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Effect of mifepristone in the different treatments of endometriosis

Y.X. Zhang

Department of Gynaecology, Yantaishan Hospital, Yantai (China)

Summary

Objective: To observe the effect of small-dose mifepristone conservative treatment and laparoscopic combined with mifepristone in the treatment of endometriosis. *Materials and Methods:* Sixty-five endometriosis cases were given small-dose mifepristone conservative treatment and were assessed for the effect of this treatment; 92 cases were randomly divided into control group (taking gestrinone) and observation group (mifepristone), FSH, P, PRL and E_2 levels were compared before and after treatment, and pregnancy investigation and each sex hormone level monitoring were followed-up at one year after drug withdrawal. *Results:* Using mifepristone, FSH, P, E_2, and LH levels all significantly changed six months after treatment and recovered 12 months after drug withdrawal; when comparing the pelvic symptoms, endometrial thickness showed that mifepristone was significantly effective ($p < 0.01$), and the pregnancy rate was 27.69%. Comparing the two groups, none of the total effective rate, pregnancy rate one year of follow-up, and recurrence rates were significantly different; hormone levels in the both groups were significantly decreased or increased ($p < 0.05$) after treatment. The two groups had no significant difference ($p > 0.05$), but 12 months after drug withdrawal, in the control group (not in the observation group), LH level was still significantly different ($p < 0.05$) compared pre-treatment. *Conclusions:* In the conservative treatment, mifepristone can safely improve the hormone levels, reduce the thickness of the endometrium, alleviate symptoms. With laparoscopic minimally invasive combined drug therapy, mifepristone has a significant effect, with a more followed-up pregnancy rate, less recurrence, and no drug accumulation side-effects, hence it is worthy of clinical application.

Key words: Mifepristone; Endometriosis; Laparoscopic treatment; Conservative treatment; Laparoscopic minimally invasive combined drug therapy; Gestrinone.

Introduction

Endometriosis is a hormone dependent disease [1], occurring more often in women of reproductive age. It is a benign disease with metastasis, invasion, recurrence and surrounding tissue serious adhesion malignant biological characteristics, and often causes pelvic, abdominal pain, and infertility [2]. It seriously impacts women's quality of life and the incidence rate is rising annually [3, 4]. The pathogenesis of this disease is not clear; the mainstream view considers ovarian hormones periodic change as the main reason for incidence and progression. Drug treatment is given priority to hormone regulation [5]. Mifepristone is a synthetic steroid drug commonly used in gynaecology, with anti-progesterone and anti-glucocorticoid function, can effectively inhibit ovulation, interfere endometrial integrity, downregulate the ectopic foci of progesterone and cortisol receptors, and block the endometrial response to estrogen and progesterone, so that patients' endometrium atrophy [6-7]. It is the most widely used drug in current clinic; for severe symptoms, patients were treated by using laparoscopy combined with drug treatment. The purpose of this study was to observe the effect of small-dose mifepristone conservative treatment and laparoscopic combined with mifepristone in the treatment of endometriosis, in order to provide the reference for clinical application.

Materials and Methods

Patients were chosen according to criteria for the diagnosis of endometriosis [8], had not used hormone drugs for six months before treatment, and liver and kidney function was normal. Women with adenomyosis of uterus, pregnant or lactating, had hysterectomy and/or single, bilateral ovarian resection or that had a mifepristone allergy were excluded from the study. The patients were recruited with informed consent, were willing to cooperate with the doctor for examination and treatment and abide by the follow-up system.

Sixty-five endometriosis cases between January 2010 to November 2013 in the present hospital. The women were aged 22-43 years, with a course of disease of 35 ± 27 months. Of these 65 patients, 40 cases had dysmenorrhea, 28 cases had menstrual disorder, and 19 cases had sexual pain (*mifepristone conservative treatment*).

As control, another 92 endometriosis cases were selected, who underwent treatment between June 2010 to January 2014. These patients aged 25-44 years with a course of disease of 39 ± 22 months, among which 63 cases had dysmenorrhea, 47 cases had menstrual disorder, and 26 cases had sexual pain. According to symptoms, they were randomly divided into control group (taking gestrinone) and observation group (mifepristone), with 46 cases in each group. These two groups of patients were comparable for no significant difference by general information ($p > 0.05$) (*laparoscopic minimally invasive operation combined with mifepristone*).

Patients in the first day of the menstrual cycle began taking mifepristone 12.5 mg / (time·d), for six months (*mifepristone conservative treatment*). The control group was given gestrinone 2.5mg/time, two times/week; the observation group was given mifepristone 12.5mg/time, one time daily. Two groups of patients started taking the drug in the first week after laparoscopic opera-

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Table 1. — *Comparison of pelvic symptoms, symptom scores, and endometrial thickness.*

Observation time	Pelvic symptoms	Symptom score	Endometrial thickness(mm)
Pre-treatment	4.8±1.5	3.4±1.4	40.0±16.0
Post-treatment	0.5±0.3**	0.6±0.3**	20.0±9.0**

Note: compared with pre-treatment group, *$p < 0.05$, **$p < 0.01$.

