



Adjuvant Therapy of HIFU Ablation for Adenomyosis

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At present, many studies have confirmed that HIFU is a safe, effective, and non-invasive method for treating adenomyosis. Still, at the same time, we also realize that this HIFU treatment also has certain limitations. One of them is similar to all other uterine preservation treatment for adenomyosis; patients will face problems of poor results and recurrence. Clinical studies have confirmed that the effective rate of HIFU alone in treating adenomyosis is about 80%–90%, and there are still 10%–20% of patients whose symptoms do not improve significantly. Besides, there are still some patients with symptoms soon recur after treatment. Liu et al. [1] reported that 45 of the 173 patients with adenomyosis after HIFU treatment had symptoms recurred; the recurrence rate was about 26%, and the median time to relapse is 12 months.

In the same situation, when it faces the problems of poor treatment results and recurrence by conservative surgery for adenomyosis, some studies have demonstrated that adjuvant drug treatment can effectively reduce and delay the recurrence of symptoms of adenomyosis [2]. Also, some guidelines clearly state that in adenomyosis, long-term medical treatment is recommended to prevent the recurrence of symptoms after conservative treatment. Therefore, the need for long-term management of HIFU for adenomyosis has also been widely recognized in the treatment of adenomyosis.

At present, the long-term adjuvant treatment commonly used with HIFU to treat adenomyosis is mainly medical treatments, including mifepristone, gonadotropin-releasing hormone agonist (GnRH-a) and levonorgestrel-releasing intrauterine system (LNG-IUS), progesterone, etc. These medical treatments are described as follows:

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16.1 Mifepristone

Mifepristone is an estrogen and progesterone receptor antagonist that can inhibit follicular development and ovulation, inhibit the hypothalamic-pituitary-ovarian axis, and cause amenorrhea. At present, a few researchers have tried to combine mifepristone with HIFU to treat adenomyosis and achieved good results. Jiang et al. [3] compared the efficacy of HIFU alone and HIFU combined with mifepristone in the treatment of adenomyosis. Their results suggested that compared with before treatment, the degree of dysmenorrhea, menstrual flow, and the uterine volume were all decreased at 6 months after treatment. The total clinical effective rate of the combined treatment group was significantly higher than that of the HIFU alone group. Mao et al. [4] studied 100 patients with adenomyosis, who were randomly allocated into a HIFU-mifepristone study group and a HIFU control group and compared their clinical symptoms, uterine volume, and lesion size of the two groups before and after treatment. The results showed that the proportion of grade V to VI (severe) pain in all patients decreased from 22% before treatment to 7% at 12 months after treatment; the average uterine volume decreased by 18%, and the lesion volume decreased by 26%. Compared between the two groups, the dysmenorrhea remission rate of the study group after 6 months and 12 months of treatment was significantly higher than that of the control group, and the anemia remission rate of the study group was also significantly higher than the control group.

At present, the specific drug regimen of HIFU combined with mifepristone in the treatment of adenomyosis has different protocols reported in the literature. Many used mifepristone 12.5 mg taken daily from 1 to 2 months before HIFU treatment or starting from 1 to 5 days at the first menstrual period after HIFU treatment for 3 months.

16.2 Gonadotropin-releasing Hormone Agonist (GnRH-a)

GnRH-a is a synthetic hormone and endocrine drug, which can inhibit ovarian function but also bind to GnRH receptors in the pituitary, endometrium, myometrium, etc., and inhibit adenomyosis by exhausting its receptor. It can also reduce the blood supply to the uterus, reduce the volume of the uterus, improve the symptoms of dysmenorrhea and menorrhagia, etc. It is a commonly used conservative treatment for adenomyosis, and it is also used for long-term postoperative management.

