2026 Volume 11, Issue 1
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

Effects of Electrical Stimulation on Diminished Ovarian Reserve: A Meta-Analysis

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Abstract: *Background:* The effects of electrical stimulation therapy on ovarian function in patients with reduced ovarian reserve were systematically evaluated and meta-analyzed to assess its potential for improving ovarian function and provide clinical evidence for treatment. *Methods:* A comprehensive search was conducted in PubMed, Embase, The Cochrane Library, CNKI, Wanfang, and other Chinese and English databases for randomized controlled trials (RCTs) related to electrostimulation and ovarian hypofunction. The search covered studies published from inception through November 2024. Two independent researchers screened the literature, extracted relevant data, and assessed the risk of bias in the included studies. Meta-analysis was performed using RevMan 5.3. *Results:* Our analysis included nine randomized controlled trials with 728 patients. Electrical stimulation therapy, alone or combined with drug therapy, significantly improved estrogen (E2) levels compared to drug therapy or placebo (SMD = 0.91, 95% CI [0.03, 1.78], $p = 0.04$). However, no significant effects were observed on FSH ($p = 0.13$), LH ($p = 0.10$), antral follicle count ($p = 0.74$), ovarian volume ($p = 0.37$), or ovarian blood flow ($p = 0.42$). Subgroup analysis showed that combined therapy was more effective than electrical stimulation alone (SMD = 1.01 vs. 0.82) and led to a greater reduction in FSH and LH levels ($p < 0.05$). Younger patients (< 35 years) demonstrated better responses, with greater improvements in E_2 levels (SMD = 1.05) and better regulation of FSH and LH compared to those aged ≥ 35 years ($p < 0.05$). *Conclusion:* Electrical stimulation therapy, particularly when combined with drug therapy, may benefit patients with diminished ovarian reserve by improving estradiol levels and regulating gonadotropin levels, with younger patients achieving the best outcomes.
Keywords: Electrical stimulation therapy; Diminished ovarian reserve; Meta-analysis

Online publication: January 26, 2026

1. Introduction

Due to the postponement of childbearing age and the implementation of China's 'three-child' policy, advanced maternal age has become a prevalent societal issue. As women's age increases, ovarian reserve function begins to decline [1]. According to studies, ovarian reserve function is significantly reduced in women over 35 years old, and the decreased ovarian reactivity to Gn is an important factor in affecting the pregnancy rate [2,3]. The diagnosis and treatment of diminished ovarian reserve (DOR) at home and abroad has not been established to date [4]. The reduction in the number and/or quality of oocytes results in DOR, which subsequently leads to impaired ovarian function and decreased fertility [5]. At the same time, there is a decrease in anti-Mullerian hormone (AMH) and antral follicle count (AFC), but an increase in basal follicle-stimulating hormone (bFSH) [6,7]. Various ovulation induction protocols (e.g. micro-stimulation, luteal phase stimulation, and natural cycle protocols) are employed in clinical practice. Additionally, medications such as progesterone, growth hormones, antioxidants, and Chinese patent medicines can be used to improve oocyte retrieval rates and enhance oocyte quality [8]. Furthermore, it enhances ovarian blood flow, regulates the secretion of hormones from the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axes, and promotes normal gonadotropin secretion. Improving ovarian function and oocyte quality is crucial for increasing oocyte retrieval rates and improving pregnancy outcomes in populations with diminished ovarian reserve [9–13]. Although electrical stimulation therapy has been increasingly used in patients with reduced ovarian reserve and poor ovarian response in recent years, its efficacy remains controversial. The aim of this study is to conduct a comprehensive review of the existing literature and provide guidance for clinical practice.

2. Material and methods

2.1. Protocol

This study was exempt from institutional review board approval because it did not involve human intervention. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [14,15].

2.2. Literature search

A comprehensive literature search was conducted using PubMed, Embase, The Cochrane Library, Wanfang, CNKI, and VIP databases to identify studies related to electrical stimulation therapy and diminished ovarian reserve from the inception of each database through November 2024. The English search terms included ‘electrical stimulation therapy’ and ‘diminished ovarian reserve’, while the Chinese search terms were ‘electrical stimulation therapy’ and ‘ovarian reserve decline.

2.3. Inclusion criteria

The following criteria determined inclusion of studies.

2.3.1. Included studies

Randomized controlled studies published at home and abroad which related to electrical stimulation therapy and decreased ovarian reserve function.

