

Clinical Observation of Chinese Medicine Treatment on Secondary Dysmenorrhoea Associated with Endometriosis

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ABSTRACT

Background: Secondary dysmenorrhoea associated with endometriosis affects many women and is the leading cause of work and school absenteeism, with considerable impact on quality of life. This study evaluates the possible role of Chinese medicinal herbs in relieving the menstrual pain associated with endometriosis. **Methods:** A prospective clinical observational pilot study involving twenty-five patients with endometriosis with Chinese medical diagnosis of stagnation of qi and blood who were recruited at the Guangdong Women's and Children's Hospital during the period of January 2004 to December 2006 to participate in a three-month Chinese medicinal herbs study. **Results:** Sixteen patients reported nil dysmenorrhoea during the treatment period. The mean CA125 at the study entry was 59.67 ± 28.32 u/ml, compared to 34.83 ± 16.34 u/ml post-treatment. The positive EMAB before the commencement of treatment was noted in 22 of 25 cases (88%), while 5 of 25 cases (20%) remained positive after treatment. **Conclusion:** Short-term administration of Chinese medicinal herbs may be effective in alleviating secondary dysmenorrhoea associated with endometriosis in qi and blood stagnation pattern. It may provide an alternative treatment option for the management of pelvic pain associated with endometriosis and further research in the area is required.

KEYWORDS endometriosis, Chinese medicine, Chinese medicinal herbs, dysmenorrhoea, pelvic pain, treatment.

Introduction

Endometriosis is defined by the **European Society of Human Reproduction and Embryology (ESHRE) as the 'presence of endometrial like tissue outside the uterus'**.¹ As ESHRE guidelines state, **endometriomas 'may involve the uterosacral ligaments, vagina, bowel, bladder or ureters'**.¹ Even though a large number of studies in endometriosis has been done

in western medicine, the incidence, aetiology, pathological development and optimal treatment of endometriosis remain controversial. Deligeorgiou writes that 'the cause of menstrual cramps and associated symptoms in primary dysmenorrhoea is related to prostaglandin production. In secondary dysmenorrhoea, there is documented pelvic pathology that causes the painful menstrual cramps, and treatment is cause related.'²

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Pain is the most common symptom associated with endometriosis and approximately 75% of symptomatic patients experience pelvic pain and/or dysmenorrhoea.^{1,3} Patients with endometriosis experience chronic pelvic pain which is worse during menstruation or at ovulation; dysmenorrhoea; subfertility; deep dyspareunia; cyclical bowel or bladder symptoms; abnormal menstrual bleeding; and chronic fatigue.^{1,3}

CA125

CA125 is the ovarian cancer antigen. As Muyldermans stated, 'in normal women, plasma concentrations of CA125 are increased slightly at ovulation and significantly during menstruation. Plasma concentrations of CA125 are markedly elevated in women with cystic ovarian endometriosis and/or deeply infiltrating endometriosis.'⁴ The clinical correlation between the value of CA125 to the diagnosis of endometriosis has been studied extensively.⁵⁻⁹ Studies have suggested that women with endometriosis often have high (greater than 35 IU/ml) serum CA125 concentrations.^{10,11}

EMAb

In addition to being a gynaecological condition, endometriosis is considered to be an autoimmune disease.¹² Several studies suggest that there is a correlation between anti-endometrial antibodies (EMAb) and endometriosis.¹³⁻³⁴ EMAb was found in the peritoneal fluid of patients with endometriosis through methods like passive hemagglutination,¹³⁻¹⁶ immunodiffusion,¹⁷⁻¹⁸ western blot,¹⁹⁻²³ immunofluorescence,²⁴⁻²⁶ immunohistochemical,²⁷⁻²⁹ and enzyme-linked immunosorbent assays.³⁰⁻³⁴

This study aimed to evaluate the possible role of Chinese medicinal herbs in relieving the menstrual pain associated with endometriosis. A prospective clinical observational pilot study was employed. Rather than only measuring physical symptoms of relief as in many other studies, quantitative items of CA125 and EMAb were also used in our study.

Methods

From January 2004 to December 2006, twenty-five cases of laparoscopic confirmed endometriosis, diagnosed with Chinese medicine syndrome differentiation of stagnation of qi and blood, consented to take part in this Chinese medicinal herbs study at the Department of Gynaecology, Guangdong Women's and Children's Hospital.

