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Original Article

Optimization of an integrated traditional Chinese and western medicine regimen for thin endometrium using motherwort injection combined with different doses of CPET - evaluating endometrial receptivity and clinical pregnancy outcomes

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Abstract: Objective: Thin endometrium (TE) is an important factor associated with embryo implantation failure and adverse pregnancy outcomes during assisted reproductive treatment. This study investigated the clinical efficacy of fixed-dose motherwort injection (MI) combined with different doses of compound estradiol/dydrogesterone tablets (CPET) in the treatment of TE, evaluated its effects on endometrial receptivity, and determined the optimal therapeutic dose of CPET. Methods: A retrospective propensity score-matched cohort study was conducted. Patients with TE treated between August 2024 and October 2025 were included. After 1:1:1 PSM, patients were matched into a control group, a low-dose CPET group, and a high-dose CPET group, with 58 patients in each group. The control group received MI alone, whereas the low- and high-dose CPET groups received different doses of CPET in addition to MI. The intervention lasted for three consecutive cycles. Endometrial morphology and hemodynamic parameters were assessed by transvaginal ultrasonography. Serum sex hormones and cytokines were measured by ELISA, and peripheral-blood mRNA expression of receptivity-related genes was detected by qPCR as an exploratory systemic molecular marker. Clinical pregnancy outcomes, safety, and cost-effectiveness were also analyzed. Results: After treatment, all three groups showed improvements in endometrial thickness, endometrial volume, the proportion of type A endometrium, and blood perfusion. The high-dose group exhibited the greatest improvement, followed by the low-dose group and the control group. In the high-dose group, serum VEGF, IGF-1, and LIF levels increased, whereas TGF-β1 levels decreased; meanwhile, peripheral-blood mRNA expression levels of ITGAV, ITGB3, HOXA10, SPP1, and KDR increased in a dose-dependent manner ($P<0.05$), providing exploratory transcriptional evidence rather than direct confirmation of protein expression in endometrial tissues or signaling pathway activation. The clinical pregnancy rate and live birth rate in the high-dose group reached 51.7% and 44.8%, respectively, both higher than those in the control group. No significant differences were observed in early or late miscarriage rates among the three groups ($P>0.05$). Adverse reactions were mainly mild, and the overall incidence of adverse reactions did not differ significantly among groups ($P>0.05$). The high-dose group also showed a more favorable cost-effectiveness profile. Conclusion: MI combined with low- or high-dose CPET may improve endometrial receptivity and pregnancy outcomes in patients with TE. In this retrospective cohort, the high-dose regimen showed favorable short-term efficacy, tolerability, and cost-effectiveness. However, further studies using endometrial tissue samples are required to verify protein-level changes and the specific signaling pathways underlying the observed clinical effects.

Keywords: Thin endometrium, motherwort injection, femoston, endometrial receptivity, clinical pregnancy outcome, propensity score matching

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Introduction

Infertility remains a major clinical concern among couples of reproductive ages. Although assisted reproductive technology has markedly improved the treatment outcomes of infertility, recurrent implantation failure remains one of the major factors limiting the success rate of IVF/ICSI [1]. Thin endometrium (TE) is usually defined as an endometrial thickness of ≤7 mm or <7 mm, and different studies have reported an incidence of approximately 2.4%-8.5% in assisted reproductive treatment cycles [2]. Previous studies have reported lower clinical pregnancy and live birth rates in patients with reduced endometrial thickness, indicating a close association between TE and adverse outcomes after assisted reproduction [3].

At present, estrogen therapy remains a commonly used pharmacological strategy for TE management. The choice of preparation, route of administration, and dosage regimen is usually guided by the endometrial preparation protocol and the patient's response [4]. Existing studies suggest that different 17β-estradiol regimens may lead to differences in serum estradiol levels, endometrial thickness, and pregnancy outcomes. However, no universally accepted optimal dose has yet been established. Therefore, clinical treatment still requires a balance between the benefits of endometrial proliferation and the safety risks related to estrogen use [5]. Intrauterine perfusion, stem cell therapy, and platelet-rich plasma therapy have yielded encouraging results in some small studies. However, their clinical use remains limited by cost, procedural invasiveness, and uncertainty regarding reproducible efficacy [6]. Traditional Chinese medicine (TCM) may improve the endometrial microenvironment through multi-target and multi-pathway regulation [7]. Motherwort injection (MI) is a purified single-herb preparation derived from the traditional Chinese medicine motherwort. Leonurine is regarded as one of its main active components, and in TCM theory, MI is considered to promote blood circulation, remove blood stasis, induce diuresis, and reduce swelling. Clinically, it has been widely used for gynecological hemorrhagic diseases and endometrial injury repair [8]. In China, MI is also one of the commonly used drugs for TE, postpartum hemorrhage, uterine subinvolution, and other gynecological conditions [9, 10]. Recent pharmacological studies suggest that MI may improve endometrial blood perfusion and alleviate fibrosis, thereby potentially enhancing estrogen-related endometrial proliferation [11]. However, the optimal dose of CPET when used in combination with MI remains unclear. Meanwhile, although some studies have explored the feasibility of integrated traditional Chinese and Western medicine in the treatment of TE, the current evidence remains insufficient. For example, many studies have been limited by small sample sizes and insufficient long-term follow-up of pregnancy outcomes [12]. In addition, efficacy evaluation has often focused mainly on endometrial thickness, which may not fully reflect the complex changes in endometrial receptivity [13].

Therefore, this study systematically compared the clinical efficacy of fixed-dose MI combined with different doses of CPET in the treatment of TE. Endometrial receptivity was comprehensively evaluated from three aspects: morphology, hemodynamics, and molecular markers. Safety and health economic outcomes were also assessed, with the aim of providing evidence for optimizing an integrated traditional Chinese and Western medicine regimen in clinical practice.

