2.24, high certainty), EA-TTP (OR 1.42, 95% CrI 1.02 to 1.98, low certainty), and EA-OTP (OR 1.41, 95% CrI 1.02 to 1.91, moderate certainty) were better than AC-ET. WA-TTP (OR 2.68, 95% CrI 1.41 to 5.15, moderate certainty), AC-OTP (OR 2.03, 95% CrI 1.19 to 3.45, moderate certainty), and AC-TTP (OR 1.74, 95% CrI 1.04 to 2.91, moderate certainty) were better than AC + AA-ET. Compared with the treatment of TEAS-ET, WA-TTP (OR 2.40, 95% CrI 1.31 to 4.47, moderate certainty), AC-OTP (OR 1.81, 95% CrI 1.11 to 2.98, moderate certainty), and TEAS-OTP (OR 2.06, 95% CrI 1.53 to 2.78, low certainty) were more effective. Statistically significant inconsistencies

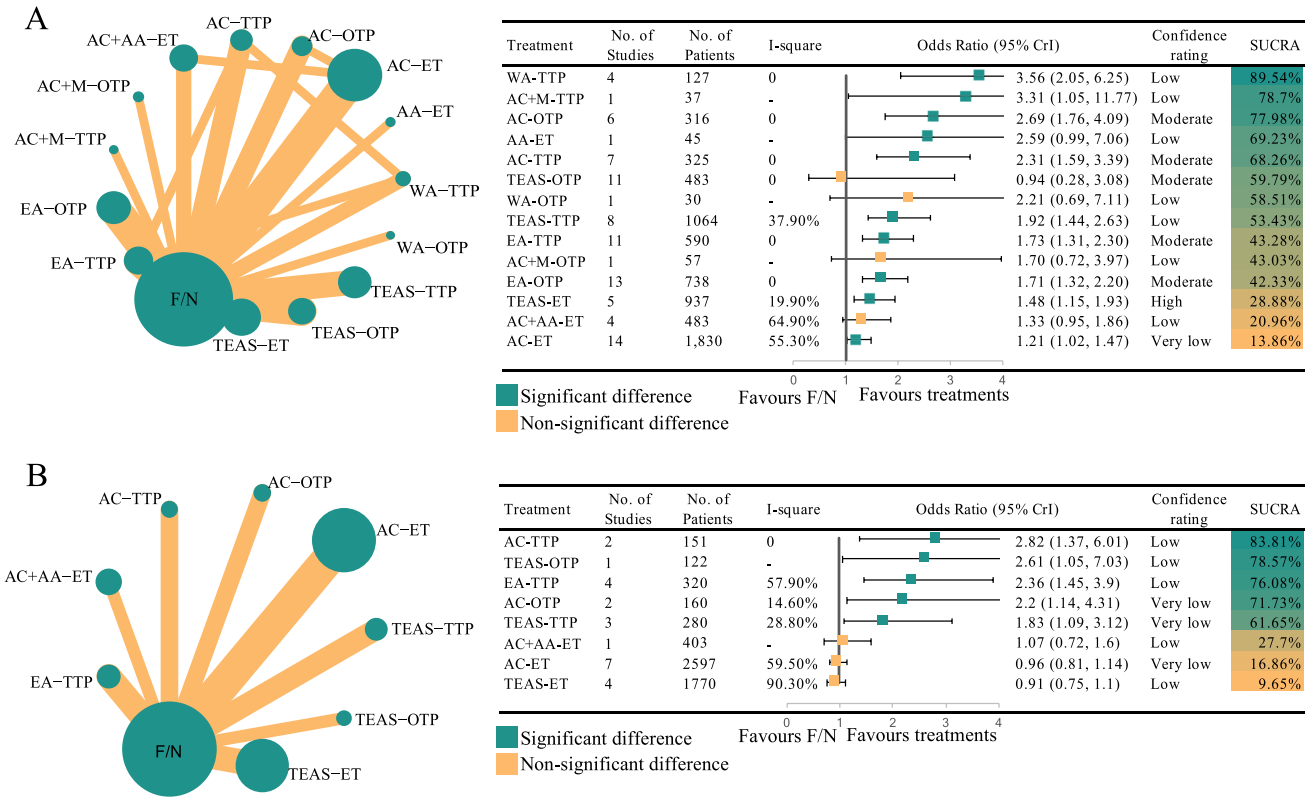

Fig. 2 Network plot and forest plot based on the outcome of clinical pregnancy rate and live birth rate. **A** Network plot and forest plot of the clinical pregnancy rate. **B** Network plot and forest plot of the live birth rate. CrI, credible intervals; SUCRA, surface under the cumulative ranking curve; AC, acupuncture; WA, warm acupuncture; TEAS, transcutaneous electrical acupoint stimulation; EA, electroacupuncture; AA, auricular acupressure; AC +M, acupuncture combined with moxibustion; AC +AA, acupuncture combined with auricular acupressure; F/N, false acupuncture or no treatment; ET, several sessions before or after embryo transfer; OTP, one menstrual cycle before oocyte retrieval; TTP, three menstrual cycles before oocyte retrieval

