Chin J Integr Med 2013 Nov;19(11):820-825

ORIGINAL ARTICLE

Controlling the Recurrence of Pelvic Endometriosis after A Conservative Operation: Comparison between Chinese Herbal Medicine and Western Medicine*

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ABSTRACT **Objective:** To compare the clinical effect of Chinese medicine (CM) and Western medicine (WM) for controlling the recurrence of pelvic endometriosis after a conservative operation. **Methods:** The study was a multi-center, randomized, parallel controlled and prospective clinical trial. Patients were randomly divided into two groups: CM group (106 cases) and WM group (102 cases). Drugs were given to patients during 1–5 days of the first menstruation after a conservative operation in both groups. Patients with stages Ⅰ and Ⅱ (revised American Fertility Society) were treated for 3 months, while the patients with stages Ⅲ and Ⅳ were treated for 6 months. The patients in the CM group were treated using three types of Chinese herbal medicine based on syndrome differentiation. Patients in the WM group were treated using gonadotropin releasing hormone agonist (GnRH-a) or gestrinone. Patients treated with GnRH-a received add-back therapy of Tibolone Tablets once a day after 4 months of treatment. Any cases of dysmenorrheal chronic pelvic pain, menstruation and any adverse reactions of patients were recorded once a month during the preoperative and postoperative periods and once every 3 months during the follow-up period. During the preoperative, postoperative and the follow-up periods, patients underwent type B ultrasonography of the pelvis and measurements of serum CA125 levels, gynecologic examination, routine evaluations of blood, urine, hepatic function (glutamate pyruvate transaminase), renal function (blood urea nitrogen) and electrocardiograms. During the follow-up period they underwent type B pelvic ultrasonography, measurement of serum CA125 levels and further gynecologic examinations. The two treatments were compared for clinical recurrence rates, pregnancy rates and the incidence of adverse reactions. **Results:** The incidence and timing of recurrence of endometriosis were not significantly different between the two groups. The first pregnancy achieved by the patient in the CM group was significantly earlier than that in the WM group ($P<0.05$). Moreover, the incidence of adverse reactions in the WM group was significantly higher than in the CM group ($P<0.01$). **Conclusions:** Treatment with Chinese herbal medicines prevented the recurrence of endometriosis after a conservative operation, improved the conception rate and showed fewer and lighter adverse reactions than did treatment with WM therapy. Treatment with Chinese herbal medicine meets the need of patients wishing to have a child following endometriosis and is an appropriate form of clinical treatment.

KEYWORDS endometriosis, infertility, fertilization *in vitro*, embryo transfer, recurrence rate, pregnancy rate

Endometriosis (EMs) is an estrogen-dependent disease that is common frequently encountered and stubborn in women of childbearing age. In recent years, the morbidity of EMs has increased significantly, reaching 10% to 15% in the general

*Supported by the Key Projects of the National Science and Technology Pillar Program during the 11th Five-Year Plan Period (No. 2006BA104A)

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DOI: 10.1007/s11655-012-1247-z

population and exceeding 30% among patients with chronic pelvic pain or infertility.[1] Surgery is the first treatment for pelvic EMs, but it is difficult to control postoperative recurrence. Some studies reported that the recurrence rate reached 36% by 5 years after surgery[2] and the recurrence rate after a conservative operation with preservation of fertility can be as high as 50%.[3] Surgery for recurrence is difficult and causes major bleeding; moreover, recurrence of EMs is still possible after surgery.[4] Thus, drug treatment after the operation is the key to eliminate or suppress any residual lesions and to prevent recurrence. The treatment of EMs recurrence with Chinese herbal medicine is now an active research field. To compare the clinical effec of controlling the recurrence of pelvic EMs after a conservative operation between Chinese medicine (CM) and Western medicine (WM), we ran a multi-center, randomized, parallel controlled and prospective clinical trial. We measured the rates of recurrence and successful pregnancy and the incidence of adverse reactions between the two therapies.