Table 2. — *Changes in sex hormones.*

Observation time	FSH (μg/L)	LH (U/L)	P (nmol/L)	E_2 (pmol/L)
Pre-treatment	9.8±2.5	7.4±3.4	298.0±144.2	288.3±53.6
Treatment for 6 months	8.0±2.3*	10.6±2.3**	110.5±99.7**	207.5±50.4**
Drug withdrawal for 12 months	9.5±2.3	7.6±3.3	290.2±149.1	280.3±53.0

Note: compared with pre-treatment group, *$p < 0.05$, **$p < 0.01$.

tion, treatment for six months (*laparoscopic minimally invasive operation combined with mifepristone*).

Observation index and efficacy criterion [9]

According to the degree of the pelvic symptoms (dysmenorrhea, dyspareunia, pelvic pain) and signs (pelvic tenderness and induration) score, each of which was scored 0-3 for both before treatment and six months after treatment. B-ultrasound, observed improvement in endometrial thickness, fasting blood, FSH, LH, P, and E_2 levels, and adverse reactions were recorded.

The clinical signs and symptoms that disappeared was considered complete remission; clinical signs and symptoms that still had mild pelvic pain were considered improved; the clinical signs and symptoms that did not obviously improve were considered invalid. One year after drug withdrawal, pregnancy investigation and each sex hormone level monitoring were followed-up (*mifepristone conservative treatment*);

For both groups, FSH, P, PRL and E_2 levels were checked both before and after treatment, and pregnancy investigation and each sex hormone level monitoring were followed-up one year after drug withdrawal (*laparoscopic minimally invasive operation combined with mifepristone*).

Statistical analysis

SPSS19.0 statistical software was adopted. Measurement data were represented by ($\bar{x} \pm s$), the t-test comparison was used to compare the mean difference between the two groups and between before and after treatment in group. A $p < 0.05$ was defined as statistical significance.

Results

Effect of mifepristone in the conservative treatment

After six months of treatment, 20 cases had complete remission, 33 cases improved, 12 cases were ineffective; the total effective rate was 81.54%. At 12 months after drug withdrawal, 19 cases had complete remission, 35 cases improved, 11 cases were ineffective; the total effective rate was 83.08%. At the follow-up, 18 cases resulted in a pregnancy (27.69%), and four cases had recurrence (6.15%). ALT and/or AST slightly increased in five cases that were given liver treatment. Irregular vaginal bleeding in small quantity occurred in 12 cases, five cases had lumbar expansion, and one case with breast pain all self-improved with no treatments.

Pelvic symptom score, symptom score, and endometrial thickness were (4.8 ± 1.5)%, (3.4 ± 1.4)%, (40 ± 16) mm, respectively, before treatment, while they were (0.5 ± 0.3)%, (0.6 ± 0.3)%, (20 ± 9) mm after treatment (p <0.01) (Table 1).

Before treatment, FSH, LH, P, E_2 levels were (9.8 ± 2.5) μg / L, (7.4 ± 3.4) U/L, (298.0 ± 144.2) nmol/L, and (288.3 ± 53.6) pmol/L, respectively. At six months after treatment they were (8.0 ± 2.3) μg/L, (10.6 ± 2.3) U/L, (110.5 ± 99.7) nmol/L, and (207.5 ± 50.4) pmol/L, respectively. At 12 months after withdrawal they were (9.5 ± 2.3) μg/L, (7.6 ± 3.3) U/L, (290.2 ± 149.1) nmol/L, and (280.3 ± 53.0) pmol/L (Table 2).

Effect of laparoscopy combined with mifepristone treatment

Before treatment, comparing the two groups of patients with FSH, LH, P, and E_2 levels, there was no significant difference ($p > 0.05$); after treatment, FSH, P, E_2 in the two groups were significantly decreased ($p < 0.05$), and LH was significantly increased ($p < 0.05$), but in control group 12 months after drug withdrawal, the LH level was still significantly different from the pre-treatment level ($p < 0.05$), and significantly different from the observation group ($p <$ 0.05) (Table 3).

After treatment, the control group of 19 cases had complete remission, 24 cases improved, three cases were ineffective, and the total effective rate was 93.48%. After one year of follow-up, 17 cases resulted in a pregnancy (36.96%), and one cases had recurrence (2.17%). In the observation group, 21 cases had complete remission, 23

Table 3. — *Changes in hormone levels.*

Observation time		FSH (μg/L)	LH (U/L)	P (nmol/L)	E_2 (pmol/L)
Control group (n=46)	Pre-treatment	6.8±1.5	6.7±1.4	198.0±45.2	178.3±54.3
	Treatment for 6 months	5.1±2.0 *	10.5±2.0 *	103.5±39.1*	127.5±33.4*
	Drug withdrawal for 12 months	6.5±1.3	9.0±1.3 *	190.2±49.5	175.5±52.6
Observation group (n=46)	Pre-treatment	6.4±1.7	6.5±1.6	190.8±40.2	175.8±54.5
	Treatment for 6 months	4.8±1.6 *#	9.9±1.7 *#	100.4±41.3*#	120.3±30.7*#
	Drug withdrawal for 12 months	6.5±1.2	6.7±1.2	189.5±39.4	172.4±51.5

Note: Compared with pre-treatment group, *$p < 0.05$; compared with control group, #$p < 0.05$.