Table 2. League table for clinical pregnancy rate

89.54%															
WA-TTP	**78.70%**														
1.06 (0.27, 3.89)	**AC+M-TTP**	**77.98%**													
1.32 (0.66, 2.7)	1.25 (0.36, 4.6)	**AC-OTP**	**69.23%**												
1.37 (0.45, 4.22)	1.28 (0.28, 6.4)	1.04 (0.35, 2.95)	**AA-ET**	**68.26%**											
1.53 (0.82, 2.93)	1.44 (0.43, 5.34)	1.16 (0.66, 2.04)	1.12 (0.4, 3.26)	**AC-TTP**	**59.79%**										
1.72 (0.93, 3.28)	1.61 (0.48, 5.91)	1.31 (0.78, 2.19)	1.26 (0.46, 3.56)	1.12 (0.7, 1.84)	**TEAS-OTP**	**58.51%**									
1.61 (0.45, 5.94)	1.51 (0.3, 8.24)	1.22 (0.35, 4.15)	1.17 (0.25, 5.48)	1.05 (0.32, 3.57)	1.69 (1.19, 2.4)	**WA-OTP**	**53.43%**								
1.85 (0.98, 3.48)	1.73 (0.52, 6.28)	1.41 (0.83, 2.31)	1.35 (0.49, 3.83)	1.2 (0.74, 1.96)	1.55 (0.99, 2.44)	1.15 (0.34, 3.79)	**TEAS-TTP**	**43.28%**							
2.06 (1.13, 3.78)	1.92 (0.59, 6.94)	1.56 (0.93, 2.54)	1.5 (0.55, 4.23)	1.33 (0.85, 2.12)	1.21 (0.5, 3.02)	1.28 (0.39, 4.19)	1.11 (0.74, 1.68)	**EA-TTP**	**43.03%**						
2.09 (0.76, 5.77)	1.96 (0.47, 8.73)	1.58 (0.61, 4.12)	1.52 (0.43, 5.63)	1.36 (0.55, 3.47)	1.2 (0.82, 1.78)	1.29 (0.31, 5.56)	1.13 (0.47, 2.87)	1.02 (0.42, 2.54)	**AC+M-OTP**	**42.33%**					
2.07 (1.13, 3.85)	1.93 (0.59, 7.01)	1.57 (0.96, 2.58)	1.52 (0.55, 4.3)	1.35 (0.86, 2.15)	1.19 (0.8, 1.79)	1.29 (0.39, 4.24)	1.12 (0.77, 1.68)	1.01 (0.7, 1.48)	0.99 (0.4, 2.43)	**EA-OTP**	**28.88%**				
2.4 (1.31, 4.47)	2.24 (0.69, 8.12)	1.81 (1.11, 2.98)	1.75 (0.64, 4.95)	1.56 (0.99, 2.48)	2.06 (1.53, 2.78)	1.49 (0.45, 4.95)	1.29 (0.89, 1.96)	1.17 (0.79, 1.72)	1.15 (0.46, 2.8)	1.16 (0.8, 1.65)	**TEAS-ET**	**20.96%**			
2.68 (1.41, 5.15)	2.5 (0.75, 9.2)	2.03 (1.19, 3.45)	1.96 (0.7, 5.65)	1.74 (1.04, 2.91)	1.39 (0.93, 2.06)	1.66 (0.5, 5.61)	1.44 (0.94, 2.31)	1.3 (0.84, 2.02)	1.28 (0.51, 3.19)	1.29 (0.85, 1.97)	1.12 (0.73, 1.72)	**AC+AA-ET**	**13.86%**		
2.93 (1.64, 5.3)	2.72 (0.85, 9.82)	2.21 (1.41, 3.43)	2.13 (0.79, 5.92)	1.9 (1.25, 2.89)	1.07 (0.69, 1.61)	1.81 (0.56, 5.9)	1.58 (1.13, 2.24)	1.42 (1.02, 1.98)	1.4 (0.58, 3.31)	1.41 (1.02, 1.91)	1.22 (0.88, 1.66)	1.1 (0.75, 1.57)	**AC-ET**	**2.23%**	
3.56 (2.05, 6.25)	3.31 (1.05, 11.77)	2.69 (1.76, 4.09)	2.59 (0.99, 7.06)	2.31 (1.59, 3.39)	0.94 (0.28, 3.08)	2.21 (0.69, 7.11)	1.92 (1.44, 2.63)	1.73 (1.31, 2.3)	1.7 (0.72, 3.97)	1.71 (1.32, 2.2)	1.48 (1.15, 1.93)	1.33 (0.95, 1.86)	1.21 (1.02, 1.47)	**F/N**	