METHODS

Diagnostic Criteria

Methods on the Manual on the Diagnosis and Therapy of Endometriosis[5] and Chinese Obstetrics and Gynecology[6] were used to establish the diagnostic criteria. The clinical stages were graded according to the revised scheme published by the revised American Fertility Society (r-AFS) in 1985.[6] The criteria of symptoms and signs for syndrome differentiation were established based on the published references[7,8] and the clinical experience of our group.

Inclusion Criteria

Patients were included according to the following screening criteria: (1) meet the diagnostic criteria and CM syndrome differentiation criteria; (2) without a history of serious drug hypersensitivity; (3) have never undergone an open operation or laparoscopic operation for EMs; (4) have not taken any other drugs to treat EMs for 6 months before the operation; (5) have no serious primary disease in the cardiovascular, cerebrovascular, hepatic, renal or hematopoietic systems and lacked any history of psychiatric illness; (6) non-lactating woman aged from 18 to 45 years.

According to the above screening criteria, patients with clinical and pathological features of ovarian EMs and/or deep infiltrating EMs were assigned to treatment groups during the first to fifth days of the first menstruation after a conservative operation. All patients signed informed consent forms.

Exclusion Criteria

Patients with EMs combined with adenomyosis and any patients using other drugs to treat EMs after the operation were excluded.

Patients

A total of 208 patients with pelvic EMs after a conservative operation were recruited from outpatient and inpatient departments of eight centers in China from March 2008 to May 2010. The centers were Guang'anmen Hospital; Beijing Friendship Hospital Affiliated to Capital Medical University; Beijing Hospital of the Ministry of Health; Beijing Tiantan Hospital Affiliated to Capital Medical University; Fuxing Hospital Affiliated to Capital Medical University; Wangjing Hospital of the China Academy of Chinese Medical Sciences; Second Affiliated Hospital to Tianjin University of Traditional Chinese Medicine and the PLA Navy General Hospital. The patients were randomly assigned to two groups by randomized blocks method. There were 106 patients in the CM group and 102 patients in the WM group.

Treatment

Drugs began to be given to the patients during days 1–5 of their first menstruation in both groups. The patients with r-AFS stages Ⅰ and Ⅱ EMs were treated for 3 months, while the patients with stages Ⅲ and Ⅳ were treated for 6 months.

The patients in the CM group were treated using three types of Chinese herbal medicine (Kangmei Pharmaceutical Co., Ltd., China) treatment based on syndrome differentiation. The herbs were decocted with water and given to the patients by oral administration twice a day, with 21 days as one course. The decoction was given again during days 1–5 of the next menstrual period. Modified Guifu Decoction (桂附饮, *Radix Aconiti lateralis Preparata*, 10 g; *Ramulus Cinnamomi* 10 g; *Radix Linderae* 10 g; *Rhizoma Sparganii* 10 g; *Rhizoma Curcumae* 10 g; *Spina Gleditsia* 14 g and *Radix Salviae Miltiorrhizae* 25 g) was given to patients with syndrome of cold congeal and blood stasis to the warm meridians and dissipate cold, activate blood and resolve stasis. Modified Danchi

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Decoction (丹赤饮, *Radix Bupleuri* 10 g; *Rhizoma Cyperi* 14 g; *Radix Salviae Miltiorrhizae* 25 g; *Radix Paeoniae rubra* 15 g; *Rhizoma Curcumae* 10 g; *Spina Gleditsia* 14 g and *Rhizoma Sparganii* 10 g) was given to the patients with syndrome of qi stagnation and blood stasis to sooth the Liver (Gan) and regulate qi, activate blood and resolve stasis. Modified Qidan Decoction [芪丹饮, *Astragalus membranaceus* (Fisch.) Bge. *Preparata* 30 g, *Salvia Miltiorrhizae* 25 g, *Radix Paeoniae rubra* 15 g, *Rhizoma Curcumae* 10 g, *Poria* 15 g and *Rhizoma Atractylodes Macrocephala* 15 g] was given to the patients with syndrome of qi deficiency and blood stasis to invigorate Spleen (Pi) and replenish qi, activate blood and resolve stasis. Drugs were added or omitted in the CM group depending on patients' symptoms. Thus, the patients with dysmenorrheal were treated by adding *Rhizoma Corydalis* 10 g, *Radix Linderae* 10 g; the patients with anal pain upon bearing down were treated by adding *Rhizoma* et *Radix Notopterygii* 8 g. The patients with lumbago were treated by adding *Radix Dipsaci* 30 g and *Cortex Eucommiae* 10 g.

