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Effect of multimodal electrical stimulation combined with low-intensity focused ultrasound on endometrial receptivity and clinical pregnancy outcomes in infertile women undergoing freeze-thawed embryo transfer

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Abstract

We aimed to investigate the effect of multimodal electrical stimulation combined with low-intensity focused ultrasound on endometrial receptivity as well as clinical pregnancy outcomes in infertile women. One hundred women undergoing in vitro fertilization-frozen-thawed embryo transfer were randomly divided into a treatment group and a control group. The treatment group received multimodal electrical stimulation combined with low-power focused ultrasound treatment for 30 min/times per day, once a day, for 7-10 days; the control group did not receive the treatment, and at the end of the treatment each of the two groups underwent frozen embryo transfer. The effect was assessed by the following indicators: endometrial thickness and volume, type of endometrium, endometrial blood flow, uterine artery pulsatility index, resistance index, and uterine arteria peak systolic velocity/end-diastolic velocity values, endometrial peristaltic wave frequency and endometrial volume; biochemical pregnancy rate, clinical pregnancy rate, and embryo implantation rates. uterine artery S/D and uterine artery RI were significantly increased after treatment with statistical differences. The rest of the indicators showed positive changes but no statistical differences. We conclude that multimodal electrical stimulation combined with low-frequency focused ultrasound therapy is effective in improving endometrial receptivity and clinical pregnancy outcomes in infertile women undergoing frozen-thawed embryo transfer *(Afr J Reprod Health 2026; 30 [11]: 51-62).*

Keywords : Multimodal electrical stimulation, pelvic floor electric muscle stimulation, focused ultrasound, embryo transfer, endometrial receptivity, infertility

Résumé

Nous avons cherché à évaluer l'effet de la stimulation électrique multimodale associée à une échographie focalisée de faible intensité sur la réceptivité endométriale ainsi que sur les résultats de grossesse clinique chez des femmes infertiles. Cent femmes bénéficiant d'une fécondation in vitro avec transfert d'embryons congelés-décongelés ont été réparties aléatoirement en un groupe traitement et un groupe témoin. Le groupe traitement a reçu une stimulation électrique multimodale combinée à une échographie focalisée de faible puissance pendant 30 minutes par séance, une fois par jour, durant 7 à 10 jours. Le groupe témoin n'a reçu aucun traitement supplémentaire. À l'issue de cette période, les deux groupes ont subi un transfert embryonnaire congelé-décongelé. L'efficacité a été évaluée à l'aide des paramètres suivants : épaisseur et volume de l'endomètre, type d'endomètre, flux sanguin endométrial, indice de pulsatilité de l'artère utérine, indice de résistance, rapport entre la vitesse systolique maximale et la vitesse télédiastolique de l'artère utérine, fréquence des ondes péristaltiques endométriales, taux de grossesse biochimique, taux de grossesse clinique et taux d'implantation embryonnaire. Après traitement, le rapport systole/diastole de l'artère utérine ainsi que l'indice de résistance de l'artère utérine ont montré une amélioration statistiquement significative. Les autres paramètres ont présenté des évolutions favorables sans atteindre la signification statistique. Nous concluons que la stimulation électrique multimodale combinée à une échographie focalisée de basse fréquence pourrait être efficace pour améliorer la réceptivité endométriale et les résultats de grossesse clinique chez les femmes infertiles subissant un transfert d'embryons congelés-décongelés *(Afr J Reprod Health 2026; 30 [11]:51-62).*

Mots-clés: Stimulation électrique multimodale ; stimulation électrique musculaire du plancher pelvien ; échographie focalisée ; transfert embryonnaire ; réceptivité endométriale ; infertilité.

