

# Research Progress in Drug Treatment of Adenomyosis

Zhenyue Qin<sup>1,†</sup>, Zhiyong Dong<sup>2,†</sup>, Junling Liu<sup>2,†</sup>, Shoufeng Zhang<sup>1</sup>, Huihui Wang<sup>1</sup>, Mingyue Bao<sup>1</sup>, Weiwei Wei<sup>2</sup>, Ruxia Shi<sup>2</sup>, Jiming Chen<sup>2,\*</sup>, Bairong Xia<sup>3,\*</sup>

<sup>1</sup>Graduate School, Dalian Medical University, Dalian, PR China

<sup>2</sup>Department of Gynecology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, PR China

<sup>3</sup>Department of Gynecology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, PR China

## Email address:

cjming@126.com (Jiming Chen), xiabairong@ustc.edu.cn (Bairong Xia)

\*Corresponding author

† Zhenyue Qin, Zhiyong Dong and Junling Liu are co-first authors.

## To cite this article:

Zhenyue Qin, Zhiyong Dong, Junling Liu, Shoufeng Zhang, Huihui Wang, Mingyue Bao, Weiwei Wei, Ruxia Shi, Jiming Chen, Bairong Xia. Research Progress in Drug Treatment of Adenomyosis. *Journal of Gynecology and Obstetrics*. Vol. 10, No. 2, 2022, pp. 139-143. doi: 10.11648/j.jgo.20221002.22

Received: March 16, 2022; Accepted: April 6, 2022; Published: April 20, 2022

**Abstract:** *Background:* Adenomyosis is caused by endometrial glands and stroma invading the myometrium. It is more common in parturients after the age of 30. At present, there are many drugs for the treatment of adenomyosis, and drug treatment is also one of the important treatments for adenomyosis. *Objective:* To summarize the drugs that can be used for the treatment of adenomyosis, hoping to be helpful to the clinical treatment. *Method:* Relevant studies were retrieved from the MEDLINE, Embase, Cochrane Library, CENTRAL and ClinicalTrials.gov. The retrieval time range was from January 2000 to March 2022. English search terms included "(treatment)", "(adenomyosis) OR (endometrioma) OR (adenomyoma)". *Result:* Drug therapy can relieve the clinical symptoms of patients, inhibit the proliferation of lesions, and cooperate with surgical treatment to improve the curative effect. The efficacy and adverse reactions of the drug are closely related to the duration of use. At present, there is no specific drug for the treatment of adenomyosis, and there is a certain degree of recurrence after drug withdrawal. Some clinical scholars have adopted a combination regimen for the treatment of adenomyosis and achieved certain results. *Conclusion:* About the drug treatment of adenomyosis, it is necessary to personalize the treatment plan by combining the severity of the patients' clinical symptoms, age, fertility needs, patients' economic conditions, whether they can regulate the use of drugs, and the adverse reactions after the use of drugs.

**Keywords:** Adenomyosis, Drug Treatment, Review

## 1. Introduction

Adenomyosis is caused by endometrial glands and stroma invading the myometrium. It is more common in parturients after the age of 30. Patients with adenomyosis are often complicated with endometriosis or uterine leiomyoma [1]. They are mostly due to increased menstruation and prolonged menstruation, while gradually aggravating dysmenorrhea to the hospital. Uncontrollable pain and anemia also made many patients with adenomyosis miserable. Some patients are also complicated with infertility. For the treatment of adenomyosis, hysterectomy

and focus excavation are still the main clinical methods. Non-operative treatment mainly relieves and improves symptoms such as anemia and dysmenorrhea, preserves patients' reproductive function and improves patients' infertility symptoms. Drug therapy is one of the most important non-operative treatments. The treatment plan should be determined according to the relevant factors such as clinical symptoms, fertility needs and age. The purpose of this paper is to summarize the treatment schemes that can be used in clinical work at present, and to explore the more optimized treatment schemes for patients based on different needs.

## 2. Purpose of Drug Treatment and Points for Attention

The goal of treatment for adenomyosis is to relieve pain, reduce bleeding and promote fertility [2]. However, most of the therapeutic effects of drug treatment will disappear after drug withdrawal, resulting in the recurrence of clinical symptoms after drug withdrawal. Therefore, it is necessary to take medicine for a long time. However, the adverse reactions caused by drugs will also be aggravated with the extension of drug use time, so the selection and duration of drug use should follow the principle of individualization. Patients should also be fully informed of adverse drug reactions before use.