The patients in the WM group received hypodermic or intramuscular injections of 3.75 mg GnRH-a (Triptorelin Acetate for Injection, Ipsen Pharma-Biotech, France, No. H20030577) once monthly or 2.5 mg oral Gestrinone (Beijing Zizhu Pharmaceutical Co., Ltd., China, No. H19980020) twice a week. Patients treated with gonadotropin releasing hormone agonist (GnRH-a) received add-back therapy of 1.25 mg Tibolone Tablets (Livial, Nanjing Organon Pharmaceutical Co., Ltd., No. H20051085) once a day after 4 months of treatment.

February 28, 2008, it had passed the ethic review of the 11th Five Year Plan; August 21, 2008, it had passed the ethic review of Guang'anmen Hospital, China Academy of Chinese Medical Sciences for changing clinical investigation plans.

Outcome Measures

The EMs recurrence rate, the pregnancy rate and the incidence of adverse reactions were recorded. Evaluations of dysmenorrheal, chronic pelvic pain, menstruation conditions and the degree of adverse reactions were based on "Guiding principle of clinical research on new drugs of traditional Chinese medicine."[9] The incidences of dysmenorrheal, chronic pelvic pain, menstruation and any adverse reactions were recorded once a month during the preoperative and postoperative periods and once every 3 months during the follow-up period. Patients underwent preoperative, postoperative and post-treatment evaluation of safety indices including type B pelvic ultrasonography, measurement of serum CA125 levels, gynecologic examinations, and routine evaluations of blood, urine, hepatic function [glutamate pyruvate transaminase (GPT) levels], renal unction [blood urea nitrogen (BUN) levels] and electrocardiograms. During the follow-up period they underwent type B pelvic ultrasonography, measurement of serum CA125 levels and further gynecologic examinations.

Evaluation Criteria

The diagnosis of recurrence was made by referring to a manual on the diagnosis and therapy of endometriosis. These were as follows: (1) recurrence and aggravation after postoperative symptoms had been relieved for 3 months; (2) the pelvic signs returned after disappearing or were aggravated to the preoperative level; (3) after operation, the type B ultrasound scans showed a new focus of infection or EMs; (4) The serum CA125 level increased again after declining and other diseases were excluded. The patients had a diagnosis of recurrence, fitting one of the criteria (2–4) above with or without concomitant criteria. The three-point scoring criteria for adverse reactions were as follows: (1) mild (1 point): minimal reaction, work and life activities were unaffected; (2) moderate (2 points): light reaction, work and life activities were affected but could be tolerated; (3) severe (3 points): severe reaction, work and life activities were badly affected and could not be tolerated.

Statistical Analysis

The data were analyzed using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). Comparison of the recurrence rate between two groups was performed using χ^2 test and the relative risk (RR), odds ratio (OR) and the 95% confidence intervals (CI) were calculated. The difference of count data or measurement data between groups was compared by Student's *t*-test or χ^2 test, respectively. Statistical significance was assumed at $P<0.05$.

