Clinical Efficacy and Immunohistochemical Changes Following Guizhi Fuling Decoction Combined with Metronidazole in the Treatment of Chronic Endometritis

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Abstract

Objective: To evaluate the clinical efficacy and safety of Guizhi Fuling Decoction combined with metronidazole in patients with chronic endometritis. Methods: A total of 100 women with histopathologically and immunohistochemically confirmed chronic endometritis were enrolled between January 2020 and October 2022. All participants were treated at the Department of Reproductive Medicine, the Second Affiliated Hospital of Xingtai Medical College, and randomly allocated to an experimental group or a control group (n=50 per group). Results: Both groups showed improvement after treatment. However, the experimental group demonstrated significantly greater increases in endometrial thickness and blood flow scores, accompanied by more pronounced improvement in pathological findings compared with the control group ($P<0.05$). In addition, key immunohistochemical markers associated with chronic inflammation showed a substantial reduction in the experimental group, indicating stronger suppression of endometrial inflammatory activity. The clinical pregnancy rate was significantly higher in the experimental group than in the control group (50.00% vs. 24.00%, $P<0.05$). The overall incidence of adverse reactions was lower in the experimental group (12.00%) compared with the control group (22.00%) ($P=0.048$). Conclusion: Guizhi Fuling Decoction combined with metronidazole effectively improves endometrial morphology, blood flow, inflammatory status, and clinical pregnancy outcomes, while demonstrating a favorable safety profile. This combined regimen represents a promising and safe therapeutic approach for patients with chronic endometritis.

Keywords

Guizhi Fuling Decoction, Metronidazole, Chronic endometritis (CE), Combined diagnosis and treatment

Introduction

Guizhi Fuling Decoction, a time-honored traditional Chinese medicinal formula, has been widely applied in the management of gynecological disorders. It exerts multiple therapeutic effects, including clearing heat and detoxifying, promoting blood circulation and resolving stasis, as well as regulating qi and blood. Recent clinical observations have shown that Guizhi Fuling Decoction produces significant improvement in alleviating symptoms of chronic endometritis, enhancing endometrial morphology, and increasing pregnancy rates [1].

Metronidazole, on the other hand, is a broad-spectrum antimicrobial agent that has demonstrated favorable clinical efficacy in the treatment of various infectious diseases, particularly gynecological infections. A combined therapeutic approach employing both Guizhi Fuling Decoction and metronidazole may therefore provide complementary effects, offering a more effective strategy for reducing symptoms of chronic endometritis and improving overall therapeutic outcomes [2].

The present study aims to evaluate the clinical

efficacy and safety of the combined use of Guizhi Fuling Decoction and metronidazole, with the objective of exploring a new therapeutic option for this condition. The findings are reported as follows.

Study population and eligibility criteria

A total of 100 patients with chronic endometritis were included and randomly assigned to an experimental group (n=50) and a control group (n=50). In the control group, patients were aged 20-45 years, with a mean age of 32.56±5.02 years. Disease duration ranged from 6 months to 8 years, with a mean duration of 24.32±5.87 months. In the experimental group, patients were aged 21-46 years, with a mean age of 33.12±4.98 years. Disease duration ranged from 7 months to 9 years, with a mean duration of 23.85±6.12 months. Statistical analysis showed no significant differences between the two groups in terms of sex composition (all female), mean age, or disease duration ($P>0.05$), indicating good baseline comparability.

Inclusion criteria:

(1) Diagnosis of chronic endometritis confirmed by histopathology and immunohistochemistry, in accordance with the diagnostic criteria established by the International Federation of Gynecology and Obstetrics.

(2) Age between 20 and 45, with a desire for pregnancy or existing infertility.

(3) No severe internal medical diseases or other complications that might affect treatment; general condition sufficient to tolerate the proposed interventions.

(4) Voluntary participation with signed informed consent.

