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CASE REPORT

Hysteroscopic Myomectomy for Type 2 Submucosal Myoma Pretreated by HIFU and Mifepristone Treatment: A Case Report and Literature Review

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Abstract: Hysteroscopic myomectomy is the first-line treatment for the removal of submucosal myoma in women facing fertility requirements. However, in the face of large diameter type 2 submucosal myoma, patients are at greater risk of complications such as uterine perforation and fluid overload during hysteroscopy. When the diameter of type 2 submucous myoma is greater than 4cm, the three-phase treatment of high intensity focused ultrasound (HIFU), drugs and hysteroscopy is effective and safe. We shared a case of a 30-year-old non-pregnant woman, who had a history of uterine submucous myoma for more than 4 years with symptoms of heavy menstruation, prolonged menstruation and secondary severe anemia. The patient's initial pelvic magnetic resonance results suggested a type 2 uterine submucous myoma with a diameter of more than 4cm. We first performed HIFU on the patient, followed by the patient's oral intake of mifepristone tablets for 3 months, and prior to hysteroscopic surgery, the patient's fibroid type was shifted to type 0, and finally successfully completed hysteroscopic myomectomy (HM). Finally, we conclude that when the diameter of type 2 submucosal myoma exceeds 4 cm, preoperative application of HIFU combined with drug treatment should be considered to maximize the reduction of fibroids, improve symptoms such as anemia and dysmenorrhea, reduce the time required for hysteroscopic surgery, and improve the safety of surgery.

Keywords: high intensity focused ultrasound, hysteroscopic myomectomy, mifepristone, submucous myoma of uterus, uterine fibroid

Introduction

Uterine fibroids are the most common benign tumors in women, and submucous myoma is a uterine fibroid that protrudes into the uterine cavity. Submucous myoma accounts for about 5.5% to 10% of the total disease group, and the age of onset tends to be younger.[1–3] The symptomatic women show increased menstrual flow, prolonged menstrual periods, abdominal pain during menstruation, purulent leukorrhea, secondary anemia, infertility or miscarriage.[1,4] The International Federation of Obstetrics and Gynecology classified uterine submucosal myoma into 3 subtypes based on the proportion of the lesion in the myometrium in 2011; a pedunculated submucosal myoma is type 0, a non-pedunculated submucosal myoma that extends ≤50% into the myometrium is type 1, a non-pedunculated submucosal myoma that extends › 50% into the myometrium is type 2, and Intramural myomas located near the uterine cavity and with the outer edge of the fibroid at a distance of ≧5mm from the uterine serosal layer are classified as type 3.[5,6]

Hysteroscopic myomectomy (HM) is the treatment of choice for patients with symptomatic or fertile submucosal myoma. As the size of the myoma increases, surgical treatment alone is accompanied by an increased risk of common hysteroscopic procedures such as uterine perforation.[7] Therefore, some researchers have used drugs such as mifepristone

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or gonadotropin releasing hormone analogue (GnRH-a) to reduce the size of the myoma prior to hysteroscopic surgery, but most leiomyomas' volumes return to their original size quickly after the drug is discontinued.[8] High-intensity focused ultrasound (HIFU) is a non-invasive treatment for uterine fibroids. So far, there has been no universal protocol for how to pre-treat type 2 submucosal myoma with a diameter greater than 4 cm preoperatively for HM. Most of the pretreatment regimens reported in the studies are single use of GnRH-a as a representative of drug treatment or HIFU treatment.[9,10] Preoperative HM pretreatment via HIFU combined with medication has not appeared in previous reports. In this report, we share a successful case of HM preoperative application of HIFU combined with drug pretreatment in the treatment of submucosal myoma larger than 4cm in diameter. In the meantime, we conducted a systematic review of the literature to better understand the modalities and outcomes of pre-treatment of type 2 submucosal myoma before hysteroscopic myomectomy.

Case Report

An unpregnant woman in her early thirties went to the gynecological clinic for treatment because of her heavy menstrual volume, prolonged menstrual period, secondary anemia and other symptoms that lasted for a year. The patient's initial menstrual cycle was 28 to 30 days, and the menstrual period was 5 to 7 days, with symptoms of dysmenorrhea. So far, the longest menstrual period is 15 days. The patient herself told us that the results of a transvaginal ultrasound performed 4 years ago indicated a submucosal myoma of approximately 20×20 × 30 mm.The patient had no other medical history and had not been taking specific medications for the past year. Prior to visiting our hospital's clinic, the patient's last ultrasound was performed in February 2023, and she self-reported that her ultrasound diagnosis at that time was also suggestive of uterine submucous myoma of unknown size. The menstrual volume of her last menstrual period was on the heavy side and could saturate 8 daily sanitary napkins per day. On the seventh day of the patient's menstrual cycle, there was no tendency for the menstrual flow to decrease, as well as the patient presented with an anemic countenance, pale paw nails, fatigue, and an unsteady gait, at which time her hemoglobin was 60 g/L (reference range, 115–150 g/L).

