Am J Transl Res 2023;15(8):5519-5527
www.ajtr.org /ISSN:1943-8141/AJTR0150165

Original Article

Acupuncture combined with mifepristone improves sex hormones and inflammatory factors in patients with uterine fibroids

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Received March 15, 2023; Accepted July 15, 2023; Epub August 15, 2023; Published August 30, 2023

Abstract: Objective: To analyze the therapeutic effect of acupuncture combined with mifepristone on uterine fibroids and its influence on sex hormones and inflammatory factors. Methods: Data of 102 patients with uterine fibroids admitted to Shanxi Provincial Hospital of Chinese Medicine from January 2019 to January 2022 were retrospectively analyzed. Among them, there were 50 patients treated with mifepristone alone (control group) and 52 patients undergoing combined treatment of acupuncture and mifepristone (observation group). After 2 months of continuous treatment, the therapeutic efficacy, volume of uterine fibroids and uterus, levels of inflammatory factors (C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α)), as well as levels of estradiol (E2), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), along with hemodynamic levels and incidence of adverse reactions were recorded and compared between the two groups. Logistic analysis was employed to identify the independent risk factors for the recurrence of uterine fibroids in patients. Results: Compared with the control group, the observation group was identified with significantly higher overall response rate ($P < 0.05$). The uterine fibroid volume and uterine volume significantly improved in both groups after treatment, and the improvements were more prominent in the observation group than in the control group ($P < 0.05$). After treatment, the serum CRP and TNF-α were both evidently decreased in the two groups, while levels of E2, FSH, LH and peak blood flow velocity were significantly ameliorated, and the improvements in the observation group were more significant than those in the control group ($P < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). Alcohol intake and treatment regime were independent risk factors for the recurrence of uterine fibroids in patients. Conclusion: Combining acupuncture with mifepristone can significantly improve uterine fibroids, estrogen and progesterone levels, as well as reduce inflammation, with a high level of safety, making it a promising treatment for clinical use.

Keywords: Acupuncture, mifepristone, uterine fibroids, sex hormones, inflammatory factors

Introduction

Uterine leiomyoma is a common benign tumor of the female reproductive system, often accompanied by symptoms such as abdominal pain and menstrual disorders. Without timely treatment, it can cause adverse events such as infertility and abortion, which seriously affect patients' physical and mental health, as well as their quality of life [1, 2]. At present, surgical and drug treatments are the most commonly adopted methods for the clinical treatment. Myomectomy is highly suitable for patients who wish to preserve fertility. Laparoscopic surgery,

on the other hand, is characterized by low trauma, mild pain and minimal blood loss, with confirmed efficacy and safety in clinical practice [3]. However, certain physical and mental damage cannot be avoided during surgery, thereby limiting its clinical application [4].

However, as research advances and medical technology develops, some scholars have found that adding appropriate drug therapy after surgery can further improve the therapeutic effects for patients. Mifepristone, a progestogen antagonist that can induce premature delivery and abortion, has favorable clinical efficacy because of its high bioavailability and plasma protein binding of up to 90% [5, 6]. However, it mainly competes for progesterone receptors, and acts less on estrogen receptor sites, resulting in longer later treatment cycles [7]. According to Traditional Chinese Medicine (TCM) theory, uterine fibroids are caused by qi deficiency and manifest as blood stasis, falling under the category of "Zheng Gan", which should be treated by activation of blood circulation [8]. Acupuncture and moxibustion have long been used in the treatment of uterine fibroids. Based on the theory of meridians and acupoints, they work to promote meridians and regulate qi and blood [9], but there is currently no study addressing the effect of acupuncture and moxibustion combined with western medicine on sex hormones and inflammatory factors in patients with uterine fibroids.

Therefore, this retrospective analysis aimed to analyze the efficacy of this combined treatment and its effect on sex hormones and inflammatory factors in patients with uterine fibroids.