Exclusion criteria:

(1) Concomitant gynecological disorders such as uterine fibroids or ovarian cysts.

(2) Severe immune system disorders, hematologic diseases, or other systemic illnesses that could interfere with treatment outcomes.

(3) History of allergic reactions to components of the prescribed traditional Chinese medicine (TCM) formula or to metronidazole.

Methods

A control group and an experimental group were established.

Control group

Patients in the control group received standard anti-infective therapy with oral doxycycline. The specific regimen was 100 mg doxycycline orally, twice daily, for 14 consecutive days. During treatment, patients were regularly reviewed to evaluate efficacy and monitor potential adverse reactions. Clinical status was closely supervised throughout the course, and the dosage or type of antibiotic was adjusted when necessary.

Experimental group

Patients in the experimental group were treated with Guizhi Fuling Decoction combined with intrauterine perfusion of metronidazole, as follows:

(1) Guizhi Fuling Decoction

Patients took Guizhi Fuling Decoction orally once daily, using a standard decoction formulation. The dosage was adjusted according to body weight and disease severity; adult patients received 1 dose per day, divided into two administrations, for a total course of 14 days. The prescription consisted mainly of Ramulus Cinnamomi (Guizhi), Poria (Fuling), Radix Paeoniae Alba (Baishao), Semen Persicae (Taoren), and Cortex Moutan (Mudanpi), which exert the effects of promoting blood circulation, resolving blood stasis, and harmonizing qi and blood [3]. These actions help improve endometrial function and accelerate the resolution of inflammation.

(2) Intrauterine perfusion of metronidazole

On days 1, 7, and 14 of treatment, patients received intrauterine perfusion of metronidazole. At each session, 20-40 mg of metronidazole was dissolved in 30-50 mL of sterile solution and infused into the uterine cavity under aseptic conditions. As a broad-spectrum antimicrobial agent with strong activity against anaerobic bacteria, metronidazole effectively reduces pathogenic microorganisms at the lesion site, mitigates inflammatory symptoms, and promotes repair and regeneration of the endometrium [4,5]. After perfusion, patients were

advised to remain in the supine position for approximately 30 minutes to facilitate drug absorption by the uterine tissues.

During treatment, patients in the experimental group were followed up weekly to monitor changes in clinical symptoms and potential adverse reactions. After completion of therapy, all patients were followed up at 1 month and 3 months to assess treatment efficacy and to record any delayed adverse events or complications.

Observation indicators

(1) Endometrial thickness: measured by transvaginal ultrasonography, expressed in millimeters (mm). Measurements were performed before and after treatment to evaluate changes.

(2) Endometrial blood flow: assessed using color Doppler ultrasonography. Blood flow velocity, volume, and the visibility of blood flow signals were evaluated, and a blood flow score was assigned according to the overall perfusion status.

(3) Pathological assessment of the endometrium: Endometrial samples were obtained at different time points before and after treatment and analyzed histopathologically. Inflammatory response, cellular proliferation, and tissue repair were evaluated following a predefined pathological grading system to determine therapeutic efficacy.

(4) Clinical pregnancy rate: Within 6 months after treatment, patients were followed to record pregnancy outcomes. Successful intrauterine pregnancy was defined as a treatment success; failure to conceive within the follow-up period was regarded as treatment failure.

(5) Adverse drug reactions: Adverse events were monitored by combining patients' self-reports with clinical examinations, including but not limited to allergic reactions, gastrointestinal discomfort, local pain, and other drug-related symptoms.

(6) Immunohistochemical markers: Endometrial specimens were collected before and after treatment for immunohistochemical evaluation of plasma cells, CD38, CD138, and CD163 positivity. The percentage of positive cells was used to quantify inflammatory activity and therapeutic response.

