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Current Status of the Diagnosis and Treatment of Adenomyosis

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Abstract: Adenomyosis refers to the endometrial glands and mesenchyme that invade the myometrium through the basal layer, and under the action of hormones, repeated bleeding, myofibrous connective tissue hyperplasia formed by diffuse or limited lesions. It is a common disease in women of childbearing age and is more common in women over 40 years of age with menstruation. In recent years, the age of onset of the disease tends to be younger, which may be related to the various uterine surgical operations in clinical work, such as abortion, childbirth, curettage, chronic endometritis, and so on. The mechanism of the disease is currently thought to be due to the invasion of the basal endometrium into the myometrium for growth, but the ectopic endometrium is immature, has reactive changes to estrogen, and is insensitive to progesterone. Its main symptoms are increased menstrual flow, dysmenorrhea, and low fertility, which seriously affect the quality of life of patients. Among them, the incidence of excessive menstrual flow is 40%–50% and the incidence of dysmenorrhea is 15%–30%. There are numerous treatments available for adenomyosis aimed at reducing menstrual flow, relieving dysmenorrhea, and improving fertility. A brief review of the various treatments available for adenomyosis in the clinic is as follows.

Keywords: Adenomyosis; Dysmenorrhea; Treatment

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1. Uterine artery interventional embolization

Interventional procedures used to be one of the more popular treatments. The mechanism of action of uterine artery embolization (UAE) in the treatment of adenomyosis is to cause ischemia, hypoxia, and necrosis of the ectopic endometrial lesion by embolization of the uterine artery, which is then absorbed [1]. UAE is now recognized as an alternative to hysterectomy. A retrospective study showed that after uterine artery embolization for uterine adenomyosis, the patients' symptoms of dysmenorrhea and increased menstruation were significantly relieved after 2 years of follow-up, and that the recent therapeutic effect was better [5]. Considering the mechanism of action of this treatment, the disadvantages of this treatment modality were mapped out to be the high incidence of postoperative complications and postoperative recurrence. In actual clinical work, uterine artery embolization is currently applied to a few patients for the treatment of adenomyosis; it is considered only when other methods of treatment are ineffective or when the use of other methods is contraindicated. In patients

who require fertility preservation, UAE may have potential adverse effects on endometrial and ovarian function, so it is not recommended to be applied to patients with fertility requirements. It is also suggested in the 2018 expert consensus that the UAE should be used with caution in patients with symptomatic adenomyosis who have fertility requirements [6].

2. Levonorgestrel intrauterine extended-release system

Levonorgestrel-releasing intrauterine system (LNG-IUS) under the trade name of Mannitol, is now widely used in clinical practice. It is a T-type IUD containing a high-potency progestin, which is located in the longitudinal arm of the device and contains 52 mg of levonorgestrel-18-methyl norethindrone, which slowly releases approximately 20 μg of levonorgestrel per day. The recommended duration of use of the device is 5 years. Its mechanism of action is to relieve dysmenorrhea and reduce menstrual flow by down-regulating the levels of estrogen receptors in the endometrial tissue glands and interstitium, causing the endometrium to molt, inducing apoptosis of the endometrial glandular cells and interstitial cells, reducing the release of prostaglandins from the endometrium, and shrinking the foci of adenomyomatous disease. The principle of contraception of LNG-IUS is to interfere with the implantation of fertilized eggs by affecting the endometrium. LNG-IUS is a long-term conservative treatment for adenomatous menstruation. IUS is the preferred option for long-term conservative treatment of adenomyosis. The Levonorgestrel Intrauterine System (LNG-IUS) is specifically indicated for patients who are infertile and require uterine preservation. Since LNG-IUS has been used in clinical practice, several studies have shown that it can significantly improve the discomfort and quality of life of patients with adenomyosis. Currently, the treatment of LNG-IUS is mainly focused on the management of its side effects. The common side effects of the levonorgestrel intrauterine release system include irregular bleeding, menstrual changes, displacement, such as subluxation of the embedded birth control device, and others like lower abdominal discomfort, breast distension, lumbar pain, and so on. Clinically regarding its side effects, some patients can achieve or improve the therapeutic effect by combining LNG-IUS with other treatments. However, in the case of displacement after placement of the levonorgestrel intrauterine extended-release system, a study by Liu Diem et al. showed that the position of the device did not affect the metamorphosis of the endometrium by its progesterone and that even if the position was changed, there was still a significant effect on the symptoms of dysmenorrhea and menstrual cramps in patients with adenomyosis and the difference was not statistically significant [7]. It was also shown that despite the displacement of LNG-IUS, there were no cases of unwanted pregnancy. This study shows that LNG-IUS can significantly improve the symptoms of dysmenorrhea and increased menstrual flow in patients with adenomyosis and that the therapeutic effect of LNG-IUS has little relationship with its position, so patients with LNG-IUS displacement can be closely followed up without any special treatment for the time being. In addition to the displacement of LNG-IUS in the course of treating adenomyosis, detachment of the device can also occur, which is related to the large size of the uterine cavity and excessive menstrual flow [8]. Some studies have shown that the incidence of detachment is 17.5%–19.1% [9]. Several clinical trials have also investigated how to prevent menstrual dislodgement [10–11]. In the study, a combination of endometrial ablation in patients with a history of previous failed menstrual device placement resulted in a normal position of the menstrual device, with no further dislodgement events. Another study showed that pretreatment with gonadotropin-releasing hormone agonists before LNG-IUS in patients with adenomyosis with a large uterus combined with heavy menstrual flow reduced the rate of LNG-IUS detachment in patients with adenomyosis [12]. Several studies have clarified that levonorgestrel intrauterine system (IUS) is effective in improving symptoms of dysmenorrhea and heavy menstrual flow in patients with adenomyosis [10–11].