SUCRA values
Interventions
NO-significant pairwise comparisons
Significant pairwise comparisons

SUCRA, surface under the cumulative ranking curve; *AC*, acupuncture; *WA*, warm acupuncture; *TEAS*, transcutaneous electrical acupoint stimulation; *EA*, electroacupuncture; *AA*, auricular acupressure; *AC+M*, acupuncture combined with moxibustion; *AC+AA*, acupuncture combined with auricular acupressure; *F/N*, false acupuncture or no treatment; *ET*, several sessions before or after embryo transfer; *OTP*, one menstrual cycle before oocyte retrieval; *TTP*, three menstrual cycles before oocyte retrieval

were observed between TEAS-OTP and WA-OTP (OR 1.69, 95% CrI 1.19 to 2.40, low certainty). Additionally, WA-TTP was found to be more effective than EA-TTP (OR 2.06, 95% CrI 1.13 to 3.78, moderate certainty). The remaining treatments did not show significant differences.

In general, potential superiority was demonstrated by WA-TTP (SUCRA = 89.54%), AC + M-TTP (SUCRA = 78.70%), and AC-OTP (SUCRA = 77.98%). The four least effective interventions were F/N (SUCRA = 2.23%), AC-ET (SUCRA = 13.86%), AC + AA-ET (SUCRA = 20.96%), and TEAS-ET (SUCRA = 28.88%). The three groups (ET, OTP, and TTP) were categorized based on the dosage of acupuncture-related therapies. In the ET group, interventions were ranked as follows: AA > TEAS > AC + AA > AC. In the OTP group, interventions were ranked as follows: AC > TEAS > WA > AC + M > EA. In the TTP group, interventions were ranked as follows: WA > AC + M > AC > TEAS > EA. The ranking probabilities are shown in Table 2.

Secondary outcomes

Live birth rate

There were 24 RCTs (2900 participants) that reported the live birth rate including 8 interventions (Fig. 2B). AC-TTP resulted in a significantly better live birth rate to AC + AA-ET (OR 2.65, 95% CrI 1.16 to 6.22, low certainty), AC-ET (OR 2.94, 95% CrI 1.39 to 6.40, low certainty), TEAS-ET (OR 3.10, 95% CrI 1.47 to 6.75, low certainty), and F/N (OR 2.82, 95% CrI 1.37 to 6.01, low certainty). The results of other comparisons are presented in Supplementary File 5Table1. The confidence ratings by CINeMA are presented in Supplementary Table 5. According to SUCRA probability results, the AC-TTP, TEAS-OTP, EA-TTP, AC-OTP, TEAS-TTP, AC + AA-ET, F/N, AC-ET, and TEAS-ET were 83.81%, 78.57%, 76.08%, 71.73%, 61.65%, 27.70%, 23.95%, 16.86%, and 9.65%, respectively Supplementary File 5Table1).

The number of oocytes retrieved

There were 39 RCTs (2076 participants) that reported the number of oocytes retrieved including 7 interventions Supplementary File 4Fig.1). AC-OTP (MD 1.58, 95% CrI 0.07 to 3.04, low certainty) and TEAS-TTP (MD 1.28, 95% CrI 0.04 to 2.53, low certainty) resulted in a significantly higher number of oocytes compared to EA-OTP. AC-OTP (MD 1.64, 95% CrI 0.43 to 2.79, low certainty) and TEAS-TTP (MD 1.34, 95% CrI 0.48 to 2.19, low certainty) resulted in a significantly higher number of oocytes compared to F/N. No significant differences were observed among the interventions in other comparisons Supplementary File 5Table3). The confidence ratings by CINeMA are presented in Supplementary Table 6. According to SUCRA probability results, the AC-OTP, TEAS-TTP, AC + M-OTP, TEAS-OTP, AC-TTP, EA-TTP, EA-OTP, and F/N were 83.41%, 75.21%, 62.06%, 60.64%, 55.13%, 28.13%, 20.48%, and 14.94%, respectively Supplementary File 5Table3).

Endometrial thickness

A total of 32 two-arm RCTs and one three-arm RCT (1392 participants) reported the outcome of endometrial thickness included 11 interventions Supplementary File 4Fig.2). AC-TTP significantly increased endometrial thickness compared to F/N (MD 2.01, 95% CrI 0.61 to 3.42, low certainty). The confidence ratings by CINeMA are presented in Supplementary Table 7. Based on SUCRA probability results, AC-TTP (SUCRA = 78.91%) was the most effective intervention for improving endometrial thickness, WA-TTP (SUCRA = 77.72%) ranked second, and TEAS-TTP (SUCRA = 63.88%) third. Except for F/N, EA-TTP was the least effective at improving endometrial thickness (SUCRA = 28.31%) Supplementary File 5: Table 3.