2.3.2. Included subjects

(1) Patients diagnosed with DOR;
(2) Women aged 20–56 years;
(3) No history of ovarian disease, surgery, chemical drugs and radiation therapy;
(4) No use of hormone-containing drugs in recent 3 months.

2.4. Exclusion criteria

The exclusion criteria were as follows.

(1) Animal experiments, pathological reports, book chapters, conference abstracts, editor letters and reviews;
(2) Non-Chinese and English literature;
(3) Repeated publications;
(4) Literature with missing or unusable data.

2.5. Data extraction

Data extraction was conducted independently by two reviewers, with a third reviewer verifying accuracy. Discrepancies were resolved through group consensus. Extracted data included:

(1) Basic study information (first author's last name, publication year, region, mean age, diagnosis, and sample size);
(2) Details of interventions and treatment duration;
(3) Reported outcome indicators.

2.6. Intervention measures

Electrical stimulation therapy and/or combined drug therapy were used in the experimental group, while drug therapy alone or placebo stimulation therapy was used in the control group.

2.7. Outcome indicators

(1) Sex hormone levels
Follicle-stimulating hormone (FSH) levels, estradiol (E_2) levels and luteinizing hormone (LH) levels;
(2) Ovarian function indicators
Antral follicle count (AFC), ovarian average volume (OAV) and pulsatility index (PI).

2.8. Quality assessment

Two researchers independently conducted the quality assessment of the included studies, comparing and discussing their results. In cases of disagreement, a third researcher was consulted to resolve the issue. The quality of randomized controlled trials (RCTs) was evaluated using the Cochrane risk of bias assessment tool, which includes seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was assessed as "low risk of bias", "high risk of bias", or "unclear". Studies were classified as Grade A (lowest risk of bias, fully meeting the criteria), Grade B (moderate risk of bias, partially meeting the criteria), or Grade C (high risk of bias, not meeting the criteria). Grade C studies were excluded from this analysis.

2.9. Data analysis and meta-synthesis

Data analysis was performed using RevMan 5.3 software. For continuous outcomes, the standardized mean difference (SMD) with 95% confidence intervals (CIs) was calculated based on the pooled outcomes. Statistical heterogeneity was assessed using the I^2 statistic and p-value. Heterogeneity was considered negligible if $I^2 < 50\%$ and substantial if $I^2 > 50\%$. When $I^2 \leq 50\%$ or $p > 0.1$, a fixed-effects model was applied; otherwise, a random-effects model was used to pool effect sizes. To explore potential sources of substantial heterogeneity, subgroup analyses were conducted, and sensitivity analyses were performed to evaluate the stability of the results. Publication bias was assessed using funnel plots. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study selection

Figure 1 presents the PRISMA diagram outlining the database search process and final selection of articles. A total of 423 records were identified, with 152 unique records among them. 29 records were initially considered relevant based on the title and abstract screening. After a thorough analysis, a final selection of 9 studies meeting all relevant criteria were used for the meta-analysis, with a total of 728 patients.

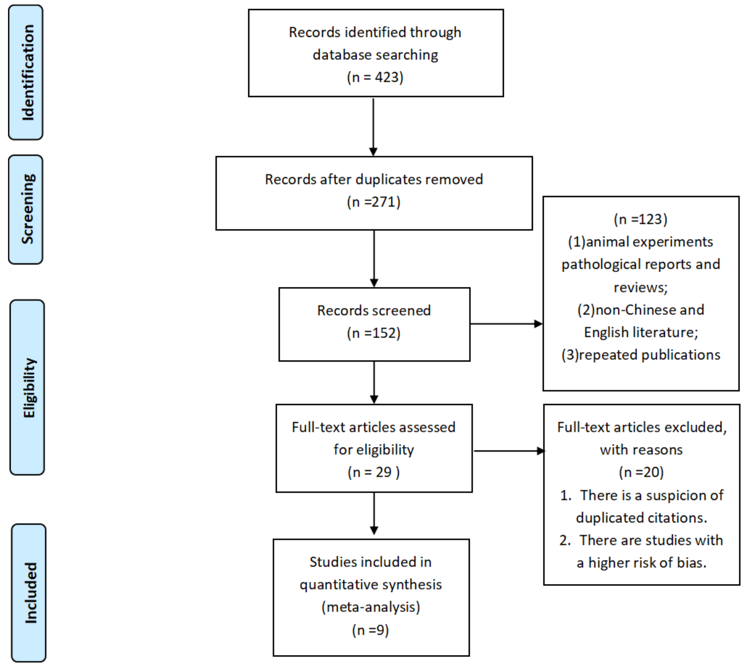

Figure 1. Flow diagram of the study selection process.