Introduction

With the increase in work pressure of modern people, changes in living and eating habits, environmental degradation and other factors, the incidence of infertility is a rapidly rising trend, China's infertility rate of couples of childbearing age from 20 years ago, 2.5% to 3% climbed to about 15% in recent years, of which the number of female infertility patients is higher than the number of male patients with infertility.[1-3] The development of assisted reproductive technology and its derivatives has made In Vitro Fertilization and Embryo Transfer (IVF-ET) an option for many infertile women. Freeze-thawed embryo transfer (FET) is widely used in assisted reproductive technology (ART) because of its effectiveness in improving cumulative pregnancy rates in IVF-ET patients and as a strategy to delay embryo transfer due to inadequate ovarian and endometrial preparation.[4] Ideal pregnancy outcome depends on a favorable endometrial environment and quality embryos, of which endometrial receptivity is one of the key factors.[5] For women who are receiving frozen embryo transfer, poor endometrial receptivity is an important factor leading to embryo transfer failure or even repeated implantation transfer failure (RIF), which is generally defined medically as the failure to achieve a clinical pregnancy after the transfer of four or more embryos.[6] Therefore, how to improve the receptivity of the endometrium becomes a key issue in the treatment of female infertility.[7-9]

Endometrial receptivity refers to the ability of the endometrium to allow blastocysts to localize, adhere, invade, and ultimately implant. Poor endometrial receptivity is manifested by thin endometrium, abnormal endometrial blood flow and morphology, and recurrent miscarriages[10,11], Low endometrial receptivity severely reduces the capacity for natural conception and assisted reproduction.[12,13] Currently, the endometrial receptivity can be improved to some extent by oral medication or surgical treatment[9], but medication has many side effects and surgical treatment is very invasive, so the search for an efficient solution to reduce the endometrial receptivity has become a research hot spot and a difficult problem.

In recent years, physical therapy techniques have become a research highlight in improving endometrial receptivity treatment due to their advantages of being non-invasive, simple, economical and safe. Physical therapy modalities commonly used in the clinic include acupuncture, transcutaneous electrical acupoint stimulation and pelvic floor electric muscle stimulation, acupuncture is through the mechanical stimulation of specific acupoints, activating nerve endings, generating action potentials, the resulting stimulation signals along the nerve trunk into the central nervous system, regulating the nervous system, to achieve therapeutic effects, belonging to the neuromodulation technology.[14] Studies have suggested that acupuncture has some efficacy in improving endometrial receptivity[13], but traditional acupuncture invades the skin, is traumatic, and the maneuvers vary from person to person, making it difficult to replicate the therapeutic effect. Transcutaneous electrical acupoint stimulation is non-invasive and simple to operate compared to traditional acupuncture therapy, and stimulates subcutaneous nerve endings through the electric current generated by electrode pads attached to acupoints on the surface of the body, and the results of the study showed that transcutaneous electrical stimulation improves endometrial receptivity and enhances the rate of conception.[14,15] It can also be stimulated by different frequencies of electric current to form a penetrating electric current magnetic field, which can make the cell membranes and the macromolecules around them resonate, improve the metabolism, increase blood perfusion, accelerate tissue repair and physiological function repair, improve the uterine environment, so as to achieve the purpose of preventing the uterine cavity from re-adhesion.[16] Pelvic floor electric muscle stimulation involves placing electrodes in the pubic area to produce different electric current stimulation, which in turn promotes pelvic blood circulation and improves pelvic floor muscle function. It has been proven effective in treating a range of pelvic problems such as pelvic pain, uterine adhesions and stress urinary incontinence.[17,18]

In addition to being widely used in diagnostic imaging, ultrasound also has great potential in physical therapy.[19] Focused ultrasound, as a new non-invasive therapeutic technology, is the use of ultrasound technology to stimulate acupoints and deliver vibratory energy to soft tissues by means of stimulation with biological effects such as mechanical and thermal effects generated in the body to increase blood flow[20], which will not damage the skin as acupuncture, can be non-invasive, accurate treatment, the effect is consistent with acupuncture, the patient caused by a sense of unhappiness and pain is much lower than that of acupuncture.[21] Currently, although some studies have demonstrated the improvement of endometrial receptivity and clinical pregnancy rates in women with electrical stimulation versus focused ultrasound[22,23], there are no studies combining this three treatments of transcutaneous electrical acupoint stimulation, pelvic floor neuromuscular stimulation, and low-intensity focused ultrasound for the treatment of female infertility.

Based on the clinical data of the previous generation of products, our research group found that the application of electrical stimulation with a certain frequency and pulse width can stimulate the contraction of uterine smooth muscle, improve blood circulation, reduce the endometrial blood flow resistance index, increase the thickness of the endometrium, and increase the blood supply to the ovaries, which improves the clinical pregnancy rate to a certain extent.

