*Original Article*

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# Acupuncture and Bushen Quyu decoction improved endometrial receptivity, hormone secretion, and uterine artery blood flow for repeated implantation failure patients undergoing *in vitro* fertilization and embryo transfer

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**SUMMARY** Acupuncture and traditional Chinese medicine (TCM) have shown certain benefits in assisted *in vitro* fertilization and embryo transfer (IVF-ET). In this study, we evaluated the efficacy and safety of the combination of acupuncture combined with the Bushen Quyu decoction in patients with failures of IVF-ET. This study was conducted at Shanghai Yangpu District Hospital of TCM from May to November of 2021. Patients with failed IVF-ET received either combined therapy or the routine procedure (control group). The main outcomes were implantation rate and clinical pregnancy rate. Radioimmunoassay was used to detect serum levels of estradiol (E2) and progesterone on the day of injection of human chorionic gonadotropin (hCG). The endometrial thickness, resistance index (RI), and pulsatility index (PI) of bilateral uterine arteries were measured by color Doppler ultrasound. Safety was assessed in all participants. After 3 months of treatment, the implantation rate (61.9% *vs*. 47.7%, $P = 0.187$) and clinical pregnancy rate (52.4% *vs.* 36.4%, $P = 0.135$) of patients with IVF-ET failure receiving acupuncture therapy combined with Bushen Quyu decoction appeared to be higher than those of the routine procedure group, although the increase was not statistically significant. However, the serum E2 level and endometrial thickness of patients in the combined therapy group increased significantly than those of the control group after hCG injection. The RI and PI values of bilateral uterine arteries in the combined therapy group were significantly lower than those in the control group after hCG injection. No difference of adverse events was observed between combined therapy group and control group (11.9% *vs.* 11.36%, $P = 0.962$). Acupuncture therapy combined with TCM treatment may improve endometrial receptivity and hormone secretion, and increase uterine artery blood flow.

***Keywords*** endometrial receptivity, *in vitro* fertilization embryo transfer, acupuncture, Bushen Quyu decoction, pregnancy rate

## 1. Introduction

Infertility has become a global social and health problem. According to statistics, infertility accounts for 10-15% of married couples of childbearing age in China (*1*). The rapid development of *in vitro* fertilization and embryo transfer (IVF-ET) technology has brought hope to infertile patients and improved the success rate of infertility treatment (*2*). After decades of development, IVF and its derivative technologies have made great progress through improving the ovulation promotion program and developing the laboratory culture system. However, the implantation rate and clinical pregnancy rate of embryos have not been satisfactory (*3*).

Endometrial receptivity is the ability of endometrium to accept embryos during a specific time period, and is a key factor affecting the outcome of IVF-ET. It is estimated that embryo factors account for about one third

of implantation failures, and the remaining two thirds of implantation failures are caused by poor endometrial receptivity or abnormal interaction between embryo and endometrium (*4*). How to improve the pregnancy outcome of patients with repeated IVF-ET transplantation failure by regulating endometrial receptivity is an urgent clinical problem.

An increasing number of infertile couples have chosen acupuncture, traditional Chinese medicine (TCM) and other auxiliary methods to improve the success rate of IVF-ET. Studies have found that acupuncture was helpful to increase the pregnancy rate (*5*). Compared to those without acupuncture or TCM treatment, acupuncture can help reduce the rate of miscarriage. In addition, TCM has certain feasibility in improving endometrial receptivity and the blastocyst on endometrium (*6*). Worldwide, there is an increasing trend of implementing acupuncture as a complementary therapy during IVF. Acupuncture has been applied for regulating hormone secretion, increasing uterine blood flow and stimulating secretion of endogenous opioids (*7*). Bushen Quyu decoction is commonly prescribed in our hospital, and retrospective data have shown that the majority of cases who have been treated with combined acupuncture and TCM have had more success in pregnancy than cases with no TCM or acupuncture treatment. However, its clinical efficacy lacks the support of evidence-based medicine. Therefore, we conducted a single center observational study to evaluate the clinical efficacy and safety of acupuncture combined with TCM in patients with IVF-ET failure of the kidney deficiency and blood stasis type.

