

Adenomyosis - Is a new treatment solution available?

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Adenomyosis is increasingly common up to 20% to 30% of reproductive-aged women who present with menorrhagia, dysmenorrhoea, infertility, and related pregnancy complications. It is often diagnosed by the clinical symptoms and ultrasound examinations. MRI, if available, will give a more detailed confirmation of adenomyosis. There are many medical treatments available for adenomyosis, e.g., oral contraceptives, LNG-IUS, GnRH-a, and progestin, while surgery is often either conservative adenomyomectomy or hysterectomy. All these treatments either impact on the fertility of these patients or not readily accepted by them because of the invasiveness of the surgery and side effects of medication. High Intensity Focused Ultrasound (HIFU) ablation treatment discussed in the paper offers an alternative non-invasive treatment for adenomyosis. The early results of HIFU ablation are satisfactory and well accepted by patients. However, long term follows up, with a combination of medical treatments after HIFU ablation, may offer a new treatment solution for adenomyosis.

Keywords

Adenomyosis; HIFU; Medical treatment; Adenomyomectomy

Adenomyosis occurs most often in women between the reproductive ages of 30 and 45, with an incidence of about 20% to 30% of all women. However, it can vary according to the particular population. In recent years, there appears to have a significant increase in the incidence with a younger age onset. The pathogenesis of adenomyosis is due to the invasion or presence of endometrial glands in the uterine myometrium accompanied by hyperplasia and hypertrophy of the surrounding muscle cells, forming either a diffuse or localized lesion. It can lead to dysmenorrhoea, heavy menstrual bleeding, infertility, and obstetric complications [1].

Ultrasound and Magnetic Resonance Imaging (MRI) are commonly used to diagnose adenomyosis nowadays. MRI gives a very good resolution of tissue layers, and it is non-technical dependence [2]. However, it is not widely available or affordable. The ultrasound scan can provide a cost-effective approach to diagnose adenomyosis. Therefore a pelvic ultrasound scan is still commonly used for the diagnosis of adenomyosis.

Good symptomatic treatment is often necessary because

firstly, adenomyosis involves younger aged patients whose parents always concern about their health. Secondly, some patients may have fertility demands, which both surgery and hormonal treatment could adversely impact on their reproductive outcome. Thirdly, the result of medical or surgical treatment is not reassured with patients' satisfaction. Surgical complications and side effects of long term medications are also unwelcomed by patients.

Regarding the treatment of adenomyosis, at present, there is no international guideline for surgical or medical treatment of adenomyosis. As adenomyosis, if mainly suffered by women in the reproductive age group, there is a growing consensus that effective long term management plan is needed either for symptomatic relief or fertility improvement. Medical treatment with progestin, gonadotropin-releasing hormone agonists (GnRHa), nonsteroidal anti-inflammatory drugs (NSAIDs), levonorgestrel intrauterine system (LNG-IUS), and combined oral contraceptives can be used as first-line therapy for a short duration until there is a wish to conceive. Nonetheless, medical therapy is not without side-effects and often not preferred when fertility is of concern.

The treatment of adenomyosis depends on the symptoms, severity, and fertility desire. Conventionally the indications of surgery for adenomyosis should include (a) dysmenorrhoea and hypermenorrhoea that failed to control with medication; (b) intolerable or contraindications to long-term medication. For older patients who do not have fertility requirements, they can choose a total hysterectomy; for younger patients who desire to preserve fertility or the uterus, they can select conservative surgery, that is, fertility-sparing operations. Conservative surgery for adenomyosis was first reported in 1952. The purpose of the conservative surgery is to remove the lesion, preserve the uterus, and fertility. Conservative surgery for adenomyosis is divided into (a) adenomyomectomy for focal adenomyosis, (b) cytoreductive surgery for diffuse adenomyosis, and (c) endometrial ablation or resection. However, conservative surgery for adenomyosis is difficult to perform and may not achieve a good result. Although conservative surgery is effective in relieving symptoms; however, the recurrence of symptoms after surgery is due to the

presence of residual adenomyosis lesion, because it is difficult to remove completely. The uterine wound healing is also poor compared to myomectomy. Therefore the risk of uterine rupture (6.0%) in pregnancy [3] after conservative adenomyosis surgery is much higher than that for uterine fibroid removal (about 0.26%) [4]. Although hysterectomy is still the ultimate treatment for women with severe symptoms, conservative surgical options should be offered for women who wish to maintain fertility.

