META-ANALYSIS OF THE EFFECTS OF TRADITIONAL CHINESE MEDICINE ON ENDOMETRIAL RECEPTIVITY

NA LIU1, NA LONG1, LU HAN2, XIA CAI1
1The Reproductive Center of the First Affiliated Hospital of Xinjiang Medical University, Xinjiang Urumqi - 2Gynecology department of the Affiliated Traditional Medical Hospital of Xinjiang Medical University, Xinjiang Urumqi, China

ABSTRACT

Objective: Use evidence-based medicine approach to evaluate the efficacy of traditional Chinese medicine (TCM) treatment on endometrial receptivity in infertility patients.

Materials and methods: Search and analyze the clinical research literature which has focused on the treatment of infertility patients from January 1999 to August 2012. These studies used TCM and adopted the Cochrane system to review outcomes. Cases meeting these criteria were collected and were analyzed using the meta-statistical method.

Results: Thirteen papers were selected, including a total of 1,122 cases. The meta-analysis showed that TCM can effectively treat infertility patients and can significantly improve endometrial receptivity and improve pregnancy rates. Funnel plots showed symmetry, suggesting there was no publication bias.

Conclusion: TCM may be an effective way to improve endometrial receptivity. The caveat is that these randomized controlled trials are not of high quality.

Key words: infertility, endometrial receptivity, meta-analysis, traditional Chinese medicine (TCM).

Received February 18, 2014; Accepted March 24, 2014

Introduction

Since the first test-tube baby was born in 1978, assisted reproductive technology (ART) research has made considerable progress; however, implantation failure still limits success rates. One of the major factors affecting the success of ART is endometrial receptivity. Thus, this subject has drawn attention from numerous researchers and clinicians.

TCM (traditional Chinese medicine) holds that a decline in endometrial receptivity is part of “infertility”. Women are blood-based, and the possession of blood ultimately depends on the abundance of kidney energy1-7. The kidney is the birth place of the essence, the source of essence, and is responsible for reproduction8-9. The strength of kidney energy determines the fullness of hormones and the cycle of menstruation8. If kidney energy is deficient, essence cannot be accumulated into a pregnancy, thus leading to infertility8-10.

If kidneys’ positive energy (yan) is weak, the fire from the gate of life is down and the uterus is in need of warmth. If kidneys’ negative energy (yin) is deficient, penetrating vessel and conception vessel are weak and the uterus lacks enough nutrients, thus leading to infertility. In “Fu Qingzhu Gynecology - Gynecology Top Volume- Seed” from a famous Qing Dynasty Doctor Fu Qingzhu, it is stated that “if the essence is full, the uterus is easy to extract essence11. If blood is rich, it is easy for the uterus to hold. This is the mechanism of having babies”. Therefore, nourishing the kidney, enriching essence, and improving qi and blood are essential to improve endometrial receptivity and increasing the pregnancy rate11. Other studies have found that kidney-nourishing tradition medicines can increase blood supply to the uterus, and can also increase the endometrial epithelium, carbohydrate, protein, and lipid content, and increase endometrial stromal nutrition12.
Medicines nourishing yin can increase uterine estrogen receptor (ER) and progesterone receptor (PR) levels. Blood circulation drugs not only regulate the circulation, but improve the nutritional status of the endometrium\(^\text{10}\). In this study, a systematic evaluation method was used to retrieve the studies regarding the impact of TCM on endometrial receptivity in randomized controlled trials. Meta-analyses of these studies further evaluated the impact of medicine on endometrial receptivity to provide support for evidence-based clinical treatment.

**Methods**

**Inclusion criteria**

*Study type*: We focused on TCM treatment in randomized or quasi-randomized controlled clinical trials, whether or not the studies were blinded; the language was not restricted.

*Observed objects*: The patients had a confirmed diagnosis of infertility.

*Interventions*: The treatment group was treated with TCM. The control group was treated with Western medicines as the positive control. There was good balance between the two groups and the groups were comparable.

*Outcomes*: Pregnancy was considered a clinical cure, while no pregnancy was considered a failure.

**Exclusion criteria**

Patients with deformities and lesions of the uterus and vagina caused by congenital physical defects were not eligible for the study.

In the case of repetitive publications, only one was selected and the remaining studies were excluded. The main interventions for clinical trials were other treatments, literature reviews of non-clinical studies, animal studies, adverse reaction reports and pharmacology, and pharmacokinetics.

Other exclusion criteria were: absence of control group, poor balance between the groups, and impossibility to compare the groups.

**Search strategy**

A computer search alone was conducted. The sources included VIP medical information systems, Wanfang Data, China Academic Journal, and PubMed. The cut-off date for the search was September 2012. We tracked retrieved literature references. If references met the inclusion criteria, further reading determined whether or not abstracts or full-text documents will be included. Qualified studies were recorded in unified form. Papers were retrieved by authors independently and were scored with the Jadad scoring method based on the following criteria: whether or not random methods were used; whether or not blinding was adopted; whether or not the baseline conditions of the treatment and control groups were recorded; whether or not intention-to-treat (ITT) analysis was performed; and whether or not there were lost cases.