Materials and methods

Study design

This was a single-center retrospective cohort study using propensity score matching (PSM). Patients with TE who received standardized treatment at the Reproductive Medicine Center of The Central Hospital of Yongzhou between August 2024 and October 2025 were included. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of The Central Hospital of Yongzhou (Approval number: 2023110807).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age 20-40 years, with a regular menstrual cycle (28±7 days); (2) endometrial thickness <7 mm confirmed by ultrasonography for two consecutive cycles on the ovulation day of a natural cycle or on the day of hCG injection in an artificial cycle; (3) first treatment with in vitro fertilization-embryo transfer (IVF-ET) or intracyto-

plasmic sperm injection (ICSI) due to infertility; (4) complete clinical data available in the electronic medical record system, including treatment records, ultrasound reports, laboratory results, and follow-up data on pregnancy outcomes; and (5) follow-up duration ≥6 months from the date of embryo transfer. The exclusion criteria were as follows: (1) congenital uterine malformation, submucosal uterine fibroids, endometrial polyps, endometrial hyperplasia, or malignant lesions; (2) grade III-IV intrauterine adhesions according to the American Society for Reproductive Medicine classification; (3) uncontrolled thyroid dysfunction, diabetes mellitus, hyperprolactinemia, or other endocrine and metabolic diseases; (4) use of estrogen, progesterone, gonadotropins, or other drugs affecting endometrial growth within 3 months before enrollment; (5) severe dysfunction of the heart, liver, kidney, hematopoietic system, or other organs, defined as liver enzymes >2 times the upper limit of normal or creatinine >133 μmol/L; (6) allergy to any component of CPET or MI; (7) psychiatric disorders or inability to complete follow-up; (8) participation in another clinical trial during the same period; and (9) use of traditional Chinese medicine preparations with blood-activating and stasis-resolving effects within 3 months before enrollment.

Grouping and matching

According to the actual treatment regimens recorded in the electronic medical records, the original cohort was divided into three groups: the control group, the low-dose CPET group, and the high-dose CPET group. PSM was performed using a 1:1:1 nearest-neighbor matching method. Matching variables included age, BMI, duration of infertility, type of infertility, number of induced abortions, and other relevant factors. The matching caliper was set at 0.05. After matching, the balance of covariates among groups was assessed using standardized mean differences (SMDs), with SMD <0.2 considered to indicate good balance. A total of 227 patients were included in the original cohort. After matching, 58 patients were included in each group, and 174 patients entered the final statistical analysis.

Sample size calculation

Sample size estimation was performed using G-Power 3.1.9.7 software (Heinrich-Heine-Universität Düsseldorf, Germany). The clinical pregnancy rate was used as the primary outcome. Based on the results of a preliminary small-sample study conducted at our hospital, the clinical pregnancy rate was approximately 32% for MI combined with low-dose CPET, increased to 52% with a medium dose, and reached 56% with a high dose. With a two-sided significance level of $\alpha=0.05$, a statistical power of $1-\beta=0.80$, and an effect size of $w=0.35$ for comparison among three groups, the calculated minimum sample size was 52 patients per group. Considering an anticipated loss to follow-up rate of approximately 10%, the final sample size was set at 58 patients per group, with a total sample size of 174 patients.

Treatment regimens

All patients started treatment on day 1 of menstruation and continued treatment for three menstrual cycles. During treatment, the use of other drugs affecting endometrial growth was prohibited. Concomitant medications were limited to basic nutritional supplements such as vitamin D and folic acid. All three groups received a fixed dose of MI (National Medical Products Administration approval No. Z51021447, Sichuan Shenghe Pharmaceutical Co., Ltd.) by intramuscular injection at 2 ml per injection, containing 20 mg total alkaloids, once daily for 14 consecutive days starting from day 1 of menstruation during the proliferative phase. Low-dose group: on this basis, patients received oral CPET (compound estradiol/dydrogesterone tablets, Abbott Healthcare Products B.V., Netherlands), 1 tablet daily for the first 14 days containing 1 mg estradiol, followed by 1 tablet daily for the next 14 days containing 1 mg estradiol + 10 mg dydrogesterone. High-dose group: patients received 2 tablets daily for the first 14 days containing 2 mg estradiol, followed by 2 tablets daily for the next 14 days containing 2 mg estradiol + 10 mg dydrogesterone.

During treatment, transvaginal ultrasonography was performed on day 21 of each menstrual cycle to assess endometrial growth. If endometrial thickness remained <5 mm after two treatment cycles, the treatment was considered ineffective, and the patient was advised to switch to another treatment regimen and withdraw from this study. After completion of treatment, all patients underwent a uniform

artificial-cycle protocol for endometrial preparation before frozen-thawed embryo transfer. CPET 1 mg/d was started on day 1 of menstruation. On day 14, when ultrasonography confirmed that endometrial thickness was ≥7 mm, dydrogesterone 10 mg bid was added for endometrial transformation. A single blastocyst was transferred on the fifth day after endometrial transformation.

Observation indicators and detection methods

Detection of endometrial morphological and hemodynamic indicators: All ultrasound examinations were performed by the same senior sonographer who had received standardized training. The examiner was blinded to patient grouping. A GE Voluson E8 color Doppler ultrasound diagnostic system (GE Healthcare, USA; serial number: E8-20220915) was used with a transvaginal probe at a frequency of 5-9 MHz. Examinations were performed before treatment and on day 21 of treatment cycles 1, 2, and 3.

Endometrial thickness was measured as the maximum vertical distance between the uterine cavity line and the junction of the anterior and posterior myometrium when the uterine cavity line was clearly displayed on the longitudinal uterine section. The measurement was repeated three times, and the mean value was recorded. Endometrial pattern was classified according to the Gonen criteria as type A (triple-line pattern), type B (homogeneous intermediate echogenicity), or type C (homogeneous hyperechogenicity). Endometrial volume was measured using three-dimensional ultrasound mode. After the endometrial boundary was manually outlined layer by layer, the system automatically calculated the volume. Endometrial echogenicity uniformity was graded from 0 to III. Endometrial peristaltic wave frequency was recorded as the number of spontaneous uterine contractions during a continuous 5-minute observation period.

Uterine artery blood flow parameters were measured by detecting bilateral uterine artery flow spectra 1 cm lateral to the level of the internal cervical os. The pulsatility index (PI) and resistance index (RI) were measured, and the average values from both sides were used. Subendometrial blood flow was graded according to the Applebaum criteria from 0 to III. The endometrial blood perfusion area was calculated using power Doppler mode, with gain, filtering, velocity range, and other parameters kept consistent during all examinations.