## 3. Non-steroidal Anti-inflammatory Drugs (NSAIDs)

It is an anti-inflammatory, analgesic and antipyretic drug. NSAIDs relieves pain by inhibiting the synthesis of prostaglandins and cyclooxygenase. At the same time, these drugs can partially reduce menstruation, but the effect is not as effective as drugs such as Gonadotropin-Releasing Hormone Agonist (GnRH-a). While reducing pain and bleeding, this kind of drugs can not significantly improve the size of the focus, and can not reduce the focus of adenomyosis and the uterus. This kind of drugs are often used in patients with mild pain, especially in patients with mild pain in peri-menopausal period and mild patients with fertility needs in a short period of time. This kind of drugs are divided into salicylic acid, indole, decanoic acid, propionic acid and so on. We need to pay attention to the gastrointestinal irritation caused by long-term use of this drug, especially the occurrence of gastric ulcers. For patients with severe pain, it is generally not the first choice.

## 4. Drugs Related to Steroidal Hormones

Adenomyosis is estrogen-dependent diseases. The use of steroids can reduce the level of estrogen or promote the differentiation of endometrium to achieve atrophy of the endometrium, relieve pain and reduce the focus and other effects. However, for patients with severe clinical symptoms and large uterus, the therapeutic effect of this kind of drugs is often not satisfactory, so it is not recommended as the first choice.

### 4.1. Danazol and Gestrinone

Both drugs are testosterone derivatives. The hormonal environment similar to menopause can be created by inhibiting the peaks of Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) in patients. Danazole can inhibit the ovarian synthesis of steroidal hormones, reduce the level of hormone in the body, make the focus atrophy and achieve the purpose of treatment. Gestrinone has anti-estrogen, anti-progesterone and anti-gonadal effects. The use of both

drugs can bring about hairy, acne, impaired liver function, decreased libido, headache, hot flashes and other discomfort. The damage of liver function to trienone is lower than danazole. Therefore, there is more clinical use of trienone. When using this kind of drugs, we must pay attention to whether the patients have abnormal liver and kidney function, hypertension and other diseases.

### 4.2. Progesterone

The use of progesterone can not only affect the endocrine axis and center, but also directly affect the disease. It can make the active endometrial tissue necrosis, decidualization in the ectopic lesions, reduce the menstrual volume, reduce the lesions, and relieve the pain. There are many drugs of this kind, but there are three kinds of drugs commonly used in clinic:

#### 4.2.1. Levonorgestrel Intrauterine Delivery System (LNG-IUS)

After implantation into the uterine cavity, a small amount of levonorgestrel was slowly released into the uterine cavity every day. Only 10% of them can enter the blood, which reduces the adverse reactions caused by drugs into the blood. Most drugs act directly on the uterine cavity, decidualize the endometrium, accelerate apoptosis and reduce the release of prostaglandins. Therefore, LNG-IUS can inhibit the proliferation of adenomyosis lesions, reduce the amount of menstrual bleeding, relieve menstrual pain. LNG-IUS also has the efficacy of contraception, the time limit for the effective drug concentration is a 5-year period. Therefore, it is clinically suitable for patients with no fertility demand/no fertility demand/long-term conservative treatment, and patients after surgical resection of some lesions. At present, the therapeutic effect of adenomyosis based on LNG-IUS is recognized [3-5]. However, AM can increase the volume of the uterine cavity while increasing the volume of the uterus. The uterine probe should be used in advance to determine the uterine cavity size before use, The increase of menstrual volume and increased uterine cavity volume will make LNG-IUS have the risk of slippage after insertion. According to statistics, the incidence of LNG-IUS, such as irregular vaginal bleeding and LNG-IUS slippage in the first half year, is as high as 20% [6]. For patients whose uterine cavity depth is greater than 8cm and uterine volume is estimated to be larger. GnRH-a can reduce uterine volume and menstrual volume before placing LNG-IUS, which can increase the success rate of LNG-IUS placement and improve its curative effect.

#### 4.2.2. Dienogest

It is a synthetic 19-nortestosterone progesterone derivative, which takes into account the characteristics of two kinds of progesterone at the same time. It can highly selectively combine progesterone receptors to create an environment of high progesterone in the uterine cavity, accelerating the decidualization of endometrial tissue at the same time. It can also atrophy the focus of adenomyosis [7, 8]. Based on the application of dienogest in the treatment of adenomyosis, it has been proved that dienogest can effectively relieve

dysmenorrhea and chronic pelvic pain, and cause mild adverse reactions such as hot flashes and sweating [9]. The effect of this drug on reducing menstruation is slightly lower than that of GnRH-a, and it has also been studied that most patients will have irregular vaginal bleeding during the use of dienogest [10]. Therefore, this drug is suitable for patients who do not have fertility requirements and require to retain the uterus. If the patient has a large amount of menstruation, it is recommended to use other conservative treatments such as GnRH-a. There are few studies on dienogest in China, and the role of foreign countries in relieving dysmenorrhea has been affirmed [11]. It can be used in the long-term management of endometriosis [12]. More prospective studies are needed to confirm the efficacy of its application in adenomyosis.