All patients were tested for CA125 (Abbott testing kit) and Antiendometrial Antibody (EMAb) (Mercury Interactive testing kit) before and after treatments. 5 ml of blood in a plain tube was obtained from each subject to test for CA125 by immunoassay. Sera from subjects involved were tested by cell enzyme-linked immunosorbent assay (ELISA) for EMAb.

A four-point categorical pain intensity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) and a 10 cm visual analog scale (VAS) were used to assess the pain intensity of dysmenorrhoea reported before and during treatment periods. Patients were asked to complete the pain intensity scale and VAS at the follow-up visits. Clinic visits were scheduled at screening, once a week for the duration of the three-month treatment, and once a month during the three-month follow-up period. Adverse events were recorded throughout the study.

Inclusion and Exclusion Criteria

To be eligible for the study, patients were required to have a history of regular 28-day menstruation cycle (± 7 days). In addition, patients also needed to have at least four clinical presentations of premenstrual abdominal discomfort, abdominal bloating sensation, intermittent pelvic pain, dysmenorrhoea, dyspareunia, menstrual bleed with clots, or breast tenderness. In order to fulfil the Chinese medicine diagnosis of stagnation of qi and blood, potential subjects were required to have purplish tongue with white coating and string taut pulse on palpation. Patients recruited must have been otherwise healthy, with a negative serum pregnancy test at the time of enrolment. They were also required to use a barrier contraceptive method during the study period and should not have used any oral contraception in the six months before study entry or during the study.

Patients were excluded from the study if they had a known history of diabetes mellitus, hypertension, cardiovascular disease or systemic disease; were using a hormonal implant in the six months prior to screening or an injectable or intrauterine contraceptive system within three months of screening and during the study; had abnormal results noted from full blood count, kidney function and liver function tests. In order to avoid confounding results, recruited subjects were asked to refrain from taking any form of analgesia during the treatment period.

Treatment

Patients meeting the eligibility criteria received *Shengdihuang* (*Radix Rehmanniae*) 12 g, *Danggui* (*Radix Angelicae sinensis*) 12 g, *Chishao* (*Radix Paeoniae rubrae*) 15 g, *Chuanxiong* (*Radix Ligustici wallichii*) 10 g, *Taoren* (*Semen Pruni persicae*) 10 g, *Honghua* (*Flos Carthami*) 10 g, *Chaihu* (*Radix Bupleuri*) 12 g, *Zhike* (*Fructus Citri aurantii*) 12 g, *Danshen* (*Radix Salviae miltiorrhizae*) 30 g, and *Huangqi* (*Radix Astragali*) 10 g, one week after the diagnostic laparoscopy for ongoing pelvic pain, dysmenorrhoea and dyspareunia. For patients who were menstruating during the treatment period, *Puhuang* (*Pollen Typhae*) 10 g and *Wulingzhi* (*Excrementum Troglodyteri seu peromi*) 15 g were added to the formula. All patients were

asked to take the herb concoction twice a day for three months and were followed up for improvements on a monthly basis for three months after the cessation of treatment. All herbs were cooked for 30 minutes duration after boiling and the cooking procedures were uniformly carried out at the hospital central pharmacy. Patients were given individual packages of herb concoction.

Results

All 25 patients who completed the screening received treatments. Paired t-tests were used to assess the significance for pain-related outcome measures, CA125 and EMAb. The mean age of patients was 34.5 years old. According to the revised American Society of Reproductive Medicine (r-ASRM) classification, there were 9 cases in Stage I–II, 12 cases in Stage III and 9 cases in Stage IV. Sixteen out of 25 patients (64%) reported no experience of dysmenorrhoea during the treatment period. The results were consistent in the four-point categorical pain intensity scale and the 100 mm visual analog scale (VAS) (Tables 1 and 2). The mean VAS before the treatment was 7.04 ±1.98 while reduced to 1.68 ±2.88 after the conclusion of treatment ($p < 0.05$). As illustrated in Table 3, the mean CA125 level before treatment was 59.67 ±28.32 u/ml, compared with 34.83 ±16.34 u/ml post-treatment

($p < 0.05$). The positive EMAb before the commencement of treatment was noted in 22 cases (88%) while 5 cases (20%) ($p < 0.05$) remained positive after the treatment.

