European Review for Medical and Pharmacological Sciences 2023; 27: 2971-2979

Efficacy of Traditional Chinese Herbs combined with bioelectrical stimulation on patients with kidney deficiency and blood stasis type thin endometrium: a retrospective observational study

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Abstract. – OBJECTIVE: This study aimed to investigate the efficacy of Traditional Chinese Herbs (TCH) combined with bioelectrical stimulation (BES) on patients with kidney deficiency and blood stasis type thin endometrium.

PATIENTS AND METHODS: A retrospective observational study was conducted on 83 patients diagnosed with thin endometrium, treated in our hospital from August 2019 to August 2021. The clinical data of the patients were reviewed, and 60 eligible patients were categorized into two groups based on the treatment they received: the TCH-BES group (n=30, patients received Femoston, TCH and BES treatment) and the control group (n=30, patients received Femoston only). The endometrial thickness (EMT), uterine artery resistance index (RI) and pulsatility index (PI), serum reproductive hormone levels, traditional Chinese medicine (TCM) syndrome scores, and clinical pregnancy outcomes between the two groups were compared. Continuous data were described as mean ± standard deviation ($\bar{X}$ ± S). Student's *t*-test was used for comparison between the two groups and paired-sample *t*-test was used for comparison within the same group before and after the treatment.

RESULTS: A total of 60 patients with thin endometrium, aged 20-35 years (average, 31.67±3.19 years), were included in this study. After the treatment, the EMT, E2 and progesterone (P) levels of the TCH-BES group were higher than that of the control group ($p<0.001$, $p<0.05$ and $p<0.001$, respectively), the PI, RI level and TCM syndrome scores of the TCH-BES group were lower than those of the control group ($p<0.001$). The clinical efficacy and pregnancy rate in the TCH-BES group were significantly higher than those in the control group ($p<0.05$).

CONCLUSIONS: TCH combined with EBS has a satisfactory efficacy on patients with kidney deficiency and blood stasis type thin endometrium, and improves EMT, E_2 and P levels, reduces PI, RI and TCM syndrome, and eventually leads to a favorable clinical pregnancy outcome.

Key Words:
Traditional Chinese Herbs, Thin endometrium, Bioelectrical stimulation, Kidney deficiency, Blood stasis.

Introduction

Thin endometrium, an endometrium thickness that cannot reach the threshold for embryo implantation, is widely recognized as the most common cause of infertility[1,2]. Successful embryo implantation requires proper embryo development, and appropriate endometrium thickness is essential for implantation. It has been reported that the incidence of thin endometrium in patients undergoing *in vitro* fertilization (IVF) is about 2.4%, and it could be as high as 38-66% in ovarian stimulation cycles, which seriously challenges reproductive health[3,4].

There are many treatments available for thin endometrium, including estrogen therapy, intrauterine perfusion, vitamins C and E, drugs to improve endometrial blood flow, L-arginine supplement, acupuncture, and bioelectrical stimulation therapy[5-8]. Of these, estrogen therapy is widely used in clinical practices as it can directly act on estrogen receptors, is rapidly absorbed after oral administration, and facilitates the increase of endometrial thickness[9]. However, estrogen therapy is not satisfactory for refractory thin endometrium. Furthermore, it is well established that long-term high-dose estrogen application will not only increase the risk of thrombosis, but also causes adverse reactions such as abnormal lipid metabolism, breast hyperplasia and insomnia[9,10]. Therefore, it is of great significance to seek more safe and effective treatment options.

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In traditional Chinese medicine (TCM), there is a saying that goes "Kidney governs reproduction". "Qi" in TCM is a general term for all the invisible subtle energy substances and functional activities of internal organs that are in constant motion in the human body, which can stimulate and promote the functional activities of entrails and control the process of the human body[11]. From the theoretical analysis of TCM, thin endometrium is caused by the deficiency of kidney essence and kidney-qi, and the lack of nourishment of qi and blood, which eventually leads to kidney deficiency and blood stasis[12]. TCM believes that this can be treated by tonifying the kidneys, filling the essence, benefiting the qi and nourishing the blood. Ding and Lian[13] and Ried[14] have demonstrated that Traditional Chinese Herbs (TCH) can increase the thickness of endometrium. In addition, Yuan et al[15] reported that bioelectrical stimulation can improve the blood perfusion of thin endometrium and improve the endometrial receptivity (ER). However, as far as we know, only a few studies, exclusively from China, evaluated the effect of TCH combined with bioelectrical stimulation (BES) on thin endometrium[16-18]. Therefore, in this study, we aimed to evaluate the efficacy of TCH combined with BES on patients with thin endometrium to provide data support for further use in clinical setting.