Materials and methods

Clinical data

Data of 102 patients with uterine fibroids who visited the Shaanxi Provincial Hospital of Chinese Medicine from January 2019 to January 2022 were retrospectively analyzed. Among them, 50 patients treated with mifepristone were assigned in a control group and 52 patients undergoing a combined treatment of mifepristone and acupuncture were in an observation group. Inclusion criteria: (1) Patients with uterine fibroids confirmed by imaging [10]; (2) Patients who did not receive any previous treatment for uterine fibroids; (3) Patients with complete data. Exclusion criteria: (1) Patients with submucous myoma, adenomyosis or endometriosis; (2) Patients who were pregnant, lactating, or in menopause; (3) Patients with pituitary tumor, diabetes, hyperthyroidism or other endocrine system diseases; (4) Patients with mental or consciousness disorders who were unable to cooperate with the treatment. This study conformed to the Helsinki Declaration and was approved by the ethics committee of Shanxi Provincial Hospital of Chinese Medicine.

Treatment regimens

Patients in the control group received oral mifepristone tablets (Hubei Gedian Humanwell Pharmaceutical Co., Ltd., GYZZ H20033551), 25 mg, once per day, continuously for 2 months. Patients in the observation group were treated with additional acupuncture. Tianshu, Guanyuan and Uterine were selected as the main acupoints. Additionally, Qihai was taken for patients with qi stagnation, Zusanli for those who suffered from qi and blood deficiency, Xuehai for those with menstrual volume, and Zhigou for those with constipation. After emptying the bladder, the acupoints were needled to a depth of approximately 1.5 mm, and the needles were left in place for 30 to 45 min. The treatment consisted of a total of 3 courses, with each course lasting for 10 days and treatment sessions conducted once daily. A 3-day rest period was taken between each course.

Outcome measures

(1) The therapeutic response was evaluated and compared between the two groups. Specifically, the response was categorized as markedly effective (disappearance of clinical symptoms, menstruation returned to normal, and tumor reduction > 50%), effective (significantly ameliorated symptoms, improment in menstruation and tumor reduction of 20%-50%), and ineffective (no improvement in symptoms). Overall response rate = (markedly effective + effective)/total number of cases × 100%.

(2) Uterine and uterine fibroid volumes were measured using a color Doppler ultrasound diagnostic apparatus (American GE, Voluson S6, USA) before and after 3 months of treatment.

Table 1. Comparison of general data

Variables	Observation Group n = 52	Control Group n = 50	t/X^2	P
Age (years)			0.002	0.975
≥ 35	30 (57.69)	29 (58.00)		
< 35	22 (42.31)	21 (42.00)		
BMI (kg/m^2)			0.001	0.981
≥ 23	29 (55.77)	28 (56.00)		
< 23	23 (44.23)	22 (44.00)		
Smoking history			0.002	0.968
Yes	21 (40.38)	20 (40.00)		
No	31 (59.62)	30 (60.00)		
Alcohol history			0.002	0.964
Yes	28 (53.85)	27 (54.00)		
No	24 (46.15)	23 (46.00)		
Disease duration (months)			0.037	0.846
≥ 5	27 (51.92)	25 (50.00)		
< 5	25 (48.08)	25 (50.00)		
Myoma site			0.179	0.915
Intramural	19 (36.54)	20 (40.00)		
Submucous membrane	20 (38.46)	19 (38.00)		
Other	13 (25.00)	11 (22.00)		

BMI: body mass index.

(3) Enzyme-linked immunosorbent assay (ELISA) was adopted to measure the levels of sex hormones, including estradiol (E2), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), before and 3 months after treatment.

(4) Inflammatory factors (C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), Shanghai enzyme-linked biotechnology, ml05-7570, ml064303) were determined using ELISA before and after treatment.

(5) Color Doppler ultrasound was adopted to detect changes in peak blood flow velocity (PSV) and resistance index (RI) before and after treatment.

(6) The incidence of adverse reactions during treatment were recorded, including headache, gastrointestinal reactions, hot flashes, and abdominal pain.

Statistical methods

The collected data were analyzed and visualized using SPSS 20.0 and GraphPad Prism 8, respectively. The measurement data were expressed as ($\bar{x} \pm S$). Student t-test was used for inter-group comparison, and paired t-test for intra-group comparison. Enumeration data (expressed as percentage) were subjected to chi-square test. Statistical differences were significant when $P < 0.05$.