After admission to the hospital, the patient was placed on an intravenous drip of 6U of suspended red blood cells. In order to understand the characteristics of the abnormal intrauterine mass, the physician performed enhanced contrast pelvic magnetic resonance imaging (MRI) on the patient before the treatment was carried out, the results showed multiple nodules and mass shadows within the myometrium and submucosa, showing T1W1 low signal and T2W2 high signal, some of the nodules showing clumping changes along with unclear margins, and some of the lesions protruding into the uterine cavity, of which the transverse extent of the largest nodule was about 42×41mm in size, with obvious inhomogeneous enhancement after enhancement (Figure 1A–D). The mass was thought to be a type 2 submucosal myoma. Based on the MRI images, the adenomyosis foci were small, and the submucosal myoma was the main factor causing the patient's menstrual and anemia symptoms. After thorough communication with the patient about several treatment options, she wanted to undergo fertility preservation treatment, and because of the large diameter of type 2 submucosal leiomyoma, she finally chose HIFU combined with drug therapy as the preoperative pretreatment for HM.

Treated with blood transfusion, the patient's rechecked hemoglobin was 89 g/L. Prior to HIFU treatment, the patient underwent a rigorous bowel preparation, including the intake of fluid for 3 days and a 12-hour fast preceding treatment. The patient was treated with HIFU under sedation and analgesia on March 23, 2023, with a ratio of 1:3 for the frequency of the treatment (1 second for the delivered energy and 3 seconds for the rest of the day), a duration of 148 minutes, an irradiation time of 896 seconds, an average power of 400 watts, an intensity of 363 seconds/hour, and a therapeutic dose of 358,000 joules. The whole procedure went smoothly and the patient did not experience any uncomfortable symptoms after the operation, such as swelling and pain in the lumbosacral region, abdominal injury or abnormal sensation in both lower limbs. Following two hours of HIFU treatment, the patient resumed normal life. Because type 2 submucosal myoma can appear uterine cavity effusion after ablation, and vaginal fluid may flow for a long time, so the patient took antibiotics orally for 7 days for preventive treatment. The patient's liver and kidney functions were rechecked on the second postoperative day and showed no abnormalities. On the fourth day after HIFU treatment, she was discharged from the hospital.

Previous reports noted that the effects of mifepristone and GnRH-a were comparable, and the patient expressed agreement to the choice of mifepristone for pharmacologic treatment by considering it in conjunction with the economic