Detection of serum indicators: Serum estradiol (E2), progesterone (*P*), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-β1 (TGF-β1), and leukemia inhibitory factor (LIF) levels were detected by enzyme-linked immunosorbent assay (ELISA). The ELISA kits used in this study were as follows: estradiol (E2; R&D Systems, a Bio-Techne brand, Cat. No. KGE014), progesterone (*P*; Novus Biologicals, a Bio-Techne brand, Cat. No. NBP2-60124), vascular endothelial growth factor (VEGF; R&D Systems, a Bio-Techne brand, Cat. No. DVE00), insulin-like growth factor-1 (IGF-1; R&D Systems, a Bio-Techne brand, Cat. No. DG100B), transforming growth factor-β1 (TGF-β1; R&D Systems, a Bio-Techne brand, Cat. No. DB100C), and leukemia inhibitory factor (LIF; R&D Systems, a Bio-Techne brand, Cat. No. DLF00). The procedures were performed strictly according to the manufacturers' instructions. Absorbance was measured at 450 nm using a Multiskan FC microplate reader (Thermo Fisher Scientific, USA), and the concentration of each indicator was calculated according to the standard curve. Blank controls, negative controls, and positive controls were set for each plate. The intra-assay coefficient of variation was <5%, and the inter-assay coefficient of variation was <10%.

Peripheral blood mRNA expression analysis by qPCR: Total RNA was extracted from blood using the Trizol method (Invitrogen, USA). After RNA concentration and purity were verified, 1 μg of total RNA was reverse-transcribed into cDNA using a reverse transcription kit (Takara, Japan). Real-time quantitative PCR (qPCR) was performed to detect the mRNA expression levels of genes related to endometrial receptivity, including integrin αv (ITGAV), integrin β3 (ITGB3), osteopontin (SPP1), homeobox gene A10 (HOXA10), and vascular endothelial growth factor receptor 2 (KDR). GAPDH was used as the internal reference gene. The forward and reverse primer sequences, amplicon lengths, and target genes are listed in **Table 1**. All primers were synthesized by Sangon Biotech (Shanghai) Co., Ltd. The qPCR reaction system was 20 μl in total, containing 10 μl SYBR Green Premix Ex Taq II (Takara, Japan; batch No.

Table 1. Primer sequences used for quantitative real-time PCR analysis

Gene Name	Forward Primer (5'→3')	Reverse Primer (5'→3')	Product Length (bp)
GAPDH	GAAGGTGAAGGTCGGAGTC	GAAGATGGTGATGGGATTTC	226
ITGAV	GACAAGCCCTGGAACGAGAT	GGTGATGGTGATGGTGATGG	147
ITGB3	CAGTGGCTGCTGCTGCTG	GCTGCTGCTGCTGCTGCTG	146
SPP1	AGCTGCTGCTGCTGCTGC	GCTGCTGCTGCTGCTGCT	133
HOXA10	GAAGCTGAGCAAGCCAAGAG	GGTGGTGGTGGTGGTGGTG	156
KDR	GCTGCTGCTGCTGCTGCT	GCTGCTGCTGCTGCTGCT	170

Note: qPCR: Quantitative real-time polymerase chain reaction, bp: base pair, GAPDH: glyceraldehyde-3-phosphate dehydrogenase, ITGAV: integrin αv, ITGB3: integrin β3, SPP1: secreted phosphoprotein 1, HOXA10: homeobox A10, KDR: kinase insert domain receptor.

RR820A), 0.8 μl each of forward and reverse primers, 2 μl cDNA template, and 6.4 μl RNase-free water. The reaction conditions were as follows: pre-denaturation at 95°C for 30 seconds; denaturation at 95°C for 5 seconds and annealing/extension at 60°C for 30 seconds, for 40 cycles; melting curve analysis at 95°C for 15 seconds, 60°C for 1 minute, and 95°C for 15 seconds. Each sample was tested in triplicate, and the relative expression level of each gene was calculated using the $2^{-\Delta\Delta Ct}$ method. As endometrial tissue was not collected, this analysis evaluated peripheral-blood transcriptional changes only, and did not confirm protein-level expression or signaling pathway activation within endometrial tissue.

Embryo transfer cycle and pregnancy outcome indicators: All embryo transfers were performed using a standardized hormone-replacement artificial-cycle protocol. Endometrial morphology and hemodynamic parameters were evaluated by a senior sonographer who was not involved in treatment allocation or pregnancy follow-up and who remained blinded to group assignment during ultrasound assessment. Pregnancy outcomes were obtained from objective clinical records according to prespecified definitions, including ultrasound reports, follow-up records, miscarriage records, and delivery records. However, because this was a retrospective study, complete blinding of pregnancy outcome assessment could not be fully ensured. Detailed parameters of the embryo transfer cycle were recorded for all patients, including the number of oocytes retrieved, number of mature oocytes (M II oocytes), number of fertilized oocytes, number of cleaved embryos, number of high-quality embryos (D3 embryo score ≥8 and fragmentation rate <20%), number of transferred embryos, and serum E_2 and P levels on the day of transfer. The fertilization rate and high-quality embryo rate were then calculated.

Pregnancy outcomes were followed until delivery or 3 months after miscarriage. The main outcome indicators included clinical pregnancy rate, defined as visualization of an intrauterine gestational sac by ultrasonography 4 weeks after transfer; early miscarriage rate, defined as the number of spontaneous miscarriages before 12 weeks of gestation divided by the number of clinical pregnancies ×100%; late miscarriage rate, defined as the number of spontaneous miscarriages at 12-28 weeks of gestation divided by the number of clinical pregnancies ×100%; live birth rate, defined as the number of live infants delivered after 28 weeks of gestation divided by the total number of transfer cycles ×100%; and full-term delivery rate, defined as the number of live infants delivered after 37 weeks of gestation divided by the number of live births ×100%. The time interval from the start of the first treatment to confirmation of clinical pregnancy was also recorded.

Safety indicators: At each follow-up visit during treatment, patients were carefully asked about adverse reactions, and the type of adverse reaction, time of onset, duration, severity, and outcome were recorded. The severity of adverse reactions was classified into three levels: mild, defined as slight symptoms requiring no special treatment and not affecting treatment; moderate, defined as obvious symptoms requiring medication but not affecting continuation of treatment; and severe, defined as serious symptoms requiring treatment discontinuation and symptomatic management. Considering the dose difference in estrogen expo-

sure, estrogen-related safety signals were specifically reviewed, including abnormal vaginal bleeding, breast tenderness, headache or dizziness, edema, gastrointestinal discomfort, liver and renal function abnormalities, and symptoms suggestive of thromboembolic events. When clinically available, records of breast examination, coagulation-related testing, and endometrial evaluation were also reviewed. However, routine long-term surveillance for endometrial hyperplasia, breast stimulation, and thrombotic risk was not performed in all patients because of the retrospective design.