This study innovatively proposes a neuro-humoral dual-regulation therapy. The mechanism of action involves the combination of multimodal electrical stimulation and low-intensity focused ultrasound. Specifically, the multimodal electrical stimulation consists of vaginal-cervical electrical stimulation combined with surface circulatory electrical stimulation. The vaginal-cervical electrical stimulation applies electrical stimulation to the uterine body and pelvic muscle groups, thereby accelerating blood supply to the pelvis, uterus, and ovaries. The surface circulatory electrical stimulation enhances peripheral hemodynamics along the anatomical pathways of human blood vessels, thereby exerting a humoral regulatory effect. The surface acupoint focused ultrasound stimulation converges ultrasonic energy through the body surface to the peripheral nerves at subcutaneous acupoints, stimulating the nerves at the corresponding acupoints and regulating the hypothalamic-pituitary-ovarian axis, thereby exerting a neuroregulatory effect. As a novel physical therapy modality, neuro-humoral dual-regulation therapy offers the advantages of being safe, non-invasive, simple to operate, and free of side effects, and is expected to be applied in the treatment of infertility.According to the above clinical treatment data, this clinical trial was conducted to investigate uterine artery blood flow index, endometrial thickness, etc., as well as the implantation rate and pregnancy rate after frozen embryo transfer in the IVF-ET infertility population before and after receiving multimodal electrical stimulation combined with low-intensity focused ultrasound on endometrial receptivity, and to record the observational data to analyze the clinical effectiveness of this treatment method.

Methods

Study design and participants

The trial was conducted from September 2020 to February 2022 at Reproductive and Genetics Hospital of CITIC-XIANGYA. One hundred subjects who failed the first frozen embryo transfer cycle or repeated frozen embryo transfer were enrolled.

Inclusion and exclusion criteria

Inclusion criteria: 1) Subjects who have failed their first frozen embryo transfer cycle or who have failed repeated frozen embryo transfers continue with frozen embryo transfer cycles; 2) Patients clinically diagnosed with ovulation disorders, tubal impassability, resection, post ligation reversal, endometriosis, immunological infertility, primary infertility; or patients with infertility due to insufficient hormone levels; 3) The intima thickness of the ovulation day or intimal transformation day was <8 mm in the previous frozen embryo cycle; 4) Age≤37 years; 5) 18≤BMI<28 kg/m^2; 6) Menstrual cycle≥25 days;Exclusion criteria: 1) Patients with contraindications to low-frequency electrical stimulation therapy, such as those with implantable cardiac pacemakers, with large metal foreign bodies at the treated site; 2) women with malignant tumor, tuberculosis, antiphospholipid syndrome, thrombophlebitis, multiple sclerosis and other diseases; 3) those with abnormal uterine morphology (uterine fibroids, uterine adenomyoma significantly compressed uterine line, uterine mediastinum 10mm), or previous severe intrauterine adhesion; 4) women with severe underlying endocrine disorders, such as diabetes mellitus; 5) women with severe inflammation of the genito-urinary tract; and 6) those with abnormal chromosome examination on one or both sides of the couple or either party did not have a chromosome examination.

Randomization

In this study, a block randomization method was used to generate a randomization allocation table, which contained randomization information including the random seed, block length, and number of blocks. The randomization allocation table was prepared in duplicate, sealed, and kept by the leading research unit responsible for the clinical trial (the sealed randomization allocation table could not be opened before the end of the trial). At the same time, a corresponding randomization allocation envelope was prepared for each participant, with the participant's identification number marked on the envelope. The sealed letter inside specified the treatment assignment allocated to that participant.

The statistical unit was responsible for distributing the randomization allocation envelopes to the research unit. The research unit was required to open the sealed envelopes sequentially in the order of participant enrollment, and to administer treatment according to the group assignment and corresponding treatment method specified in the enclosed letter. The date and time of opening were required to be recorded, and the person opening the envelope was required to sign.

A total of 100 patients were enrolled in this trial, and they were randomly assigned to two experimental groups, treatment group and control group.a.Treatment group: 50 people in the treatment group received clinical routine superovulation therapy, and then received treatment with electro-ultrasound therapeutic apparatu (Medlander Medical Technology Inc. C4000).b. Control group: 50 people in the control group received routine superovulation therapy.