PI and RI

Ten trials, involving 381 patients and five interventions, reported outcomes for PI and RI in the network meta-analysis Supplementary File 4Fig.3–4). No significant differences were found between pairwise comparisons for two outcomes. And the certainty of the evidence is low or very low. The confidence ratings by CINeMA are presented in Supplementary Table 8–9. Based on the outcome of PI, the SUCRA values for AC-TTP, TEAS-OTP, AC + M-TTP, TEAS-TTP, and WA-TTP were 69.30%, 67.38%, 53.82%, 45.54%, and 43.69%, respectively Supplementary File 5: Table 4. For the RI outcome, the SUCRA values evaluated for the five adjuvant treatments were 86.09% (TEAS-OTP), 55.58% (AC-TTP), 51.67% (AC + M-TTP), 48.89% (TEAS-TTP), and 35.42% (WA-TTP) Supplementary File 5: Table 5.

Subgroup analysis

Based on subgroup analysis by choice of control groups, all studies reported the comparison of acupuncture-related treatment with the no acupuncture invention control. The results of the network meta-analysis showed that all acupuncture-related treatments showed significant efficacy compared with no acupuncture invention control ($p < 0.05$), except for WA-OTP, AC + M-OTP, and AC + AA-ET. Only seven acupuncture treatments included a false or placebo acupuncture control, and the results showed that TEAS-TTP, TEAS-OTP, and TEAS-ET were superior to placebo treatment ($p < 0.05$).

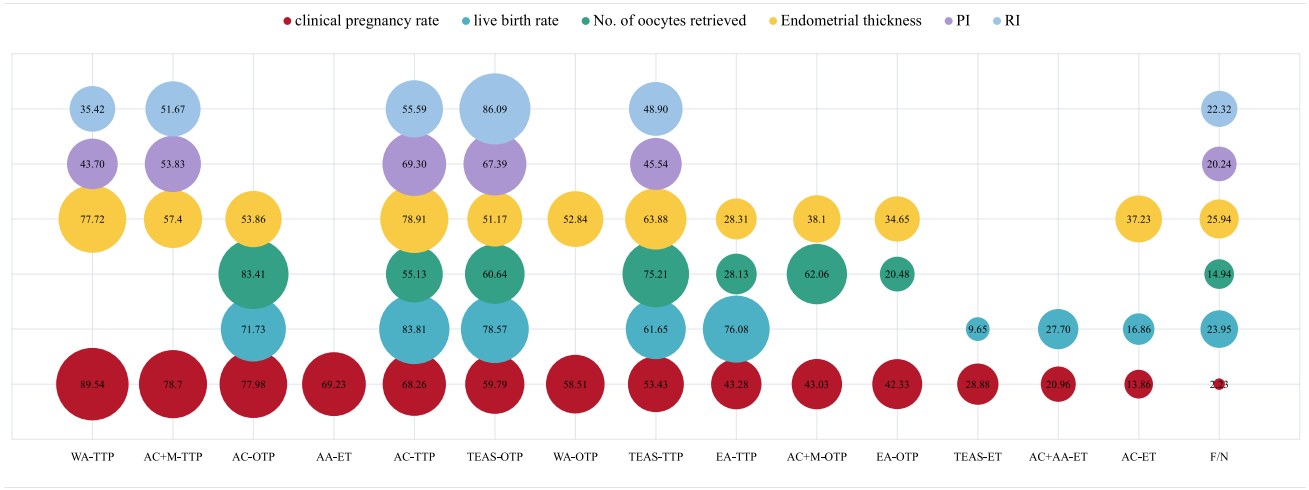

Fig. 3 Two-dimensional bubble diagram for the six outcomes based on the SUCRA results. SUCRA, surface under the cumulative ranking curve; PI, pulsation index; RI, resistance index; AC, acupuncture; WA, warm acupuncture; TEAS, transcutaneous electrical acupoint stimulation; EA, electroacupuncture; AA, auricular acupressure; AC + M, acupuncture combined with moxibustion; AC + AA, acupuncture combined with auricular acupressure; F/N, false acupuncture or no treatment; ET, several sessions before or after embryo transfer; OTP, one menstrual cycle before oocyte retrieval; TTP, three menstrual cycles before oocyte retrieval