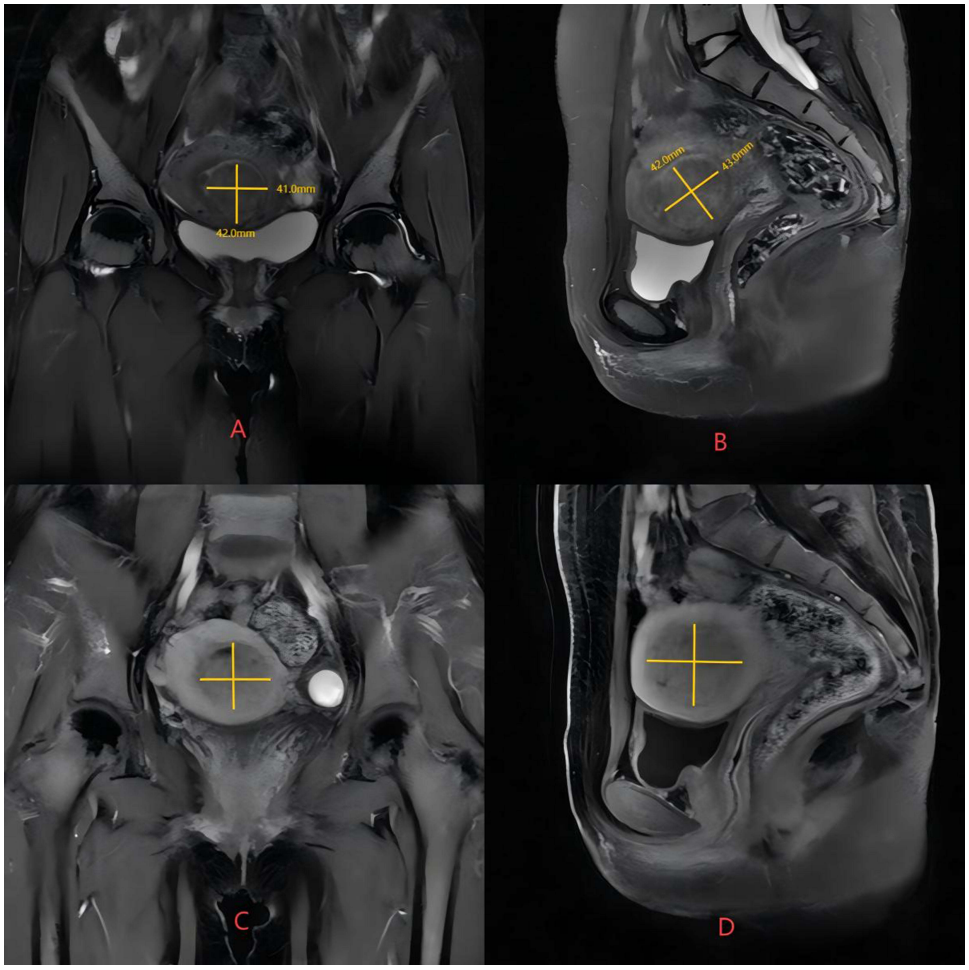

Figure 1 Magnetic resonance imaging of the largest myoma in the uterine cavity before HIFU treatment (**A** and **B**). Magnetic resonance imaging of the largest myoma in the uterine cavity after contrast enhancement (**C** and **D**).
Abbreviation: HIFU, high-intensity focused ultrasound.

cost. The patient was discharged from the hospital and started on oral mifepristone with a dosing regimen of 10 mg once daily for 3 months. To understand the condition of the lesions after HIFU, we performed enhanced contrast pelvic magnetic resonance imaging on the patient again on April 6, 2023, and the results showed multiple irregular nodular and mass shadows within the myometrium and submucosa, exhibiting isometric T1 and isometric T2 signals. Some of them appeared to be wart-like and nodular, protruding toward the uterine cavity, and the size of the transverse extent of the larger ones was about 36cm×37mm, and the lesions were partially non-enhanced after enhancement, and the irregular solid components of the margins appeared to be inhomogeneously enhanced (Figure 2A–F). During mifepristone administration, the patient underwent a total of three transvaginal ultrasound scans, and all three imaging results were suggestive of an inhomogeneous, strongly echogenic mass detected in the uterus. The size of the echogenic mass from the first scan was 43×22×26 mm, the second was 41×19×23 mm, and the third was 41×28 × 18 mm, and the echogenic mass was characterized by an irregular morphology and protruded mostly into the uterine cavity. Through the images we found that the patient's submucosal myoma gradually changed from type 2 to type 0 (Figure 3A–E).

The patient was readmitted to the hospital for hysteroscopy on July 5, 2023, and the blood sampling results after admission did not reveal any particular abnormality. Before HM, we used Carboprost Methyl Pessary to soften her cervix. During the surgery, we saw a nodule that looks like a myoma, about 40×30× 20 mm in size connected to the anterior wall of the uterine cavity, with a root tip of about 15 mm wide, and another nodule of about 10 × 10×10 mm in

Figure 2 Magnetic resonance imaging of uterus after HIFU treatment (**A,C** and **E**). Uterine magnetic resonance imaging after contrast enhancement (**B,D** and **F**). The picture shows that uterine myoma is located in the cervical canal.

size on the right wall of the uterine cavity protruding into the uterine cavity. We considered the submucosal myoma to have become type 0, so we performed a hysteroscopic submucosal myomectomy and the excised tissue was placed in a collection bag for postoperative histopathologic analysis. The total duration of the procedure was 35 minutes, the estimated blood loss was 2 mL, the total volume of the swelling medium used was approximately 1000 mL of 0.9% saline, and the patient showed no signs of water intoxication. Pathological examination revealed that the nodules seen during the operation were consistent with stroke leiomyoma, and the immunohistochemical results of tumor cells were Ki-67 (+, about 4%), ER (+), CD34 (-), SMA (+), demsin (+), CD10 (-) (Figure 4A–D).