Patients and Methods

Patients

A retrospective observational study was conducted on patients diagnosed with thin endometrium and treated in the Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine from August 2019 to August 2021. The clinical data of 83 patients aged 20-35 years (average, 31.67±3.19 years) were reviewed. Patients were screened for eligibility and categorized into two groups based on the treatment they received: the TCH-BES group (n=30, patients received a combination of estrogen (Femoston), TCH and BES) and the control group (n=30, patients received Femoston) (Figure 1). The study was approved by the ethics committee of the Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine (No. 2020-018-02, Date: 03-May 2021) and complied with the Declaration of Helsinki. Patient informed consent was waived because of the retrospective nature of the study.

Diagnostic Criteria of Thin Endometrium

Western medicine diagnostic criteria[4,19]: The definition of thin endometrium has not been standardized, so we defined thin endometrium as an endometrial thickness (EMT) less than 7 mm when the maximum follicle diameter in natural cycle is ≥ 18 mm based on data from previous studies[19,20].

TCM diagnostic criteria for kidney deficiency and blood stasis type thin endometrium[21]:

1) Primary symptoms: low menstrual flow or amenorrhea; EMT <7 mm when the maximum follicle diameter is ≥18 mm.
2) Secondary symptoms: soreness and weakness of the waist and knees; dizziness and tinnitus; fatigue; dark or purple color of menstruation; Frequent urination or clear urination at night.
3) Tongue and pulse: pale tongue or with ecchymosis; thin or astringent pulse.

For the TCM diagnosis of infertility with kidney deficiency and blood stasis, the primary symptoms are necessary, there are two or more secondary symptoms, and the tongue and pulse are examined to identify the type of kidney deficiency and blood stasis.

Inclusion Criteria

1) Patients of childbearing age who are 20-35 years old and met both the western and the TCM diagnostic criteria of thin endometrium[4,19-21].
2) Patients with regular menstruation (menstrual cycle of 28-35 days) and menstruation that clears within 7 days.
3) Patients without a history of infertility.
4) Patient's body mass index (BMI) of 18-24 kg/m^2.
5) The basic endocrinology of the patients within the normal range.
6) Ultrasound examination of the patients showed normal uterine morphology.
7) Patients with hysterosalpingogram (HSG) results suggesting bilateral tubal patency.

Exclusion Criteria

1) Patients with congenital reproductive system diseases or premature ovarian failure;
2) Patients with contraindications to low-frequency electrical stimulation;
3) Patients with mental illness or severe major organ diseases (e.g., heart, liver, kidney, etc.);
4) Patients who have taken hormonal drugs and vasodilators such as aspirin within the last three months;
5) Patients dropped out due to adverse reactions or lost to follow up;
6) Patients with poor compliance.