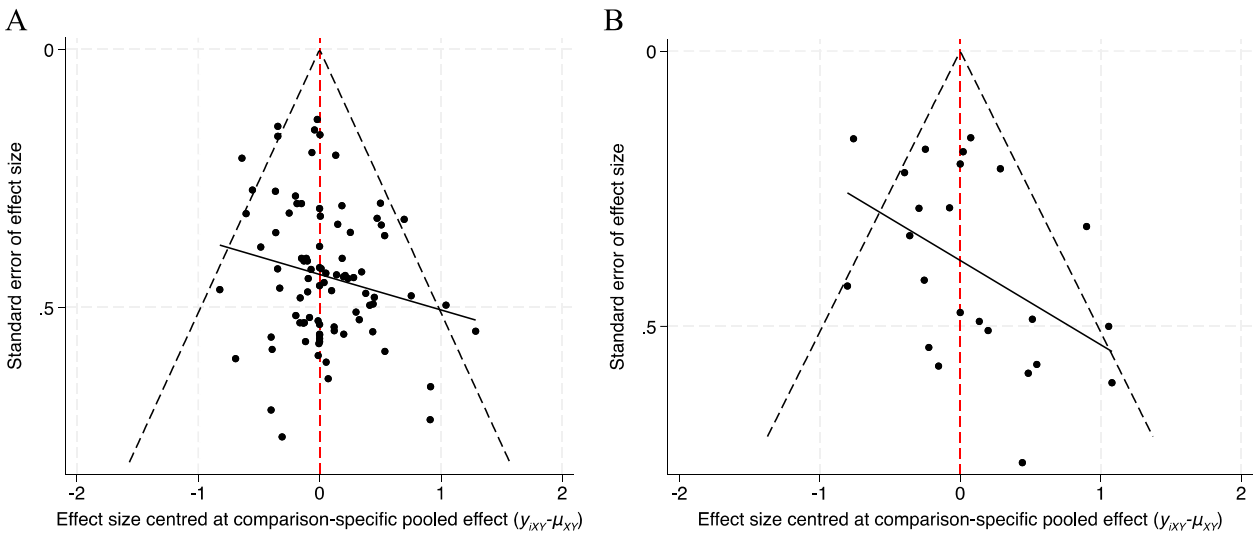

Fig. 4 Funnel plot of the clinical pregnancy rate and live birth rate. **A** Funnel plot of the clinical pregnancy rate. **B** Funnel plot of the live birth rate

Subgroup analysis according to embryo transfer strategy showed that AC-OTP, WA-TTP, TEAS-OTP, AC-TTP, and EA-OTP showed good efficacy in both ET and FET ($p < 0.05$). In addition, TEAS-TTP and EA-TTP were found to similarly improve clinical pregnancy rates in FET ($p < 0.05$).

Subgroup analysis based on the study sample size showed that the majority of acupuncture regimens showed significant efficacy when the sample size was < 100, and the TEAS-ET regimen showed significant efficacy only when the sample size was > 100 ($p < 0.05$).

According to the comparative analysis of region, the vast majority of studies focused on China, where WA-TTP, AA-ET, TEAS-TTP, AC-TTP, AC-OTP, TEAS-OTP, EA-TTP, EA-OTP, and TEAS-ET had a significant clinical efficacy ($p < 0.05$). Analysis of no-China studies showed that there are currently four treatment regimens AC-OTP, EA-OTP, AC-ET, and AC + AA-ET applied in this field, but only AC-OTP was observed to have efficacy ($p < 0.05$).

Subgroup analysis based on age showed that the clinical pregnancy rates of WA-TTP, TEAS-TTP, TEAS-OTP, and EA-TTP were lower in > 35 than < 35. Also, the result

analysis revealed that AC-TTP and EA-OTP were not significant in the advanced age group ($p < 0.05$). Details of subgroup analysis are presented in Supplementary File 6Table1–5.

Bubble diagram and publication bias

We performed a two-dimensional bubble diagram for the six outcomes based on the SUCRA results (Fig. 3). The results showed that WA-TTP has obvious advantages in increasing clinical pregnancy rate and the number of retrieved oocytes. AC-TTP demonstrated a greater efficacy in improving live birth rates, increasing endometrial thickness, and reducing pulsation index. AC-OTP has the best efficacy in increasing the number of retrieved oocytes, and its efficacy in clinical pregnancy rate ranks second. For clinical pregnancy rates, AC-OTP was more effective than AC-TTP, and TEAS-OTP outperformed TEAS-TTP, whereas EA-OTP was less effective than EA-TTP. Regarding endometrial thickness outcomes, AC-TTP was superior to AC-OTP, TEAS-TTP exceeded TEAS-OTP, and EA-TTP was less effective than EA-OTP. The funnel plot of the clinical pregnancy rate and live birth rate show the publication bias in Fig. 4. The funnel diagram of clinical pregnancy rate showed that most studies were symmetrically distributed around the $X = 0$ line (Fig. 4A). However, four studies fell outside the funnel, providing evidence for small samples' effect in the research network. The left–right distribution of the live birth rate funnel plot was asymmetrical, indicating the possibility of publication bias (Fig. 4B). Supplementary Fig. 1shows the funnel plot for four secondary outcomes.