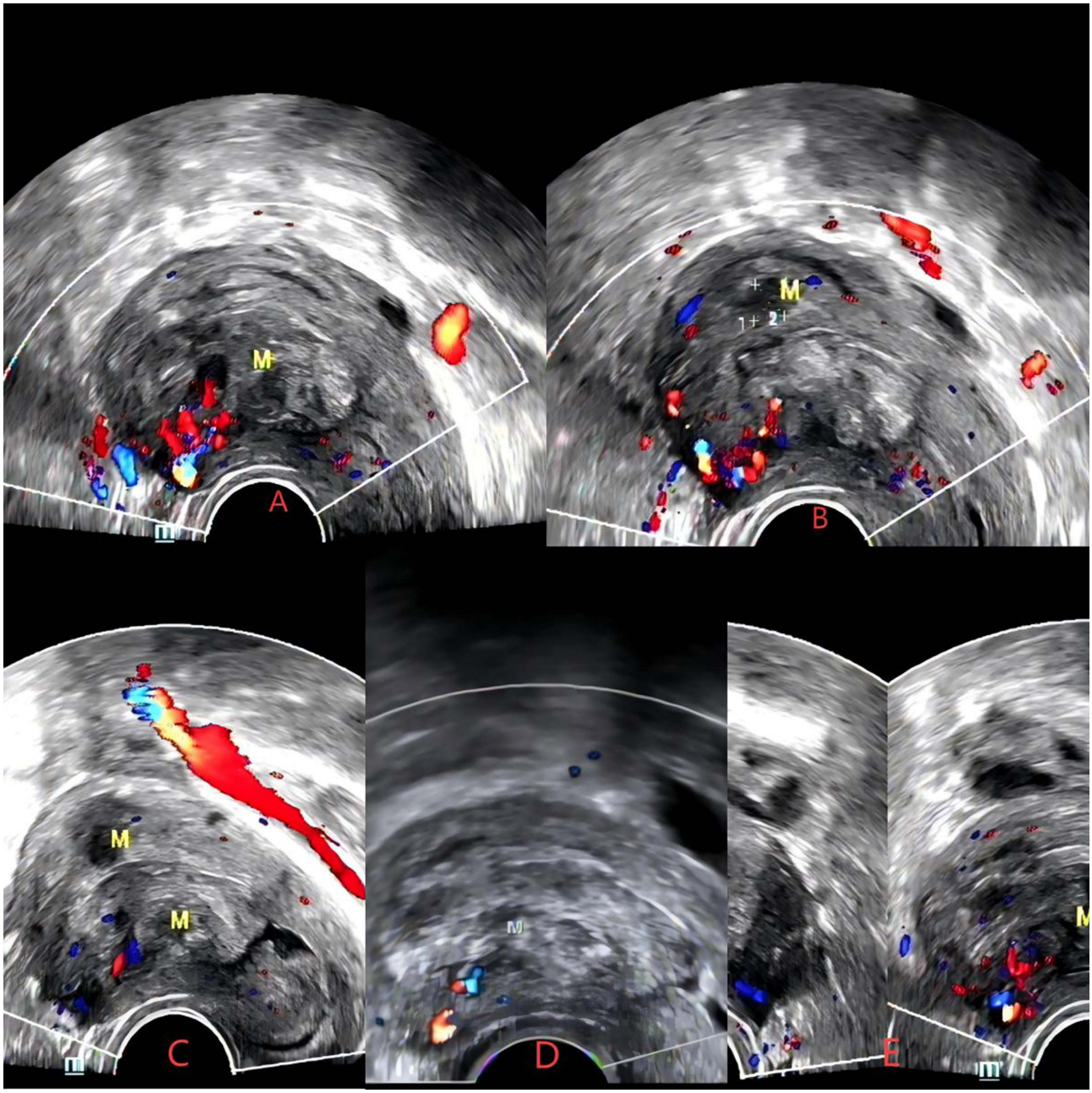

Figure 3 Ultrasound scan results of the uterus after one month of mifepristone treatment (**A** and **B**). The ultrasound scan results of the uterus after two months of mifepristone treatment (**C, E**). Ultrasound scan results of the uterus after three months of mifepristone treatment (**D**). The "M" in the Figure 3 represents a leiomyoma. According to the ultrasound results, the majority of the patient's submucosal myoma was located in the uterine cavity, and it was considered to be converted to type 0.

Considering that the patient's uterine focus were completely removed, we recommended regular follow-up and reexamination of the patient. During telephone and outpatient follow-up, the patient informed that the symptoms of heavy menstrual flow and prolonged menstrual period had disappeared. The patient underwent transvaginal ultrasound examinations at the 1st, 3rd, and 6th months after surgery, and the results showed that there was no residual submucosal myoma (Figure 5). The patient expressed satisfaction with the results of this treatment and had no recurrence during the follow- up period.