Health economic indicators: Per-patient medical costs in the three groups were calculated from the patient perspective. The calculation period covered the time from the start of the first treatment to 3 months after embryo transfer. Costs included direct medical costs, such as ultrasound examination fees, laboratory examination fees, drug costs, embryo transfer fees, and endometrial biopsy fees, as well as indirect medical costs, including lost wages, transportation expenses, and accommodation expenses. Lost wages were calculated as the local average daily wage multiplied by the number of medical visit days. The clinical pregnancy rate and live birth rate were used as effectiveness indicators, and the cost-effectiveness ratio (C/E) was calculated.

Statistical analysis

SPSS 26.0 statistical software (IBM, USA) was used for data analysis. Continuous variables were first assessed for normality using the Shapiro-Wilk test and for homogeneity of variance using Levene's test. Normally distributed variables with homogeneous variances were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared among groups using one-way analysis of variance. LSD tests were used for pairwise comparisons only when the homogeneity of variance assumption was met. When variances were unequal, Welch's analysis of variance followed by the Games-Howell post hoc test was used. Continuous variables that did not conform to a normal distribution were expressed as median and interquartile range [M (P25, P75)] and compared using the Kruskal-Wallis H test. Categorical variables were expressed as frequency and percentage [n (%)]. The χ^2 test was used when the expected frequencies met the assumptions for χ^2 analysis, whereas Fisher's exact test was used when any expected cell count was less than 5. After PSM, standardized mean differences were used to evaluate the balance of covariates among groups. All statistical tests were two-sided, with α=0.05 as the significance level. P<0.05 was considered statistically significant.

Results

Analysis of baseline data balance

After matching, no statistically significant differences were observed in the measured baseline covariates among the three groups (P> 0.05), suggesting improved comparability after PSM. However, several standardized mean differences remained slightly above 0.2, and residual imbalance in measured covariates could not be completely excluded. These findings suggested that major confounding factors commonly encountered in retrospective studies were reasonably controlled, although residual imbalance in some measured covariates could not be completely excluded. As shown in **Table 2**, there were no statistically significant differences among the three groups in age, BMI, duration of infertility, type of infertility, number of induced abortions, or other variables (P>0.05) (**Table 2**).

Effects of treatment on endometrial morphological indicators

Before treatment, the three groups had comparable baseline endometrial morphology, and none of the measured indicators differed significantly among groups (P>0.05). As treatment progressed, endometrial thickness gradually increased in all three groups, but the increase was greater in the combined treatment groups than in the monotherapy group. After three treatment cycles, the mean endometrial thickness in the high-dose group reached (7.66±0.83) mm, which was higher than that in the low-dose group and the control group (P<0.05). The trends in endometrial volume, proportion of type A endometrium, endometrial echogenicity uniformity, and peristaltic wave frequency were consistent with those of endometrial thickness. After three treatment cycles, the proportion of type A endometrium in the high-dose group reached

Table 2. Baseline characteristics of patients with thin endometrium after propensity score matching

Variable	Control Group	Low-dose Group	High-dose Group	F or χ^2	*P*	SMD
Age (years)	31.95±3.91	31.17±3.69	30.84±4.34	1.17	0.313	0.269
BMI (kg/m^2)	22.11±2.85	22.19±2.37	22.84±2.97	1.232	0.294	0.251
Duration of infertility (years)	3.79±2.20	3.83±1.92	4.03±1.83	0.249	0.78	0.119
Primary infertility [n (%)]	26 (44.8)	23 (39.7)	28 (48.3)	0.885	0.642	0.174
Number of induced abortions	2.16±0.93	1.97±1.09	2.10±1.10	0.601	0.51	0.188
Smoking [n (%)]	16 (27.6)	12 (20.7)	15 (25.9)	0.803	0.669	0.161
Alcohol consumption [n (%)]	10 (17.2)	12 (20.7)	7 (12.1)	1.572	0.456	0.233

Note: BMI: Body mass index, SMD: standardized mean difference. Data are expressed as mean ± standard deviation or n (%), as appropriate.

Table 3. Comparison of endometrial morphological parameters before and after treatment among the three groups

Variable	Time Point	Control Group	Low-dose Group	High-dose Group	F	*P*
Endometrial thickness (mm)	Before treatment	5.34±0.60	5.22±0.45	5.36±0.66	1.024	0.361
	After treatment	6.33±0.66$^{\&}$	7.12±0.64$^{*,\&}$	7.66±0.83$^{*,\#,\&}$	51.241	<0.001
Endometrial volume (ml)	Before treatment	2.03±0.56	2.15±0.54	2.07±0.45	0.743	0.477
	After treatment	2.89±0.64$^{\&}$	3.50±0.77$^{*,\&}$	4.20±0.79$^{*,\#,\&}$	45.733	<0.001
Type A endometrium	Before treatment	12 (20.7)	15 (25.9)	14 (24.1)	0.447	0.800
	After treatment	23 (39.7)$^{\&}$	35 (60.3)$^{*,\&}$	42 (72.4)$^{*,\#,\&}$	13.03	0.002
Endometrial echogenic uniformity	Before treatment	2.22±0.77	2.33±0.66	2.05±0.63	2.357	0.098
	After treatment	1.52±0.57$^{\&}$	1.10±0.55$^{*,\&}$	0.84±0.37$^{*,\#,\&}$	26.251	<0.001
Endometrial peristaltic wave frequency (times/5 min)	Before treatment	4.22±1.34	4.22±1.01	4.14±1.15	0.105	0.901
	After treatment	3.19±0.76$^{\&}$	2.50±0.78$^{*,\&}$	1.88±0.68$^{*,\#,\&}$	45.541	<0.001

Note: $^{*}P$<0.05, compared with control group; $^{\#}P$<0.05, compared with low dose group; $^{\&}P$<0.05, compared with before treatment.

72.4%, and the endometrial peristaltic wave frequency decreased to (1.88±0.68) times/5 min (P<0.05). Overall, the morphological indicators improved in a dose-dependent manner (**Table 3**).