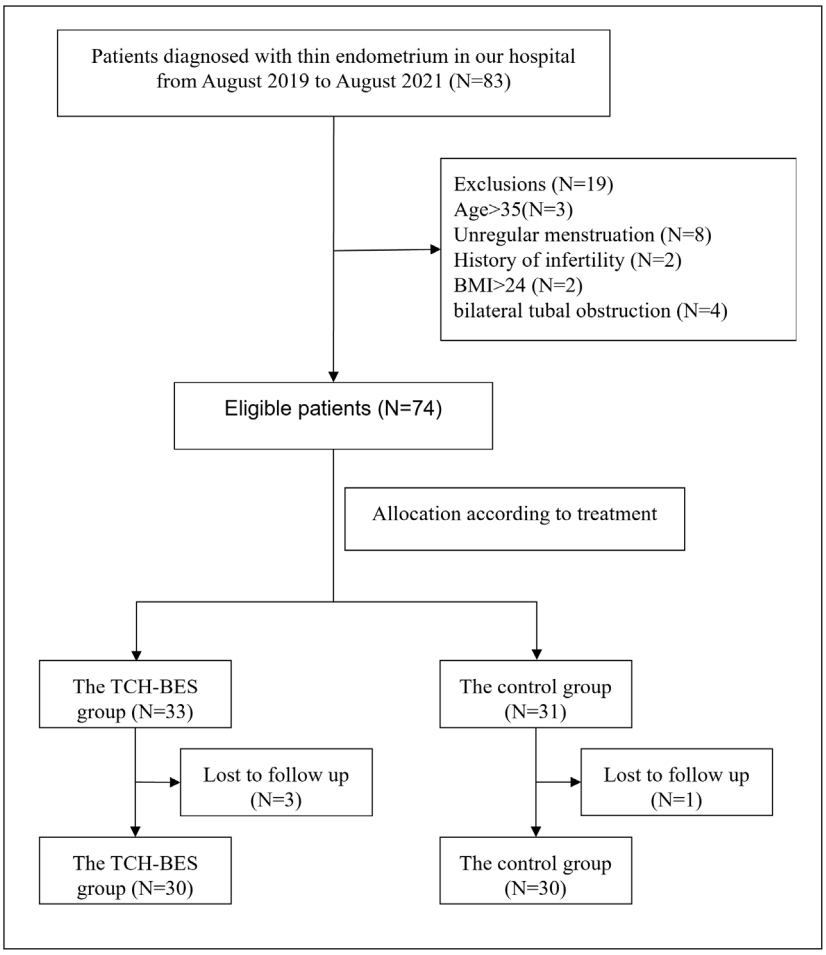

Figure 1. Study enrolment flowchart.

Treatment

Patients in the Control group were treated with Femoston (Bayer Healthcare Ltd. Guangzhou, China; Approval NO.: JX20130024) orally on the 3rd day of menstruation, 2 mg/day for 28 days, for 3 consecutive menstrual cycles.

Patients in the TCH-BES group were treated with Femoston (Bayer Healthcare Ltd. Guangzhou, China; Approval NO.: JX20130024) orally on the 3rd day of menstruation, 2 mg/day for 28 days, with additional kidney-tonifying TCH after menstruation. The TCH preparation (200 ml/bag, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Shandong, China) consists of Amethyst 30 g, Rehmannia glutinosa 12 g, Cistanche 15 g, Epimedium 15 g, Dodder Seed 15 g, Codonopsis 15 g, Astragalus 18 g, Atractylodes 15 g, Poria 15 g, Tangerine peel 12 g, Cyperus Rotundus L. 10 g, Suberect Spatholobus Stem 15 g, Angelica 15 g, Red Peony 12 g, Chuanxiong 12 g and Radix Glycyrrhizae Preparata 6 g[22]. Patients took one bag of TCH preparation in the morning and one bag in the evening, stopped taking it during the menstruation, and received BES by bioelectrical feedback device Urostym® (Labory Medical Technology Co., Ltd., Mississauga, Canada) three days after the menstruation. BES was performed as follows[6]: patients emptied the bladder before treatment and took the supine position; a probe was inserted intravaginally after connecting the A1 channel. The current frequency and pulse width were 40 Hz and 250 μs, respectively, with a duration of 5 s and an interval of 10 s. The current intensity was the maximum threshold that the patient could tolerate, with an adjustment range of 10 to 50 mA, to ensure both the therapeutic effect and patient safety. BES was given once a day for 30 min for three to five days for three consecutive menstrual cycles.

Data Collection and Indicators

The general data of patients were collected, and EMT, uterine hemodynamics, serum reproductive hormone levels, TCM syndrome scores

and menstrual blood loss (MBL) before and after the treatment were collected. Patients were followed up for three months after the treatment and pregnancy outcomes were collected.