Intervention

Treatment group: The patients received the treatment of electro-ultrasound technology from the eighth day of the menstrual cycle from the eighth day of the menstrual cycle, and the patients were treated with 30 min/time every day, once a day, and treated continuously for 7~10 days according to the doctor's instructions, and the frozen embryo transfer was performed. Prior to treatment, a vaginal-cervical probe was inserted and surface electrode patches were applied for humoral regulation, while an ultrasound transducer was placed at surface acupoints for neuroregulation.

Vaginal-Cervical Electrical Stimulation: The vaginal-cervical probe was inserted into the vagina with the distal electrode positioned against the cervical os, and the circumferential electrodes in full contact with the vaginal wall. Electrical stimulation was applied to the uterine body and pelvic muscle groups to accelerate blood supply to the pelvis, uterus, and ovaries. Cervical electrical stimulation parameters:

Frequency: 5Hz; Current: 7mA; Pulse width: 500μs; On/off cycle: 2s/2s. Vaginal electrical stimulation parameters: Frequency: 40Hz; Current: 22.5mA; Pulse width: 300μs; On/off cycle: 5s/5s.Surface Circulatory Electrical Stimulation: Electrical stimulation was applied along the anatomical pathways of human blood vessels to enhance peripheral hemodynamics.

The electrode placements were as follows:

One pair of electrodes: positive electrode placed over the abdominal surface projection of the abdominal aorta; negative electrode placed over the corresponding posterior renal region on the back.

One pair of electrodes: positive electrode placed over the left external iliac artery projection; negative electrode placed over the left inguinal region.

One pair of electrodes: positive electrode placed over the right external iliac artery projection; negative electrode placed over the right inguinal region.

One pair of electrodes: positive electrode placed over the surface projection of the left femoral artery on the thigh; negative electrode placed over the surface projection of the left gastrocnemius muscle on the lower leg.

One pair of electrodes: positive electrode placed over the surface projection of the right femoral artery on the thigh; negative electrode placed over the surface projection of the right gastrocnemius muscle on the lower leg.Surface circulatory electrical stimulation parameters: Frequency: 2Hz; Current: 20mA; Pulse width: 1000μs; On/off cycle: 5s/5s.

Surface Acupoint Focused Ultrasound Stimulation: Coupling gel was applied to the ultrasound transducer, which was then placed over the following surface acupoints: Guanyuan (CV4), Zhongji (CV3), Zigong (bilateral, EX-CA1), Sanyinjiao (bilateral, SP6), and Zusanli (bilateral, ST36). The focused ultrasound converged energy through the body surface to the peripheral nerves at subcutaneous acupoints, stimulating the nerves at the corresponding acupoints and regulating the hypothalamic-pituitary-ovarian (HPO) axis.

Focused ultrasound parameters: Output power: 1.5W; On/off cycle: 5s/5s.

Control group: Patients underwent frozen embryo transfer after receiving clinical superovulation therapy.

Frozen-Thawed Embryo Transfer procedures are as follows:

Embryo Cryopreservation. Embryos are dehydrated in a high-concentration cryoprotectant solution. The treated embryos are then loaded into straws and rapidly plunged into liquid nitrogen for long-term storage. Each straw is clearly labeled with the patient's information, embryo grade, and cryopreservation date.

Embryo Thawing: The straws containing the embryos are retrieved from the liquid nitrogen tank and warmed gradually according to a standardized protocol. A gradient dilution solution is used to remove the cryoprotectant. Embryo survival rate and morphology are assessed under a microscope. If necessary, a brief period of in vitro culture is performed to evaluate embryonic development.

Embryo Transfer. The patient is instructed to maintain adequate bladder filling and is positioned in the lithotomy position. The embryo is aspirated into a transfer catheter, which is then advanced through the cervix into the uterine cavity under ultrasound guidance, and the embryo is injected.

Data collection

Population characteristics: age, infertility years, infertility type, Body Mass Index (BMI), basal follicle-stimulating hormone (FSH), basal luteinizing hormone (LH), basal estradiol (E2), basal progesterone (P), anti-mullerian hormone (AMH), number of antral follicles (AFC), endometrial preparation program (hormone replacement therapy (HRT) and GnRH-a down-regulation in combination with hormone replacement therapy (GnRH-a-HRT)), number of embryos transferred, embryonic stage.