## 2. Methods

### 2.1. Study design and participants

This study is a single center observational study. Women who underwent IVF-ET from May to November of 2021 at the gynecology clinic of Shanghai Yangpu District Hospital of TCM were recruited. The diagnostic criteria of infertility is that the couples have normal sexual life after marriage, and have not been pregnant for more than one year without contraception (*8*). The syndrome diagnostic criteria of kidney deficiency and blood stasis syndrome in infertility and blood stasis syndrome in hypomenorrhea were formulated according to the Criteria for the Diagnostic Efficacy of TCM Diseases and Syndromes issued by the Chinese Medicine Administration in 2012 (*9*), and the TCM Gynecology edited by Ma Baozhang (*10*). All patients experienced one or more IVF-ET transplant failures.

Inclusion criteria were: (*i*) meeting the diagnostic criteria of infertility; (*ii*) conforming to kidney deficiency and blood stasis syndrome; (*iii*) patient's age was 23-42 years old; (*iv*) embryos to be transferred were of high quality, and frozen thawed embryo transfer was planned; (*v*) given informed consent. Exclusion criteria were: (*i*) confirmed obvious and serious other organic diseases in the reproductive organs, which cannot bear pregnancy; (*ii*) infertility caused by genetic factors; (*iii*) women suffering from serious mental illness, acute infection of urogenital system, and sexually transmitted diseases; (*iv*) women with a history of habitual abortion.

### 2.2. Ethics

This study has been approved by the Ethics Committee of Yangpu District Hospital of TCM (Ethics No.: YPZY-2018-LC-02), and each patient has provided written informed consent. This study was conducted in accordance with the principles of the 2000 Declaration of Helsinki.

### 2.3. Procedures

Natural cycle or semi natural cycle were used to prepare endometrium for frozen embryo transfer for both groups. Natural cycle is suitable for those with regular menstrual cycle and ovulation; semi natural cycle is suitable for those with irregular or no ovulation. Oral letrozole 2.5-5 mg/d was administrated for 3-5 days after menstruation. The hCG injection day of the two schemes is the date of maximum diameter of the main follicle reaching 18 mm.

The control group was operated according to the routine procedure of frozen thawed embryo transfer, and the combined therapy group was treated with acupuncture combined with the Bushen Quyu decoction before transplantation on the basis of the routine procedure of frozen thawed embryo transfer.

Acupuncture scheme: point positioning were chosen based on the 7$^{th}$ edition of Meridian Acupuncture (*11*). Select the following acupoints: CV4 (Guanyuan), CV6 (Qihai), CV3 (Zhongji), EX-CA1 (Zigong), SP6 (Sanyinjiao), LI4 (Hegu, both sides), BL23 (Shenshu), DU4 (Mingmen), BL32 (Ciliao) and SP10 (Xuehai, both sides). Needles: according to the regulations of the special clinical research team of the "Acupoint Code", 30 # 1.5 inch disposable sterile needle (Huatuo brand, Suzhou, China) was selected, with a specification of 0.25 × 40 mm. Operation: refer to the operation method of "Meridians and Acupoints" compiled by Shen Xueyong, the textbook of the national planning of Chinese medicine colleges and universities in the new century. The patient first emptied the urine and then took the supine position, fully exposed the site of the operation, after local routine disinfection at selected acupoints, quickly pierced the needle at a 90-degree angle into 0.8-1.2 inches, and the above acupoints were repeatedly inserted and twisted using the flat supplement and diarrhea technique until the patient felt local numbness and heaviness, then the needle was left for 30 minutes after obtaining the gas. The above acupuncture treatment was performed 2-3 times/week except during

menstruation, and was stopped after transplantation. The patients were treated with medicine and acupuncture for 3 menstrual cycles, and the patients who received frozen embryo transfer during the treatment period or within 2 months after the treatment were eligible to be included in the group.

The Bushen Quyu decoction was prepared by the TCM pharmacy of Yangpu District Hospital of TCM. The basic herbs and dosage were as follows: Dangshen (tangshen) 15g, Baizhu (Largehead Atractylodes Rhizome) 15g, Tusizi (Chinese Dodder seed) 15-30g, Nvzhenzi (Glossy privet fruit) 10g, Danggui (Chinese Angelica) 15g, Sanqi (*Sanchi*) 3-5g and Danshen (Dan-Shen Root) 9g. Patients received one full dose (taking at two half-doses: morning and evening) per day orally. Each dose was decocted with water, and taken after warming. The administration was stopped during menstruation, or immediately after detection of pregnancy.