Results

Comparison of general data

No significant differences were identified in age and body mass index and other baseline data between the two groups ($P > 0.05$), indicating that the two groups are comparable (**Table 1**).

Comparison of treatment efficacy

The overall response rate of the observation group was 96.30%, which was markedly higher than that of control group (76.47%), as shown in **Table 2**.

Comparison of uterine and uterine fibroid volumes

There was no significant difference regarding the volume of uterus and uterine fibroids before treatment between the two groups. However, after 3 months of treatment, both groups

Table 2. Comparison of overall response rate between the two groups [n (%)]

Efficacy	Observation Group n = 52	Control Group n = 50	X^2	P
Markedly effective	35 (67.31)	26 (52.00)	-	-
Effective	15 (28.85)	12 (24.00)	-	-
Ineffective	2 (3.85)	12 (24.00)	-	-
Overall response rate (%)	50 (96.15)	38 (76.00)	8.743	0.003

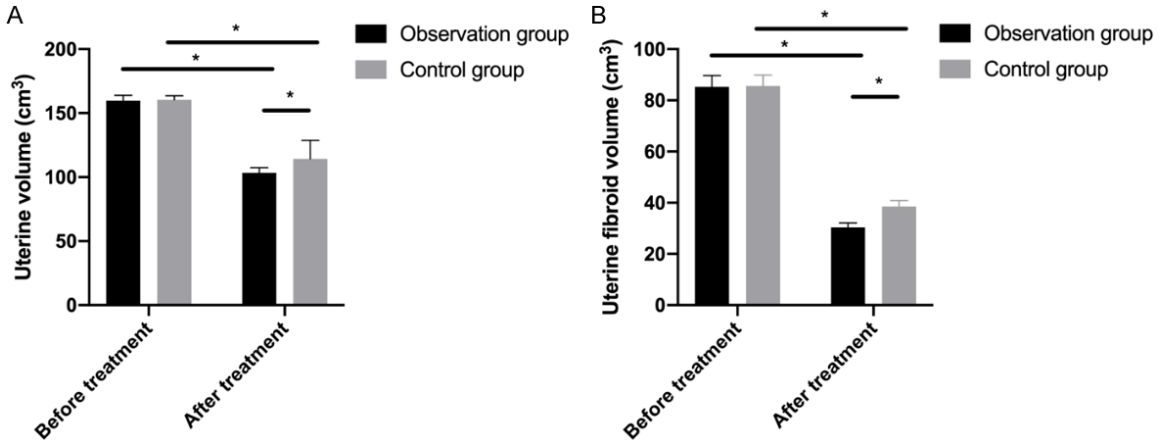

Figure 1. Comparison of uterine and uterine fibroid volumes before and after treatment between the two groups. A: Comparison of uterine volume; B: Comparison of uterine fibroid volume. * indicates P < 0.05.

showed a decrease in the volume of uterus and uterine fibroids. The reductions in the observation group were more prominent than those in the control group (all P < 0.05, **Figure 1**).

Comparison of sex hormone levels

Before treatment, no significant difference was identified in E2, FSH and LH levels between the two groups. After 3 months of treatment, the hormone levels were evidently lower in both groups, and the decreases were more prominent in the observation group than those in the control group (all P < 0.05, **Figure 2**).

Comparison of serum inflammatory factors

Before treatment, no significant difference was observed in CRP and TNF-α levels between the two groups (P > 0.05). After treatment, the two levels declined evidently, and the decreases were more significant in the observation group than those in the control group (all P < 0.05, **Figure 3**).

Comparison of uterine hemodynamics

Before treatment, there was no significant difference in PSV and RI between the two groups (P > 0.05). While after treatment, both PSV and RI increased significantly in the two groups (P < 0.05), and the observation group exhibited higher PSV than control group did (P < 0.05), but there was no statistical difference observed in RI between the two groups (P > 0.05). Details are displayed in **Figure 4**.