EMT and uterine hemodynamics

Color Doppler ultrasound (CDU, Model: HI VISION Preirus, Hitachi Medical Co., Ltd., Tokyo, Japan) was used to detect EMT, uterine artery resistance index (RI) and pulsatility index (PI)[23,24]. CDU was performed by the physicians of the Ultrasound Department of our hospital on the 8th day of the menstrual cycle, and re-examination was carried out every day or every other day depending on the follicular development until the maximum follicle diameter reached ≥18mm.

Serum reproductive hormones[25]

Serum of all patients was collected on the third day of the menstrual cycle, and the levels of serum reproductive hormones before and after the treatment were measured, including estradiol (E_2) and progesterone (P).

TCM syndrome scores

Patients' symptoms and changes in tongue and pulse were observed, and a TCM syndrome scale was developed for scoring by the same physicians before and after the treatment.

Pregnancy outcomes

The pregnancy outcomes of the patients three months after the treatment were recorded. Pregnancy rate = (pregnancy number/total number of patients) × 100%.

Assessment of Clinical Efficacy of TCM Treatment

The treatment outcomes were divided into four categories as follows: cured; remarkable effective; effective; ineffective.

Cured

EMT ≥8 mm when the maximum follicle diameter is ≥18 mm, menstrual flow >50 mL, and disappearance of symptoms (efficacy index ≥ 95%).

Remarkable effective

EMT ≥8 mm when the maximum follicle diameter is ≥18 mm, menstrual flow >40 mL, and significant reduction of symptoms (70% ≤ efficacy index < 95%).

Effective

EMT ≥7 mm when the maximum follicle diameter is ≥18 mm, menstrual flow >20 mL, and slight relief of symptoms (30% ≤ efficacy index < 70%).

Ineffective

EMT <7 mm when the maximum follicle diameter is ≥18 mm, no change in menstrual flow and no reduction in symptoms (efficacy index < 30%).

Total effective rate (%) = (Number of cured patients + Number of remarkable effective patients+ Number of effective patients) / Total number of patients × 100%.

Calculation of efficacy index: Efficacy index = (total pre-treatment score – total post-treatment score) / total pre-treatment score × 100%.

Menstrual flow: The amount of MBL was assessed by Pictorial Blood Loss Assessment Chart (PBAC)[26,27], and the score, number and days of sanitary napkin were collected. The assessment method has been detailed by Xu et al[28].

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Continuous data were described as mean ± standard deviation ($\bar{X} \pm S$). Student's *t*-test was used for comparison between the two groups and paired-sample *t*-test was used for comparison within the same group before and after the treatment. Categorical data were described as frequency and percentage (n, %), and the differences between the two groups were compared by χ^2 test. The Wilcoxon rank sum test was used for comparison of ordinal data. All statistical tests were two-sided, and $p<0.05$ indicated a statistically significant difference.

Results

Baseline Characteristics

A total of 60 patients with thin endometrium were included in this study, with 30 patients in each group.

The mean age and disease duration of patients in the TCH-BES group were (31.00±3.48) years and (2.31±1.28) years, respectively. The average age and disease duration of patients in the control group were (32.33±2.77) years and (2.10±1.31) years, respectively. There were no significant differences in age, BMI, and disease duration between the two groups ($p>0.05$), which indicated comparability (Table I).

Table I. Baseline characteristics of the patients.

Groups	N	Age, mean (SD), year	BMI, mean (SD), kg/m²	Disease duration, mean (SD), year
TCH-BES group	30	31.00-3.48	23.73-1.61	2.31-1.28
Control group	30	32.33-2.77	22.85-2.25	2.10-1.31
t		1.641	-1.727	-0.623
p		0.106	0.089	0.536

Comparison of EMT

There was no significant difference in EMT, between the two groups before the treatment (p>0.05). After the treatment, the EMT of both groups was higher than that before the treatment (p< 0.001), and the EMT of the TCH-BES group was higher than that of the control group (p<0.001) (Table II).