Human chorionic gonadotropin (hCG) injection was performed when the maximum diameter of the main follicle grew to 18 mm. On the day of hCG injection, the peripheral blood of patients was drawn. The levels of estradiol (E2) and progesterone in the peripheral serum of patients were detected by radioimmunoassay. The endometrial thickness, resistance index (RI), and pulsatility index (PI) of bilateral uterine arteries were measured on the day of hCG injection by ultrasound using the GE Volkswagen E8 color Doppler, RM6C7.5MHz transvaginal probe model (General Electric Medical Systems, Milwaukee, WI, USA). Adverse events including breast pain, nausea, rash, headache and other symptoms were recorded.

### 2.4. Outcomes

The main outcomes of this study were implantation rate and clinical pregnancy rate. Blood test β-hCG positive patients 14 days after transplantation were regarded as biochemical pregnancy, which indicated successful implantation. The implantation rate was calculated as: number of successful implantation/number of patients ×100%. Four weeks after transplantation, ultrasound monitoring was performed. Those who detected with gestational sac, embryo bud and fetal heart beat were regarded as clinical pregnancy. The clinical pregnancy rate was calculated as: number of clinical pregnancies/ number of patients ×100%.

In addition, serum levels of E2 and progesterone, endometrial thickness, RI and PI of bilateral uterine arteries were compared between the two groups on the day of hCG injection.

### 2.5. Statistical analysis

Categorical variables were expressed by rate (%), and compared using the Chi-square test or Fisher's exact test. The continuous data that conform to the normal distribution were expressed by mean ± SD, and compared using Student's *t*-test. Continuous variables that do not conform to the normal distribution were expressed as median (interquartile range) [M (IQR)], and compared using Mann-Whitney *U* test. All statistical analyses were conducted using SPSS 24.0 statistical software. A two-sided $P < 0.05$ denoted as statistical significance.

## 3. Results

### 3.1. Patient characteristics

A total of 86 participants were recruited, including 42 women received combined therapy, and 44 women received routine treatment (the control group). Before treatment, there was no significant difference between the two groups in terms of age, infertility years, IVF-ET times and body mass index (BMI) ($P > 0.05$ for all). In addition, there was no significant difference between the two groups in terms of the causes of assisted pregnancy ($P = 0.991$) (Table 1).

### 3.2. Pregnancy rate of patients with IVF-ET failure

As shown in Table 2, the implantation rate of patients with IVF-ET failure receiving combined treatment appeared to be higher than those of the routine procedure group, although the increase was not statistically significant (61.9% *vs.* 47.7%, $P = 0.187$). In addition, although not reaching statistical significance, the clinical pregnancy rate appeared to be higher of the combined therapy group than the control group (52.4% *vs.* 36.4%, $P = 0.135$).

### 3.3. Hormone levels and endometrium thickness after hCG injection

As shown in Table 3, there was no difference of the E2 level between the two groups before hCG injection. After

**Table 1. Population characteristics**

| | Combined therapy group ($n = 42$) | Control group ($n = 44$) | *P* |
|---|---|---|---|
| Age | 31.88 ± 4.27 | 30.84 ± 3.46 | 0.22 |
| Infertility years | 3 (3-4) | 3 (3-4) | 0.84 |
| IVF-ET times | 2 (2-3) | 3 (2-4) | 0.28 |
| BMI | 22.62 ± 1.48 | 22.32 ± 2.22 | 0.46 |
| Cause of assisted pregnancy | | | 0.991* |
| Fallopian tube | 21 | 24 | |
| Ovulation disorder | 5 | 5 | |
| Endometriosis | 3 | 3 | |
| Spouse factor | 12 | 11 | |
| Unknown cause | 1 | 1 | |

BMI, body mass index; IVF-ET, *in vitro* fertilization and embryo transfer. *Fisher's exact test.

**Table 2. Comparison of pregnancy rate between the two groups**

| | Combined therapy group ($n$ = 42) | Control group ($n$ = 44) | $P$ |
|---|---|---|---|
| Implantation | | | 0.187 |
| Yes | 26 (61.9%) | 21 (47.7%) | |
| No | 16 (38.1%) | 23 (52.3%) | |
| Clinical pregnancy | | | 0.135 |
| Yes | 22 (52.4%) | 16 (36.4%) | |
| No | 20 (47.6%) | 28 (63.6%) | |