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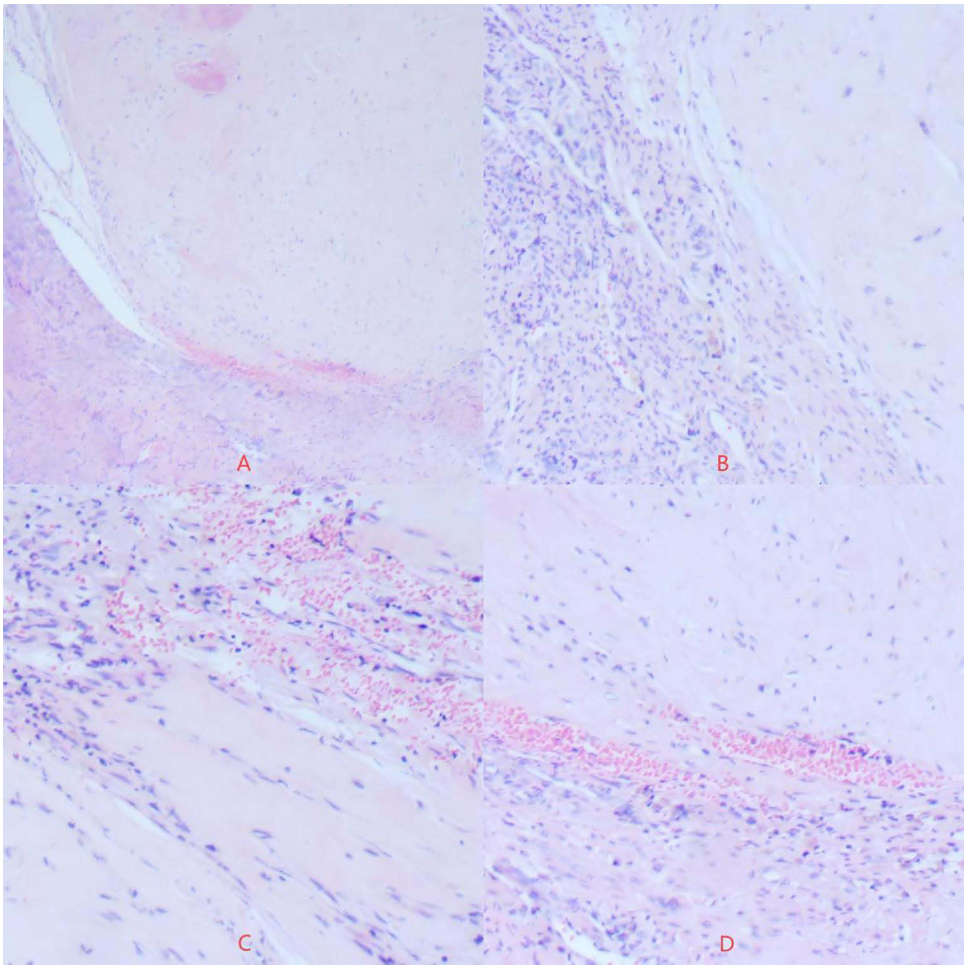

Figure 4 (**A**–**D**) Submucosal myoma removed in the uterine cavity during hysteroscopy. Immunohistochemical staining showed that Ki-67, er, SMA and demsin were positive, while CD34 and CD10 were negative.

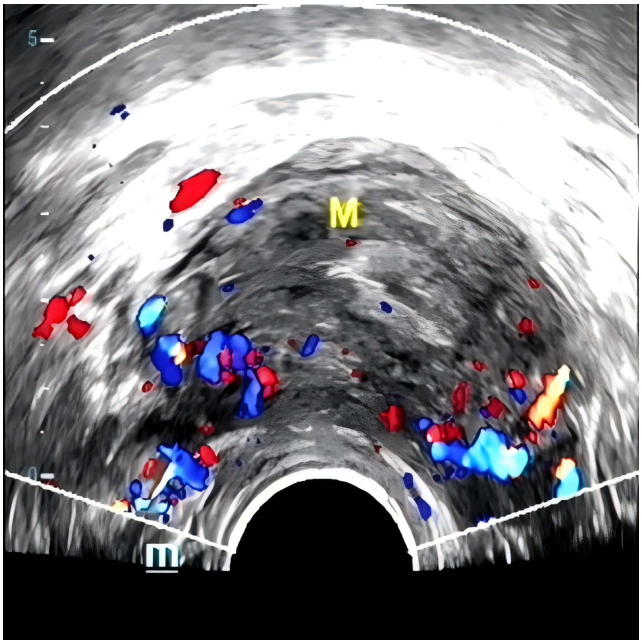

Figure 5 Two months after the completion of all treatments, the patient's ultrasound results showed complete removal of submucosal myoma. The "M" in the Figure 5 represents a leiomyoma.