Analysis of risk factors affecting the prognosis of patients

According to the recurrence 1 year after treatment, the patients were divided into a good prognosis group (n = 71) and a poor prognosis group (n = 31). Univariate analysis showed that alcohol intake and treatment regimen were both factors affecting the prognosis (**Table 3**). After assigning the values (**Table 4**), further logistics regression analysis showed that alcohol intake and treatment regimen were independent risk factors affecting the prognosis of patients (**Table 5**, P < 0.05).

Comparison of adverse reactions during treatment

The incidence of adverse reactions in the observation group was negligibly higher than

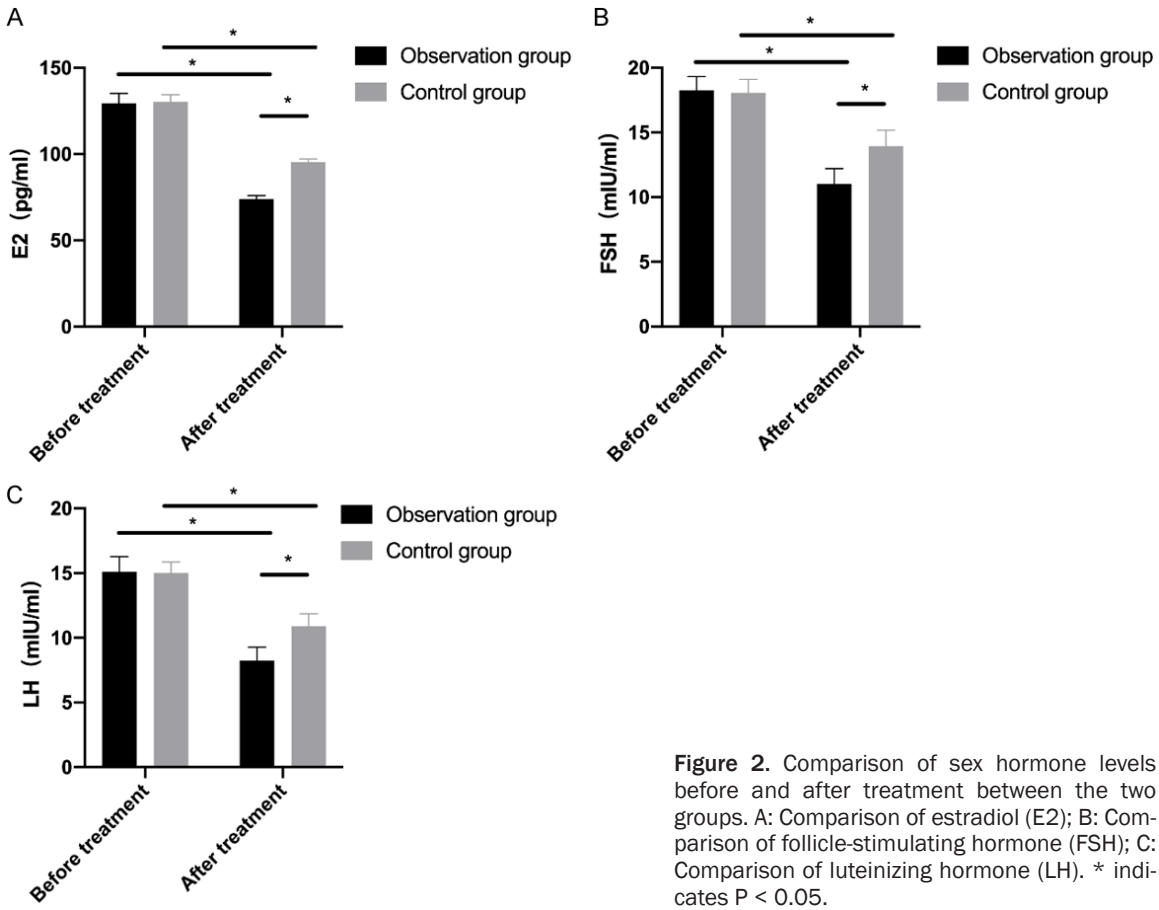

Figure 2. Comparison of sex hormone levels before and after treatment between the two groups. A: Comparison of estradiol (E2); B: Comparison of follicle-stimulating hormone (FSH); C: Comparison of luteinizing hormone (LH). * indicates $P < 0.05$.

