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Original Article

Traditional Chinese medical herbs staged therapy in infertile women with endometriosis: a clinical study

Zhaorong Ding[1], Fang Lian[2]

[1]*Department of Traditional Chinese Medicine, Jinan Central Hospital Affiliated to Shandong University, China;* [2]*The Affiliated Hospital of Shandong Traditional Chinese Medical University, China*

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Abstract: Background: Endometriosis is a common gynecological disease defined as the presence of endometrioid tissue (glands and stroma) outside the uterus. About 30 to 40% patients with endometriosis are infertile. In traditional Chinese medical system, endometriosis associated infertility is mostly caused by kidney deficiency and blood stasis. The herb of reinforcing kidney and removing blood stasis is designed to treat the disease. Material and methods: All the 80 up-to-standard patients were divided into two different groups exactly according to the random principle. They were treated with hormone and traditional Chinese medical herb separately. After half year's therapy, all the patients received one year's follow-up. Their transvaginal ultrasonographic changes, serum hormone levels and pregnancy rate were recorded to analysis the effect. Results: No significant difference happened in two groups' demographic and clinical characteristics ($P > 0.05$). After the treatment, the effect on serum hormone levels and specific markers are significant ($P < 0.05$). The transvaginal ultrasonographic changes were positive, too. The text on hepatic and renal function confirmed to the safety of the herb. Compared to hormone therapy, the traditional Chinese medical herb is safe and effective for endometriosis patients with infertility. Conclusion: Compared with hormone therapy, traditional Chinese medical herb's two-staged therapy is effective and safe for endometriosis patients with infertility.

Keywords: Endometriosis, infertility, traditional Chinese medicine, mifepristone

Introduction

Endometriosis is a common gynecological disease defined as the presence of endometrium-like tissue (glands and stroma) outside the uterus. The ectopic endometria can be found in different areas like ovary, uterosacral ligament, uterus-rectum fossa, myometrium and even organs outside the pelvic cavity [1]. They will induce a chronic inflammatory reaction, scar tissue, and adhesions. Patients with endometriosis mainly complain of pelvic pain, dysmenorrhea, and dyspareunia. The associated symptoms can impact the patient's general physical, mental, and social wellbeing [2]. Apart from the impact on their living quality, it also can have an impact on the potential of these women to have a family. Endometriosis occurs in over 10% of the general female population. About 30 to 40% patients with endometriosis are infertile, and 25 to 50% of infertile women have endometriosis [3, 4].

The pathogenesis still remains unknown. Possible causes include metaplasia, cellular immunity, distance metastasis. Another possibility is that the chronic inflammatory reaction disturbed the ova's maturity and excretion, which leads to the infertility. Treatment options include expectant management, analgesia, hormone therapy, surgical intervention, and combined medical treatment before and/or after surgery. It is acknowledged that laparoscopy is the preferred surgery to treat infertility caused by endometriosis. The fertility could be restored in a short time, while the initial risk is the impact of ovarian function [5]. Because of the high morbidity and infertility rate, it is important and impending to explore an effective and safe treatment to solve the problem. Drug therapy can control the symptoms well, but there is no evidence on the effect of infertility. The previous treatment was administration of gestagens, later danazol and gonadotropin releasing hormone (GnRH) analogues [6]. Hughes's study

showed that in infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility [6].

Traditional Chinese medicine exists thousands years in the world and still plays a great role in modern Chinese medical work. In traditional Chinese medical system, Endometriosis belongs to the category of blood stasis. In the opinion of syndrome differentiation and treatment system, endometriosis associated infertility is mostly caused by kidney deficiency and blood stasis. The herb of reinforcing kidney and removing blood stasis is designed, but the medicine for removing blood stasis always increase the risk of abortion after ovulatory phase. This shortage limits patients' progress of natural conception at the right moment. The aim of our study is to observe the efficacy of the herb's stage therapeutics based on different periods of menstrual cycle.

Materials and methods

Patients

Our study was approved by the Ethical Committee of Jinan Central Hospital Affiliated to Shandong University China. Each patient signed an informed consent form for the use of related data. All up-to-standard patients were divided into two different groups exactly according to the random principle. Finally, a total of 80 patients were collected between January and August in 2013. All the participants were infertile women with minimal or mild endometriosis confirmed by laparoscopy, according to the revised American Fertility Society (r-AFS) classification (r-AFS score < 16) [7]. At the same time, they were eligible to participate this study if 1) the patients in the child-bearing period (20-40 years old) who have birth plans and had failed to get pregnant after at least 12 months; 2) the patients were able to understand the study content and provide consent; 3) the patients were willing to accept the necessary follow-up, therapy and laboratory examination. The exclusion criteria included 1) previous surgery or hormone therapy for endometriosis; 2) the infertility was credited with other diseases but not endometriosis; 3) the patients with uterine fibroid, severe cardiovascular, cerebrovascular diseases, or hepatic or renal dysfunction; 4) the patients who participate in other study program in the meantime.