Discussion

Submucosal myoma is a steroid hormone-dependent tumor and its prevalence is as high as 70–80% in women at the age of 50 years.[1] Epidemiological studies have found a trend towards a younger patient population, and the annual global cost exceeds that of diseases such as breast and ovarian cancer.[2,3] Submucosal fibroids are suspected clinically for abnormal uterine bleeding or colicky dysmenorrhea, and the diagnosis is usually supported by ultrasonography and MRI. Depending on the type of submucosal myoma and the severity of symptoms, the choice of treatment options varies. Hysteroscopic myomectomy is the first line of minimally invasive conservative treatment for submucosal myoma, especially for women who still have reproductive requirements. In comparison to laparoscopic surgery, young patients undergoing hysteroscopic surgery have better fertility and outcome as well as faster recovery of ovarian function postoperatively.[11] Nevertheless, hysteroscopic surgery has certain limitations, and the risk of intraoperative complications such as water intoxication, uterine perforation, and hemorrhage increases with the duration of the procedure and the amount of distended fluid.[12] A foreign retrospective study with a case number of 1244 cases showed that 100% of type 0 myoma, 88.59% of type 1 myoma, and 82.55% of type 2 myoma could be completed by hysteroscopic surgery in one operation, while type 2 myoma with a diameter larger than 3.0 cm had a high risk of secondary or multiple operations.[13] Compared with type 0, type 1 or type 2 submucosal myoma that is oversized or has an abundant blood supply to thmyoma may require multiple surgeries, and it also increases the risk of uterine perforation, endothelial injury, uterine adhesions, and excessive fluid resorption, especially for type 2 submucosal myomas with a diameter greater than 4 cm.[14,15]

For type 2 submucosal myoma with large diameter, researchers are exploring how to reduce the occurrence of secondary surgery. Therefore, some researchers choosed to use drugs such as mifepristone or gonadotropin releasing hormone analogue (GnRH-a) to reduce the size of leiomyoma and improve the symptoms of anemia to reduce the difficulty of surgery and complications before HM.[16–19] Drug therapy is divided into two categories, those that only improve the symptoms of menorrhagia, such as hormonal contraceptives, tranexamic acid, and non-steroidal anti-inflammatory drugs, and those that improve symptoms as well as reduce the size of leiomyoma, such as GnRH- a and progesterone inhibitors. Although Friedman AJ and Murphy reported respectively that GnRH-a and mifepristone could shrink the fibroids as soon as possible, and even the fibroid volume could be reduced by 50% to 77%, but they could not eradicate the fibroid, meanwhile, the fibroid volume started to increase again after stopping the drug.[20] Drug-only pretreatment has the risk of interfering with the human endocrine system, and prolonged application produces perimenopausal symptoms such as hot flashes, night sweats, and palpitations, and after discontinuing the drug, most of the leiomyomas' volumes return to their original size within 6 months.Meanwhile, it was reported that the use of GnRH-a before hysteroscopy had no advantage in terms of operative time, fluid absorption and complications.[7,20–23]

In recent years, innovative alternatives have emerged for the treatment of uterine fibroids. S G Vitale employed hysteroscopic laser ablation to treat 20 patients with type 0, 1, or 2 uterine fibroids, each less than 7 cm in diameter.[24] Results indicated a significant reduction in the volume of uterine fibroids during a 2-month follow-up after surgery (51.6 ± 22.5 mm3 vs 33.4 ± 17.1 mm3; $p<0.001$), with a decrease in reported severe menstrual bleeding symptoms from 18/20 (90%) to 2/18 (10%; $p<0.01$). HIFU treatment has gradually appeared in the sights of researchers. HIFU is a non-invasive treatment for uterine fibroids.[25–27] Guided by ultrasound, it rapidly warms the tissue to 60–100 degrees Celsius by creating a focal point of high energy density in the target area, which results in coagulative necrosis and reduces the size of the fibroids to achieve symptomatic relief of uterine fibroids. Research results have shown that this technique is effective and safe in the treatment of uterine fibroids.[28–31] So far, there has been no universal protocol for how to pretreat type 2 submucosal myoma with a diameter greater than 4 cm preoperatively for HM. Most of the pretreatment regimens reported in the studies are single use of GnRH-a as a representative of drug treatment or HIFU treatment. The gynecology team of the Affiliated Hospital of Sichuan North Medical College collected 12 cases of HIFU combined with hysteroscopy for the treatment of type 2 submucosal myoma with a diameter of ›4 cm, and the patients' maximum diameter of the myoma averaged 55.08±9.93 mm. They found that three cases converted to type 0 and six to type 1 after HIFU treatment, concluding that HIFU can be a better pretreatment for larger type 2 submucosal myoma.[32] Da-Cheng Qu evaluated the feasibility of preoperative HIFU for the treatment of type 2 submucosal myoma with a diameter greater than 4 cm in HM, and his study found that the mean volume of uterine body and myoma was significantly reduced after