In addition, LNG-IUS can be used after conservative surgery for adenomyosis to reduce symptom recurrence and control disease progression [27].

3. Drug therapy

Medication is an important option for patients with adenomyosis who have fertility requirements. It relieves symptoms associated with adenomyosis, improves surgical outcomes, delays disease progression, and promotes fertility. Commonly used drugs include non-steroidal anti-inflammatory drugs, steroid hormones, GnRH-a, mifepristone, and so on. The effect of applying drugs for long-term treatment of adenomyosis needs to be further studied, and there is no curative drug [13].

3.1. Non-steroidal anti-inflammatory drugs

It is a class of anti-inflammatory, antipyretic, and analgesic drugs without glucocorticoids, and the mechanism of action is to reduce pain by inhibiting prostaglandin synthesis. Side effects of gastrointestinal reactions, and long-term application of peptic ulcer need to be vigilant. It is usually applied according to the patient's condition.

3.2 Steroid hormones

The ectopic endometrium in patients with adenomyosis is basal endometrium, which is immature endometrium, and this immature endometrium has reactive changes to estrogen but is unresponsive or insensitive to progesterone. Steroid hormones can reduce the level of estrogen and promote the ectopic endothelium and endometrial metamorphosis or atrophy, which can reduce the amount of menstruation, reduce the size of the uterus, and relieve dysmenorrhea. Steroid hormones mainly include two types of oral contraceptives and progestins alone. The first type of oral contraceptives can increase the risk of thrombosis, so a detailed medical history is needed before use, including liver function, blood lipids, and other related tests to rule out contraindications to the use of drugs. Patients without contraindications can be applied for a long time, while safe and effective, but they should be closely followed up during the use of drugs. The second category is progestin drugs. It includes norethindrone, medroxyprogesterone acetate, pregnenolone, dienogest, and so on. It can effectively relieve the degree of dysmenorrhea and reduce the symptoms of increased menstruation. However, progestins are not as effective in treating adenomyosis as endometriosis. This is related to the response of the ectopic endometrium to progestins. The side effects are mainly irregular vaginal bleeding, amenorrhea, and loss of libido. In addition, a new highly effective progestin drug has been introduced, which is denogestrel, which has high progestin activity, binds only to the progestin receptor, has no estrogenic, anti-estrogenic, or androgenic activity, and has a weak anti-gonadotropin effect. However, it can slightly inhibit ovulation and slightly reduce estrogen levels; it can also inhibit endometrial cell proliferation and reduce nerve growth factor and nerve fiber density. It has been widely used in patients with endometriosis, which is effective in relieving dysmenorrhea and pelvic pain and can be used long-term until menopause in about 67% of patients, thus avoiding hysterectomy [14–15]. Its most common side effects are irregular vaginal bleeding and hot flashes, but it is generally well tolerated. Some studies have shown that the pain relief effect of dienogest is similar to that of GnRH-a, and the incidence of hot flushes is low in patients with dienogest, and it has no significant effect on bone loss, but it is not as effective as GnRH-a in terms of menstrual flow reduction and uterine volume reduction [16]. The incidence of irregular vaginal bleeding is very high in patients with dienogest, so dienogest should be used cautiously in patients with uterine adenomyosis combined with excessive menstrual flow. Further studies are needed on the use of denogestrel in the treatment of adenomyosis.