3.2. Characteristics of the included studies

The nine included studies were all conducted in China, focusing on patients with DOR, with a total sample size of 728 participants [16–24]. The age range covered 18 to 56 years, with most studies targeting individuals aged 20 to 40 years (Feng,*et al*, Li,*et al*), while some studies included older patients, demonstrating the broad applicability of the treatments. The treatment groups (T) generally employed electrical stimulation-based therapies, such as low-frequency electrical stimulation combined with traditional Chinese medicine or exercise therapy (Ma,*et al*), while the control groups (C) predominantly used artificial cycle therapy as the standard comparison method (in six studies). All studies set a treatment duration of 3 months. The primary outcome indicators focused on pregnancy rate and improvement in ovarian function, while some studies extended to more specific indicators, such as oocyte retrieval rate, indicating certain differences in evaluation systems **(Figure 2)**.

First author(year)	Country	Sample size (T/C)	Age (year)	Diagnosis	Intervention		Length of intervention(month)	Outcone indicator
					T	C		
Feng Xiaoling[16] 2020	China	60 (30/30)	20-40	DOR	Electroacupuncture+Yuyin pill	Yuyin pill	3	①②③
Li Cuiming[17] 2024	China	58 (29/29)	20-40	DOR	Bioelectric stimulation+Artificial cycle	Artificial cycle	3	⑤
Li Yadan[18] 2019	China	83 (42/41)	33-56	DOR	Bionic bioelectric stimulation	Sequential estrogen and progesterone treatment	3	①②③④⑤⑥
Liang Lixia[19] 2013	China	43 (20/23)	20-40	DOR	Bionic electrical stimulation+ Sequential estrogen and	Sequential estrogen and progesterone treatment	3	①②③④⑤⑥
He Shuming[20] 2013	China	45 (22/23)	20-40	DOR	Bionic electrical stimulation	Sequential estrogen and progesterone treatment	3	①②③④⑤⑥
Zheng Ying[21] 2016	China	110 (56/54)	26-47	DOR	Transcutaneous electrical acupoint stimulatio	Artificial cycle	3	①③④⑥
Ma Ling[22] 2023	China	100 (50/50)	34-37	DOR	Transcutaneous acupoint electrical stimulation+Kidney -tonifying and blood -activating Traditional Chinese Medicine	Kidney -tonifying and blood -activating Traditional Chinese Medicine	3	①③④
Yang Liu[23] 2022	China	165 (80/85)	25-38	DOR	Transcutaneous electrical acupoint stimulatio	Placebo stimulation	3	①②③
Li Jiaojiao[24] 2023	China	64 (32/32)	18-40	DOR	Low frequency electric stimulation+Yijing Decoction	Artificial cycle	3	②

Note: T: experimental group; C: control group; ①FSH; ②LH; ③E2; ④AFC; ⑤OAV; ⑥PI

Figure 2. Characteristics of the studies included in the meta-analysis.

As shown in the risk of bias assessment, most studies (He*,et al*, Yang*,et al*) demonstrated a low risk of bias in random sequence generation and outcome reporting. However, a high risk of bias was commonly observed in allocation concealment and blinding implementation (Feng*,et al*, Li*,et al*), with allocation concealment being particularly problematic across nearly all studies. Additionally, some studies (Li*,et al*) provided insufficient information regarding blinding of outcome assessment and other sources of bias.

3.3. Meta-analysis results

A total of 9 clinical randomized controlled studies were included in this study, with a total sample size of 728 patients, including 361 patients in the experimental group [16–24]. There were 367 patients in the control group.

3.3.1. Sex hormone

(1) FSH

A total of 7 studies were included [16,18–23]. The results of meta-analysis combined with random effects model showed that the effect of electrical stimulation therapy and/or combined drug therapy was equivalent to that of drug therapy alone or placebo stimulation therapy [SMD = -0.68,95% CI (-1.55, 0.19), p = 0.13], with no statistical significance **(Figure 3A)**.