There were no reported adverse events related to the intake of Chinese medicines throughout the study and follow-up period.

Discussion

The prevailing western medical symptomatic treatment for endometriosis is expectant therapy.³ However, it is considered ineffective, as the recurrence rate is up to 70%.⁴ Even though surgical therapy can relieve pelvic pain,⁵ the recurrence rate is still 30–40% four weeks after the surgery was performed.⁶ Given the existing limitations and high recurrence rate in western medical treatment on endometriosis, it is important to seek alternative therapies which may have a role in alleviating the symptoms for women with endometriosis.

As mentioned, women with endometriosis often have elevated (greater than 35 IU/ml) level of serum CA125.^{7,8} In a study that assessed 685 women with endometriosis, the CA125 level was noted at 19, 40, 77, and 182 IU/ml for Stage I, II, III and IV disease respectively.⁷ Even though serum CA125 is not a

TABLE 1 Pain Intensity

	No Pain (PI = 0)	Mild pain (PI = 1)	Moderate pain (PI = 2)	Severe pain (PI = 3)
Before treatment	0	8	10	7
At the conclusion of treatment	16	4	2	3

TABLE 2 Pain Intensity of Dysmenorrhoea (VAS)

	0	1-2	3-4	5-6	7-8	9-10	Total
Before treatment	0	0	4	4	10	7	25
At the conclusion of treatment	16	3	1	2	2	1	25

TABLE 3 Serum CA125 and Antiendometrial Antibody measurements

	CA125 (IU/ml)	No. of EMAb* positive cases
Before treatment	59.67 ±28.32	22
At the conclusion of treatment	34.83 ±16.34	5

* EMAb = Endometrial Antibody

sensitive indicator for endometriosis, it is shown to correlate in women with endometriosis Stage III and IV disease.⁸ In our study, both EMAB and CA125 concentrations were reduced at the conclusion of treatment period. It is consistent with our initial hypothesis that Chinese herbal therapy may have a role in offering alternative care to women with endometriosis-related dysmenorrhoea.

One of the major issues among all types of clinical care is the compliance of treatment. We aimed to reduce the potential compliance and drop-out problems in this study by asking recruited patients to be reviewed once a week in the clinic.

The liver (*dan*), thoroughfare vessel (*chong mai*) and conception vessel (*ren mai*) govern the physiology of menstruation. The smooth running of blood and qi are responsible for normal menstruation to occur. This also relies on the free flow of liver qi and qi of *chong mai*. Endometriosis in Chinese medicine may be related to stagnation of qi and blood as in painful menstruation. The formula used in this study consists of various herbal components. *Danggui* (*Radix Angelicae sinensis*), *Chuanxiong* (*Radix Ligustici wallichii*) and *Chishao* (*Radix Paeoniae rubrae*) were used to nourish and invigorate the blood. *Danggui* is a commonly known Chinese herb that has traditionally been used to treat dysmenorrhoea, irregular menstruation, and as a supportive herb for menopausal complaints.^{3,5} *Danggui* is also believed to enhance the production of endogenous oestrogen.^{3,5} Further study is needed to investigate the synergistic mechanism of action of *Danggui* in endometriosis treatment. For patients who were menstruating during the treatment period, *Pubuang* (*Pollen Typhae*) 10 g and *Wulingzhi* (*Excrementum Trogopteri seu pteromi*) 15 g were added to the formula. Both *Pubuang* and *Wulingzhi* enter the Liver meridian and disperse the blood stasis associated with menstruation.

Flower et al.³⁶ included two randomised clinical trials (altogether 158 subjects) in their Cochrane systematic review of Chinese herbal medicine for endometriosis. So far there has been no placebo-controlled clinical trial for evaluating the safety and effectiveness of Chinese herbal medicine in endometriosis treatment. Furthermore, as Flower et al.³⁶ state in their review, 'the two trials included in this review are of poor methodological quality so these findings must be interpreted cautiously.' Despite the fact that there were no statistical differences between Chinese herbal medicine and comparison groups in terms of symptom relief and pregnancy rate, both included studies revealed 100% symptom improvement as reported by participants. Flower et al.³⁶ state, 'Post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol.' In contrast to other Chinese herbal medicine studies on endometriosis, our study also attempted to incorporate quantitative measures

(CA125 and EMAB) in outcome assessments, in addition to the routine physical symptoms measurement. These measurement items will hopefully provide for objective assessment of the outcomes.