High intensity focused ultrasound (HIFU) ablation treatment

At present, surgery has evolved from open to minimally invasive surgery. Tomorrow we may be shifting from minimally invasive surgery to non-invasive focused ultrasound surgery. The "focused ultrasound surgery (FUS)" is the application of an ultrasound-guided or MRI guided High Intensity Focused Ultrasound (HIFU) ablation system which has been used to treat liver cancer, pancreatic cancer, bone tumors, soft tissue tumors and benign uterine diseases [5–8]. The principle of HIFU treatment is to focus the ultrasound energy within the body after safely penetrating the body tissue. The main therapeutic mechanisms of HIFU include thermal, cavitation, and mechanical effects. As a non-invasive treatment, the HIFU ablation produces a temperature above 60-90 °C at the focused target tissue within a very short time, and it results in coagulation necrosis at the target tissue without inflicting injury to the surrounding tissues. The necrotic tissue is gradually absorbed or becomes a fibrotic scar. The operation procedure is the same as that of HIFU ablation to uterine fibroids. The patient lies prone on the HIFU system for treatment. Under sedation and analgesia and real-time image monitoring, the focused ultrasound energy will ablate either the diffuse adenomyosis on which both or either front and back uterine walls need to be ablated; or the focal adenomyosis, where only the focal lesions are ablated.

Because the pathology of adenomyosis is completely different from that of fibroids, and the boundary is unclear, that is, there is no pseudo-capsular interface, the ultrasound energy deposition and diffusion are different and more difficult, and the required treatment dose is significantly increased by about 20 to 30% compared to a fibroid of the same size. At the same time, the apparent grayscale change appears later than that of fibroids. Technically the dose distribution has to be uniform when the grayscale change does not appear. The average energy power is preferably at 400 W. Because the adenomyosis has no pseudocapsule, the energy diffusion is easy to spread. It is then necessary to keep a safe distance from the uterine serosa (at least about 1-1.5 cm) during the ablation procedure, to avoid heat from reaching and breaking through the serosa and causing damage to surrounding tissues and organs, such as bladder and intestinal injury. For patients who wish to preserve reproductive functions, the HIFU procedure should take cautions to avoid damage to the endometrium, particularly for those who wish to have children.

During the HIFU ablation, maintain a safe distance of at least 1.5 cm between the target focal point and the endometrium. The whole procedure of HIFU ablation will take about 1-2 hours, and patients can get out of the HIFU table and leave.

The primary purpose of HIFU ablation treatment is to ablate and reduce the sizes of lesions, control the growth, relieve dysmenorrhea, and improve clinical symptoms [9]. At present, the related researches on the efficacy of HIFU in the treatment of adenomyosis are mainly based on short-term efficacy. As early as 2008, Yoon SW *et al.* [10] reported a 47-year-old patient with adenomyoma treated with HIFU. At 12 months follow up, the patient had obvious improvement in her symptoms of dysmenorrhea and increased menstrual flow. The size of the patient's uterus decreased by 35% one year after treatment. Lee JS *et al.* 2015 [11] reported the follow-up results of 346 patients with symptomatic adenomyosis who were treated with HIFU ablation. The uterine volume reduction at 3, 6, and 12 months after HIFU treatment were 43.99%, 47.01%, and 53.98%, respectively, and the severity of their symptoms was reduced by 55.61%, 52.38%, and 57.98% respectively. Their quality of life improvement scores were 80.06%, 69.39%, and 85.07% by 3, 6, and 12 months, respectively. Therefore these findings suggest that HIFU treatment of adenomyosis can reduce the uterine volume and adenomyotic lesions in the short term (at 12 months follow up) and also effectively relieve the dysmenorrhea and heavy menstrual flow. Fan *et al.* followed up 224 patients out of 350 patients with symptomatic adenomyosis treated with HIFU for two years. The symptoms of dysmenorrhoea were relieved in 82.3%, and that of menorrhagia was 78.9% [12]. Zhang *et al.* further showed that patients with diffuse adenomyosis had significantly less relief of the dysmenorrhoea than focal adenomyosis after HIFU treatment [13]. The recurrence of dysmenorrhoea symptoms can be high because of the common diffuse distributions of adenomyosis in the uterine wall. Liu *et al.* followed 208 out of 230 patients after HIFU treatment for a median time of 40 months, 83.2% reported symptomatic relief of dysmenorrhoea. However, dysmenorrhoea recurred with varying severity in 45 patients 12 months after HIFU treatment [14]. Nevertheless with increasing experience of HIFU treatment, the efficacy of HIFU ablation for adenomyosis has significantly improved and has also been widely recognized in China. The combined therapy of GnRH-a or/and Mirena with HIFU treatment can further consolidate the curative effect and reduce the recurrence of adenomyosis [15, 16]. Now the recurrence rate was significantly reduced, therefore HIFU may now become a new treatment solution for adenomyosis.