RESULTS

General Clinical Data

The demographic data of the patients in

Table 1. Demographics of Patients in the Two Groups

Item		CM (106 cases)	WM (102 cases)	Statistics	*P*-value
Basic material	Age ($\bar{x} \pm s$, year)	32.52 ± 6.16	31.70 ± 6.08	0.97	0.33
	Sexual life history [Case (%)]	84 (79.2)	80 (78.4)	0.02	0.89
	EMs course ($\bar{x} \pm s$, year)	28.80 ± 36.82	38.15 ± 56.07	–0.40	0.69
Clinical manifestation [Case (%)]	Algomenorrhea	60 (56.6)	63 (61.8)	0.57	0.45
	Chronic pelvic pain	42 (39.6)	37 (36.3)	0.25	0.62
	Irregular menstruation	15 (14.2)	11 (10.8)	0.54	0.46
	Infertility	15 (14.2)	15 (14.7)	0.01	0.91
	Pelvis positive sign	101 (95.3)	96 (94.1)	0.14	0.71
	Abnormal B-Ultrasound Scan	100 (94.3)	99 (97.1)	0.93	0.33
	Abnormal CA125	49 (46.2)	52 (51.0)	0.93	0.63
Postoperative diagnosis [Case (%)]	Ovarian endometriosis cyst	100 (94.3)	97 (95.1)	1.37	0.50
	Deep infiltrating endometriosis	6 (5.7)	4 (3.9)		
	Incorporation	0 (0.0)	1 (1.0)		
r-AFS staging [Case (%)]	Stage Ⅰ	13 (12.3)	8 (7.8)	6.36	0.10
	Stage Ⅱ	51 (48.1)	43 (42.2)		
	Stage Ⅲ	36 (34.0)	35 (34.3)		
	Stage Ⅳ	6 (5.7)	16 (15.7)		
CM Syndrome differentiation [Case (%)]	Cold stagnation cause qi blockage	4 (3.8)	10 (9.8)	3.92	0.14
	Qi stasis cause blood stagnation	69 (65.1)	68 (66.7)		
	Qi deficiency cause blood stagnation	33 (31.1)	24 (23.5)		

both groups was shown in Table 1. There was no difference of the baseline characters between the two groups.

Comparison of Recurrence Rates

There were 64 patients (60.4%) received a 3-month treatment and 42 patients (39.6%) received a 6-month treatment in the CM group. While in the WM group, there were 51 patients (50%) received a 3-month and a 6-month treatment, respectively. The mean follow-up time after operation in the CM group was 20.66 ± 6.75 months and 20.83 ± 6.65 months in the WM group with no statistical difference between groups (P>0.05). There were no statistically significant differences in the clinical recurrence rate or in the time to recurrence of pelvic EMs between the CM and WM groups (P>0.05, Tables 2 and 3).

Table 2. Comparison of the Clinical Recurrence Rates of Pelvic Endometriosis between the Two Groups

Group	Case	Recurrence [Case (%)]	χ^2	*P*-value	RR (95% CI)
CM	106	9 (8.5)	1.448	0.229	0.619 (0.280–1.366)
WM	102	14 (13.7)			

Table 3. Comparison of the Time to Recurrence of Pelvic EMs between Groups

Group	Case	Time to recurrence (Month)		*t*	*P*-value
		$\bar{x} \pm s$	Median (Range)		
CM	9	8.56 ± 4.93	6.00 (3.00–18.00)	–0.42	0.68
WM	14	7.86 ± 3.08	6.00 (3.00–12.00)		

Comparison of Pregnancy Rates

A comparison of the pregnancy rate between the two groups during the follow-up period showed no significant differences (31.1% *vs*. 28.4%, P=0.670). For those diagnosed with infertility before the operation, the pregnancy rate in the CM group [12/15 (80.0%)] was significantly higher than that in the WM group [4/15 (26.7%), P=0.003]. The mean duration to achieving the first pregnancy after the operation for the patients in the CM group was also significantly less than that in the WM group (P<0.05, Table 4).

Table 4. Comparison of the Time to First Pregnancy between the Two Groups

Group	Case	Time to first pregnancy (Month)		*t*	*P*-value
		$\bar{x} \pm s$	Median (Range)		
CM	33	5.88 ± 4.18	4.00 (1.00–17.00)	–2.09	0.04
WM	29	8.44 ± 5.34	6.00 (3.00–21.00)		

Comparison of the Incidence of Adverse Reactions

During the treatment period, there were patients with adverse reactions in both groups. A few patients in the CM group complained of mild stomach upsets but these were relieved quickly after adjusting the herbal medicines and dosages. Most of the patients in the WM group showed some prolonged adverse reactions, such as mild to moderate fever and sweating, colpoxerosis, hypaphrodisia, acne, weight gain, insomnia, bone pain, irregular bleeding, headache and skin itching. There was a statistically significant difference of adverse reactions between the two groups [9.4% *vs*. 83.3%, $P<0.01$).