Effects of treatment on endometrial hemodynamic parameters

After treatment, uterine artery blood flow resistance decreased to varying degrees in all three groups, with the most marked improvement observed in the high-dose group (P< 0.001). Meanwhile, in the high-dose group, the proportion of grade III subendometrial blood flow reached 70.7%, and the blood perfusion area reached (42.98±5.85)%, both of which were higher than those in the control and low-dose groups (P<0.05) (**Table 4**).

Effects of treatment on serum sex hormones and cytokines

Serological testing showed that sex hormone and cytokine levels were comparable among the three groups before treatment. After three treatment cycles, E_2 and P levels increased to different extents in all three groups, with the largest increase observed in the high-dose group (P<0.05). Regarding cytokines, combined treatment increased the levels of the pro-angiogenic factors VEGF and IGF-1, as well as LIF, a key factor associated with endometrial receptivity. Combined treatment also decreased the level of TGF-β1, a fibrosis-related factor, and this regulatory effect appeared to be dose-dependent (P<0.001) (**Figure 1**).

Effects of treatment on clinical pregnancy outcomes

The clinical pregnancy rate in the high-dose group reached 51.7%, which was higher than 39.7% in the low-dose group and 27.6% in the control group (P=0.029). Correspondingly, the live birth rate was also higher in the high-dose group, reaching 44.8% (P=0.006). In addition, the mean interval from the first treatment to confirmation of pregnancy was (86.47±21.62) days in the high-dose group, shorter than that

Table 4. Comparison of endometrial hemodynamic parameters before and after treatment among the three groups

Variable	Time Point	Control Group	Low-dose Group	High-dose Group	F	*P*
Uterine artery PI	Before treatment	2.70±0.52	2.63±0.43	2.81±0.47	2.319	0.102
	After treatment	2.17±0.49$^{\&}$	1.91±0.32$^{*,\&}$	1.61±0.30$^{*,\#,\&}$	31.713	<0.001
Uterine artery RI	Before treatment	0.89±0.08	0.89±0.09	0.92±0.07	2.567	0.08
	After treatment	0.75±0.08$^{\&}$	0.67±0.07$^{*,\&}$	0.61±0.05$^{*,\#,\&}$	68.234	<0.001
Grade III subendometrial blood flow	Before treatment	8 (13.8)	9 (15.5)	10 (17.2)	0.263	0.877
	After treatment	21 (36.2)$^{\&}$	33 (56.9)$^{*,\&}$	41 (70.7)$^{*,\#,\&}$	14.103	<0.001
Endometrial blood perfusion area (%)	Before treatment	18.61±3.53	17.97±2.94	17.42±3.08	2.006	0.138
	After treatment	27.75±4.36$^{\&}$	34.36±4.56$^{*,\&}$	42.98±5.85$^{*,\#,\&}$	137.2	<0.001

Note: $^{*}P$<0.05, compared with control group; $^{\#}P$<0.05, compared with low dose group; $^{\&}P$<0.05, compared with before treatment. PI: Pulsatility index, RI: resistance index.

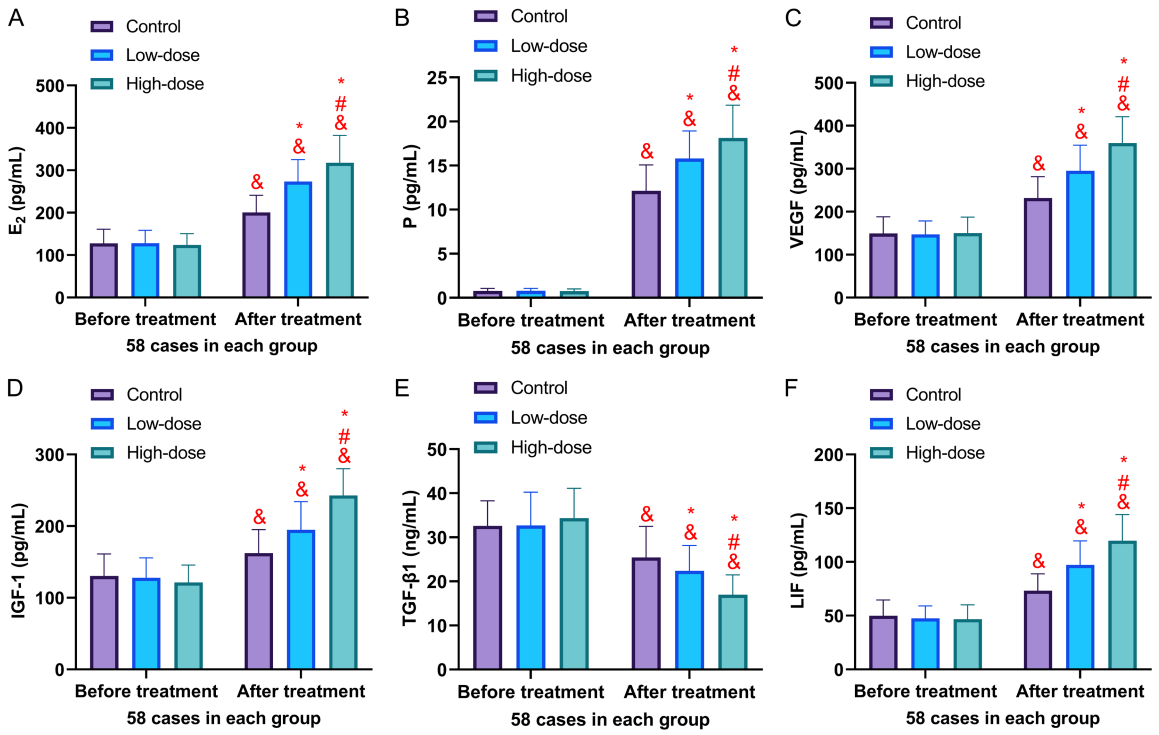

Figure 1. Effects of motherwort injection combined with CPET on serum sex hormones and cytokines in patients with thin endometrium after 3 treatment cycles. A. Serum estradiol (E2) levels. B. Serum progesterone (*P*) levels. C. Serum vascular endothelial growth factor (VEGF) levels. D. Serum insulin-like growth factor-1 (IGF-1) levels. E. Serum transforming growth factor-β1 (TGF-β1) levels. F. Serum leukemia inhibitory factor (LIF) levels. Compound estradiol/dydrogesterone tablets (CPET), estradiol (E2), progesterone (P), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-β1 (TGF-β1), leukemia inhibitory factor (LIF). $^{*}P$<0.05, compared with the control group; #*P*<0.05, compared with the low-dose group; &*P*<0.05, compared with before treatment.

in the low-dose and control groups (*P*<0.001). However, there were no significant differences in early or late miscarriage rates among the three groups (*P*>0.05) (**Table 5**). Because the numbers of early and late miscarriage events were small, Fisher's exact test was used for these comparisons.