3.3. GnRH-a

Its mechanism of action is to inhibit the secretion of luteinizing hormone and follicle-stimulating hormone by the pituitary gland by interfering with the hypothalamic-pituitary-ovarian axis, thus inhibiting the secretion of estrogen and progesterone by the ovaries, leading to the emergence of temporary amenorrhea. However, during the application, patients may experience adverse reactions such as hot flashes, sweating, and bone loss. To minimize the side effects, patients should be asked about their discomfort during treatment, blood estradiol levels should be monitored, and reverse additive therapy and calcium supplementation should be administered as appropriate. Currently, it is recommended that the duration of GnRH-a treatment is 6 months, and patients' informed consent is required for long-term use. It has been widely used in clinical practice that GnRH-a can effectively relieve dysmenorrhea caused by adenomyosis, reduce menstrual flow, and reduce the size of the uterus. However, in clinical practice, GnRH-a is often used in combination with other therapeutic methods for the long-term treatment of adenomyosis. For patients with adenomyosis close to the age of menopause, the drug can be applied alone to bring about early menopause.

4. Endometrial ablation

Endometrial ablation, which involves ablating the uterine lining through the radiofrequency action of mesh electrodes, is effective in treating excessive menstrual flow [26]. Excessive menstrual flow is present in about 40%–50% of patients with adenomyosis [4]. In patients with adenomyosis who have increased menstrual flow and possible LNG-IUS shedding, endometrial ablation in combination with LNG-IUS can be applied and has a satisfactory long-term outcome. However, several retrospective studies reported that although endometrial ablation alone can improve the symptoms of excessive menstrual flow in some patients with adenomyosis, the long-term efficacy and the improvement of the symptoms of dysmenorrhea are not obvious [17–18]. A study by Junyao Lou et al. showed that endometrial ablation combined with levonorgestrel intrauterine device (IUD) system did not have a statistically significant difference in the improvement of dysmenorrhea, but there was a statistically significant difference in the improvement of menstrual flow and the occurrence of sterilization dislodgement [10].

5. High-intensity focused ultrasound ablation

High-intensity focused ultrasound (HIFU) is a non-invasive thermal ablation technology. Its mechanism of action is through the energy ultrasound focused on the target cells, producing mechanical effects, high-temperature effects, and biochemical effects, so that the target area of the tissue coagulative necrosis, and necrosis of the tissue is gradually absorbed, to alleviate the symptoms of dysmenorrhea and increased menstrual flow. It is minimally invasive, low pain level, is safe, and has little effect on normal tissues around the lesion. HIFU treatment for adenomyosis is mainly for patients who require uterine preservation and refuse surgery. During the treatment, the physician can control the application of high-intensity focused ultrasound to ablate the ectopic lesions within the ultrasound field of view, to protect the normal tissues around the lesions from being destroyed, but it may not be able to completely and thoroughly clear the ectopic lesions, so there is still a chance of recurrence of the ectopic endometrium. Many studies also confirmed that high-energy focused ultrasound treatment of adenomyosis is reliable in relieving dysmenorrhea, reducing menstrual flow, and shrinking uterine volume [19–20]. Some studies also show that the combination of Treprostinil before HIFU is more effective and can significantly improve the quality of life of patients [19]. Therefore, its therapeutic effect has been generally recognized. However, this treatment also has disadvantages, the most important of which is that it is difficult

to exclude whether it is combined with malignant tumors. In addition, considering the other adverse effects of HIFU for adenomyosis, such as the occurrence of ablation-related skin burns, strict screening of patients and individualized protocols are required to reduce these adverse effects, so the clinical application of HIFU is limited [21].