Transvaginal three-dimensional ultrasound examination.

Detection indexes: (1) endometrial thickness; (2) type of endometrium; (3) uterine arteria peak systolic velocity/end-diastolic velocity (S/D), uterine pulsatility index (PI), and resistance index (RI) of uterine arteries; (4) endometrial peristaltic wave frequency; (5) endometrial blood flow; (6) endometrial volume.

After the end of the treatment period, the clinical pregnancy effect was verified: the pregnancy date, embryo implantation rate, clinical pregnancy rate, and biochemical pregnancy rate were recorded for 10 months, and the pregnancy outcome was tracked. Biochemical pregnancy rate = (number of biochemical pregnancy cycles / total number of embryo transfer cycles)*100%; Clinical pregnancy rate = (number of clinical pregnancy cycles / total number of embryo transfer cycles)*100%; Embryo implantation rate =(number of gestational sacs / total number of embryos transferred)*100%.

Safety indicators

Observation of adverse pregnancy outcomes: placental abruption, miscarriage, monozygotic twin rate, premature rupture of membranes, preterm birth rate, low birth weight infant rate, placenta previa, oligohydramnios, preterm birth, neonatal asphyxia, neonatal congenital macromalformation, etc. The incidence of adverse pregnancy outcomes in each group was used as the evaluation index. Incidence of adverse pregnancy outcomes = (number of adverse pregnancy outcomes/total number of cases in the group)*100%.

Statistical analysis

Data were analysed using Statistic Package for Social Science (SPSS) 19.0 statistical software (IBM, Armonk, NY, USA). Measurement information was expressed as (x±s), paired t-test was used for normality information, and non-normality information was examined by signed rank-sum test with paired design. *P*<0.05 was taken as statistically significant difference.

Ethical statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The study conformed to the US Federal Policy for the Protection of Human Subjects. The study was approved by the Ethics Committee of Reproductive and Genetics Hospital of CITIC-XIANGYA. The ethical approval number: LL-SC-2021-004-02.

Results

Clinical characteristics

The baseline data for control and treatment groups is shown in Table 1. A total of 50 people were enrolled in the treatment group and 50 people were enrolled in the control group in the experiment. It can be seen that there were no statistically significant differences between the control group and the treatment group in terms of age, infertility years, infertility type, BMI, endometrial preparation plan and number of embryos transferred (*P*>0.05).

Table 1: Comparison of clinical characteristics

Basic information	Control group	Treatment group	*P*
Age	30.96±4.23	30.96±3.55	0.904
Infertility years	2.91±2.60	3.08±1.57	0.087
Infertility type			
Primary	13（56.5%）	16（61.5%）	0.721
Secondary	10（43.5%）	10（38.5%）	
BMI	22.48±2.44	21.64±2.94	0.193
Basic FSH (IU/L)	7.10±1.84	7.58±1.90	0.561
Basic LH (IU/L)	4.83±3.16	5.98±3.93	0.296
Basic E2 (pg/mL)	56.20±75.94	46.96±30.09	0.477
Basic P (ng/mL)	0.48±0.33	0.57±0.31	0.223
AMH (ng/mL)	4.28±3.50	4.77±3.66	0.667
AFC	13.5±7.3	16.4±9.0	0.335
Endometrial preparation program			
HRT	17(73.9%)	14(53.8%)	0.146
GnRH-a-HRT	6(26.1%)	12(46.2%)	
Number of embryos transferred	1.61±0.50	1.73±0.45	0.368
Embryonic stage			
Cleavage embryo	13(56.5%)	19(73.1%)	0.224
blastocyst	10(43.5%)	7(26.9%)	

Endometrial receptivity

The endometrial thickness, type of endometrium, uterine artery S/D, uterine artery PI, uterine artery RI, endometrial peristalsis wave frequency, endometrial blood flow, endometrial volume were statistically analyzed, as shown in Table 2. The S/D and RI of the uterine artery were significantly improved after treatment, with a statistically significant difference (*P*<0.05). The endometrial thickness, type of endometrium, uterine artery PI, uterine artery RI, endometrial peristaltic wave frequency, endometrial blood flow and volume showed positive changes, but there was no statistical difference(*P*>0.05).