Even though we have obtained encouraging result from this pilot study, there are many areas for improvements regarding study design for future investigations. We consider the number of recruited subject to be fairly small in this study. Although it may be enough for a pilot study, a larger sample size in a blinded controlled study would be needed to evaluate the efficacy of Chinese herbs in relieving secondary dysmenorrhoea in endometriosis. In addition, a properly designed randomised controlled study in this area is certainly in need, as suggested by Flower et al. in their Cochrane review. Even though we have used CA125 and EMAB as quantitative outcome measures in our study, quality of life measurements should also be incorporated into any future study to assess whether Chinese herbal medicine can play a role in that aspect for women with endometriosis.

Conclusion

Short-term administration of Chinese medicinal herbs may be effective in alleviating secondary dysmenorrhoea associated with endometriosis in qi and blood stagnation pattern. It may provide an alternative treatment option for the management of pelvic pain associated with endometriosis, but further research into the area is needed. In order to evaluate the role of Chinese herbal medicine treatment as an adjuvant therapy in existing western medical treatment, properly designed placebo-controlled randomised integrative medicine trials are needed.

Clinical Commentary

Short-term administration of Chinese medicinal herbs may be effective in alleviating secondary dysmenorrhoea associated with endometriosis in qi and blood stagnation pattern. In addition to clinical assessment of physical symptoms improvement, quantitative measurement items (e.g., EMAB) should be taken into consideration.

References

1. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005;20(10):2698-704.

2. Deligeorgiou E. Dysmenorrhea. *Ann N Y Acad Sci* 2000;900:237–44.
3. Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K, et al. Differences in characteristics among 1000 women with endometriosis based on extent of disease. *Fertil Steril* 2008;89:538–45.
4. Muyldermans M, Cornillie FJ, Koninckx PR. CA125 and endometriosis. *Hum Reprod Update* 1995;1(2):173–87.
5. Hornstein MD, Harlow BL, Thomas PP, Check JH. Use of a new CA125 assay in the diagnosis of endometriosis. *Hum Reprod* 1995;10:932–4.
6. O'Shaughnessy A, Check JH, Nowroozi K, Lurie D. CA125 levels measured in different phases of the menstrual cycle in screening for endometriosis. *Obstet Gynecol* 1993;81:99–103.
7. Hornstein MD, Thomas PP, Gleason RE, Barbieri RL. Menstrual cyclicality of CA125 in patients with endometriosis. *Fertil Steril* 1992;58:279–83.
8. Koninckx PR, Riittinen L, Seppala M, Cornillie FJ. CA125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. *Fertil Steril* 1992;57:523–30.
9. Mol BWJ, Bayram N, Lijmer JG, Wiegerinck MAHM, Bongers MY, van der Veen F, et al. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998;70:1101–8.
10. Cheng YM, Wang ST, Chou CY. Serum CA-125 in preoperative patients at high risk for endometriosis. *Obstet Gynecol* 2002;99:375–80.
11. Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F, et al. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998;70:1101–8.
12. Matarese G, De Placido G, Nikas Y, Alviggi C. Pathogenesis of endometriosis: natural immunity dysfunction or autoimmune disease? *Trends Mol Med* 2003;9:223–8.
13. Mathur S, Peress MR, Williamson HO, Youmans CD, Maney SA, Garvin AJ, et al. Autoimmunity to endometrium and ovary in endometriosis. *Clin Exp Immunol* 1982;50:259–66.
14. Chihal HJ, Mathur S, Holtz GL, Williamson HO. An antiendometrial antibody assay in the clinical diagnosis and management of endometriosis. *Fertil Steril* 1986;46:408–11.
15. Badawy SZA, Cuenca V, Freliech H, Stefanu C. Endometrial antibodies in serum and peritoneal fluid of infertile patients with and without endometriosis. *Fertil Steril* 1990;53:930–2.
16. Garza D, Mathur S, Dowd MM, Smith LF, Williamson HO. Antigenic differences between the endometrium of women with and without endometriosis. *J Reprod Med* 1991;36:177–82.
17. Badawy SZA, Cuenca V, Stitzel A, Jacobs RDB, Tomar RH. Autoimmune phenomena in infertile patients with endometriosis. *Obstet Gynecol* 1984;63:271–5.
18. Meek SC, Hodge DD, Musich JR. Autoimmunity in infertile patients with endometriosis. *Am J Obstet Gynecol* 1988;158:1365–73.
19. Mathur S, Chihal HJ, Homm RJ, Garza DE, Rust PF, Williamson HO. Endometrial antigens involved in the autoimmunity of endometriosis. *Fertil Steril* 1988;50:860–3.
20. Mathur S, Garza DE, Smith LF. Endometrial autoantigens eliciting immunoglobulin (Ig)G, IgA, and IgM responses in endometriosis. *Fertil Steril* 1990;54:56–63.
21. Rajkumar K, Malliah V, Simpson CW. Identifying the presence of antibodies against endometrial antigens: a preliminary study. *J Reprod Med* 1992;37:552–6.
22. Gorai I, Ishikawa M, Onose R, Hirahara F, Minaguchi H. Antiendometrial antibodies are generated in patients with endometriosis. *Am J Reprod Immunol* 1993;29:116–23.
23. Mathur SP. Autoimmunity in endometriosis: relevance to infertility. *Am J Reprod Immunol* 2000;44:89–95.
24. Wild RA, Shivers CA. Antiendometrial antibodies in patients with endometriosis. *Am J Reprod Immunol Microbiol* 1985;8:84–6.
25. Kreiner D, Fromowitz FB, Richardson DA, Kenigsberg D. Endometrial immunofluorescence associated with endometriosis and pelvic inflammatory disease. *Fertil Steril* 1986;46:243–6.
26. Wild RA, Hirisave V, Podczaski ES, Coulam C, Shivers CA, Satyaswaroop PG. Autoantibodies associated with endometriosis: can their detection predict presence of the disease? *Obstet Gynecol* 1991;77:927–31.
27. Kennedy SH, Sargent IL, Starkey PM, Hicks BR, Barlow DH. Localization of anti-endometrial antibody binding in women with endometriosis using a double-labelling immunohistochemical method. *Br J Obstet Gynaecol* 1990;97:671–4.