6. Surgical treatment

6.1. Focal resection for adenomyosis

Conservative surgery for adenomyosis involves intraoperative removal of ectopic foci and preservation of uterine integrity to preserve fertility. However, there are risks of residual foci, susceptibility to recurrence, and inconsistent efficacy in the postoperative period. Lesion excision is divided into type I and type II surgeries. Type I surgery is for those who have formed focal adenomyomas, and the adenomyoma is removed to preserve the integrity of the uterus. Type II surgery is for those who have diffuse adenomyosis foci and undergo cytoreduction to preserve the reproductive function. The efficacy of this procedure in relieving dysmenorrhea, reducing menstrual flow, and reducing uterine size in patients with adenomyosis has been confirmed in several clinical studies. A clinical study reported that patients with adenomyosis were treated with ectopic lesion excision alone or lesion excision combined with levonorgestrel intrauterine slow-release system for 2 years, and the differences in dysmenorrhea scores and menstrual flow were statistically significant when the two groups were compared [22]. In addition, there were no shedding events of LNG-IUS in the combined treatment group and the combined treatment significantly delayed the time to recurrence. For patients with fertility requirements, Harada et al. also clarified that for pharmacological treatment of adenomyosis [23]. The 3-year postoperative clinical involvement of adenomyosis lesion excision with preservation of fertility was associated with a significant increase in the pregnancy rate and live birth rate. In addition, a study by Tan et al. showed that fertility-preserving surgery, such as adenomyectomy, is effective in improving pregnancy rates in infertile patients, and that it is more effective in focal lesions than in diffuse adenomyosis [24]. However, for the sole purpose of improving fertility, the infertility of patients with adenomyosis is due to a combination of factors, the most prominent of which is age, which means that the effect of age on fertility cannot be ignored. In addition to this, the possible complications of postoperative pregnancy, such as uterine rupture and placenta implantation, should also be taken into account. Therefore, the choice of treatment should be individualized to maximize the benefit of the patient in the clinical decision-making process.

6.2. Hysterectomy

However, in recent years, the treatment of adenomyosis has gradually evolved from hysterectomy to uterus preservation, but hysterectomy still occupies an irreplaceable position. For patients with no fertility requirements, a hysterectomy can be considered to remove the root cause of adenomyosis if the results are not obvious after treatment with a hysterectomy. This is because the uterus-preserving treatments carry a risk of recurrence. Hysterectomy is a surgical treatment that removes the lesion and the root cause of the disease to achieve a cure.

7. Other

In addition to the above treatments, the more common drug used in clinical work is mifepristone. As a progesterone receptor antagonist, mifepristone antagonizes progesterone by competing with it for the receptor. Domestic literature reports show that mifepristone can effectively relieve pain symptoms, and the efficacy is

dose-related, and the efficacy of pain relief is up to 90% [25]. However, there is a lack of large sample studies on the therapeutic effect of mifepristone in the treatment of adenomyosis, and the dosage selection and treatment course of mifepristone need to be determined by further research. In addition, abnormal expression of cyclooxygenase and aromatase has been found in ectopic adenomyosis foci, so whether inhibitors of this enzyme have a therapeutic effect on adenomyosis needs to be further confirmed [3]. However, the effectiveness of long-term drug therapy for adenomyosis needs further study [13].

8. Summary and prospect

Uterine adenomyosis is a common benign disease that affects women's lives and work. In clinical work, a clear diagnosis can be made based on the patient's typical clinical manifestations and signs, and auxiliary examinations. Although there are various clinical treatments for adenomyosis, each treatment has its advantages and disadvantages. With the improvement of people's living standards and awareness level, more and more patients choose to have uterus preservation treatment. For each patient, the provider should consider all factors together and provide the most appropriate treatment plan to maximize the benefits of clinical decision-making. In addition, it is hoped that soon a drug or a treatment modality based on uterine preservation can be discovered to improve the quality of life of patients with adenomyosis, based on the mechanism of development of adenomyosis.

Disclosure statement

The authors declare no conflict of interest.

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