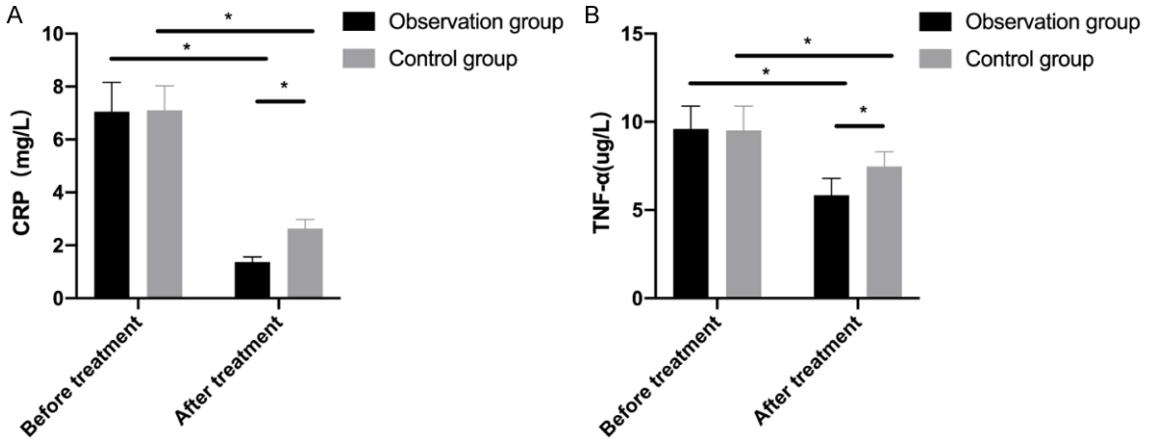

Figure 3. Comparison of serum inflammatory factors before and after treatment between the two groups. A: Comparison of C-reactive protein (CRP); B: Comparison of tumor necrosis factor-α (TNF-α). * indicates $P < 0.05$.

that in the control group (13.46% *vs* *12.00%*, $P > 0.05$, **Table 6**).

Discussion

The pathogenesis of uterine leiomyoma is associated with genetic susceptibility, imbalance of sex hormone levels and stem cell dysfunction. when symptoms such as menstrual disorders and lower abdominal pain occur due to fibroid growth, it is called symptomatic uterine leiomyoma [11]. It is critical to take active clinical measures to improve the symptoms caused by uterine fibroids. At present, western

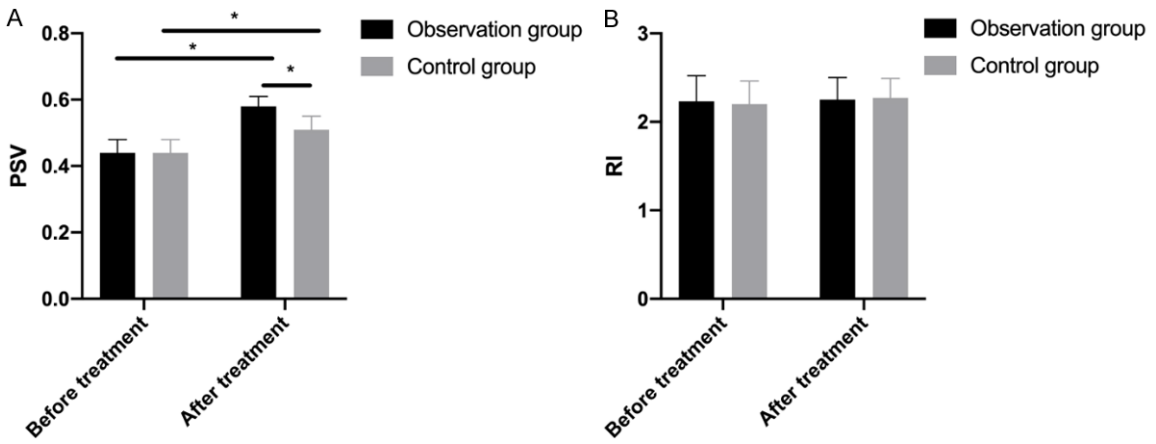

Figure 4. Comparison of uterine hemodynamics before and after treatment between the two groups. A: Comparison of peak blood flow velocity (PSV); B: Comparison of resistance index (RI). * indicates $P < 0.05$.