Comparison of key indicators in the embryo transfer cycle

To exclude the influence of embryo quality and endocrine status during the transfer cycle on pregnancy outcomes, we further analyzed key parameters of the embryo transfer cycle in the

Table 5. Comparison of clinical pregnancy outcomes among the three groups

Variable	Control Group	Low-dose Group	High-dose Group	F or χ^2	*P*
Clinical pregnancy rate	16 (27.6)	23 (39.7)	30 (51.7)*,#	7.061	0.029
Live birth rate	10 (17.2)	18 (31.0)*	26 (44.8)*,#	10.314	0.006
Early miscarriage rate	5/16 (31.3)	4/23 (17.4)	3/30 (10.0)	3.28	0.194
Late miscarriage rate	1/16 (6.3)	1/23 (4.3)	1/30 (3.3)	0.213	0.899
Time to pregnancy confirmation (days)	130.94±30.09	104.78±23.68*,#	86.47±21.62*,#	17.364	<0.001

Note: *P<0.05, compared with control group; #P<0.05, compared with low dose group. Fisher's exact test was used for early and late miscarriage rates because of small expected cell counts.

Table 6. Comparison of embryo transfer cycle parameters among the three groups

Variable	Control Group	Low-dose Group	High-dose Group	F	*P*
Number of oocytes retrieved	12.57±3.97	11.26±3.87	12.60±3.40	2.42	0.092
Number of mature oocytes	9.88±4.20	8.43±4.20	9.83±3.48	2.479	0.087
Fertilization rate (%)	79.43±7.47	79.83±8.39	80.99±7.30	0.636	0.531
High-quality embryo rate (%)	54.35±11.03	52.87±7.70	52.51±11.57	0.525	0.592
Serum E_2 on transfer day (pg/ml)	292.35±45.22	295.60±52.47	302.86±62.04	0.583	0.560
Serum P on transfer day (ng/ml)	15.14±3.10	15.67±2.80	15.49±3.58	0.416	0.66

Note: MII: Metaphase II, E2: estradiol, P: progesterone.

three groups. The results showed no statistically significant differences among the three groups in the number of oocytes retrieved, number of mature oocytes, fertilization rate, high-quality embryo rate, number of transferred embryos, or serum E_2 and P levels on the day of transfer (P>0.05). These findings suggest that the differences in pregnancy outcomes among the three groups were unlikely to be mainly explained by embryo-related factors or endocrine status during the transfer cycle, but were more likely related to treatment-associated improvement in endometrial receptivity (**Table 6**).

Effects of treatment on peripheral-blood mRNA expression of receptivity-related markers

After three treatment cycles, the peripheral-blood mRNA expression levels of five receptivity-related genes, namely ITGAV, ITGB3, SPP1, HOXA10, and KDR, increased in a dose-dependent manner. The relative expression levels of these genes in the high-dose group were higher than those in the control and low-dose groups (P<0.05). These peripheral-blood transcriptional changes were consistent with the ultrasound and serological findings and provided exploratory molecular evidence associated with the combined treatment; however, they did not directly demonstrate corresponding protein expression or signaling pathway activation in endometrial tissue (**Figure 2**).

Safety evaluation

Safety evaluation showed that the incidence of adverse reactions during treatment was low in all three groups, and no serious adverse reactions occurred. The overall incidence of adverse reactions did not differ significantly among groups (P=0.456). The main adverse reactions were mild gastrointestinal symptoms, breast tenderness, headache, and dizziness. These symptoms resolved spontaneously without special treatment and did not interrupt treatment (**Table 7**).

C/E analysis

Health economic analysis showed that although treatment costs were higher in the low-dose and high-dose groups than in the control group (P=0.007), their C/E ratios were more favorable. In the high-dose group, the costs per clinical pregnancy and per live birth were 29994.67 yuan and 34609.23 yuan, respectively, indicating a health-economic advantage (**Table 8**).

Discussion

Using a strict 1:1:1 PSM design, this study systematically evaluated the clinical value of MI combined with different doses of CPET in the

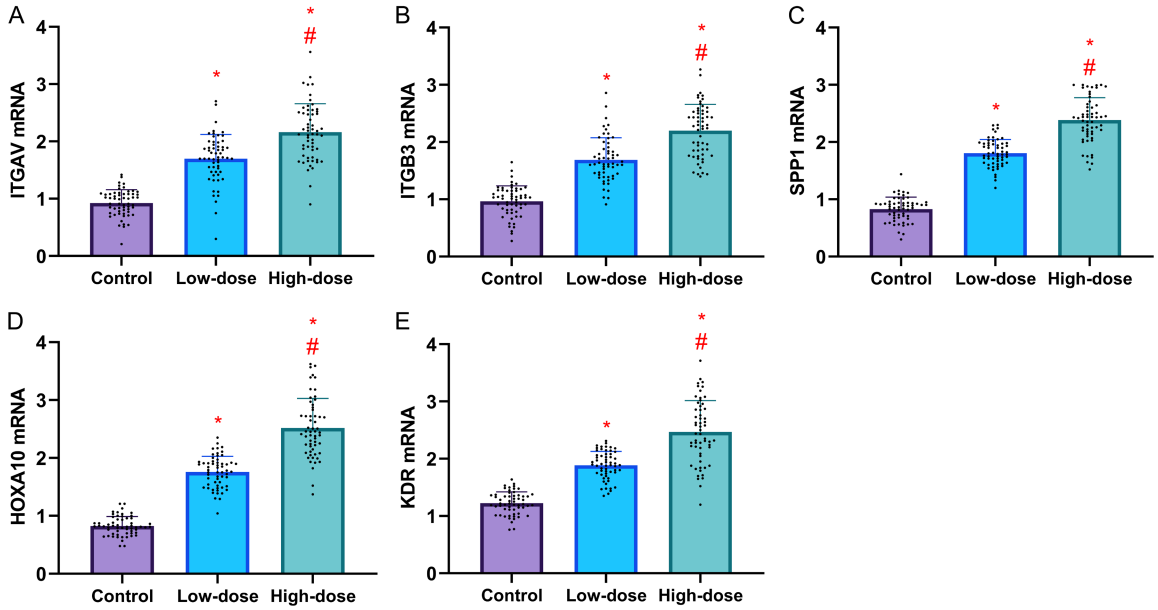

Figure 2. Effects of motherwort injection combined with CPET on peripheral-blood mRNA expression of receptivity-related genes after 3 treatment cycles. A. Relative mRNA expression of ITGAV. B. Relative mRNA expression of ITGB3. C. Relative mRNA expression of SPP1. D. Relative mRNA expression of HOXA10. E. Relative mRNA expression of KDR. Compound estradiol/dydrogesterone tablets (CPET), messenger RNA (mRNA), integrin αv (ITGAV), integrin β3 (ITGB3), secreted phosphoprotein 1 (SPP1), homeobox A10 (HOXA10), kinase insert domain receptor (KDR). *P<0.05, compared with the control group; #P<0.05, compared with the low-dose group.