Treatments

The 80 patients were divided into two different treatment groups: traditional Chinese medicine group (Group A) and hormone therapy group (Group B). Patients in hormone therapy group take 12.5 mg mifepristone orally every day. The therapy started from the first day of their menstrual cycle and lasted for six months. In traditional Chinese medicine group, two kinds of herbs were given to participants in different periods of their menstrual cycle. The first kind was used before ovulation, while the other was after ovulation. After water decoction, each herb was separately taken in the morning and evening. The course of treatment is the same with hormone therapy.

Traditional Chinese medicine prescription

The first prescription is composed by 20 g (gram) prepared radix rehmanniae, 20 g dodder, 15 g angelica, 15 g salvia, 15 g Caulis Spatholobi, 20 g cyperus rotundus, 12 g curcuma zedoary, 12 g Chuan cattle cane, 15 g poria cocos, 15 g cassia twig, 15 g rhizoma corydalis, 15 g trogopterus dung and 15 g red peony root.

The second prescription includes 20 g dodder, 20 g herbal epimedii, 10 g cornu cervi degelatinatum, 15 g angelica, 15 g Caulis Spatholobi, 25 g combined spicebush, 15 g poria cocos, 15 g folium artemisiae argyi, 15 g cassia twig, 15 g rhizoma corydalis, 15 g parched white peony root and 10 g liquorice.

Follow-up

All participants completed their one-month visit after therapy, where their menstrual status was noted. Transvaginal ultrasonography was taken every month on the third day before ovulation to observe follicular development and hyperplasia endometrial until the follicles' excretion. Because of the potential liver renal toxicity, patients need to text their hepatic and renal function before and after the therapy, so that we can evaluate its safety. In addition, they were required to text the peak value of estradiol before ovulation and follicle stimulating hormone (FSH) on day 2-3 of cycle, the serum level of CA125 and endometrial antibody (EMAb). During the 12 months follow-up, we mainly observed whether they were pregnant.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) for continuous variables and fre-

Table 1. Baseline characteristics

	Group A (n=40)	Group B (n=40)	*P* value
Age (years)	28.1±2.1	28.6±3.4	0.352
Duration of infertility (years)	2.3±1.8	2.6±1.5	0.287
BMI (Kg/m^2)	20.4±3.1	20.6±2.4	0.631
r-AFS stage (%, n)			
Stage I	57.5% (23)	65.0% (26)	0.438
Stage II	42.5% (17)	35.0% (14)	0.403
Endometrial thickness (mm)	12.6±0.9	11.9±1.1	0.552
FD (mm)	1.61±0.21	1.59±0.87	0.439
Estradiol (pg/mL)	188.5±44.3	190.3±39.4	0.296
FSH (ng/mL)	10.2±2.4	10.3±2.8	0.526
CA125 (U/mL)	84.5±18.1	90.1±21.6	0.442
EMAb (%, n)	65.0% (26)	55% (22)	0.392

r-AFS stage: according to the revised American Fertility Society (r-AFS) classification; FD: follicle diameter; Estradiol: the peak value of estradiol before ovulation; FSH: follicle-stimulating hormone; EMAb: positive rate of endometrial antibody.

Table 2. Comparison between the therapeutic effects

	Group A	Group B	*P* value
Endometrial thickness (mm)	8.6±0.6	8.9±0.7	0.552
FD (mm)	1.95±0.11	1.75±0.37	0.439
Estradiol (pg/mL)	98.5±21.9	99.6±19.4	0.296
FSH (ng/mL)	5.2±1.9	5.4±2.3	0.526
CA125 (U/mL)	36.3±12.1	42.1±13.4	0.442
EMAb (%, n)	30.0% (12)	30% (12)	0.392
PR (%, n)	52.5% (21)	37.5% (15)	0.265

FD: follicle diameter; Estradiol: the peak value of estradiol before ovulation; FSH: follicle-stimulating hormone; EMAb: positive rate of endometrial antibody; PR: pregnant rate.

Table 3. Effects of traditional Chinese medical herb

	Before treatment	After treatment	*P* value
Endometrial thickness (mm)	12.6±0.9	8.6±0.6	0.102
FD (mm)	1.61±0.21	1.95±0.11	0.219
Estradiol (pg/mL)	188.5±44.3	98.5±21.9	0.006**
FSH (ng/mL)	10.2±2.4	5.2±1.9	0.005**
CA125 (U/mL)	84.5±18.1	36.3±12.1	0.014*
EMAb (%, n)	65.0% (26)	30.0% (12)	0.045*
ALT (U/L)	28±5.6	32.1±4.4	0.456
Cr (μmol/L)	54.9±9.5	63.4±7.3	0.338

*: $p < 0.05$; **: $p < 0.01$. FD: follicle diameter; Estradiol: the peak value of estradiol before ovulation; FSH: follicle-stimulating hormone; EMAb: positive rate of endometrial antibody; ALT: glutamic-pyruvic transaminase; Cr: creatinine.

quencies for categorical variables. Differences between groups were examined by nonparametric test and chi-square test for continuous and categorical variables respectively. An alpha value of 0.05, corresponding to a *P* value < 0.05, served as criterion for establishing statistical significance. Analysis was performed using SPSS for Windows (SPSS Inc., Version 19.0, Chicago, Illinois).