Clinical pregnancy outcomes

Ultimately, participants in the treatment group and the control group received frozen embryo transfer. The comparison of clinical pregnancy outcomes

Table 2: Comparison of endometrial receptivity

The day before embryo transfer	**Control group**	**Treatment group**	***P***
Endometrial thickness (mm)	10.34±2.42	11.09±2.68	0.508
Type of endometrium			
A	5(21.7%)	8(30.8%)	0.585
B	14(60.9%)	12(46.2%)	
C	4(17.4%)	6(23.1%)	
Uterine artery S/D	7.30±1.98	6.17±1.44	0.032*
Uterine artery PI	2.40±0.46	2.22±0.40	0.118
Uterine artery RI	0.85±0.05	0.82±0.05	0.049*
Endometrial peristaltic wave frequency			
No peristalsis	1(4.3%)	0(0.0%)	0.892
Faint squirming	1(4.3%)	2(7.7%)	
squirming	21(91.3%)	23(88.5%)	
Significant peristalsis	0(0.0%)	1(3.8%)	
Endometrial blood flow			
Level 1	17(73.9%)	22(84.6%)	0.567
Level 2	6(26.1%)	4(15.4%)	
Endometrial volume (mL)	3.74±1.63	4.06±1.67	0.471

Table 3: Comparison of clinical pregnancy outcomes

Outcomes	**Control group**	**Treatment group**	***P***
Biochemical pregnancy rate	43.5%	57.7%	0.321
Clinical pregnancy rate	43.5%	50.0%	0.648
Embryo implantation rate	32.4%	28.9%	0.729

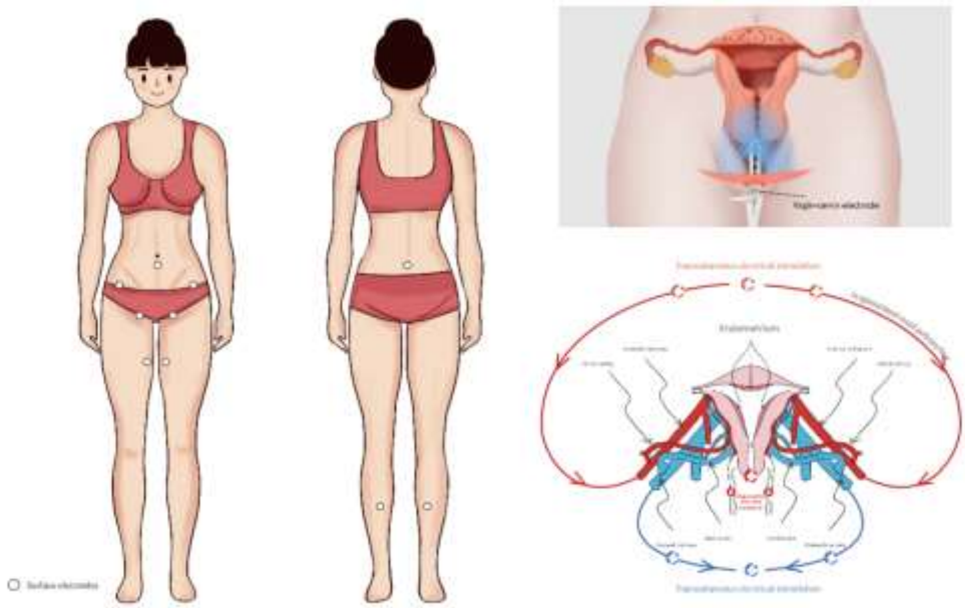

Figure 1: Transcutaneous electrical acupoint stimulation and pelvic floor electric muscle stimulation