Table 3. Univariate analysis

Variables	Good prognosis group n = 71	Poor prognosis group n = 31	X^2	P
Age	33.31±1.24	34.42±1.27	0.020	0.887
BMI			0.020	0.888
≥ 23 kg/m^2 (n = 57)	40 (56.34)	17 (54.84)		
< 23 kg/m^2 (n = 45)	31 (43.66)	14 (45.16)		
Smoking			0.083	0.772
Yes (n = 35)	25 (35.21)	10 (32.26)		
No (n = 67)	46 (64.79)	21 (67.74)		
Myoma site			1.946	0.378
Intramural (n = 39)	28 (39.44)	11 (35.48)		
Mucous membrane position (n = 39)	29 (40.85)	10 (32.26)		
Other (n = 24)	14 (19.72)	10 (32.26)		
Alcohol Intake			9.216	0.002
Yes (n = 63)	37 (44.12)	26 (56.76)		
No (n = 39)	34 (55.88)	5 (43.24)		
Treatment Regime			25.84	< 0.001
Acupuncture used (n = 52)	48 (67.61)	4 (12.92)		
No acupuncture (n = 50)	23 (32.39)	27 (26.47)		

BMI: body mass index.

Table 4. Value assignment sheet

Factor	Assignment value
Alcohol Intake	Yes = 1, No = 0
Treatment Regimen	No acupuncture = 1, using acupuncture = 0

medicines such as anti-progestogen and estrogen drugs are commonly used to reduce the volume of uterine fibroids or inhibit its growth rate, thereby relieving clinical symptoms [12].

In this study, we evaluated the efficacy of acupuncture combined with mifepristone for uterine fibroids. Mifepristone, as a type of glucocorticoid drug, is mostly used for short-term treatment of non-surgical uterine fibroids. It is administered in a dose-dependent manner and offers advantages such as fewer adverse reactions, faster body metabolism, higher plasma concentration, rapid achievement of lesions, and inhibition of progestogen [13]. Mifepristone was once considered as a new type of antiprogestogen drug, which can compete with the progesterone receptors in the body, reduce progesterone action and inhibit

Table 5. Multivariate analysis

Factor	B	S.E.	Wald	P	Exp (B)	95% C.I. of EXP (B)	
						Lower Limit	Upper Limit
Alcohol intake	2.581	0.711	12.593	0.001	13.164	3.166	53.831
Treatment Regime	3.356	0.845	16.031	0.002	26.155	5.462	147.327

Table 6. Comparison of incidence of adverse reactions between the two groups [n (%)]

Adverse Reactions	Observation Group n = 52	Control Group n = 50	X^2	P
Headache	3 (5.77)	2 (4.00)	-	-
Gastrointestinal Reactions	2 (3.85)	2 (4.00)	-	-
Hot Flashes	1 (1.92)	1 (2.00)	-	-
Abdominal Pain	1 (1.92)	1 (2.00)	-	-
Incidence of Adverse Reactions	7 (13.46)	6 (12.00)	0.949	0.825