Acupoint analysis

Figure 5 presents a heatmap of acupoints (the frequency > 2), revealing 37 distinct acupoints employed across the analyzed acupuncture interventions. Except for AC-ET, TEAS-ET, AA-ET and AC + AA-ET, among the remaining ten acupuncture protocols analyzed, Guanyuan (CV4), Zigong (Ex-CA07), and Sanyinjiao (SP6) emerged as the most predominantly utilized acupoints. A complete frequency distribution of all 68 acupoints from 14 treatments is provided in Supplementary Table 10. The top five acupoints with the highest total frequency are Guanyuan (CV4), Zigong (Ex-CA07), Sanyinjiao (SP6), Zusanli (ST36), and Qihai (CV6), collectively representing 40.89% (321/785) of the total frequency.

Discussion

We implemented our comprehensive and systematic NMA by updating the currently available data regarding acupuncture-related therapies for women undergoing in vitro

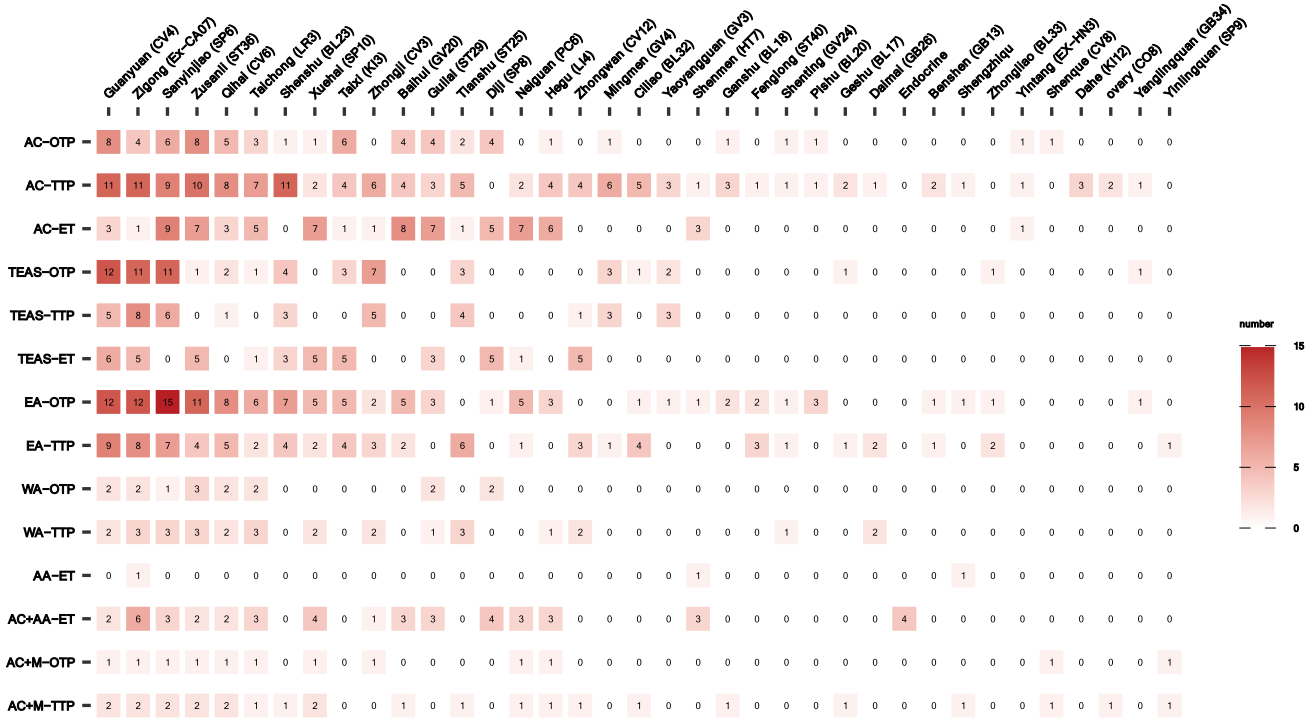

Fig. 5 Heatmap of acupoints of the included studies

fertilization and embryo transfer. Our study comprised 96 RCTs comparing 15 treatments with 14,736 participants. We found that WA for 3-month menstrual cycles during controlled ovarian hyperstimulation (COH) was most effective in improving the clinical pregnancy rate. AC-OTP has the best efficacy in improving the number of oocytes retrieved. And for the endometrial thickness, the effect of AC-TTP is better than that of other therapies. It is important to note that acupuncture-related therapies before and after embryo transfer have little clinical significance, except for AA. Moreover, the most CINeMA assessment showed very low to moderate confidence in the evidence; our findings should be interpreted with caution.

