

Feature Article

Strategies for Activating Blood Circulation-Regulating Gan (Liver)-Tonifying Shen (Kidney) Sequential Therapy of Endometriosis-Associated Infertility

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ABSTRACT Endometriosis (EM) is a major cause of infertility and has a complex pathogenesis, which brings severe challenges in both clinical treatment and scientific research. Current clinical research focuses on the difficult problem of improving the pregnancy rate of EM patients. Our studies found that Chinese medicine has significant advantages in terms of improving the pregnancy rate of EM patients.

KEYWORDS endometriosis, infertility, promoting blood circulation-regulating Gan (Liver)-tonifying Shen (Kidney) sequential therapy

Endometriosis (EM) is a common disease of females of child-bearing age concerned with infertility, and its morbidity is 35%–50%,⁽¹⁾ which is 20 times higher than that of the non-EM infertility population.⁽²⁾ In 2000, Buyalos, et al⁽³⁾ proposed the concept of "endometriosis-associated infertility". EM-associated infertility has long been a focus of attention in the medical field.

Puzzle of EM-Associated Infertility Therapy

The etiology of EM is complex. It is generally recognized that EM is the result of an interaction of many factors and multiple mechanisms. EM-associated infertility is affected by many factors. It is believed that the mechanism mainly includes four aspects: mechanical factors such as pelvic anatomical and structural changes, fallopian tube obstruction, changes in endocrine function or ovarian functions that reduce endometrial receptivity, and immune factors. These factors can affect pregnancy due to changes in ovulation, fertilization, imbedding and development, leading to infertility or early abortion through a number of mechanisms.

Modern medical treatment of EM mainly includes oral contraceptives, progesterone, testosterone derivatives and gonadotropin releasing hormone analogues (GnRH-a). These medicines can relieve symptoms but have no separate application value for infertility treatment. Currently, most guidelines

do not recommend drug treatment for patients with fertility requirements. Importantly, surgery can reduce pelvic lesions, restore the pelvic anatomical structure, change the pelvic microenvironment and increase the chances of pregnancy after surgery. However, the potential damage to ovarian function after surgery should not be ignored. In recent years, we have advocated avoiding reoperation and protecting ovarian function during operation. For those with fertility requirements or concerns about infertility, it is not recommended to use hormonal drugs to prevent recurrence after operation, and active measures should instead be taken.

Understanding Activating Blood Circulation-Regulating Gan (Liver)-Tonifying Shen (Kidney) Sequential Therapy of EM-Associated Infertility

It is generally recognized that blood stasis is the main pathogenesis of EM in Chinese medicine (CM) circles. The occurrence of this disease is closely related to constitution factors, living environment and living habits.⁽⁴⁾ Blood stasis and Shen deficiency are

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the main mechanisms responsible for EM-associated infertility. The treatment thus should combine CM and Western medicine. The diagnosis needs to combine the diagnostic criteria of Western medicine and CM syndrome differentiation. The golden period of pregnancy, which refers to the half-year period after operation, should be emphasized. Many clinical studies report that taking CM to activate blood circulation to remove blood stasis as soon as possible can not only prevent adhesion, inhibit recurrence, and improve the microenvironment of pelvic cavity, but also improve the pregnancy rate.⁽⁴⁻⁶⁾ According to my clinical experience, EM should be diagnosed as three distinct types of syndromes: qi stagnation and blood stasis, qi deficiency and blood stasis, and cold coagulation and blood stasis. The sequential treatment involves activating blood circulation before ovulation, tonifying Shen and invigorating Pi (Spleen) after ovulation, and simultaneously protecting Pi and Wei (Stomach) and balancing the patient's emotions. Through screening the clinical prescriptions of Prof. LI Guang-rong, Huoxue Xiaoyi Decoction (活血消异方, consisted of *Bupleuri Radix*, *Radix Salviae Miltiorrhizae*, *Curcuma Zedoary*, *Semen Coicis*, *Endothelium Corneum Gigeriaegalli*, *Paeoniae Radix Rubra*, *Spina Gleditsiae*, and *Rhizoma Cyperi*) was formulated.⁽⁴⁾

A total of 55 patients with EM-associated infertility were treated with CM sequential therapy to activate blood flow and tonify the Shen.⁽⁵⁾ By 1 year after drug withdrawal, the cumulative pregnancy rate reached 40%. A randomized controlled trial compared the effects of CM and GnRH-a on EM-associated infertility.⁽⁶⁾ The results showed that the pregnancy rates in the 1- and 2-year periods after operation in the CM group were significantly higher than those in the control group, and the pregnancy rate at 6 months was 50% in the CM group. For patients with fertility requirements CM had a similar level of efficacy in the 1- and 2-year periods after operation as Western medicine.⁽⁷⁻⁹⁾ However, there was no statistically significant difference between the two groups, and the recurrence rate of the two groups was the same. These results indicate that CM has advantages in improving pregnancy, with a similar success as Western medicine in inhibiting recurrence.

It was found that EM has significant adverse effects on pregnancy. EM can decrease the

expression of HOXA10 mRNA of mice during the implantation window phase,⁽¹⁰⁾ reduce the average number of superovulation events, decrease the fertility rate, limit the 2- and 4-cell embryo cleavage rates at different stages *in vitro* fertilization, and alter the modulation rate.⁽¹¹⁾ EM can also influence the quality of embryonic development of EM model mice, decrease the quantity of embryonic development and influence the pregnancy rate and live birth rate.^(12,13) However, Huoxue Xiaoyi Decoction can up-regulate the expression of HOXA10 mRNA in mice,⁽¹⁰⁾ develop the endometrial receptivity, improve the quality of embryonic development⁽¹¹⁾ and increase both the pregnancy rate and live birth rate.⁽¹³⁾

Choice of Activating Blood Circulation-Regulating Gan-Tonifying Shen for EM-Associated Infertility

The treatment of EM-associated infertility should be considered alongside a patient's age, infertility duration, size of the cyst, EM fertility index (EFI), ovarian function and intrauterine environment in order to best formulate the corresponding treatment plan.⁽¹⁴⁾ The cases can be roughly divided into the following 5 situations. (1) For younger women with a short duration of infertility, a 3–4 cm endometrial cyst and basically patent anatomy, the sequential treatment of CM should be used based on the above three types of syndrome. Meanwhile, the ovulation should be monitored by basal body temperature or ultrasonography and coitus behavior at the proper time should also be guided. Surgical treatment is recommended if non-pregnancy or enlargement of the cyst occurs for a full year. (2) For patients with cysts over 5 cm in size, surgical treatment is recommended first. The treatment after the surgery is the same as above. (3) For patients over 30 years old, fertility treatments by Western medicine should be added as appropriate. *In vitro* fertilization and embryo transfer (IVF-ET) is recommended to be combined with the sequential treatment of CM if non-pregnancy occurs for half of a year. (4) For patients over 35 years of age, IVF-ET combined with the sequential treatment of CM is recommended. (5) For patients with recurrent ovarian cysts except the canceration, the sequential treatment of CM or IVF-ET is recommended according to the degree of the lesion and the ovarian function. Reoperation should be carried out discreetly.

Summary

In recent years, the incidence of EM has

increased and has presented in younger women. The CM treatment of EM-associated infertility has significant advantages, and therapy based on activating blood circulation and regulating Gan-tonifying Shen sequence can improve follicle quality and endometrial receptivity, thus increasing pregnancy rate. The patient's age, personal will and disease conditions must be taken into account in treatment. Benefits would be increased when integrated CM and Western medicine are used and when an individual treatment plan is formulated.

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