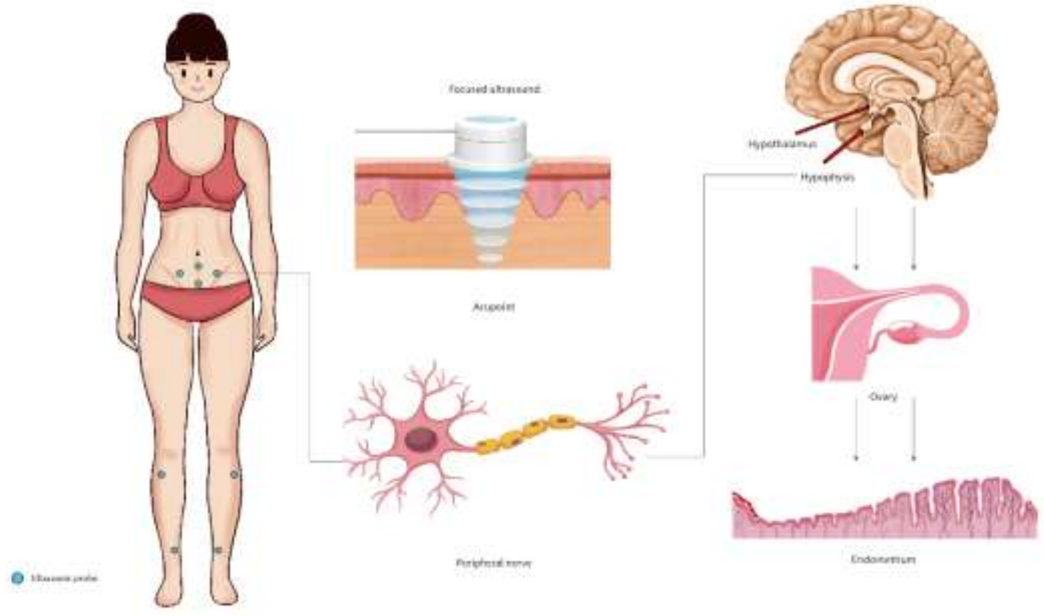

Figure 2: low-intensity focused ultrasound. The authors created the diagram, including all arrows and labels

between control and treatment groups were shown in Table 3. The biochemical pregnancy rate, clinical pregnancy rate and embryo implantation rate of treatment group were all higher in the control group, however, there was no statistical difference(P>0.05).

Safety observation

There were no adverse pregnancy outcomes in this clinical study.

Discussion

As China's fertility rate has gradually declined and the proportion of infertility has gradually increased, we used the Medlander Electro-Ultrasound Therapeutic Apparatus, which combines three therapeutic modalities: transcutaneous electrical acupoint stimulation, pelvic floor electric muscle stimulation, and low-intensity focused ultrasound. In this study, in order to improve the outcome of frozen embryo transfer and pregnancy outcomes in infertile women, we used the Medlander-Electro-Ultrasound Therapeutic Apparatus, which combines three therapeutic modalities: transcutaneous electrical acupoint stimulation, pelvic floor electric muscle stimulation and low-intensity focused ultrasound, for the treatment of patients who underwent frozen-thawed embryo transfer.As a result, although there were no significant differences between the treatment and control groups in endometrial thickness, endometrial peristalsis, endometrial blood flow, endometrial volume, uterine artery PI, or clinical pregnancy outcomes, all of which showed positive changes, there were significant differences in the uterine artery S/D and RI. This partly validates the improvement in endometrial receptivity as well as clinical pregnancy outcomes with this therapy. Shen et al.[24] have found that the electroacupuncture can improve the proportion of type A endometrium, clinical pregnancy rate, embryo implantation rate and live birth rate of the observation group (P<0.01).These results are better than the results of this study, which may be due to the fact that thet study of Shen,et al targeted a population with reduced ovarian function, whereas the population included in this study did not require ovarian status; and the much longer period of that study resulted in a more pronounced effect.

Presently, all three modalities, transcutaneous electrical acupoint stimulation, pelvic floor electric muscle stimulation and focused ultrasound, have now been shown to improve female reproductive function and increase the success rate of assisted reproduction in women. Dmochowski et al.[25] found that percutaneous electrical stimulation resulted in significantly higher serum integrins, serum progesterone, and better development of endometrial cell cytosolic synapses in women who underwent IVF-ET, and that in the final pregnancy outcome, the treated group had a higher clinical pregnancy rate and higher embryo implantation rate than the untreated group.