Comparison of Safety Indices

Before treatment, the safety indices and biochemical parameters of patients in the two groups were within normal ranges. After treatment, some of these were outside normal ranges but there were no statistically significant differences between the CM and WM groups.

DISCUSSION

The pelvic pain and infertility caused by EMs seriously affects the health and quality of life and brings great pain and suffering to the patients. Conservative operation is the choice of treatment for young patients with EMs who wish to have a child, but the recurrence rate remains persistently high. How to delay or eliminate such recurrence is an important research topic.

GnRH-a treatment causes a significant reduction in the ovarian secretion of estrogen and leads to a temporary cessation of menstruation, so it is called reversible medical oophorectomy. At present, it is the most effective Western medical treatment for patients with EMs. Some authors have argued that the treatment of EMs by combining a conservative operation with GnRH-a therapy could reduce the recurrence rate and increase the pregnancy rate.[10] However, others recommended combining a conservative operation with GnRH-a treatment for 3–6 months and following up for 6–60 months. Comparing the above-mentioned treatment with the expected treatment, there was no statistically significant in the recurrence rate.[11-13] Combined treatment with GnRH-a after operation could increase the pregnancy rate but there was no statistically significant difference in the pregnancy rate.[10,14] The adverse reactions of GnRH-a treatment mainly manifest as a low estrogen syndrome with fevers, sweats, colpoxerosis, hypaphrodisia, headache, insomnia, poor memory, emotional lability, depression, debility, arthralgia, irregular vaginal bleeding, breast haphalgesia and allergic responses. Some patients of child-bearing age even develop irreversible premature ovarian failure after treatment. It is difficult for patients to accept these side effects. In addition, the loss of bone mass is a serious adverse reaction of GnRH-a, even with short-term treatments.

Because of the high-cost of GnRH-a, a cheaper drug gestrinone has become a common medicine to prevent the recurrence of EMs after a conservative operation for EMs. Gestrinone inhibits endometrial growth to control the recurrence of EMs, and has antiestrogenic, antiprogestogenic and antigonadotropic hormone effects. Treatments with gestrinone and GnRH-a are both effective in controlling recurrence and increasing the pregnancy rate, but gestrinone induces adverse reactionsdue to the high androgenic hormone levels.[15] The best time for pregnancy is 6 months to 1 year after an operation for EMs. However, during treatment with WM, the patients cannot get pregnant, so it is easy to miss the optimal time.[16] For those patients with infertility before the operation, there is a need to use assisted reproductive technologies to increase the pregnancy rate after stopping drugs. However, this is burdensome to the patients.

By contrast, treatment with Chinese herbal medicines stresses prescription for the individual patient's syndrome pattern and attempts to adjust the body's physiology holistically. The recurrence rate of EMs following treatment with CM in this study was basically identical to treatment using WM. At the same time, it had some advantages, such as not interfering with the patient's normal physical condition. It produced a low incidence and mild symptoms of adverse reactions and showed good patient compliance. During treatment with CM, the patients could also try to get pregnant. The time to first pregnancy among the patients in the CM group was shorter than that in the WM group, especially for those patients diagnosed with infertility caused by endometriosis before the operation. The effectiveness of raising the conception rate of patients in the CM group was obviously better than in the WM group.

In this study, syndrome differentiation and treatment with CM has provided a new investigative direction and treatment for controlling the recurrence of EMs after a conservative operation. It also improved the general condition of the patients, improved the conception rate and helped them to select the best time to get pregnant. Thus, it is appropriate for general use in the clinical treatment of patients with EMs.

International registration number: ChiCTR-TRC-10000808

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(Received January 14, 2012)
Edited by YUAN Lin