**Table 3. Comparison of serum hormone levels and endometrial thickness before and after hCG injection between the two groups (mean ± SD)**

| | Combined therapy group ($n$ = 42) | Control group ($n$ = 44) | $P$ |
|---|---|---|---|
| Estradiol (pmol/L) | | | |
| Before treatment | 833.5 ± 110.8 | 805.6 ± 123.8 | 0.28 |
| After treatment | 916.2 ± 100.6 | 781.6 ± 186.0 | < 0.001 |
| Progesterone (nmol/L) | | | |
| Before treatment | 1.2 ± 0.4 | 1.3 ± 0.3 | 0.07 |
| After treatment | 1.3 ± 0.3 | 1.3 ± 0.3 | 0.81 |
| Endometrial thickness (mm) | | | |
| Before treatment | 7.8 ± 0.9 | 8.1 ± 0.9 | 0.14 |
| After treatment | 8.8 ± 0.8 | 8.4 ± 1.1 | 0.048 |

hCG injection, the E2 level in the combined therapy group was significantly higher compared with that in the control group ($P$ < 0.001). There was no statistically significant difference of the progesterone level between the two groups both before and after hCG injection.

As for the average endometrial thickness, there was no difference between the two groups before hCG injection. After hCG injection, the endometrial thickness in the combined therapy group was significantly higher compared with the control group (Table 3, $P$ = 0.048).

### 3.4. Uterine artery blood flow

As shown in Table 4, before hCG injection, all variables of uterine artery blood flow were comparable between the two groups. However, after hCG injection, bilateral uterine artery resistance index (RI) and pulsation index (PI) of patients in the combined therapy group were significantly lower than those in the control group ($P$ < 0.001 for all).

### 3.5. Adverse events

As shown in Table 5, the recorded adverse events included breast swelling and pain, nausea, rash, and headache in both groups. There was no significant difference of adverse events between the combined therapy group and the control group ($P$ = 0.962).

**Table 4. Changes of uterine artery blood flow before and after hCG injection between the two groups (mean ± SD)**

| | Combined therapy group ($n$ = 42) | Control group ($n$ = 44) | $P$ |
|---|---|---|---|
| Right RI | | | |
| Before treatment | 0.77 ± 0.15 | 0.78 ± 0.15 | 0.71 |
| After treatment | 0.58 ± 0.13 | 0.78 ± 0.17 | < 0.001 |
| Right PI | | | |
| Before treatment | 2.83 ± 0.53 | 2.90 ± 0.52 | 0.58 |
| After treatment | 2.24 ± 0.25 | 2.78 ± 0.53 | < 0.001 |
| Left RI | | | |
| Before treatment | 0.77 ± 0.17 | 0.76 ± 0.16 | 0.87 |
| After treatment | 0.55 ± 0.18 | 0.79 ± 0.15 | < 0.001 |
| Left PI | | | |
| Before treatment | 2.77 ± 0.61 | 2.84 ± 0.48 | 0.58 |
| After treatment | 2.37 ± 0.26 | 2.88 ± 0.47 | < 0.001 |

RI, resistance index; PI, pulsatility index.

**Table 5. Comparison of adverse events ($n$/%)**

| | Combined therapy group ($n$ = 42) | Control group ($n$ = 44) | $P$ |
|---|---|---|---|
| Total | 5 (11.9%) | 5 (11.36%) | 0.962* |
| Breast swelling and pain | 1 (2.38%) | 2 (4.54%) | |
| Nausea | 2 (4.76%) | 1 (2.27%) | |
| Rash | 1 (2.38%) | 1 (2.27%) | |
| Headache | 1 (2.38%) | 1 (2.27%) | |

*Fisher's exact.

## 4. Discussion

This study indicated that the implantation rate and clinical pregnancy rate of patients with IVF-ET failure receiving acupuncture therapy combined with Bushen Quyu decoction treatment appeared to be higher than those of the routine procedure group, although the increase was not statistically significant. After hCG injection, the endometrial thickness in the combined therapy group was higher than that in the control group, while PI and RI were lower than those in the control group. Our results suggested that the combined therapy increased the level of estradiol in IVF-ET patients and improved endometrial receptivity, possibly because the TCM decoction can reduce the blood flow resistance of uterine artery to promote the development of endometrium and help embryo implantation.