preoperative HIFU treatment for HM, and the mean contraction rate of myoma was 67.6±17.0%. He affirmed the effectiveness of HIFU as a pretreatment before HM.[17] Simple HIFU treatment does not immediately improve symptoms such as anemia and heavy menstrual flow. According to some researchers, for submucosal myoma, pre-treatment with representative drugs such as GnRH-a and mifepristone before hysteroscopy could reduce the size of the myoma, decrease intraoperative bleeding, shorten the operation time as well as reduce the difficulty of the operation.[7,16–18] In the meantime, it is well known that mifepristone has the ability to quickly achieve hemostasis, increase hemoglobin levels, and reduce the size of the leiomyoma. Liao Ping's study on applying GnRH-a pretreatment for type 2 submucosal myoma with large diameter showed that drug combined with hysteroscopy is efficacious in treating the type 2 submucosal myoma with a diameter greater than 4 cm[16] (Table 1). However, in earlier randomized controlled trials, the results showed no significant benefits of using GnRH analogs prior to hysteroscopic resection surgery.[33] In theory, GnRH-a pretreatment can make surgery, the reducing the size of fibroids and blood vessel formation. The longer the duration of surgery, the higher the surgical risk. Studies have found that the duration of surgery is related to the amount of fluid. Researchers have found that preoperative administration of GnRH-a is helpful in reducing fluid absorption during surgery,[34,35] and the additional advantage of preoperative treatment is the correction of anemia and the possibility of surgery at any time, as the patient is in a state of amenorrhea with significant tissue benefits.[36] Nonetheless, both of the preoperative HM pre-treatments have problems related to the embedded cervix of themyoma, secondary surgery, and long operative time.[37]

In our report, the patient's pre-HIFU pelvic cavity MRI image showed a 42×41 mm type 2 submucosal myoma in the myometrium, and the patient also had symptoms of secondary anemia. Because of the patient's fertility requirements, the large size of the submucosal myoma, the ultrasound suggesting the presence of adenomyosis, the low preoperative hemoglobin, and the concern about the risk of a second surgery, she decided to opt for the treatment plan of hysteroscopic surgery combined with preoperative preconditioning after a thorough discussion with the patient. The patient is a woman who has not yet become pregnant, and preserving her fertility to the greatest extent is a critical consideration. Postoperative uterine adhesions are closely linked to female fertility following hysteroscopy. We observed that the incidence of postoperative uterine adhesions was relatively low (9.3%) in women who underwent any form of uterine fibroid resection, such as hysteroscopy or laparoscopy, and did not vary with different surgical methods. The majority of postoperative uterine adhesions were minimal, with submucosal fibrosis identified as a risk factor for these adhesions.[38,39] However, there is currently a lack of research data on the impact of HIFU and medication combined with hysteroscopy on the incidence of uterine adhesions, warranting further analysis. Postoperative uterine myometrial healing is also crucial for preserving the reproductive function of the uterus. We already know that neurotransmitters and nerve fibers exist within the pseudocapsule of myomas, which can promote cell activation and induce muscle regeneration. During the treatment process, it is crucial to preserve as much of the pseudocapsule of myomas as possible.[40] In Da-Cheng Qu's study, they observed that the contraction of the uterine myometrium after HIFU treatment was able to repel the necrotic components, thus allowing the myoma to move into the uterine cavity, proving that HIFU could promote the transformation of type 2 submucosal myoma into type 0, type 1, and even self-discharge. Researchers compared the efficacy and safety of HIFU and GnRH-a in hysteroscopic myomectomy by including 42 cases of HIFU group and 37 cases of GnRH-a group, and after three months of pretreatment in both groups they found that the average operation time and intraoperative bleeding in the HIFU group was significantly lower than that in the GnRH-a group. They suggested that this may be correlated with the fact that after HIFU treatment, necrotic tissue was discharged and the boundary between the myoma and the myometrium was more pronounced, and that the myoma symptom scores and hemoglobin levels were improved in both groups,[16,17] but the overall effective rate of the preconditioned patients was higher in the