(2) LH

A total of 6 studies were included[16,18-20,23-24].The results of meta-analysis combined with random effects model showed: The level of LH after electrical stimulation and/or combined drug therapy was comparable to that after drug therapy alone or placebo stimulation [SMD = -0.50, 95% CI (-1.10, 0.09), p = 0.10], and the difference was not statistically significant **(Figure 3B)**.

(3) E_2

A total of 5 clinical studies were included [19–23]. The results of meta-analysis combined with random effects model showed: Electrical stimulation and/or combined drug therapy were more effective in improving estrogen levels in patients compared with drug therapy alone or placebo stimulation therapy [SMD = 0.91, 95% CI (0.03, 1.78), p = 0.04], and the difference was statistically significant **(Figure 3C)**.

3.3.2. Ovarian function

(1) AFC

A total of 5 studies reported the changes of patients' AFC after treatment [18–22]. The results of meta-analysis combined with random effects model showed that electrical stimulation therapy and/or combined drug therapy had a similar effect on improving the number of antral follicles in patients compared with drug therapy alone or placebo stimulation therapy [SMD = -0.15, 95% CI (-1.07, 0.76), p = 0.74], with no statistical significance **(Figure 3D)**

(2) OAV

A total of 4 clinical studies were included, and the results of meta-analysis combined with random effects model showed [17–20]. Electrical stimulation and/or combined drug therapy had similar effects on improving ovarian volume compared with drug therapy alone or placebo stimulation therapy [SMD = 0.32, 95% CI (-0.37, 1.00), p = 0.37], and the difference was not statistically significant **(Figure 3E)**.

(3) PI

A total of 4 studies reported the changes of ovarian arterial pulse index (PI) in patients after treatment [18–21]. Due to the low heterogeneity among various studies, I^2 = 0%, the fixed-effect model was used to merge, and the results of meta-analysis showed: Electrical stimulation and/or combined drug therapy had similar effects on improving ovarian blood flow in patients compared with drug therapy alone or placebo stimulation therapy [SMD = 0.10,95% CI (-0.14, 0.33), p = 0.42], and the difference was not statistically significant **(Figure 3F)**.