Statistical analysis

All data were analyzed using SPSS 22.0 software. Continuous variables were expressed as Mean ± Standard Deviation (Mean ± SD), and between-group comparisons were conducted with independent-samples t-tests. Categorical data were expressed as percentages (%) and compared using the χ^2-test. For within-group comparisons before and after treatment, paired t-tests were applied. A two-tailed $P<0.05$ was considered statistically significant, and $P<0.01$ indicated a highly significant difference.

Results

Comparison of endometrial parameters between the two groups

Both groups exhibited significant changes in endometrial-related parameters after treatment. However, the degree of improvement was more pronounced in the experimental group than in the control group, and the between-group differences were statistically significant ($P<0.05$). As shown in Table 1, these findings indicate that the combined treatment more effectively increased endometrial thickness, improved blood flow perfusion, and reduced pathological scores than oral doxycycline alone.

Table 1. Comparison of endometrial parameters between the two groups (Mean ± SD).

Group	n	Endometrial thickness (mm)		Endometrial blood flow score		Pathological assessment of the endometrium	
		Before	After	Before	After	Before	After
Control group	50	5.42±1.15	6.52±1.32	1.96±0.74	2.03±0.87	4.08±0.71	3.72±0.79
Experimental group	50	5.38±1.10	7.89±1.22	1.95±0.70	3.56±0.92	4.07±0.74	2.41±0.68

Group	n	Endometrial thickness (mm)		Endometrial blood flow score		Pathological assessment of the endometrium	
		Before	After	Before	After	Before	After
t	/	0.23	6.28	0.14	5.19	0.29	7.26
P	/	0.82	<0.05	0.89	<0.05	0.77	<0.05

Comparison of clinical pregnancy rates

The therapeutic regimen of Guizhi Fuling Decoction combined with metronidazole significantly improves the clinical pregnancy rate in patients with chronic endometritis. The clinical pregnancy rate in the experimental group reached 50.00%, significantly higher than the 24.00% observed in the control group, further confirming that this therapeutic strategy can substantially improve the likelihood of pregnancy in patients with chronic endometritis. Moreover, the chi-square test results (χ^2 = 8.234, P <0.05) indicate that the difference in pregnancy rates between the two groups is not caused by random error but by the therapeutic superiority of the combined regimen, as shown in Table 2.

Table 2. Comparison of clinical pregnancy rates between the two groups (n, %).

Group	n	No. of clinical pregnancies (n)	Clinical pregnancy rate (%)
Control group	50	12	24.00
Experimental group	50	25	50.00
χ^2	/	/	8.234
P	/	/	<0.05

Comparison of adverse drug reactions

Compared with oral doxycycline treatment, the combined therapeutic regimen of Guizhi Fuling Decoction and metronidazole offers superior safety in patients with chronic endometritis. The overall incidence of adverse reactions in the experimental group (12.00%) was significantly lower than that in the control group (22.00%), with a statistically significant difference (P=0.048), as shown in Table 3.

Table 3. Comparison of adverse drug reactions between the two groups (n, %).

Group	n	Allergic reactions	Gastrointestinal discomfort	Local pain	Other adverse reactions	Total incidence of adverse reactions (%)
Control group	50	3 (6.00)	5 (10.00)	2 (4.00)	1 (2.00)	11 (22.00)
Experimental group	50	2 (4.00)	3 (6.00)	1 (2.00)	0 (0.00)	6 (12.00)
χ^2	/	/	/	/	/	3.926
P	/	/	/	/	/	0.048

Changes in immunohistochemical marker expression and inflammatory cell infiltration scores

As shown in Table 4, before treatment, there were no significant differences between the two groups in the positive expression rates of plasma cells, CD38, CD138, and CD163 (P>0.05). After treatment, the positive expression rate of plasma cells in the experimental group decreased markedly from 82% to 16.0%, while CD38, CD138, and CD163 positivity decreased to 18%, 20%, and 16%, respectively. The inflammatory

cell infiltration scores also improved significantly and were consistently lower than those in the control group (P<0.05), indicating that the combined therapy effectively suppressed chronic endometrial inflammation at the molecular and cellular levels [6].