Table 1 Research on HIFU as Preprocessing

Author	Published Years	Number of Cases	Interventions
Ping Liao	2021	79	42 patients were treated with HIFU, and 37 patients were treated with GnRH-a.
Da-Cheng Qu	2019	5	5 patients with type 2 submucosal myoma undergoing HIFU treatment

HIFU group. Previous studies have repeatedly demonstrated the superiority of HIFU over GnRH-a as a pretreatment method prior to HM. Yet, some reports concluded that GnRH-a combined with HIFU pretreatment improved the efficacy of heterogeneous high-signal myoma compared to HIFU alone.[41] Thus, we chose this treatment plan for the patient, and the treatment sequence was also determined. The patient did not complain of skin damage in the treated area during treatment, and she reported mild pain in the treated area after treatment, which was less than a pain score of 3. Pelvic MRI images after HIFU treatment suggested a reduction in the size of the myoma (Figure 2).

On completion of HIFU treatment, the patient needed to be given time for drainage of necrotic tissue, with a time interval of three months from HM. The patient's intraoperative ultrasound guidance during the HIFU procedure showed more blood flow signals in the vicinity of the mass, as well as the postoperative requirement that the patient needed to be on strict contraception. Physicians considered to reduce uterine arterial blood flow by reducing the number of progesterone receptors in the fibroid tissues by mifepristone and affecting the expression of epidermal growth factor receptor and vascular endothelial growth factor in the fibroid tissues in the 3 months after the operation to enhance the therapeutic effect, and to inhibit the patient's ovulation at the same time. Mifepristone is a potent progesterone receptor antagonist, and it has been studied that sustained low-dose administration of mifepristone could result in a significant reduction in the size of uterine fibroids.[19] Reinsch et al compared the effects of GnRHa and mifepristone in the treatment of uterine fibroids and found that mifepristone treatment for three months was comparable to GnRH-a treatment for six months and had no significant side effects due to hypoestrogenism.[42] Murphy reported no significant reduction in uterine and fibroid volume with mifepristone at a dose of 5 mg.[43] On the basis of the best therapeutic effect and the lowest side effect of the drug, we found that oral mifepristone 10 mg per day was a more ideal therapeutic dose.[44,45] During the patient's medication period, we observed the patient's monthly ultrasonography and blood draw results, which showed that the patient's myoma gradually changed from type 2 to type 0, although the size of the myoma did not appear to be significantly reduced, and the patient's hemoglobin steadily increased throughout the treatment period.

The patient underwent a 105-day preoperative pretreatment phase and was readmitted to the hospital to complete removal of the submucous myoma. To minimize surgical complications, a preoperative transvaginal ultrasound was performed to assess the characteristics of the leiomyoma, which showed a type 0 submucosal myoma. No anemia was suggested by the routine blood count after admission. The surgeon completely removed the patient's submucous myoma a single hysteroscopic procedure, strictly following the standard technique of HM. The total operative time in our case was 35 minutes, which is significantly less than the average international operative time.[46,47] The shortened duration of the operation demonstrated the significance of preoperative preconditioning. In addition, we performed intraoperative ultrasound guidance to avoid complications such as uterine perforation. To adequately expose the uterine cavity, we chose 0.9% saline to control the intrauterine pressure below 100 mmHg. For women of reproductive age, fluid overload could lead to complications such as heart failure, pulmonary edema, and gas embolism.[12] In our case, the amount of fluid used throughout the procedure was approximately 1000 mL and the patient showed no signs of water intoxication.

Conclusion

When doctors are clinically confronted with type 2 submucosal myoma with a diameter greater than 4cm, they should consider applying HIFU combined with drug therapy before HM. This new treatment can minimize the size of the myoma, improve symptoms such as anemia and dysmenorrhea, reduce the time needed for hysteroscopic surgery, and improve surgical safety.

Data Sharing Statement

All data generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

The patient signed and provided written informed consent, gave consent for the publication of photograph(s) and case history and other details within the text to be published in journals used for scientific purposes.

Consent to Participate

The report of this study adheres to the CARE guidelines.[48] The Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine approved the case report and provided a written informed consent form for publication.

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Disclosure

Junjie Li is now affiliated with Traditional Chinese Medicine Department, Hunan University of Medicine General Hospital, Hunan, Huaihua, 418000, People's Republic of China. All authors declare that there is no conflict of interest in this study.

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