Quite different from open or minimally invasive surgery, the advantages of HIFU treatment for adenomyosis include (a) HIFU treatment involves no wound, no bleeding, or radiation. The treatment is safe and reliable, allowing rapid recovery. (b) HIFU treatment can keep the integrity of the uterus. It also does not interfere with women's endocrine and reproductive functions [17, 18]. Although mild complica-

tions like skin burns, leg pain, vaginal discharge, or numbness of the lower limbs could be seen in up to 38% of the treated patients in some retrospective studies [11, 14], most of these adverse effects were mild. They subsided within two weeks without any treatment or conservative treatment. Bowel injury was a rare complication that could occur in 0.02% of patients with adenomyosis [19], and while other major adverse events that occurred in 0.2% of HIFU fibroid treatment may be possible [20], but not reported in HIFU for adenomyosis. (c) HIFU treatment only needs sedation and analgesia, and the patient can keep awake and communicate with the doctor throughout the HIFU procedure. This treatment also helps to reduce anesthesia-related complications. (d) HIFU ablation for adenomyosis can be performed as day surgery in an outpatient clinic, and patients can either be discharged home after treatment or stay overnight in hospitals. A clinic set up for HIFU treatment had been reported by the author [21]. (e) HIFU ablation may improve the environment of uterus and pelvis, and increase the chances of pregnancy [22].

Recent clinical experience showed that the chance of getting pregnant and improved obstetric outcomes were encouraging and higher after HIFU treatment, compared to spontaneous pregnancy without any treatment [23–25]. Zhou *et al.* reported a follow-up study of 68 HIFU treated adenomyosis patients, 54 conceived after ten months (range 1–31 months) post-HIFU, and 21 delivered healthy babies. There was no uterine rupture during pregnancy or delivery [25]. At this early stage, any analysis of the impact on pregnancy and fertility by the HIFU treatment is compounded by the fact that there is no agreed treatment protocol and definition of the extent and severity of adenomyosis. Even though early reports of pregnancies after HIFU interventions for adenomyosis appeared to be safe. It is too early to conclude the pregnancy outcomes soon after HIFU treatment.

HIFU ablation is, however, not suitable in some situations such as (a) Bowel adhesions found in the acoustic pathway, which will increase the risk of bowel injury [19, 26]. (b) The lesion of adenomyosis is too small, because adenomyoma is without a pseudocapsule, and the ablation heat may diffuse and spread to the uterine serosa or endometrium, causing damage to bowel, bladder or endometrium. Therefore if the lesion is too small, i.e., with the lesions in the uterine wall together measured less than 3 cm, HIFU ablation might not be applicable [19]. (c) Severe abdominal keloid scars which can affect ultrasound penetration and lead to skin or keloid burn [19, 26].

Although HIFU ablation for adenomyosis has been shown to relieve period pain, heavy periods and reduce the uterine size, it may not be possible to provide a cure for adenomyosis. Therefore the prevention and treatment of adenomyosis are important. The key issues are (a) to take measures to minimize endometrial trauma, e.g., reduce the number of unnecessary uterine curettages because they are one of the pathogenesis of adenomyosis. Hopefully, medical induced miscarriage can now replace of suction curettage for

termination of pregnancy, hysteroscopy +/- directed biopsy to replace D&C, etc. These alternatives will minimize the risk of endometrial damage; (b) early diagnosis of adenomyosis by imaging technology may offer an early medical treatment to control the progression of the adenomyosis, e.g., taking pills; (c) early treatment with HIFU ablation may reduce the sizes and symptoms of adenomyosis; (d) successful early pregnancy with or without HIFU treatment may help to halt the progression of adenomyosis because of the prolonged pregnancy, and lactation period; (e) finally, more research in the effectiveness and long term relief by combining adjuvant treatments to HIFU ablation may shed new direction in the future management of adenomyosis.

To summarise, present related researches on the efficacy of HIFU ablation for adenomyosis are mainly based on short-term efficacy. The results suggest that HIFU treatment of adenomyosis can reduce the uterine volume and adenomyotic lesions in the short term, and also effectively relieve the dysmenorrhea and heavy menstrual flow. Nevertheless, we know that HIFU is not yet a perfect tool in the treatment of adenomyosis because the long term result is not known. Based on the pathogenesis of adenomyosis, the preservation of endometrium by HIFU ablation will likely associate with increased recurrence. However, because HIFU is a non-invasive treatment, patients are more likely to accept it than the conventional medical and surgical treatments, which have undesirable side effects and complications. Despite early favorable treatment results, the recurrence rate is worth closely examined. A combination with drug treatment to control the symptoms appears to be preferable. For the HIFU treatment of adenomyosis, studies with large sample sizes, randomized controlled trials, and longer-term follow up are needed before applying it widely in clinical practice.

Author contributions

M Xue provided the information, and XG Zhu collected the data from the literature. F Wong wrote the manuscript. All authors contributed to editorial changes in the manuscript and read and approved the final manuscript.

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Conflict of interest

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