Table 4. — *Comparison of the clinical effects.*

Group	Anesis	Improve-ment	Relapse	Total effective rate	Gestation
Control group (n=46)	19	24	1	43 (93.48%)	17 (36.95%)
Observation group (n=46)	21	23	1	44 (95.65%)^{NS}	18 (41.74%)^{NS}

Compared with control group, NS = not significant ($p > 0.05$).

cases improved, two cases were ineffective, and the total efficiency was 95.65%. After one year of follow-up, 18 cases resulted in a pregnancy (39.13%) and one case had recurrence (2.17%). There were no significant differences between these two groups (Table 4).

Discussion

Endometriosis is more common in women of childbearing age, seriously affecting women's quality of life and health, and the incidence rate was on the rise in recent years [10, 11]. The occurrence and development of endometriosis is closely related to endocrine disorders, and is a kind of steroid hormone dependent disease. Adjusting hormonal levels can cause ectopic endometrial atrophy and improve symptoms and the pregnancy outcome [12, 13]; thus the conservative method can be used to treat endometriosis. The traditional hormones such as contraceptives, testosterone derivatives, and gonadotropin releasing hormone agonists can ease the symptoms, reduce the lesion, but may cause obvious low estrogen symptoms, or cause damage to the liver function and bone metabolism [14, 15]. Therefore assessing the safety and efficacy of drugs is a common concern of the gynecologist. Mifepristone is a new anti-hormone drug [16], which can be combined with glucocorticoid receptor and progesterone, is five times stronger than progesterone on endometrial progesterone receptor affinity, its effective dose has no effect on cortisol [17, 18], can inhibit the ovulation cycle by acting on the hypothalamic pituitary ovarian axis, inhibit the secretion of FSH, P, PRL and E_2, reduce the contact with estrogen and progesterone receptors on ectopic endometrium, inhibit ovarian function, prevent follicular development, cause ectopic endometrial atrophy, and achieve the therapeutic effect [19, 20].

The results of this study showed that using mifepristone, FSH, P, E_2 significantly decreased six months after treatment compared with those before treatment [FSH: $p < 0.05$; P and E_2: $p < 0.01$, LH significantly increased ($p<0.01$)]. At 12 months after drug withdrawal, they all recovered to the level before treatment, thanks to mifepristone that obviously regulated sex hormone level, so as to promote endometrial atrophy. Comparing pelvic symptoms and endometrial thickness before and after the treatment, it could be seen that mifepristone could significantly reduce the pelvic symptoms and signs score ($p < 0.01$), and endometrial thickness was significantly reduced ($p < 0.01$). At one year after using mifepristone, the pregnancy rate was 27.69%.

For patients who choose surgery to treat endometriosis, laparoscopic minimally invasive operation combined with drug therapy is more advocated , for it can effectively prevent disease recurrence and significantly improve the postoperative pregnancy rate [21-23]. In this study, two groups of patients were treated with mifepristone and gestrinone, respectively, after laparoscopic minimally invasive treatment. Mifepristone is a progesterone antagonist [24], can be combined with the hypothalamus, ovary and pituitary tissues of progesterone receptors, inhibit the secretion of FSH and LH, and can inhibit ovarian function to decrease estrogen levels, cause ectopic endometrial atrophy, and improve symptoms and pregnancy results. There was no significant differences of sex hormone indexes before and after treatment, which suggested that mifepristone was safe did not cause drug accumulation [25-27]. While gestrinone belongs to a moderately strong progesterone [28], it can inhibit the LH and FSH secretion through hypothalamus-pituitary, and effectively control ovarian secretion function, and peak gonadotropin and estradiol levels to treat endo- metriosis. In addition, gestrinone can be combined with androgen contained in the blood, cause the inhibition of intimal cell receptor, causing the endometrial cells to be completely absorbed or to atrophy [29]. In this study, comparing the two groups of patients with respect to FSH, LH, P and E_2 levels after treatment, there was no significant difference and the pregnancy rate was relatively close; however, for gestrinone treatment, 12 months after drug withdrawal, LH level was still significantly different from the pre-treatment level, which indicated gestrinone caused drug accumulation; in general, mifepristone had better therapeutic effect.

In conclusion, in the conservative treatment, mifepristone can safely improve the hormonal levels, reduce the thickness of the endometrium, alleviate symptoms, and with no drug accumulation after stopping the drug, and does not affect the sex hormone levels. With laparoscopic minimally invasive combined therapy, mifepristone has significant effect, more followed-up pregnancy rate, has less recurrence, no drug accumulation, and is worthy of clinical application.

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Address reprint requests to:
Y.X. ZHANG, M.D.
Department of Gynaecology
Yantaishan Hospital
No. 91 Jiefang Road
Yantai, 264001 (China)
e-mail: yongxinzh12@163.com