Table 4. Comparison of immunohistochemical marker expression between the two groups (n, %).

Marker	Group	n	Pre-treatment	Post-treatment	*t*	*P*
Plasma Cells	Experimental group	50	41 (82.0%)	8 (16.0%)	4.78	<0.001
	Control group	50	40 (80.0%)	24 (48.0%)		
CD138	Experimental group	50	43 (86.0%)	10 (20.0%)	5.02	<0.001
	Control group	50	42 (84.0%)	28 (56.0%)		
CD38	Experimental group	50	42 (84.0%)	9 (18.0%)	4.65	<0.001
	Control group	50	41 (82.0%)	26 (52.0%)		
CD163	Experimental group	50	41 (82.0%)	8 (16.0%)	4.90	<0.001
	Control group	50	40 (80.0%)	25 (50.0%)		

Discussion

Chronic endometritis is one of the key factors leading to female infertility. It not only impairs fertility, but also can result in menstrual disorders and recurrent miscarriage [7]. Current treatment strategies mainly include antibiotic therapy and TCM interventions.

However, conventional antibiotic regimens are challenged by the emergence of bacterial resistance and often show suboptimal efficacy in managing long-standing inflammation [8]. Therefore, it is of great clinical importance to explore more effective and safer treatment options for chronic endometritis.

Guizhi Fuling Decoction, a classic formula in TCM, consists of several active ingredients, including Cinnamomi Ramulus, Poria, Paeoniae Alba Radix, Persicae Semen, and Moutan Cortex [9]. These components work synergistically to treat chronic endometritis through various mechanisms:

(1) Cinnamomi Ramulus: It is known for its ability to warm the channels, promote blood circulation, and resolve blood stasis. It enhances uterine blood flow and promotes microcirculatory improvement in the endometrium, which helps to eliminate blood stasis and supports the repair of damaged endometrial tissue. Its warming properties also aid in relieving cold-induced blood stasis, a common pathophysiological factor in chronic endometritis.

(2) Poria: It has diuretic, spleen-strengthening, and sedative properties. It helps to expel excess moisture and reduce internal dampness, thereby improving the overall internal environment. By facilitating fluid metabolism, Fuling plays a crucial role in mitigating inflammatory responses and enhancing uterine health, creating an optimal microenvironment for the endometrium and promoting the resolution of chronic inflammation.

(3) Paeoniae Alba Radix: It is renowned for its ability to regulate the liver, relieve stagnation, and alleviate pain. It improves blood circulation, harmonizes qi-blood flow, and alleviates pain or discomfort associated with chronic endometritis. Additionally, it has anti-inflammatory effects, which help mitigate local inflammation in the endometrium, enhancing tissue repair and healing.

(4) Persicae Semen: It is widely recognized for its blood-moving and pain-relieving properties. It promotes circulation of blood, addresses blood stasis, and aids in alleviating symptoms such as uterine pain, a common complaint in patients with chronic endometritis. Its effects on blood flow also contribute to the promotion of uterine repair and regeneration, improving the structural and functional integrity of the endometrial lining.

(5) Moutan Cortex: It is known for its ability to clear heat, cool the blood, and promote blood circulation. It reduces inflammatory symptoms, helping to

alleviate heat and toxicity in the uterus caused by chronic endometrial inflammation. Mu Dan Pi also helps to improve uterine perfusion, thereby enhancing the healing and regeneration of the endometrial tissue.

Together, these ingredients of Guizhi Fuling Decoction target various aspects of chronic endometritis, including the improvement of endometrial morphology, blood circulation, immune modulation, and the reduction of inflammatory activity. Specifically, the formula's ability to regulate the body's internal environment, enhance uterine microcirculation, and resolve blood stasis provides a comprehensive approach to restoring endometrial function [10]. For patients with infertility, the use of Guizhi Fuling Decoction has shown potential in increasing the likelihood of successful conception by creating favorable conditions for embryo implantation.