28. Fernandez-Shaw S, Hicks BR, Yudkin PL, Kennedy S, Barlow DH, Starkey PM. Anti-endometrial and anti-endothelial auto-antibodies in women with endometriosis. *Hum Reprod* 1993;8:310–5.
 29. Kim JG, Kim CW, Moon SY, Chang YS, Lee JY. Detection of antiendometrial antibodies in sera of patients with endometriosis by dual-colored, double-labeling immunohistochemical method and western blot. *Am J Reprod Immunol* 1995;34:80–7.
 30. Confino E, Harlow L, Gleicher N. Peritoneal fluid and serum autoantibody levels in patients with endometriosis. *Fertil Steril* 1990;53:242–5.
 31. Odukoya OA, Wheatcroft N, Weetman AP, Cooke ID. The prevalence of immunoglobulin G antibodies in patients with endometriosis. *Hum Reprod* 1995;10:1214–9.
 32. Hatayama H, Imai K, Kanzaki H, Higuchi T, Fujimoto M, Mori T. Detection of antiendometrial antibodies in patients with endometriosis by cell ELISA. *Am J Reprod Immunol* 1996;35:118–22.
 33. Palacio JR, Iborra A, Gris JM, Andolz P, Martinez P. Anti-endometrial autoantibodies in women with a diagnosis of infertility. *Am J Reprod Immunol* 1997;38:100–5.
 34. Reimand K, Talja I, Metsküla K, Kadastik Ü, Matt K, Uibo R. Autoantibody studies of female patients with reproductive failure. *J Reprod Immunol* 2001;51:167–76.
 35. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. *Menopause* 2002;9:145–50.
 36. Flower A, Liu JP, Chen S, Lewith G, Little P. Chinese herbal medicine for endometriosis. *Cochrane Database Syst Rev* 2009(3).
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