Comparison of Uterine Hemodynamics

There was no significant difference in PI or RI between the two groups before the treatment (p>0.05). After the treatment, the PI and RI of the two groups were lower than that before treatment (p<0.001), and the PI and RI of the TCH-BES group were lower than those of the control group (p<0.001) (Table III).

Comparison of Serum Reproductive Hormones

There were no significant differences in E_2 and P levels between the two groups before the treatment (p>0.05). After the treatment, the E_2 and P levels in both groups were significantly increased. In addition, E_2 and P levels in the TCH-BES group were significantly higher than those of the control group (p<0.05 and p<0.001, respectively) (Table IV).

Comparison of TCM Syndrome Scores

There was no significant difference in TCM syndrome scores between the two groups before the treatment (p>0.05). After the treatment, the TCM syndrome scores of the two groups were lower than that before treatment (p< 0.001), and the TCM syndrome scores of the TCH-BES group was lower than that of the control group (p<0.001) (Table V).

Comparison of Clinical Efficacy of Treatment for TCM Syndromes

The clinical efficacy of the TCH-BES group (90.0%) was significantly higher than that of the control group (76.7%) (p<0.05) (Table VI).

Table II. Comparison of EMT between the two groups before and after treatment (cm).

Groups	N	Before treatment	After treatment	*t*	*p*
TCH-BES group	30	0.39-0.96	1.05-0.13	-21.87	<0.001
Control group	30	0.41-0.94	0.85-0.11	-16.155	<0.001
t		-0.809	6.534		
p		0.422	<0.001		

Table III. Comparison of uterine artery PI and RI between the two groups before and after treatment.

Groups	N	PI		RI	
		Before treatment	After treatment	Before treatment	After treatment
TCH-BES group	30	3.87-0.37	2.58-0.13[a]	0.93-0.24	0.76-0.51[a]
Control group	30	3.90-0.39	3.00-0.24[a]	0.92-0.26	0.83-0.41[a]
t		-0.422	-8.257	0.367	-5.152
p		0.675	p < 0.001	0.715	p < 0.001

Compared within the same group before treatment, [a]p < 0.001.

Table IV. Comparison of uterine artery PI and RI between the two groups before and after treatment.

Groups	N	E_2 (pg/mL)		*p* (nmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
TCH-BES group	30	31.57-6.94	47.50-7.21[a]	0.75-0.22	2.85-0.34[a]
Control group	30	32.30-7.47	41.94-7.75[a]	0.77-0.20	1.93-0.28[a]
t		0.394	-2.864	0.265	11.342
p		0.695	<0.05	0.792	<0.001

Compared within the same group before treatment, [a]$p < 0.001$.

Table V. Comparison of TCM syndrome scores between the two groups before and after treatment.

Groups	N	Before treatment	After treatment	*t*	*p*
TCH-BES group	30	12.83-1.72	3.30-0.59	28.63	<0.001
Control group	30	12.03-3.38	10.80-2.80	1.535	0.130
t		1.153	-14.306		
p		0.254	<0.001		

Table VI. Comparison of clinical efficacy of treatment for TCM syndromes between the two groups [n (%)].

Groups	N	Cured	Remarkable effective	Effective	Ineffective	Total effective rate	Z	*p*
TCH-BES group	30	4 (13.3)	15 (50.0)	8 (26.7)	3 (10.0)	27 (90.0)	-2.957	0.003
Control group	30	1 (3.3)	5 (20.0)	17 (53.3)	7 (23.3)	23 (76.7)		

Comparison of Clinical Pregnancy Outcome

The pregnancy rate of the TCH-BES group (63.3%) was significantly higher than that of the control group (33.3%) ($p<0.05$) (Table VII).

Discussion

Numerous studies[29,30] show that thin endometrium is associated with lower pregnancy rates. Reproductive

endocrine hormone disturbance is one of the possible causes of thin endometrium. It leads to the decrease in E_2 and P levels, which, subsequently, affect endometrial angiogenesis, and eventually results in abnormal uterine hemodynamics[31,32]. Uterine hemodynamic abnormalities are common in patients with thin endometrium. Ultrasonography of these patients often shows markedly elevated PI and RI of the uterine arteries, which leads to insufficient endometrial circulation, affects endometrial growth, and ultimately causes infertility[24].