**Statistics**

Revman 5.0 software from the Cochrane Collaboration Group was used for data processing and analysis. A chi-square test was used for statistical heterogeneity analysis with an \(\alpha = 0.05\) and a \(P < 0.05\) being considered statistically significant. The Peto method was also used for heterogeneity testing with an \(I^2\) as the indicator of the degree of heterogeneity. An \(I^2\) is < 25% is of low heterogeneity; an \(I^2\) between 25% and 50% is of medium heterogeneity, and an \(I^2 > 50\%\) is of high heterogeneity. If homogeneity was detected between the studies, the fixed effects model was selected. If there was heterogeneity a random effects model was selected. The results included count data as calculated using the odds ratio (OR) method and 95% confidence intervals. Meta-analyses use funnel plots of the distributed morphologic analysis of clinical data to determine whether or not there was publication bias.

**Results**

**Literature Search Results**

An electronic search using the keywords, “endometrial receptivity”, and “medicine” revealed 79 papers. After screening, 13 studies met the inclusion criteria for randomized controlled trials (RCTs). The number of cases included from the various institutes ranged from 36-210. There were a total of 1122 patients in the studies. All included studies had clearly recognized diagnostic criteria. All 13 studies used randomized methods. Among the 13 studies, 4 mentioned random number (figures 1-4), 1 used ovulation order (figure 5), and no stochastic methods were mentioned in the remaining 8 studies\(^{6-13}\). Two papers reported lost cases\(^{2,3}\). Whether or not there was allocation concealment, how the sample size was calculated, whether or not the study was blinded, and whether or not ITT was followed were not reported. Therefore, all reports were of low quality. The results of the included studies are shown in Table 1.
The treatment groups had 479 cases and 145 patients were pregnant, with a pregnancy rate of 30.27%. There were 475 patients in the control group and 69 patients were pregnant, with a pregnancy rate of 14.53%. The analysis has a low degree of heterogeneity ($X^2 = 8.74$, df = 9, $P = 0.08$).
0.46, \( F = 21\% \)), thus the fixed effect model was used (OR = 2.86; 95% CL = 2.01-4.05; Z = 5.89; P < 0.00001). These results indicated that TCM can improve the pregnancy rate. Only four papers included an evaluation of treatment outcomes (5-8). Because the evaluation metrics were not consistent or because there were missing data, a meta-analysis was not performed; however, it is clear that at the conclusion of the studies, the described syndromes in the TCM treatment groups were significantly better than the control group.

**Endometrial thickness**

Ten RCTs reported human chorionic gonadotrophin (HCG) daily endometrial thickness after treatment (2,5,7,9-13).
There were 466 cases in the treatment group and 431 patients in the control group. The analysis has a high degree of heterogeneity (X² = 46.36, df = 9, P < 0.00001, I² = 81%). Therefore, a random effects model was used (Z = 3.13; P = 0.002; 95% CL of 0.52 [0.20, 0.85]). These results show that TCM can improve endometrial thickness.

2.2.3 PI and RI of endometrial blood flow
Seven RCTs reported HCG levels daily, and the pulsatility indexes (PIs) and resistance indexes (RIs) of endometrial blood flow (1-2, 4, 6-7, 9-10). There were 376 patients in the treatment group and 377 patients in the control group. The PIs and RIs were highly heterogeneous (X² = 399.54, df = 6, P < 0.00001, I² = 98%; X² = 307.52, df = 6, P < 0.00001, I² = 98%), thus the random effects model was selected (Z = 1.76, P = 0.08, 95% of CL was -1.45 [-3.05,0.16] for PI; Z = 3.39, P = 0.0007, 95% of CL was -2.39 [-3.77, -1.01] for RI). These results indicated that TCM can improve the RI of endometrial blood flow, but there was no significant improvement in the PI. Another RCT reported that luteal phase endometrial blood PI and RI in the treatment group were lower than the control group and the difference was statistically significant (8).

Endometrial type
Seven RCTs reported endometrial types (1-2, 4, 6-7, 9-10). There were 387 patients in the treatment group, of which 288 cases were type A and 108 cases were a combination of B and C types. There were 366 patients in the control group, of which 227 cases were type A and 139 cases were a combination of B and C types. They was a high level of heterogeneity (X² = 6.19, df = 6, P = 0.40, I² = 3%). Therefore, a fixed effects model was used (Z = 3.56, P = 0.0004, 95% CL were 1.77 [1.29, 2.42] and 0.57 [0.41, 0.77]).

2.4 Funnel plot analysis
The pregnancy rate ratio OR between the treatment and control groups from the meta-analysis results was plotted on the abscissa and the number of samples in the experiments was the ordinate. The funnel plot analysis will show the distribution pattern of the collected data in clinical studies to determine the presence of publication bias. As can be seen from Figure 6, the literature was normally distributed, indicating that no bias existed among the included publications.