Results

Baseline characteristics

We collected 80 patients diagnosed as endometriosis associated infertility at last. The mean age of patients in group A is 28.1±2.1, while 28.6±3.4 in group B. The comparison between the baseline information and previous medical history of two groups are concluded in **Table 1**. There were no significant differences of the possible factors which may have influence on the effect in two groups, including duration of infertility and r-AFS stage. No abnormality in routine liver and renal function examinations happened in all participants. In the same way, there were no significant differences in age, hormone levels and transvaginal ultrasonography's changes. In addition, no significant difference happened in two groups' serum level of CA125 and detection rate of EMAb. According to the results, the two groups were comparable with regard to their demographic and clinical characteristics ($P > 0.05$).

Therapeutic effect

As shown in **Table 3**, endometrial thickness was lower and follicle diameter was larger in group A. Although the improvement was not significantly different ($P > 0.05$). From the serum level of hormone of view, significant improvement happened after treatment ($P < 0.01$). Changes of CA125 and EMAb were also satisfactory ($P < 0.05$). All the results give us confidence to help endometriosis associated

infertility patients with our unique herb. Another important point we can't ignore is the safety. Traditional Chinese medical herb usually contains many different components, which leads to the complicated pharmacological effect. We used glutamic-pyruvic transaminase (ALT) and serum creatinine to evaluate the influence on hepatic and renal function. The results showed that no significant changes occurred on the serum level of ALT and creatinine ($P > 0.05$). At the same time, there were no severe adverse events happened during our follow-up. **Table 3** showed that our herb's therapeutic effect was almost equivalent to hormone therapy (all $P > 0.05$).

The pregnancy rate within 12 months of follow-up was 45.0% (36/80): 21 in Group A (52.5%, 21/40), and 15 in Group B (37.5%, 15/40). There were no cases of ectopic pregnancy, but three spontaneous abortions (one in Group A and two in Group B). No significant difference in PR and spontaneous abortion rate were observed ($P > 0.05$) (**Table 2**). At the end of our follow-up, one baby was born respectively in two groups.

Discussion

Endometriosis is the most common disease that occurs in the female pelvis, and is associated with infertility. The pathogenesis of endometriosis associated infertility is rather unclear. Traditionally, endometriosis associated infertility has been attributed to primarily advanced stages of pelvic disease, which cause lesions, that may impair normal reproductive processes. Panidis and Matalliotakis provided their thorough review of the putative mechanisms of early stage endometriosis in the etiology of subfertility [8]. Recent years, laparoscopic surgery and gonadotropin-releasing hormone agonists (GnRHas) have been widely used to treat endometriosis. Controversy remains regarding the benefit of surgical ablation of minimal-to-mild endometriosis at the time of laparoscopy. No one can deny that the laparoscopic surgery can improve patients' fecundity. However, because of the progressive nature of the disease and the potential ovarian functional affect in many patients, it appears prudent to ablate endometriotic lesions at the time of surgery in patients with minimal and mild endometriosis [5, 9, 10]. High success rates in fertility rates have been reported when surgery was carried out in conjunction with multidisciplinary approaches [11].

Traditional Chinese medicine has also long been in use for the treatment of endometriosis. In the system of traditional Chinese medicine, women's menstruation, pregnancy and delivery are closely related to blood's wax, wane, lag and unimpeded. Recently, more and more doctors believe that endometriosis results from kidney deficiency in the root, and blood stasis in the tip. Chinese nourishing kidney herbs can regulate gonad axis dual-directionally as endocrine hormone, strengthen pituitary and ovary's reactiveness and improve hypothalamus-pituitary-ovary axis' function. We add promoting-circulation drugs into nourishing kidney herbs, so that the compound preparation can improve patients' circulation and increase ovarian blood flow volume. It helps mature follicle ovulate. In our study, two different herbs were separately used in follicular phase and luteal phase. First herb was mainly used to reinforce kidney, nourish vital substance, activate blood, remove stasis and regulate ovarian function. However, since the second herb was designed to warm meridian, puissant activating blood ingredients were reduced. According to the results of our study, the treatment of traditional Chinese medicine by stage is effective for endometriosis patients. The effect manifests not only in the transvaginal ultrasonographic changes, but also significantly in the serum hormone levels ($P < 0.01$).

Several limitations of this study should be recognized. Firstly, the sample's size of our study was small, which might limit the reliability. Besides, as the popular of laparoscopic surgery, the effect is more and more widely recognized. In our study, we didn't take the surgery into account. In the meantime, laparoscopic surgery combined with traditional Chinese medicine will be our choice in the future. At last, the follow-up is too short to record each patient's pregnancy and delivery. Despite the limitations of our approach, the study provided us effective proofs that our herb's two-staged therapy is a safe and effective measure for endometriosis patients with infertility.

In conclusion, compared with hormone therapy, traditional Chinese medical herb's two-staged therapy is effective and safe for endometriosis patients with infertility.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhaorong Ding, Department of traditional Chinese Medicine, Jinan Central Hospital, 105 Jiefang Road, Jinan 250013, Shandong, China. Tel: +86 531-82076588; E-mail: dingzhaorong123456@126.com

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