Table 7. Comparison of treatment-related adverse events among the three groups

Variable	Control Group	Low-dose Group	High-dose Group	X^2	P
Overall adverse reaction rate	7 (12.1)	10 (17.2)	12 (20.7)	1.572	0.456
Gastrointestinal reactions	3 (5.2)	6 (10.3)	8 (13.8)		
Breast tenderness	3 (5.2)	3 (5.2)	3 (5.2)		
Headache/dizziness	1 (1.7)	1 (1.7)	1 (1.7)		
Mild adverse reactions	7 (12.1)	9 (15.5)	11 (19.0)	1.052	0.591
Moderate adverse reactions	0 (0.0)	1 (1.7)	1 (1.7)	1.012	0.603

Table 8. Cost-effectiveness analysis of the three treatment strategies

Variable	Control Group	Low-dose Group	High-dose Group	F	P
Direct medical cost (CNY)	12533.76±1257.36	13136.00±1092.16*	13224.33±1432.86*	5.091	0.007
Indirect medical cost (CNY)	2256.21±288.46	2232.59±265.21	2290.16±262.54	0.655	0.521
Total cost (CNY)	14789.97±1291.90	15368.59±1134.78*	15514.48±1470.24*	4.992	0.008
Cost per clinical pregnancy achieved (CNY)	53613.63	38755.57	29994.67	-	NA
Cost per live birth achieved (CNY)	85781.8	49521	34609.23	-	NA

Note: *P<0.05, compared with control group. CNY: Chinese yuan, NA: not applicable.

treatment of TE. The results showed that the CPET-based regimen containing 2 mg/d estradiol was associated with improvements in endometrial morphology, hemodynamics, and peripheral-blood transcriptional markers related to receptivity, along with higher clinical pregnancy and live birth rates. At the same time, this regimen showed acceptable safety and a more favorable cost-effectiveness profile. This finding suggests that the assumption that "higher-dose estrogen is necessarily associated with higher risk and higher cost" may not apply to all clinical settings, and it provides useful evidence for dose optimization in the

integrated traditional Chinese and Western medicine treatment of TE.

After three treatment cycles, endometrial thickness, endometrial volume, the proportion of type A endometrium, and blood perfusion in the three groups gradually improved as the CPET dose increased. The high-dose group showed better outcomes than both the control and low-dose groups. This result suggests that, in the setting of MI combination therapy, endometrial proliferation continued to improve as the estrogen dose increased, with no obvious plateau observed within the dose range examined in this study. By providing exogenous estradiol, CPET may act on estrogen receptors in endometrial epithelial and stromal cells, thereby promoting mitosis, proliferation, and differentiation. A higher estradiol dose may produce stronger activation of downstream signaling pathways, thereby promoting endometrial growth and repair [14]. Fixed-dose MI may participate in endometrial repair by improving vascular function and the local microenvironment, although the mechanism underlying this effect should still be interpreted with caution. Previous studies have shown that leonurine can inhibit calcium influx in vascular smooth muscle cells and produce a certain vasodilatory effect, while total alkaloids from motherwort have also shown angiogenic potential in experimental models [15, 16]. In addition, TE is often accompanied by increased blood flow resistance, decreased VEGF expression, and insufficient vascular development, suggesting that impaired local perfusion may be involved in the development of TE [17]. Other animal or cellular experiments have suggested that leonurine may participate in angiogenic regulation through HIF-1α/VEGF or PI3K/Akt-eNOS-related pathways [18]. However, the above evidence is mainly derived from non-TE clinical studies or non-endometrial models, and it still cannot directly prove that MI enhances the endometrial proliferative effect of CPET.

The morphological and hemodynamic improvements observed in this study were also reflected in the serological and molecular findings. It should be emphasized that the mRNA markers in this study were detected in peripheral blood rather than endometrial tissue; therefore, these findings should be interpreted as systemic transcriptional changes associated with treatment rather than direct evidence of endometrial tissue-level molecular remodeling. This study found that serum levels of the pro-angiogenic factors VEGF and IGF-1, as well as LIF, a key factor of endometrial receptivity, increased in the high-dose group, whereas the fibrosis-related factor TGF-β1 decreased. Meanwhile, peripheral-blood mRNA expression of receptivity-related genes, including ITGAV, ITGB3, SPP1, HOXA10, and KDR, also showed dose-dependent upregulation. Together, these findings support the hypothesis that the combined regimen may be associated with angiogenesis, implantation-window regulation, and fibrotic remodeling, but the present data cannot confirm the activation of these mechanisms within endometrial tissue. The possible synergistic effect of MI and CPET may be explained by their complementary actions on endometrial proliferation, vascular remodeling, and antifibrotic regulation. Estradiol in CPET provides a direct proliferative stimulus by activating estrogen receptor-dependent epithelial-stromal signaling in the endometrium. Previous evidence suggests that estrogen-mediated uterine epithelial proliferation may be regulated by stromal factors such as FGF10 and BMP8A [14]. In contrast, MI may mainly improve the local endometrial microenvironment. Leonurine, one of the major active components of motherwort, has been reported to induce vasorelaxation [15], and motherwort alkaloids have shown angiogenic activity in experimental models [16]. Experimental studies further suggest that leonurine may regulate angiogenesis through HIF-1α/VEGF activation [19] and the PI3K/Akt-eNOS signaling pathway [20]. These findings are biologically consistent with the decreased uterine artery PI and RI and the increased VEGF level observed in the present study. In addition, the reduction in TGF-β1 may indicate attenuation of profibrotic remodeling, which is supported by previous evidence that leonurine can regulate TGF-β/Smad2-related signaling in fibrosis models [21]. Therefore, CPET may promote endometrial proliferation directly, whereas MI may enhance perfusion and reduce fibrotic resistance; their combined use may improve endometrial receptivity through complementary mechanisms. Previous studies have shown that estrogen-related signaling may participate in the regulation of VEGF expression, and that LIF/LIFR plays an important role in endometrial receptivity and embryo

implantation [22, 23]. At the same time, leonurine has shown potential to regulate PI3K/Akt-eNOS and TGF-β/Smad-related pathways in endothelial cells or other fibrosis models [20, 24, 25]. Therefore, the mechanistic pathways discussed above should be regarded as biologically plausible explanations based on previous studies and current clinical associations, rather than mechanisms directly verified by the present study.