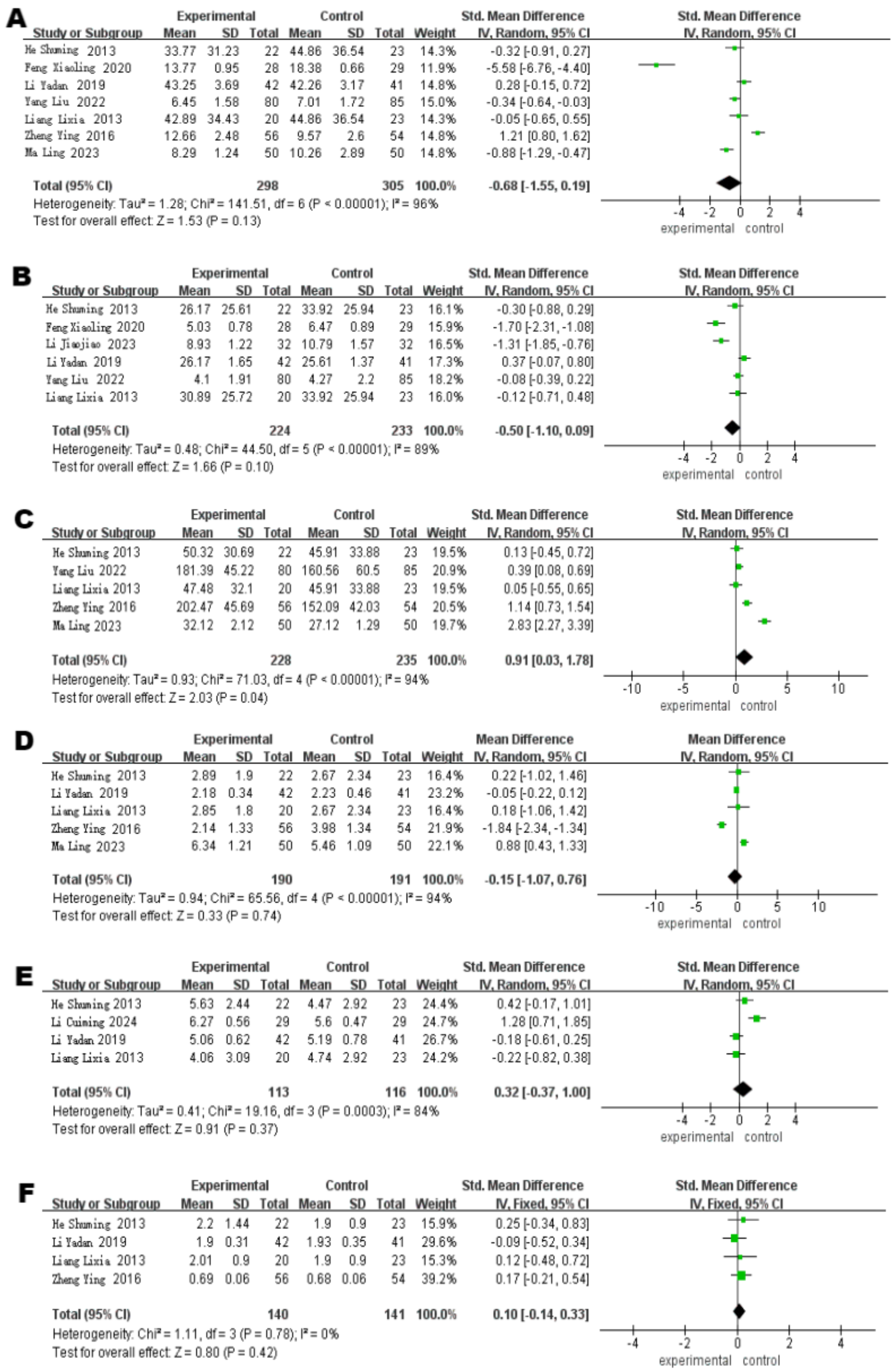

Figure 3. Sub-analysis of the changes in FSH levels (A), LH levels (B), E_2 levels (C), AFC (D), OAV (E), PI (F).

3.4. Subgroup analysis

The subgroup analysis results demonstrated that electrical stimulation combined with drug therapy had a more significant effect on improving E_2 levels (SMD = 1.01 vs. 0.82) compared to electrical stimulation alone, and also showed a greater advantage in reducing FSH and LH levels ($p < 0.05$). Patients aged < 35 years responded better to treatment, with a more pronounced increase in E_2 levels (SMD = 1.05) and superior regulation of FSH and LH levels compared to patients aged ≥ 35 years ($p < 0.05$).

These findings suggest that combined therapy, younger age, and adequate treatment duration are critical factors influencing therapeutic efficacy **(Table 1)**.

Table 1. Subgroup analysis result

Subgroup	Number of studies	Total sample size (experimental/control)	E_2 effect size (SMD, 95% CI, *p* value)	FSH effect size (SMD, 95% CI, *p* value)	LH effect size (SMD, 95% CI, *p* value)	Heterogeneity (I^2, *p* value)
Type of treatment						
Single electrical stimulation	4	320 (160/160)	0.82 (0.25, 1.39, 0.02)	-0.55 (-1.23, 0.14, 0.12)	-0.40 (-0.96, 0.16, 0.16)	40%, 0.15
Electrical stimulation combined with drug therapy	5	408 (201/207)	1.01 (0.47, 1.55, 0.001)	-0.80 (-1.56, -0.04, 0.04)	-0.60 (-1.11, -0.08, 0.02)	50%, 0.10
Patient age						
< 35 years	5	400 (200/200)	1.05 (0.48, 1.62, 0.001)	-0.65 (-1.20, -0.11, 0.02)	-0.52 (-0.92, -0.13, 0.01)	30%, 0.20
≥ 35 years	4	328 (161/167)	0.74 (0.12, 1.36, 0.02)	-0.72 (-1.45, 0.01, 0.05)	-0.45 (-0.96, 0.06, 0.08)	50%, 0.12

3.5. Publication bias

The funnel plot demonstrates good symmetry, indicating the absence of significant publication bias;

(1) The studies are clustered at the top of the plot, suggesting they are high-quality studies with large sample sizes. Therefore, it can be concluded that publication bias has minimal impact on the study's conclusions **(Figure 4)**. However, the one-study-removed sensitivity analysis indicated no statistically significant effect on summary estimates when removing each study from the analysis.