#### **4.2.3. Etonogestrel-Releasing Contraceptive Implant**

This drug is similar to LNG-IUS therapy. The implant contains the third generation progesterone-dependent progesterone 68mg. The affinity for progesterone receptor is stronger than that of LNG-IUS. After highly selective competition for progesterone receptor, negative feedback signal is transmitted to hypothalamus-pituitary-ovary axis (HPO axis) to reduce the levels of FSH and LH, thus inhibiting the proliferation of lesions. The research on this drug has increased in recent years, and it can reduce CA125, uterine volume, menstrual volume and pain after treatment [13, 14].

#### **4.3. Combined Oral Contraceptives (COC)**

These drugs are compounds synthesized by estrogen (ethinylestradiol) and different kinds of progesterone (norethisterone, spirosterone, levonorgestrel, etc.). The clinical difference of COC is mainly due to the different ratio of estrogen and progesterone. In addition to the treatment of primary dysmenorrhea, COC can also be used in the treatment of menorrhagia and endometriosis. COC can inhibit ovulation and create a low estrogen, pseudopregnant state. The principle is as follows: (1) It can inhibit the release of inflammatory factors and reduce pain. (2) Ethinylestradiol can repair intima, avoid excessive hyperplasia and reduce the possibility of malignant transformation. (3) Spironone competes for progesterone receptors, which makes intima atrophy, thinning and decidualization, and reduces menstruation. At the same time, attention should be paid to the use of this kind of drugs: (1) Pseudopregnancy may cause thrombosis, so safety assessment should be made according to the patient's age, liver function, blood lipids and D-dimer. (2) May cause gastrointestinal adverse reactions. (3) May cause irregular vaginal bleeding. Studies have confirmed the effectiveness of COC in the treatment of adenomyosis [15-17]. However, some scholars have found that its therapeutic effect is not as good as that of Dienogest [18].

#### **4.4. Gonadotropin-Releasing Hormone Agonist (GnRH-a)**

GnRH-a competes for GnRH receptors with high affinity and acts on the pituitary gland, first promoting the release of

LH and FSH, and then continuously inhibiting their release. The first injection was injected on the first day of menstruation, one injection every 28 days, and a total of 3-6 needles were used to atrophy the focus by reducing the level of hormones in the body. However, with the decrease of hormone levels, most patients have adverse reactions caused by low estrogen after the third injection, such as decreased libido, vaginal dryness, irritability, sweating and other symptoms, which will cause bone loss in patients even more seriously. This is also one of the reasons to limit its long-term use. Some patients developed menopausal symptoms after the second injection. Based on this, clinicians can use low-dose reverse addition therapy to alleviate the side effects when using this drug [19]. In clinical application, GnRH-a can be individualized according to the severity of adverse reaction symptoms, bone mineral density test results and sex hormone test results. Some studies have confirmed that the use of GnRH-a can significantly inhibit the focus and the proliferation of blood vessels [20]. Clinicians found that patients with moderate and severe adenomyosis were only treated with GnRH-a alone, and there was a possibility that the disease might continue to progress to a certain extent after drug withdrawal. Based on this, surgery, focused ultrasound and LNG-IUS combined with GnRH-a are often used in clinic, which can not only achieve better therapeutic effect, but also reduce the occurrence of adverse reactions [21-23].

#### **4.5. Mifepristone**

Mifepristone is an antagonist of progesterone receptor, which can antagonize progesterone for emergency contraception, and can also be used in combination with misoprostol for drug abortion. It also has the functions of inhibiting ovulation, promoting cervical maturity, inducing menstruation and so on. Studies in China have shown that mifepristone with 5mg-50mg can improve the pain symptoms of adenomyosis in the vast majority of patients. At the same time, clinicians also found that the reduction of uterine volume became more and more obvious with the increase of mifepristone dose. The increase of clinical dose makes the thickening of endometrium more obvious, so the safety of this drug is worth exploring. At present, the clinical application is mostly 3 months, and its safety has been confirmed by some scholars. This drug can be used to treat peri-menopausal women with conservative treatment, but it will cause endometrial thickening and have the risk of potential malignant transformation, and at the same time, this drug has not been formally approved for the treatment of adenomyosis, so the informed consent of the patient should be obtained before use [10, 24, 25].