The results indicated that WA-TTP constituted the most effective regimen for improving clinical pregnancy rates, aligning with findings from prior research. Warm acupuncture, as an acupuncture therapy, delivers dual stimulation of acupoints via the warming effect of needling and moxibustion, targeting the activation of blood circulation, the removal of blood stasis, and the energization of meridians and collaterals [39]. Clinical studies have demonstrated that WA effectively increases endometrial thickness [40], enhances ovarian function, stabilizes sex hormone levels, boosts clinical pregnancy rates, and lowers miscarriage rates [41], though the underlying mechanism warrants further investigation. At present, widely used interventions in clinical studies primarily comprise AC, EA, and TEAS, favored for their high degree of standardization. While the efficacy of WA is acknowledged, its deployment in the field of IVF-ET remains limited owing to its complexity. Advancements in technology are anticipated to streamline the operational procedures of WA and promote the widespread use of this therapy. Acupuncture points will be selected based on the Zang-fu organ system, Yin-Yang theory, and clinical rules for infertility acupoint selection. The top three acupoints Guanyuan (CV4), Zigong (Ex-CA07), and Sanyinjiao (SP6) are indicated as preferred for treating female infertility [42]. SP6 (spleen/kidney/liver channel intersection) and CV4 (conception vessel) are believed to improve uterine [43], while Zigong (extra point) directly stimulates uterine microenvironmental remodeling. Acupuncture-related therapies are adjunctive interventions in IVF-ET, with acupoint selection primarily targeting the Ren Meridian, spleen and kidney channels, and qi-blood regulating meridians.

Numerous factors contribute to the low clinical pregnancy rates in IVF-ET, chiefly among these are embryo quality and endometrial receptivity. While embryo quality in ART has been significantly optimized, enhancing endometrial receptivity continues to be a formidable challenge [44]. Endometrial receptivity represents a focal point of research within assisted reproductive technology, with numerous scholars positing that its enhancement is crucial to augmenting pregnancy outcomes. The assessment indices for endometrial receptivity encompass endometrial thickness, volume, type (categorized as type A, B, and C based on echogenicity differences), hemodynamic parameters (PI, RI), and peristaltic waves, among others [45]. Lower PI and RI values signify a more abundant blood supply to the uterus and ovaries.

At present, endometrial thickness serves as the primary index for assessing endometrial receptivity. AC-TTP demonstrates the highest efficacy in enhancing endometrial thickness. AC-TTP and TEAS-OTP represent the most effective measures for reducing PI and RI levels. Acupuncture has been shown to enhance the outcomes of IVF-ET, primarily by regulating the hypothalamic-pituitary-ovarian axis (HPOA), augmenting blood flow to the ovaries and endometrium, and facilitating the maturation and release of ova [46]. Furthermore, it is associated with a reduction in the frequency of endometrial peristalsis [47], inhibition of uterine contractions [48], and alleviation of depression, anxiety, and stress. Its capacity to modulate immune function has also been demonstrated to contribute to improved IVF-ET outcomes. TEAS, a novel acupuncture therapy, employs electrical rather than mechanical stimulation, exerting therapeutic effects through the application of pulsed currents to acupoints via electrode pads on the skin's surface [49]. The results of a meta-analysis [50] that incorporated nine randomized controlled trials demonstrated that TEAS treatment significantly improved embryo implantation rates, clinical pregnancy rates, and live birth rates in patients undergoing IVF-ET. TEAS offers the advantages of being safe, non-invasive, painless, highly reproducible, and increasingly acceptable to clinical patients, anticipating its widespread application in assisted reproduction technology processes in the future.

Currently, the use of acupuncture is mainly concentrated in Asia, and the consensus [49] published in 2017 emphasized the great potential of acupuncture therapy in IVF-ET, which will hopefully expand the international use of acupuncture. Our team explored the most appropriate treatment protocols for different situations through subgroup analysis, among which AC-OTP had significant efficacy in most cases, was easy to perform, and was highly scalable. The results of subgroup analysis by choice of control groups showed that the effects of the false acupuncture group and no acupuncture invention group were both inferior to those of other acupuncture-related therapies. Based on the results of the embryo transfer strategy, it was suggested that AC-OTP was most effective in fresh embryo transfer. Some studies have reported that certain electrical stimulation can stimulate cellular activity, so this may be one of the reasons why TEAS-TTP and EA-TTP regimens have better efficacy among FET regimens [51]. For both natural and assisted reproduction, age is a key factor affecting clinical pregnancy rates.