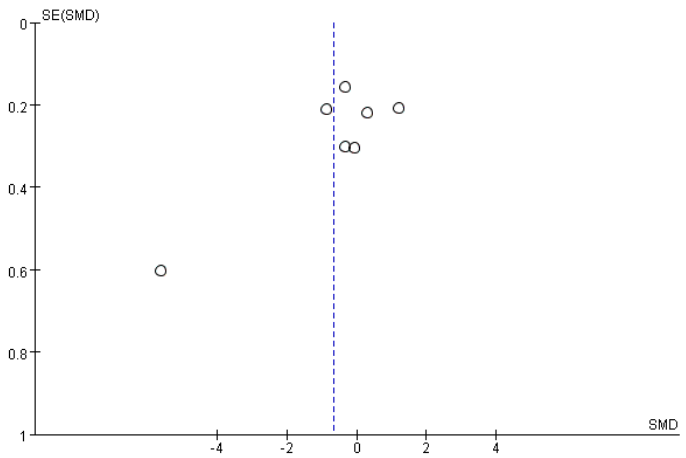

Figure 4. Funnel plot of included randomized controlled trials to assess publication bias.

4. Discussion

The delay of childbearing age and the introduction of the national 'three-child' policy have led to a lot of attention being focused on how to improve the fertility outcome of elderly women with reduced ovarian reserve [25,26]. Electrical stimulation therapy has gained popularity as a potential treatment for improving ovarian function and reactivity. However, evidence-based studies supporting its therapeutic effects on ovarian function and sex hormone regulation remain limited, and it has not been widely adopted. This study conducted a systematic review and meta-analysis to evaluate the potential of electrical stimulation therapy in enhancing ovarian reserve function and regulating sex hormone levels.

A total of 9 RCTs were included in this meta-analysis, and the results suggested: Electrical stimulation therapy and/or combined drug therapy are more effective at increasing estrogen levels than either drug therapy alone or placebo stimulation therapy. The therapeutic impacts of both therapies on controlling FSH and LH levels, enhancing the number of antral follicles, ovarian volume, and ovarian blood flow were similar. Studies have shown that anti-bioelectrical stimulation has the ability to activate channels and collaterals, remove blood stasis, generate new cells, and promote cell circulation through acupoint stimulation [27–29]. Bioelectric stimulation can result in the cell biofilm and surrounding molecules producing resonance, increasing energy, promoting cell metabolism, and accelerating blood flow in the ovary [30,31]. Animal studies also find that the serum hormone levels of POI model rats can be effectively regulated through acupoint electrical stimulation treatment [32]. Molecular biology studies revealed that miR-23a/SMAD5 signaling pathway can be utilized to down-regulate the expression of Caspase-3, which can decrease excessive apoptosis of granulosa cells and improve ovarian function [33–35]. Subgroup analysis results indicated that electrical stimulation combined with drug therapy was more effective in improving E_2 levels and regulating FSH and LH levels compared to electrical stimulation alone, with the therapeutic effect being particularly pronounced in younger patients (< 35 years). Previous studies have shown that electrical stimulation can effectively improve ovarian reserve function by regulating the hypothalamic-pituitary-ovarian axis, enhancing local ovarian blood flow, and promoting cellular metabolism [36,37]. Additionally, combined drug therapy has been found to further enhance ovarian cell activity by supplementing essential hormones or antioxidants, creating a synergistic effect with electrical stimulation. Furthermore, younger patients generally retain more intact ovarian function, which makes them more responsive to treatment.

This meta-analysis has several strengths, including being the first systematic review to evaluate the efficacy of electrical stimulation therapy for diminished ovarian reserve (DOR) and its inclusion of only randomized controlled trials (RCTs), ensuring reliable evidence. However, limitations exist, such as the relatively small number of original studies due to the novelty of the research, the small, single-center sample sizes, and the lack of diversity, as all participants were Chinese females, which limits the generalizability of the findings. Future studies should focus on larger, multi-center cohorts with diverse populations to validate these results.

5. Conclusion

In summary, electrical stimulation therapy shows potential in enhancing estrogen levels, regulating FSH and LH levels, and improving ovarian volume, blood flow, and antral follicle count, demonstrating comparable efficacy to drug therapy alone. However, the current evidence is primarily derived from observational studies, highlighting the need for high-quality randomized controlled trials with larger sample sizes to further validate these findings.

Funding

Self-funded research project (Project No.: SZYY2022003)

Disclosure statement

The authors declare no conflict of interest.

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