The differences in clinical pregnancy outcomes were consistent with the observed improvement in endometrial receptivity. The clinical pregnancy rate and live birth rate in the high-dose group reached 51.7% and 44.8%, respectively, both higher than those in the control and low-dose groups. The interval from the first treatment to confirmation of pregnancy was also the shortest in the high-dose group. More importantly, there were no statistically significant differences among the three groups in the number of oocytes retrieved, number of mature oocytes, fertilization rate, high-quality embryo rate, or serum sex hormone levels on the day of transfer. These findings made it less likely that embryo-related factors were the main explanation for the differences in pregnancy outcomes and suggested that the higher pregnancy rate was more likely related to improved endometrial receptivity in the high-dose group. These findings are consistent with previous reports showing that thin endometrium is associated with impaired local perfusion, increased vascular resistance, reduced glandular epithelial growth, and decreased VEGF expression [17]. They are also in line with studies indicating that VEGF, LIF, HOXA10, and integrin family molecules are closely related to endometrial receptivity and embryo implantation [13, 26]. Compared with regenerative approaches such as platelet-rich plasma or growth hormone, which have been reported to improve endometrial function but remain limited by heterogeneity of protocols, additional procedures, and uncertain reproducibility [27, 28], the MI plus CPET regimen may be easier to standardize in routine clinical practice. However, unlike randomized controlled trials or mechanistic experiments, the present retrospective clinical study can only suggest an association between the combined regimen and improved receptivity. Further studies are required to verify whether the observed clinical benefit is mediated through the VEGF-related angiogenic pathway, LIF-mediated implantation-window regulation, HOXA10/integrin-related receptivity regulation, or TGF-β1-related antifibrotic remodeling. In the health economic analysis, although the direct drug cost in the high-dose group was higher than that in the control and low-dose groups, the cost for achieving one clinical pregnancy and one live birth was the lowest, at 29994.67 yuan and 34609.23 yuan, respectively. This finding can be explained clinically: the high-dose regimen may have improved the success rate of a single treatment course and reduced the need for repeated examinations, additional medication use, and repeated embryo transfer caused by treatment failure, while also shortening the treatment cycle and reducing indirect costs such as lost wages and transportation expenses. Compared with many previous studies that primarily focused on efficacy and paid less attention to economic evaluation [27-29], the present study further suggests that the high-dose regimen may be more economical from the perspective of overall patient treatment cost. In terms of safety, there was no statistically significant difference in the overall incidence of adverse reactions among the three groups. All adverse reactions were mild, including gastrointestinal reactions, breast tenderness, and slight discomfort at the injection site, and no serious adverse events occurred. These findings suggest that short-term use of 2 mg/d estradiol combined with MI was well tolerated in this cohort and did not appear to increase estrogen-related adverse reactions. Nevertheless, these safety findings reflect short-term tolerability only. They do not provide definitive long-term safety evidence. This study did not include systematic long-term monitoring of endometrial hyperplasia, breast stimulation, coagulation function, or thromboembolic events. Therefore, the present results are insufficient to support widespread clinical use of the high-dose regimen without further safety verification. In clinical practice, individualized risk assessment and appropriate monitoring are still required when high-dose estrogen is used, particularly because the optimal estrogen regimen for thin endometrium remains uncertain and should be balanced against potential safety concerns [4, 12]. However, this result should be interpreted with caution because of the relatively small sample size and the possibility of statistical uncertainty. Therefore, safe-

ty should be further verified in studies with larger sample sizes.

In addition, as a single-center retrospective study, although PSM was used to control for major confounding factors, selection bias and information bias could not be completely eliminated. In particular, all embryo transfers were performed in an artificial-cycle setting, and the retrospective nature of the study limited the possibility of complete blinding during pregnancy outcome assessment. Although ultrasound assessment was performed by a sonographer blinded to group assignment and pregnancy outcomes were defined according to objective clinical criteria, residual observer bias and information bias could still have affected the interpretation of the results. Moreover, this study did not include a placebo control group and did not adopt a double-blind design, which may have introduced patient-reported bias. The molecular analyses in this study were limited to peripheral-blood mRNA expression of receptivity-related markers. Endometrial tissue was not collected for immunohistochemistry, Western blotting, proteomic analysis, or pathway-level assays. Therefore, the present findings cannot confirm whether the corresponding proteins or signaling pathways were altered in the endometrium. These results should be considered hypothesis-generating and require validation in prospective studies using endometrial tissue-based molecular assays. Finally, this study included only patients undergoing IVF-ET for the first time. Its efficacy in patients with refractory TE and repeated implantation failure still requires further validation. In addition, the lack of long-term follow-up data prevented us from evaluating the long-term effects of the combined treatment on offspring health.

Conclusion

In this retrospective cohort, MI combined with high-dose CPET showed favorable short-term efficacy, tolerability, and cost-effectiveness in selected patients with TE. This regimen was associated with improvements in endometrial morphology, blood perfusion, peripheral-blood receptivity-related mRNA expression, and pregnancy outcomes. However, because molecular assessment was limited to peripheral-blood mRNA markers, the present study cannot confirm protein-level changes or specific signaling pathway activation in endometrial tissue. These findings provide clinical evidence for optimizing TE treatment strategies and support further evaluation of this regimen in clinical practice. Future large-sample randomized controlled trials incorporating endometrial tissue-based protein detection and signaling pathway analyses are needed to further verify the efficacy, safety, and underlying mechanisms of this regimen.

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Disclosure of conflict of interest

None.

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