the growth of uterine fibroids [14]. However, studies have shown that mifepristone has some limitations, such as the tendency of fibroids to regrow after drug withdrawal, adverse reactions during medication, and the possibility of endometrial thickening [15]. Uterine fibroids is not exactly a term nor an illness within the scope of TCM. It can be attributed to the category of "phlegm" according to the clinical symptoms. According to the detailed records of the disease, uterine fibroids are mainly caused by emotional depression and stagnation of liver-qi, resulting in stagnation of qi and blood stasis, internal accumulation of uterus, and the formation of phlegm over time. Additionally, they can be caused by deficiency of qi in the spleen and the stomach, deficiency of blood, insufficient endowment, and overwork, which lead to more qi and blood consumption and blood stasis during menstrual pregnancy and breastfeeding. Therefore, promoting blood circulation, removing blood stasis and breaking blood stasis should be emphasized in the treatment [16]. Acupuncture at Guanyuan point can tonify qi of the kidney and benefit the essence blood; uterine point can adjust and manage qi; Qihai point can dispel dampness and cold, as well as regulate meridians and the belt vessel; Zhongji point can dissipate qi and water; Xuehai point can generate blood, promote blood circulation and remove blood stasis; Zusanli point can activate meridians and dispel wind-cold and dampness; Sanyinjiao point can reconcile qi and blood, tonify kidney and nourish liver; Hegu point can enhance the energy, expel turbidity and dispel wind-cold; and Neiguan point can soothe the breathing. The principle of acupuncture treatment is to stimulate acupoints, thereby regulating hormone levels in the body and inhibiting the development and growth of fibroids. This study revealed prominently better therapeutic efficacy by acupuncture combined with mifepristone than by mifepristone alone, with evidently smaller volume of uterus and uterine fibroids in the observation group after treatment.

Studies have shown that the growth of uterine fibroids is inextricably linked to the elevated hormone levels [17]. Estrogen and progesterone levels are positively correlated with FSH levels, and high levels of estrogen and progesterone can stimulate the endocrine regulation of the hypothalamic-pituitary-ovarian axis via the neuro-humoral network regulatory system and promote synthesis of FSH. Conversely, low levels of estrogen and progesterone can inhibit synthesis of FSH [18, 19]. In this study, we observed that E2, FSH and LH went significantly lower in both groups after treatment, and the decreases were more significant in the observation group than in the control group. It is indicated that mifepristone combined with acupuncture treatment could regulate body hormone levels more effectively. This is also the first time to show that the combined treatment was more effective in reducing sex hormones. It has been revealed that acupuncture can improve cellular immunity and play a therapeutic role by reducing E2 [20], which is also consistent with our results. In addition to body hormones, inflammatory response was also identified to be closely related to the occurrence and

development of uterine fibroids, the pathogenesis of which is associated with inflammatory factors such as hs-CRP [21, 22]. A decline of serum inflammatory factors was identified in both groups after treatment, and the decreases were more significant in the observation group than in the control group. The reason may be that the combined treatment can play a synergistic therapeutic role, thereby enhancing the immunity and regulating the secretion of cytokines in the body [23], but the specific mechanism of action still needs further analysis. In addition to hormonal effects, microcirculatory disturbances and hemodynamic disturbances in the body are also closely related to the development of uterine fibroids [24]. The results of this study showed that PSV and RI increased in both groups after treatment, and PSV in the observation group was significantly higher than that in the control group, indicating that mifepristone combined with acupuncture can increase the blood flow resistance inside the uterine fibroids to a certain extent and reduce the blood supply, thereby reducing the size of fibroids and promoting the rehabilitation of patients. In addition, we compared the incidence of adverse reactions between the two groups and only found a negligible difference, indicating that mifepristone combined with acupuncture not only exhibited better efficacy, but was also of satisfying safety performance. Finally, we analyzed the risk factors for poor prognosis and found that alcohol consumption and no acupuncture were the independent risk factors leading to recurrence in patients. A previous study [25] also pointed out that alcohol intake was associated with the occurrence of uterine fibroids.

In summary, combining acupuncture with mifepristone is effective in the treatment of uterine fibroids. It can not only significantly improve the hormone levels and inflammation in patients, but also benefit patients with a high level of safety, making it a promising treatment in clinical practice. However, there are some limitations in this study. On the one hand, we did not use other drugs to compare the effect of mifepristone combined with acupuncture, which may allow us to find an alternative treatment regimen. On the other hand, the sample size included in this study was limited, so the study findings remain to be further verified. We will further conduct multicenter large-sample studies to support the conclusions with more sufficient data.

Disclosure of conflict of interest

None.

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