In the treatment of adenomyosis, many studies have confirmed that HIFU combined with GnRH-a treatment can improve the therapeutic effect. Guo et al. [5] showed that HIFU treatment alone compared with HIFU combined with GnRH-a treatment; there is no significant difference in the efficacy at 1 month after treatment. Nevertheless, at 6 and 12 months after treatment, there was a significant improvement of dysmenorrhea, heavy menstrual flow, and lesion size reduction in the combined treatment group than the HIFU treatment alone.

Tan and Li [6] also compared the efficacy of HIFU alone and HIFU combined with GnRH-a in the treatment of adenomyosis. Eighty-four patients were

randomized into two groups (42 patients each) and found that the total effective rate of the combined treatment group was 90.48% and the HIFU alone group 73.81%. The volume of the lesions in the two groups was significantly reduced at 1 month, 3 months, and 6 months after treatment, and the volume of the lesions in the combined treatment group at 3 months and 6 months was more obvious than that in the HIFU treatment group. All serum CA125, menstrual volume, and dysmenorrhea visual analog scale (VAS) scores were significantly decreased after HIFU treatment. There was no statistically significant difference in adverse effects between the two groups during treatment.

At present, there is no standardization of GnRH-a usage for the treatment of adenomyosis after HIFU ablation. GnRH-a is generally given on the first day of the next menstrual period after HIFU treatment. Depending on the size of the uterus and the severity of symptoms, 4–6 courses of treatment are given. Besides, studies have confirmed that pre-treatment of adenomyosis with GnRH-a can improve the efficacy of HIFU treatment. Zhang et al. [7] confirmed that 1 to 3 courses of GnRH-a treatment before HIFU treatment of adenomyosis could obtain a larger ablation volume and effective ablation rate than the HIFU treatment group alone, and at 3 and 6 months follow-up, patients had a higher rate of symptom relief.

16.3 Levonorgestrel-Releasing Intrauterine System (LNG-IUS)

The LNG-IUS is also known as Mirena IUD, a new type of hormone-containing intrauterine birth control device, which can evenly release the high-efficiency progesterone, levonorgestrel (LNG), which can provide a long-term conservative medical treatment for adenomyosis. It is also one of the commonly used adjuvant treatments after HIFU ablation for adenomyosis.

Huang et al. [8] studied 42 cases of HIFU treatment, 44 cases of LNG-IUS intrauterine placement, and 43 cases of adenomyosis treated with HIFU combined with LNG-IUS. They found that the uterine volume, dysmenorrhea score, menstrual volume, and endometrial thickness were significantly reduced in the HIFU with LNG-IUS group at 3 months and 6 months after treatment than the other two groups. Wu et al. [9] studied 15 cases of adenomyosis patients treated with HIFU combined with LNG-IUS and 15 cases of HIFU alone and found that compared with the same group before treatment, the dysmenorrhea score and the uterine fibroid symptom-quality of life (UFS-QOL) score were significantly reduced; when compared with the HIFU alone group, the dysmenorrhea score was significantly decreased at 3, 6, and 12 months, the UFS-QOL score and serum CA125 level also significantly decreased at 6 and 12 months after HIFU combined with LNG-IUS treatment. Therefore, compared with HIFU alone, HIFU combined with LNG-IUS is more effective in improving patients' dysmenorrhea and improving quality of life. At present, the specific protocol of HIFU combined with Mirena for the treatment of adenomyosis has not standardized. Most of the Mirena IUD placement is at 2–5 days after the first or third menstrual period after HIFU treatment.