TCM has a long history in the treatment of gynecological diseases. As one of the classic prescriptions in TCM, Guizhi Fuling Decoction is well known for its ability to regulate qi and blood, promote blood circulation, and resolve blood stasis. In the context of chronic endometritis, Guizhi Fuling Decoction can improve the blood supply to the endometrium and accelerate the absorption of inflammatory exudates, thereby facilitating recovery [11]. Numerous clinical studies have confirmed these benefits. The main mechanism is believed to involve modulation of the internal milieu, enhancement of immune function, and improvement of microcirculatory status, ultimately restoring normal endometrial function [12]. Recent research further suggests that Guizhi Fuling Decoction may increase the likelihood of successful pregnancy in patients with infertility, underscoring its potential value in female reproductive health.

Metronidazole is a broad-spectrum antimicrobial agent with potent activity against anaerobic bacteria and plays an important role in the treatment of gynecologic infections. When administered via intrauterine perfusion for chronic endometritis, metronidazole can act directly at the lesion site. It effectively reducing local microbial load, alleviating inflammation-related symptoms, and promoting regeneration and repair of damaged endometrial tissue. This mode of administration achieves high drug concentration at the target site, thereby enhancing efficacy while reducing systemic adverse reactions [13].

The combination of Guizhi Fuling Decoction with metronidazole integrates the advantages of TCM and Western medicine. Guizhi Fuling Decoction helps to regulate the patient's constitution and optimize the microenvironment of the endometrium, whereas metronidazole directly combats infection. Together, they act on both the internal environment and the local lesion, leading to multidimensional improvement of the pathological changes associated with chronic endometritis and facilitating conception.

The present study showed that patients in the experimental group who received Guizhi Fuling Decoction plus intrauterine metronidazole exhibited significantly greater improvements in endometrial thickness, blood flow, and pathological scores compared with those treated with doxycycline alone. Specifically, endometrial thickness increased from 5.38 mm to 7.89 mm; the blood flow score improved from 1.95 to 3.56; and the pathological score decreased markedly. Indicating more thorough recovery of endometrial structure and function. These findings suggest that the combined regimen effectively promotes endometrial repair and improves uterine perfusion, thereby creating more favorable conditions for embryo implantation and pregnancy.

In addition, the marked reduction in plasma cell, CD38, CD138, and CD163 positivity in the experimental group provides immunohistochemical support for the anti-inflammatory advantage of the combined therapy. These markers are closely associated with chronic endometrial inflammation, and their decline indicates a meaningful decrease in immune activation and cellular infiltration. This suggests that the integration of Guizhi Fuling Decoction with intrauterine metronidazole not only improves endometrial morphology but also helps

restore a more stable local immune environment, which may further contribute to improved reproductive outcomes.

In terms of reproductive outcomes, the clinical pregnancy rate of the experimental group was significantly higher than that of the control group. This further confirms that the treatment strategy can substantially improve the pregnancy potential of patients with chronic endometritis. In terms of safety, the overall incidence of adverse reactions in the experimental group was lower than that in the control group, indicating that Guizhi Fuling Decoction combined with metronidazole not only improved the therapeutic effect but also exhibited better tolerability.

Conclusion

In summary, Guizhi Fuling Decoction combined with metronidazole shows excellent clinical efficacy in the treatment of chronic endometritis. It significantly improves endometrial thickness, blood circulation, and pathological status, and markedly increases the clinical pregnancy rate, with a relatively low incidence of adverse reactions. This combined regimen represents a safe and effective therapeutic option worthy of further promotion and application in clinical practice.

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Conflicts of Interest

The author declares no conflict of interest.

References

[1] Sfakianoudis, K., Simopoulou, M., Nikas, Y., Rapani, A., Nitsos, N., Pierouli, K., Pantos, K. (2018) Efficient treatment of chronic endometritis through a novel approach of intrauterine antibiotic infusion: a case series. *BMC Women's Health*, 18(1), 197.