The endometrial thickness refers to the total length of the endometrium of the anterior and posterior walls of the uterus and the uterine space, and changes periodically with the menstrual cycle. A moderate endometrial thickness is easy for embryo implantation, while a thin endometrium can significantly reduce the rate of embryo implantation (*12*). Estrogen and progesterone are hormones that play a leading role in the periodic development and transformation of endometrium. Estrogen is essential to maintain the proliferation of endometrium in follicular stage, and can

promote the proliferation and growth of endometrium, as well as repair and restore the damaged endometrium. Meanwhile, estrogen and progesterone also regulate uterine artery blood flow. A high level of estrogen can expand uterine artery blood vessels, increase compliance of uterine artery wall, reduce arterial blood flow resistance, and accelerate uterine artery blood flow speed (*13-14*). Previous studies have reported that for patients who failed IVF-ET receiving treatment of warm acupuncture at abdominal and lumbosacral points for 3 menstrual cycles, the endometrial thickness and uterine blood perfusion increased significantly, while bilateral PI values decreased. Warm acupuncture can improve the clinical pregnancy rate of patients who failed high-quality frozen thawed embryo transfer after re-transplantation (*15*).

With the development of ultrasound diagnostic technology, it is possible to study and evaluate endometrial receptivity by measuring uterine hemodynamic parameters with transvaginal color Doppler ultrasound, a non-invasive method (*16*). In assisted reproductive technology, Doppler ultrasound has been applied to monitor parameters such as endometrial thickness, morphology, arterial blood flow, and endometrial blood flow perfusion, which are reliable indexes of endometrial receptivity and pregnancy outcome. Endometrial blood flow is the main nutrient vessel of the endometrium. Rich blood flow indicates favorable internal environment of the endometrium during the transplantation window, which is associated with a better outcome of embryo pregnancy. It was found that more blood flow branches in the endometrium and under endometrium were associated with higher success rate of embryo implantation (*17*). For patients with poor endometrial blood flow, TCM can be applied to improve the uterine artery and endometrial blood flow, increase the clinical pregnancy rate of FET, and reduce the waste of embryos. Of the Bushen Quyu decoction, Nvzhenzi (Glossy privet fruit) and Tusizi (Chinese Dodder seed) are the principal medicines dedicating to nourish kidney energy. Baizhu (Largehead Atractylodes Rhizome) and Dangshen (tangshen) are adjuvant drugs with the effect of strengthening the spleen. When the spleen is healthy, the Qi and Blood are active. The addition of Danggui (Chinese Angelica), Sanqi (Sanchi) and Danshen (Dan-Shen Root) have the effect of activating blood and eliminating stasis.

The acupoints selected in this study, including CV4 (Guanyuan), CV6 (Qihai), CV3 (Zhongji), EX-CA1 (Zigong), SP6 (Sanyinjiao), LI4 (Hegu), BL23 (Shenshu), DU4 (Mingmen), BL32 (Ciliao), SP10 (Xuehai) and other acupuncture points can play the roles of warming the womb, recuperating Chong Ren, and cultivating Yuan Qi. The acupuncture treatment can enhance the blood supply of the ovary and uterus, enhance the contraction of smooth muscle, accelerate blood circulation, stimulate the formation of ovarian capsule, promote the rupture of follicle wall, help mature follicles to discharge, and regulate the autonomic nervous system to enhance endometrial receptivity. Previous studies have shown that warming needle can improve the local temperature of the lower abdomen, accelerate the blood circulation around the uterus and accessories, promote the absorption of endometrial effusion, improve the uterine environment and endometrial receptivity, and increase the clinical pregnancy rate (*18*). It is also worth noting that the adverse events of the combined therapy were relatively mild, since the herbs used in the Bushen Quyu decoction in general have no obvious toxic and side effects.

This study has a few limitations. First, the retrospective nature of the study may introduce certain biases, although comparison of baseline characteristics showed there were no significant differences between the two groups. Second, our sample size is limited, which may explain why we did not detect a significant increase of the implantation rate and clinical pregnancy rate of patients with IVF-ET failure. However, we did detect improvements of endometrial receptivity and hormone secretion, as well as uterine artery blood flow, which are consistent with previous studies. In the future, a well-designed randomized clinical trial with sufficient sample size is needed to fully evaluate the efficacy of the combined treatment.

In summary, the combined therapy of Bushen Quyu decoction and acupuncture can improve endometrial receptivity and hormone secretion, and increase uterine artery blood flow of patients receiving IVF-ET, although the combined treatment did not significantly improve implantation rate and clinical pregnancy rate. In addition, this combination treatment is safe and does not increase adverse reactions.

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*Conflict of Interest*: The authors have no conflicts of interest to disclose.

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