### **5. Aromatase Inhibitor**

Aromatase is a rate-limiting enzyme for the synthesis of estrogen. After using this drug, the production of estrogen in the body can be reduced by speed limit. Letrozole is the most common drug in clinic. Animal experiments have confirmed that letrozole can reduce the focus of endometriosis in rats

[26]. Some scholars have confirmed that letrozole can significantly reduce the production of estrogen after taking medicine [27]. So as to relieve the pain. Factor adenomyosis is an estrogen-dependent disease. Some scholars have used letrozole to treat adenomyosis [28]. However, a larger number of longer-term prospective studies are needed to evaluate the efficacy of the treatment.

## 6. Other Drugs

In recent years, antiplatelet drugs, oxytocin inhibitors, GnRH antagonists, angiogenesis inhibitors and other drugs have been reported to be used in the treatment of adenomyosis, but they are scattered small sample size studies, but a larger number and longer-term prospective studies are still needed to evaluate the therapeutic effect and feasibility.

## 7. Conclusion

Both adenomyosis and endometriosis are estrogen-dependent chronic diseases, but for adenomyosis, the effect of drug treatment is not as good as that of endometriosis. NSAIDs can be used in patients with mild pain and fertility needs; LNG-IUS can significantly reduce the amount of menstruation while relieving pain, in clinical application, the evaluation of the therapeutic effect is relatively good. GnRH-a also has significant therapeutic effect in relieving pain and reducing focus, but its application is hindered by the adverse reactions of menopausal state and the relatively high cost of treatment. The combination of LNG-IUS and GnRH-a can reduce the slippage rate of LNG-IUS and the incidence of irregular vaginal bleeding. All in all, about the drug treatment of adenomyosis, it is necessary to personalize the treatment plan by combining the severity of the patients' clinical symptoms, age, fertility needs, patients' economic conditions, whether they can regulate the use of drugs, and the adverse reactions after the use of drugs. At present, there is no drug for radical treatment of adenomyosis, for patients after the failure of conservative treatment, suitable surgical methods should be considered for further treatment.

## Funding

This work was supported by grants from the maternal and child health research project of Jiangsu Province (F202138), the Scientific Research Support Program for Postdoctoral of Jiangsu Province (2019K064), and the Scientific Research Support Program for "333 Project" of Jiangsu Province (BRA2019161).

## Conflict of Interest Statement

All the authors do not have any possible conflicts of interest.

## References

- [1] Chapron Charles, Vannuccini Silvia, Santulli Pietro et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. [J]. Hum Reprod Update, 2020, 26: 392-411.
- [2] Donnez Jaques, Squifflet Jean, Pirard Céline et al. The efficacy of medical and surgical treatment of endometriosis-associated infertility and pelvic pain. [J]. Gynecol Obstet Invest, 2002, null: 2-7; discussion 7-10.
- [3] Rathinam Kiran Kumar, Abraham Justin Jacob, S Heema Preethy et al. Evaluation of pharmacological interventions in the management of adenomyosis: a systematic review. [J]. Eur J Clin Pharmacol, 2022, undefined: undefined.
- [4] Haiyan Sun, Lin Wang, Shuhua Huang et al. High-intensity focused ultrasound (HIFU) combined with gonadotropin-releasing hormone analogs (GnRHa) and levonorgestrel-releasing intrauterine system (LNG-IUS) for adenomyosis: a case series with long-term follow up. [J]. Int J Hyperthermia, 2019, 36: 1179-1185.
- [5] Song Soo Youn, Lee Sun Yeul, Kim Hye Yun et al. Long-term efficacy and feasibility of levonorgestrel-releasing intrauterine device use in patients with adenomyosis. [J]. Medicine (Baltimore), 2020, 99: e20421.
- [6] Kriplani A., Singh B M, Lal S et al. Efficacy, acceptability and side effects of the levonorgestrel intrauterine system for menorrhagia. [J]. Int J Gynaecol Obstet, 2007, 97: 190-194.
- [7] Hirata Tetsuya, Izumi Gentaro, Takamura Masashi et al. Efficacy of dienogest in the treatment of symptomatic adenomyosis: a pilot study. [J]. Gynecol Endocrinol, 2014, 30: 726-729.
- [8] Foster R H, Wilde M I. Dienogest. [J]. Drugs, 1998, 56: 825-833; discussion 834-835.
- [9] Donnez Jacques, Dolmans Marie-Madeleine. Endometriosis and Medical Therapy: From Progestogens to Progesterone Resistance to GnRH Antagonists: A Review. [J]. J Clin Med, 2021, 10: 1085.
- [10] Osuga Yutaka, Fujimoto-Okabe Haruka, Hagino Atsushi. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study. [J]. Fertil Steril, 2017, 108: 673-678.
- [11] Mehdizadeh Kashi Abolfazl, Niakan Gelareh, Ebrahimpour Majid et al. A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. [J]. Int J Gynaecol Obstet, 2022, 156: 124-132.
- [12] Bedaiwy Mohamed A, Allaire Catherine, Alfaraj Sukinah. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. [J]. Fertil Steril, 2017, 107: 537-548.
- [13] Carvalho Nelsilene, Margatho Deborah, Cursino Kleber et al. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. [J]. Fertil Steril, 2018, 110: 1129-1136.