A recent study by Chen et al[18] showed that combined treatment of thin endometrial infertility with TCH decoction (Bushen Peiyuan Yanggong decoction) and BES can improve EMT, ameliorate endometrial hemodynamics, and ultimately have a favorable clinical pregnancy outcome. Our study supports these findings. We show that the combination of TCH and BES can improve reproductive endocrine hormone disturbance and uterine hemodynamics. Zhao and Shi[16] also reported that a TCH

Table VII. Comparison of pregnancy outcomes between the two groups after treatment [n (%)].

Groups	N	Non pregnancy	Clinical pregnancy	χ^2	*p*
TCH-BES group	30	11 (36.7)	19 (63.3)	5.406	0.038
Control group	30	20 (66.7)	10 (33.3)		

pill (called "Jinfeng Pill") combined with BES can improve EMT and endometrial hemodynamics. We may speculate that BES plays an auxiliary role in improving endometrial hemodynamics. BES is a non-invasive, safe and effective treatment modality that has been demonstrated to enhance blood perfusion of thin endometrium and improve ER without side effects that are associated with estrogen treatment, and without burdening the liver[6,15,33]. It releases electric currents of different frequencies through external electrode patches, thus accelerating the recovery of damaged muscles and nerves, relaxing muscle tension, and reducing vascular resistance, which consequently increases the blood supply to the pelvic floor and uterus, promotes blood circulation, increases tissue nutrition, accelerates tissue repair and physiological function recovery, and eventually promotes endometrial growth[15]. While clinical efficacy of BES alone for thin endometrium is not satisfactory[30], it can be used as an adjunctive treatment for patients with thin endometrium.

A study[34] has found that TCM is associated with higher success rate of pregnancy in infertile women. In our study, TCH played a major role in improving EMT, reproductive endocrine hormone disturbance, leading to favorable clinical pregnancy outcome. Our study showed that the TCM syndrome scores were decreased after the treatment and the TCH-BES group had a higher pregnancy rate, which was consistent with the results of Xie et al[17]. Traditional Chinese medicine approaches the treatment of thin endometrium by nourishing the kidney and promoting blood circulation[12]. Therefore, in our study, Chinese herbs in the TCH preparation mainly had the effect of tonifying the kidney and promoting blood circulation. According to TCM, *Amethyst* warms the uterus; *Rehmannia glutinosa*, *Angelica, Red Peony* and *Suberect Spatholobus Stem* can promote blood circulation and regulate menstruation; *Codonopsis*, *Astragalus* and *Chuanxiong* can promote qi so as to activate blood; *Cistanche*, *Epimedium* and *Dodder Seed* can improve kidney yang deficiency by regulating hypothalamus-pituitary-adrenal axis[35-38]. The combination of all these components makes TCH a multi-target action system, which can act on various parts of the human body on different levels in a multi-target manner[8]. It acts on the out-of-balance neuroendocrine immune network, harmonizing and returning the body to a stable state, and thus improving uterine health.

Limitations

There are several limitations of the study. First, it was a retrospective observational study with a small sample size. Second, the TCM syndrome scores were assessed by physicians, which introduces a potential variability in terms of subjectivity and the degree of expertise of each physician. Last, the follow-up period in our study was relatively short (three months), and further studies with longer-term follow-up are required to validate the findings of our study.

Conclusions

TCH combined with EBS has a satisfactory efficacy on patients with kidney deficiency and blood stasis type thin endometrium, which improves EMT, E_2 and P levels, reduces PI, RI and TCM syndrome, and eventually has a favorable clinical pregnancy outcome.

Conflicts of Interest

The authors have nothing to disclose.

Acknowledgments

None.

Ethics Approval

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine (No.:2020-018-02).

Informed Consent

Patient informed consent was waived because of the retrospective nature of the study.

Authors' Contribution

HF was the principal investigator in the study. HF, SC, and LH designed the study. HF and XL performed data collection. LH carried out data analysis. All authors have contributed to, written, revised, and approved the final manuscript.

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