[2] Kitaya, K., Yasuo, T. (2023) Commonalities and disparities between endometriosis and chronic endometritis: therapeutic potential of novel antibiotic treatment strategy against ectopic endometrium. *International Journal of Molecular Sciences*, 24(3), 2059.

[3] Gao, J., Yang, J., Lu, Z., Dong, X., Xu, Y. (2022) The Multiple pharmacologic functions and mechanisms of action of guizhi fuling formulation. *Evidence-Based Complementary and Alternative Medicine*, (1), 6813421.

[4] Chadchan, S. B., Cheng, M., Parnell, L. A., Yin, Y., Schriefer, A., Mysorekar, I. U., Kommagani, R. (2019) Antibiotic therapy with metronidazole reduces endometriosis disease progression in mice: a potential role for gut microbiota. *Human Reproduction*, 34(6), 1106-1116.

[5] Kimura, F., Takebayashi, A., Ishida, M., Nakamura, A., Kitazawa, J., Morimune, A., Murakami, T. (2019) Chronic endometritis and its effect on reproduction. *Journal of Obstetrics and Gynaecology Research*, 45(5), 951-960.

[6] Kravchenko, E. N., Novitskaya, E. L., Sabitova, N. L., Lisitsa, E. V. (2025) Evaluation of the effectiveness of complex treatment for chronic endometritis resulting in thin endometrium in patients with impaired reproductive function. *Obstetrics and Gynecology*, (4), 138-144.

[7] La, X., Wang, W., Zhang, M., Liang, L. (2021) Definition and multiple factors of recurrent spontaneous abortion. *Environment and Female Reproductive Health*, 231-257.

[8] Petrina, M. A., Cosentino, L. A., Wiesenfeld, H. C., Darville, T., Hillier, S. L. (2019) Susceptibility of endometrial isolates

recovered from women with clinical pelvic inflammatory disease or histological endometritis to antimicrobial agents. *Anaerobe*, 56, 61-65.

[9] Liu, Z., Peng, Z., Zheng, P., Xu, L. (2023) Clinical efficacy of Xiaochaihu decoction combined with Guizhi Fuling Pill in adjuvant treatment of AECOPD and its influence on inflammatory factors in patients. *Journal of Experimental and Clinical Application of Chinese Medicine*, 10-16.

[10] Wang, D., Cheng, X., Fang, H., Ren, Y., Li, X., Ren, W., Yang, C. (2020) Effect of cold stress on ovarian & uterine microcirculation in rats and the role of endothelin system. *Reproductive Biology and Endocrinology*, 18(1), 29.

[11] Efendieva, Z., Vishnyakova, P., Apolikhina, I., Artemova, D., Butov, K., Kalinina, E., Sukhikh, G. (2023) Hysteroscopic injections of autologous endometrial cells and platelet-rich plasma in patients with thin endometrium: a pilot randomized study. *Scientific Reports*, 13(1), 945.

[12] Rungsiwiwut, R., Virutamasen, P., Pruksananonda, K. (2021) Mesenchymal stem cells for restoring endometrial function: an infertility perspective. *Reproductive Medicine and Biology*, 20(1), 13-19.

[13] Pessoa de Farias Rodrigues, M., Lima Vilarino, F., de Souza Barbeiro Munhoz, A., da Silva Paiva, L., de Alcantara Sousa, L. V., Zaia, V., Parente Barbosa, C. (2020). Clinical aspects and the quality of life among women with endometriosis and infertility: a cross-sectional study. *BMC Women's Health*, 20(1), 124.

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Research direction: Clinical efficacy of Guizhi Fuling Decoction combined with metronidazole in the treatment of infertility caused by endometritis (infertility, endometritis, Guizhi Fuling Decoction combined with metronidazole).