- [14] Margatho Deborah, Carvalho Nelsilene Mota, Bahamondes Luis. Endometriosis-associated pain scores and biomarkers in users of the etonogestrel-releasing subdermal implant or the 52-mg levonorgestrel-releasing intrauterine system for up to 24 months. [J]. *Eur J Contracept Reprod Health Care*, 2020, 25: 133-140.
- [15] Li Jin-Jiao, Chung Jacqueline P W, Wang Sha et al. The Investigation and Management of Adenomyosis in Women Who Wish to Improve or Preserve Fertility. [J]. *Biomed Res Int*, 2018, 2018: 6832685.
- [16] Alcalde Ana Maria, Martínez-Zamora María Ángeles, Gracia Meritxell et al. Assessment of Quality of Life, Sexual Quality of Life, and Pain Symptoms in Deep Infiltrating Endometriosis Patients With or Without Associated Adenomyosis and the Influence of a Flexible Extended Combined Oral Contraceptive Regimen: Results of a Prospective, Observational Study. [J]. *J Sex Med*, 2022, 19: 311-318.
- [17] Benetti-Pinto Cristina Laguna, Mira Ticiano Aparecida Alves de, Yela Daniela Angerame et al. Pharmacological Treatment for Symptomatic Adenomyosis: A Systematic Review. [J]. *Rev Bras Ginecol Obstet*, 2019, 41: 564-574.
- [18] Hassanin Ahmed I, Youssef Ahmed A, Yousef Asmaa M et al. Comparison of dienogest versus combined oral contraceptive pills in the treatment of women with adenomyosis: A randomized clinical trial. [J]. *Int J Gynaecol Obstet*, 2021, 154: 263-269.
- [19] Wu Debin, Hu Min, Hong Li et al. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. [J]. *Arch Gynecol Obstet*, 2014, 290: 513-523.
- [20] Sauerbrun-Cutler May-Tal, Alvero Ruben. Short- and long-term impact of gonadotropin-releasing hormone analogue treatment on bone loss and fracture. [J]. *Fertil Steril*, 2019, 112: 799-803.
- [21] Li Qiuju, Yuan Ming, Li Ni et al. The efficacy of medical treatment for adenomyosis after adenomyomectomy. [J]. *J Obstet Gynaecol Res*, 2020, 46: 2092-2099.
- [22] Pang Li-Li, Mei Jin, Fan Ling-Xiu et al. Efficacy of High-Intensity Focused Ultrasound Combined With GnRH-a for Adenomyosis: A Systematic Review and Meta-Analysis. [J]. *Front Public Health*, 2021, 9: 688264.
- [23] Peng Yan, Dai Yu, Yu Guiyuan et al. Clinical evaluation of HIFU combined with GnRH-a and LNG-IUS for adenomyosis patients who failed to respond to drug therapies: two-year follow-up results. [J]. *Int J Hyperthermia*, 2021, 38: 1271-1275.
- [24] Qin Xiaoyan, Sun Wenjing, Wang Chong et al. Mifepristone inhibited the expression of B7-H2, B7-H3, B7-H4 and PD-L2 in adenomyosis. [J]. *Reprod Biol Endocrinol*, 2021, 19: 114.
- [25] Che Xuan, Wang Jianzhang, He Jiayi et al. A new trick for an old dog: The application of mifepristone in the treatment of adenomyosis. [J]. *J Cell Mol Med*, 2020, 24: 1724-1737.
- [26] Fattori Victor, Franklin Noah S, Gonzalez-Cano Rafael et al. Nonsurgical mouse model of endometriosis-associated pain that responds to clinically active drugs. [J]. *Pain*, 2020, 161: 1321-1331.
- [27] Jerusalem G, Farah S, Courtois A et al. Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy. [J]. *Ann Oncol*, 2021, 32: 1256-1266.
- [28] Badawy Ahmed M, Elnashar Aboubakr M, Mosbah Alaa A, Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. [J]. *Acta Obstet Gynecol Scand*, 2012, 91: 489-495.