Bodombossou-Djobo et al.[26] treated dozens of women with a history of infertility and thin endometrium with pelvic floor neuromuscular electrical stimulation (NMES) and found that 60% of the women who received NMES in the middle of the treatment had a significant increase in the thickness of the endometrium and had a higher rate of pregnancy than the patients in the group that did not receive NMES. Guo *et al.*[27] found that long-acting gonadotropin-releasing hormone agonists combined with transvaginal ultrasound-guided cyst aspiration were effective in improving endometrial receptivity, implantation rates, and clinical pregnancy rates in IVF-ET patients with ovarian endometriosis. This may also demonstrate the effectiveness of the treatment modality used in this study on endometrial receptivity and frozen embryo transfer outcomes in women.

The mechanism of electrical stimulation therapy combined with focused ultrasound therapy adopted in this study mainly utilizes the dual regulatory effects of neuromodulation and humoral regulation, as shown in Figure 1 and Figure 2. Multimodal electrical stimulation therapy directly drives pelvic blood circulation through the simultaneous action of surface electrodes and cervical electrodes on the cervix, the abdominal aorta, the external iliac arteries, the femoral arteries, the inguinal groin, the gastrocnemius muscle, the lumbar-sacral area and other blood perfusion hubs. It directly drives the pelvic blood circulation, accelerates the blood flow in the lower limbs, and increases the pelvic blood supply directionally; while focused ultrasound therapy applies principles of traditional Chinese medicine, stimulates corresponding acupoints, activates deep nerves through ultrasound mechanical effects, regulates the hypothalamic-pituitary-ovarian axis, and improves reproductive endocrine function as a whole.[28]

Strengths and limitations

This study possesses several methodological strengths. First, the randomized controlled design with sealed envelope allocation minimizes selection bias and enhances internal validity. Second, the multimodal intervention integrates three distinct physical therapy modalities—transcutaneous electrical acupoint stimulation, pelvic floor neuromuscular stimulation, and low-intensity focused ultrasound—into a unified neuro-humoral dual-regulation protocol, representing a novel and theoretically comprehensive approach to improving endometrial receptivity. Third, the use of standardized, objectively measurable hemodynamic and ultrasonographic parameters (uterine artery S/D, RI, PI, endometrial thickness, volume, and blood flow) provides quantifiable evidence of physiological effects.

However, these strengths must be weighed against substantial limitations. The most critical limitation is the small sample size (n=100), which severely constrains statistical power. In assisted reproductive technology trials, modest effect sizes are common; with only 50 participants per group, the study is markedly underpowered to detect small-to-moderate differences in pregnancy rates. Post-hoc power analysis based on the observed clinical pregnancy rate difference (43.5% vs. 50.0%) indicates that the achieved power was well below the conventional 80% threshold, substantially increasing the risk of type II error. Consequently, we cannot definitively conclude that the intervention is ineffective; rather, we can only state that it failed to demonstrate efficacy under the conditions of this trial.

Additional limitations include the single-center design, which restricts generalizability to broader clinical populations with varying demographic and clinical characteristics. The inclusion of heterogeneous infertility etiologies—ovulation disorders, tubal factors, endometriosis, immunological infertility, and primary infertility—without stratification or subgroup analysis may have introduced confounding variability, potentially masking treatment effects in specific patient populations. The treatment duration (7–10 days) and parameter settings were fixed and not individually titrated; it remains unknown whether extended treatment, higher stimulation intensities, or modified protocols might yield different outcomes.Furthermore, we did not perform a formal apriori sample size calculation based on expected clinical pregnancy rates, which compromises the interpretability of the negative findings and precludes robust efficacy claims.

Conclusion

In conclusion, although multimodal electrical stimulation combined with low-intensity focused ultrasound improved uterine artery blood flow indices, this study failed to demonstrate a significant beneficial effect on endometrial receptivity parameters or clinical pregnancy outcomes in women undergoing FET. The negative findings, compounded by insufficient statistical power and a single-center design, preclude any recommendation for clinical adoption at this time. Hemodynamic improvements alone do not guarantee enhanced implantation success. Future large-scale, adequately powered, multicenter randomized trials with optimized protocols, longer treatment durations, and predefined subgroup analyses are warranted to definitively evaluate whether this intervention holds clinical value for specific infertile populations.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this research.

Authors contribution

Yixin Sun: Conceptualization; data curation; formal analysis; investigation; project administration. Xun Zhang: Investigation; writing-original draft preparation. Yun Ge: Investigation; writing-review and editing. Chao Yang: data curation; investigation; writing-review and editing.

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