Although the utilization of acupuncture-related therapies in IVF-ET has been widely discussed, the evaluation of acupuncture protocols, dosages, and intervention phases in randomized controlled trials is relatively lacking [52]. To date, an absence of expert consensus or evidence-based guidance prevails, hindering the systematic summarization of acupuncture point selection. The "Paulus protocol" [53], the most frequently implemented randomized controlled trial protocol for acupuncture-assisted IVF-ET, mandates acupuncture application 25 min before and after embryo transfer. Subsequently, this protocol has been adopted as the recommended IVF-assisted treatment by a majority of international fertility clinics. However, clinical studies employing this acupuncture protocol have occasionally failed to reproduce previous results [54–57]. Traditional Chinese Medicine (TCM) practitioners contend that this standardized protocol does not facilitate individualized treatment according to evidence-based principles, and that the acupuncture dosage is inadequate [58]. It has been suggested that the dosage of acupuncture used in some of the randomized trials included in a systematic review was very low and that higher dosages could have improved the efficacy of acupuncture [52]. The proliferation of research has uncovered several inherent challenges in acupuncture studies, including study design, sample size, and the selection of appropriate control groups [59]. This study aimed to systematically evaluate the impact of acupuncture-related therapies on pregnancy outcomes, with detailed analysis of their dosage and intervention phases. The findings indicated that administering AC and TEAS in several sessions before and after transplantation had a minimal effect on enhancing clinical pregnancy rates, while AA-ET ranking fourth in effectiveness. Magarelli et al. [60] conducted a prospective cohort clinical study which reported that a total 11 electrostimulation procedure sessions (9 sessions before oocytes retrieval, 24 h before ET and 1 h after ET) significantly improved clinical pregnancy rates in IVF cycles compared to control. While their work was not an RCT, the dose–response trend they identified corroborates our conclusion that sustained acupuncture regimens (e.g., WA-TTP, AC-OTP) yield superior outcomes compared to peri-transfer interventions. Developing a long-term treatment plan necessitates not merely a comprehensive assessment by healthcare practitioners of the patient's disease type, duration, and symptoms but also consideration of the patient's acceptance of acupuncture, financial status, and proximity to the clinic.

Currently, IVF-ET technology, both domestically and internationally, is undergoing popularization and development. Within this context, acupuncture interventions in TCM demonstrate broad application prospects and are anticipated to make significant breakthroughs. This study compares and ranks the clinical efficacy of various acupuncture intervention protocols within IVF-ET using network meta-analysis, with the goal of furnishing an objective and rigorous evidence-based foundation for the formulation of international clinical guidelines.

The innovations and limitations of this study

This study represents the inaugural network meta-analysis of randomized controlled trials examining acupuncture intervention in IVF-ET, utilizing Bayesian methodology. This approach has a rigorous study design and yields results of substantial reference value. The study furnishes a robust evidence base, crucial for guiding future research directions and minimizing resource wastage. A comprehensive literature search and manual screening across multiple databases, regardless of language and publication date, significantly minimized the risk of overlooking relevant studies. Engaging at least two reviewers in the data extraction and quality assessment processes guaranteed the reliability of the findings. Each study's risk of bias was assessed, and well-established tools were employed to ensure the evidence's reliability. Additionally, subgroup analyses, considering factors such as publication year, participant age, region, total sample size, control group selection, and embryo transfer strategies, were undertaken to investigate the impact on IVF pregnancy outcomes.

Although this study has certain significant limitations, they are primarily inherent to the study design rather than the methodology. First, RCTs included multiple infertility types, encompassing ovulation disorder, ovarian dysfunction, recurrent implantation failure, thin endometrium, and other unexplained infertility. Variations in infertility type and duration were significant across the studies, with some lacking more detailed descriptions. We recognize that heterogeneity among studies is inevitable, potentially impacting the outcomes. Second, studies possessing a high risk of bias or with small sample sizes could result in the overestimation of efficacy. Furthermore, an imbalance in participant numbers between WA-TTP and other acupuncture interventions could affect the reliability of study results.

Conclusion

Acupuncture-related therapies have the potential to enhance clinical pregnancy rates among women undergoing IVF-ET, with WA-TTP, AC + M-TTP, and AC-OTP demonstrating potential superiority. AC-TTP demonstrated a greater efficacy in improving live birth rates, increasing endometrial

thickness, and reducing pulsation index. Our findings emphasize that acupuncture-related therapies with a limited number of sessions before or after embryo transfer show minimal clinical benefit except auricular acupressure. This underscores the necessity of standardize the protocol of acupuncture-related therapies to improve pregnancy outcomes. As technology advances and research methods become more standardized, it is anticipated that future randomized double-blind controlled trials focusing on individualized acupuncture protocols will further validate these findings.

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Author contribution BCL served as principal author and had full access to all the data in the study and took responsibility for the accuracy of the data analysis and the integrity of the data. ZHZ and ZSP contributed to the conception and design. LYP, SJL, and BCL contributed to the data acquisition and interpretation. BCL contributed to draft of the manuscript. All authors contributed to the critical revision of the manuscript on important intellectual content. LMY and WSB contributed to the revision of the article and gave final approval.

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Wei Shaobin,National Famous Old Chinese Medicine Expert Inheritance Studio,CJJ2022126,Shaobin Wei

Data availability The original contributions presented in the study are included in the article/Supplementary, further inquiries can be directed to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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