Discussion

Western medicine understanding of endometrial receptivity
Embryo quality and endometrial receptivity are two important elements in the success of assisted reproduction. With the maturation of controlled ovarian hyperstimulation programs and the improvement in embryo culture conditions, > 95% of patients have qualified embryos for implantation (10). However, the clinical pregnancy rate has persisted at approximately 40%. It is evident that endometrial receptivity is the key to the success of ART (15, 16).

Synchronization between endometrial receptivity and growth of the fertilized egg is the key to implantation success. The use of ovulation drugs during in vitro fertilization-embryo transfer (IVF-
ET) cycles will induce multiple follicle maturation. After fertilization, several quality embryos can be used for implantation(15). In contrast, after ovulation induction, the balance of endogenous steroids and the expression of hormone receptors were disturbed. Thus, the physiologic effects of endogenous hormones on the endometrium, the correlation factor with receptor expression, and the endometrial morphology were asynchronous.

This will affect endometrial receptivity during the embryo implantation period and decrease the pregnancy rate. Pinopode is the gold standard for endometrial receptivity; however, pinopode involves endometrial biopsy, an invasive and traumatic examination procedure. This feature limits its application in IVF-ET cycles. In clinical practice, endometrial thickness and perfusion monitored by ultrasound are commonly used to assess endometrial receptivity(15-17).

**TCM understanding of endometrial receptivity**

TCM holds that kidney essence deficiency and kidney qi weakness are the basic pathologies of infertility. The kidney, where essence resides, is the innate hidden internal organ of essence. The kidney dominates human growth and development and reproductive functions. “Suwen - Elder naive theory papers” states that “when women are seven years old, kidney qi is strong and teeth and hair grow. When they are 14, menstruation arrives; conception vessel clears; and essence is full. It’s time to have babies”. Women’s reproductive capacity and the kidney are closely related with the coordination among the kidney qi - menstruation penetrating vessel and conception vessel - uterus along the shaft as a precondition(8-11). If kidney qi is abundant, menstruation will come, Chong and Ren will clear, and men and women become reproductively mature.

Men begin to excrete sperms and women begin to menstruate. When yin and yang are in harmony, two essences combine, leading to pregnancy. In clinical practice, the weakness of kidney can often be caused by the following factors: inadequate endowment; malnutrition; sexual indulgence; panic; multiple pregnancies; chronic illness; ovarian surgery radiotherapy; chemotherapy; pelvic infection exposure to environmental toxicants; and other kidney diseases. When kidney essence is absent, kidney qi is deficient, the division between Chong and Ren is lost, menstruation becomes less and dries, and reproductive function is gone(8-11).

IVF-ET induces down-regulation and ovarian hyperstimulation may further aggravate kidney weakness, leading to a vicious cycle. Down-regulation is an important part of controlled ovarian hyperstimulation in an IVF-ET long program, which puts the pituitary gland in the desensitization state, suppresses gonadotropin secretion to a low level, reduces the incidence of premature luteinizing hormone peaks, improves egg quality so that follicle synchronization develops and more mature follicles are produced, and the success rate of IVF-ET improves. Although there are many different causes of infertility with unique symptoms for IVF-ET patients, upon down-regulation, the characteristic clinical signs can be observed and syndromes can be treated following certain rules in TCM(15-17).

After pituitary down-regulation therapy, kidney yin and yang dynamic equilibrium is destroyed so that the body sex fluid loses its moisture, yang cannot be materialized, and menstruation becomes difficult due to the relative lack of red blood. In addition, dry mouth and throat, as well as sore joints and back occur. Menstruation is weak and the color is dark. Mental fatigue, loss of libido, hot flashes, vaginal dryness, pale tongue, thin tongue coating, and a thin and weak pulse are other symptoms. Experimental studies have revealed that the kidney weakens during down-regulation. From a microscopic point of view, the symptoms after down-regulation with gonadotropin-releasing hormone agonists match the characteristics of kidney weakness. Controlled ovarian hyperstimulation treatment causes extraordinary hormone levels, changes the internal environment, and disrupts the natural cycles of cytokines, receptors, and various regulatory factors. Hyperovulation interferes with the internal environment and is an artificial and relative deficiency disease. Using the controlled ovarian hyperstimulation long program, pituitary down-regulation leads to the syndrome of iatrogenic kidney yin deficiency during menstrual periods.

Hyperstimulation requires the development of multiple eggs at the same time, which makes the yin less common. The disease can be traced back to Chong and Ren. The pathogeneses is the relative lack of kidney yin, deficient kidney essence which cannot nurture eggs, poor yin qi which needs moisture, and yan qi which cannot materialize. These cause difficult menstruation and Chong and Ren dystrophy.
Through this study we believe that TCM may be an effective way to improve endometrial receptivity and improve pregnancy rates; however, the quality of randomized controlled clinical trials is methodologically poor. Future research should improve the quality of clinical research, strengthen the consistency of clinical trials, and use blinded studies, such as double-blind or a double-blind, double-dummy study. Attention should be paid to reports of negative outcomes of clinical trials to generate more reliable results and guide future clinical applications.

References