16.4 Other Single Adjuvant Therapy with HIFU

There are a few papers that reported other adjuvant treatments associated with HIFU ablation. Luo et al. [10] studied the efficacy of HIFU combined with gestrinone in the treatment of adenomyosis. In their study, the efficacy of HIFU alone and HIFU combined with gestrinone in 30 patients with adenomyosis was analyzed. Among them, patients in the combined treatment group started taking gestrinone 2.5 mg, two times weekly after HIFU ablation. After taking it for 3 months, the follow-up results showed that the improvement in menstrual flow and dysmenorrhea scores at the 6 and 12 months after treatment was statistically significant. Compared with the HIFU control group, the raised hemoglobin level of the combined treatment group was statistically significant 6 months after treatment. There are also studies suggesting that HIFU combined with absolute alcohol injection [11]; Chinese herbal medicine [12] can also improve the efficacy of HIFU in its treatment of adenomyosis. Even more, Hou et al. [13] had studied HIFU combined with metformin in the treatment of adenomyosis. The improvement of the menstrual flow and pain, as well as the reduction of serum inflammatory factors, was significantly better than the HIFU treatment group alone.

16.5 Combined Adjuvant Therapies with HIFU

In addition to the single adjuvant treatment approach in the above studies, some studies reported the use of combined adjuvant treatment together with HIFU for treating adenomyosis, and its effect is obvious. Sun et al. [14] reported the result of 142 patients with adenomyosis treated with HIFU combined with GnRH-a and LNG-IUS. They were followed up for 5 years. At 12 months after treatment, the size of the uterus shrinks obviously with an average reduction of about 45% and then slightly increases and stabilizes at a reduction rate of about 35%. The volume of uterine adenomyosis, dysmenorrhea scores, and menstrual volume also had similar declines. During this long-term 5 years follow-up, the recurrence rate of dysmenorrhea and menorrhagia are also low, approximately 5.68% and 7.91%, respectively. It is suggested that HIFU combined with GnRH-a and LNG-IUS is a safe and effective method for the treatment of adenomyosis. Yang et al. [15] also treated 466 patients with HIFU combined with GnRH-a and LNG-IUS. After treatment, both the dysmenorrhea and menstrual symptoms were significantly relieved, the uterine volume basically returned to normal, and the serum CA125 level also dropped to normal. Ye et al. [16] retrospectively analyzed the efficacy of HIFU ablation, HIFU combined with GnRH-a, HIFU combined with LNG-IUS, and HIFU combined with GnRH-a + LNG-IUS in treating dysmenorrhea of adenomyosis and found that long-term efficacy of HIFU combined with LNG-IUS + GnRH-a in the treatment of dysmenorrhea of adenomyosis is significantly better than that of HIFU alone and HIFU combined with GnRH-a. The difference is statistically significant.

Regarding HIFU and its combination therapy, there is currently no unanimous opinion. The present experience showed that (1) if the patient's symptoms are

mainly dysmenorrhea, and the uterus enlargement is less than 2 months of pregnancy, and there is no fertility requirement in a short period, LNG-IUS can be placed after the menstruation 3 months after HIFU treatment; (2) if the uterus is more than 2 months of pregnancy, with heavy menstrual flow, but without fertility requirements within a short period, it is recommended to give GnRH-a treatment for 4–6 months after HIFU treatment. LNG-IUS can be placed 1–2 months before GnRH-a is stopped; (3) for patients with obvious uterine enlargement and fertility requirements, 4–6 courses of GnRH-a treatment is given further to reduce the size of the uterus after HIFU treatment, and patients should be encouraged to get pregnant soon a few months after HIFU and GnRH-a treatment.

In summary, after HIFU treatment of adenomyosis, long-term management should be maintained for symptomatic relief. Various methods and drugs have been used as adjuvant treatments for adenomyosis treated with HIFU, and studies have shown that combined treatment methods often have better efficacy in both short and long term than HIFU treatment alone. However, at present, there is still a lack of agreed standards and specific treatment plans for adjuvant treatments, because patients have a different extent of diseases, associated conditions, and variations of symptoms. When selecting appropriate adjuvant treatment, it is necessary to follow the individualized principle according to the specific situation of the patient. Hopefully, in the future, large-scale multicenter prospective studies can be conducted to confirm the efficacy of HIFU in the treatment of adenomyosis, to clarify the indications of various adjuvant treatments, and guide a better clinical practice.

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