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REVIEW ARTICLE

Current Medical Therapy for Adenomyosis: From Bench to Bedside

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Abstract
Adenomyosis, characterized by the growth of endometrial tissue within the uterine wall, poses significant challenges in treatment. The literature primarily focuses on managing abnormal uterine bleeding (AUB) and dysmenorrhea, the main symptoms of adenomyosis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid provide limited support for mild symptoms or symptom re-exacerbation during hormone therapy. The levonorgestrel-releasing intrauterine system (LNG-IUS) is commonly employed in adenomyosis management, showing promise in symptom improvement and reducing uterine size, despite the lack of standardized guidelines. Dienogest (DNG) also exhibits potential benefits, but limited evidence hinders treatment recommendations. Danazol, while effective, is limited by androgenic side effects. Combined oral contraceptives (COCs) may be less effective than progestins but can be considered for contraception in young patients. Gonadotropin-releasing hormone (GnRH) agonists effectively manage symptoms but induce menopausal symptoms with prolonged use. GnRH antagonists are a recent option requiring further investigation. Aromatase inhibitors (AIs) show promise in alleviating AUB and pelvic pain, but their safety necessitates exploration and limited use within trials for refractory patients. This review highlights the complexity of diagnosing adenomyosis, its coexistence with endometriosis and uterine leiomyomas, and its impact on fertility and quality of life, complicating treatment decisions. It emphasizes the need for research on guidelines for medical management, fertility outcomes, long-term effects of therapies, and exploration of new investigational targets. Future research should optimize therapeutic strategies, expand our understanding of adenomyosis and its management, and establish evidence-based guidelines to improve patient outcomes and quality of life.

1 Introduction

Adenomyosis is a common benign condition affecting women and is characterized by dysmenorrhea, menorrhagia, abnormal uterine bleeding (AUB), infertility, and chronic pelvic pain. This disease occurs when the endometrium invades the myometrium, resulting in a diffuse uterine enlargement. Microscopic examination reveals non-neoplastic ectopic endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium [1, 2]. The disruption of the normal junction between the basal endometrium and myometrium is hypothesized to be the primary event leading to the development of adenomyosis [3, 4].

Although the exact cause of this junction disruption is not fully understood, it has been suggested that forceful and uncoordinated myometrial contractions, often seen in women with heavy menstrual flow [5] may contribute to the pathogenesis of adenomyosis. Additionally, the disease onset may be favored by disruption of the endometrial–myometrial border due to spontaneous, induced abortion or uterine dilatation and curettage, although the pathogenic action of these factors is controversial [6, 7].

Adenomyosis is frequently associated with endometriosis [8, 9]. While they share similarities, adenomyosis is considered a distinct entity from endometriosis, and there are clinical and pathological features that differentiate them [8, 10, 11]. Adenomyosis can also coexist with uterine leiomyomas [12] or congenital uterine anomalies [13], making their differentiation challenging on ultrasound examination [14]. In some cases, these associations may require surgical intervention rather than medical treatment alone. Furthermore, depending on a woman's age, desire for fertility, and reported symptoms, adenomyosis may necessitate long-term medical therapy that extends until menopause [15].

Currently, there are no established guidelines for the treatment of adenomyosis. However, like endometriosis,

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Key Points

Adenomyosis presents significant challenges in treatment, with current literature primarily focusing on managing abnormal uterine bleeding (AUB) and dysmenorrhea, the main symptoms associated with the condition.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid have limited roles in therapy, mainly providing support for mild symptoms or symptom re-exacerbation during hormone therapy. Progestins such as LNG-IUS (levonorgestrel-releasing intrauterine system) and oral dienogest are commonly used in adenomyosis management, showing promise in improving symptoms and reducing uterine size. However, the lack of guidelines hampers their standardized use.

Literature evaluating the medical treatment of adenomyosis-related infertility is very limited.

Further research is needed to establish evidence-based guidelines for the medical management of adenomyosis. Additionally, the investigation of new treatment targets, including GnRH antagonists and aromatase inhibitors, holds promise but requires more exploration for their potential in adenomyosis treatment.

which is also a hormone-dependent inflammatory condition, various hormonal and nonhormonal treatments are being used off-label to manage adenomyosis (Fig. 1). While these treatments can effectively control symptoms in many cases [16–18], their efficacy may vary. The aim of the current narrative review is to give an overview of the main drugs employed or under investigation for treating adenomyosis.

2 The Role of Medical Therapy for Treating Symptoms Related to Adenomyosis

2.1 Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are nonhormonal compounds that act by blocking the activity of the enzyme cyclooxygenase (COX), thereby inhibiting the production of prostaglandins, thromboxanes, and other molecules involved in the inflammatory cascade.

To date, the available literature lacks specific studies on the use of NSAIDs for adenomyosis. However, due to their anti-inflammatory and pain-relieving effects, NSAIDs are commonly used in symptomatic therapy to alleviate the symptoms of dysmenorrhea, pelvic pain, and AUB associated with adenomyosis [16]. Nonetheless, approximately 20% of women with adenomyosis experience dysmenorrhea that does not respond to NSAID treatment [19].

A Cochrane systematic review [20] concluded that NSAIDs can effectively treat dysmenorrhea. However, the same review does not provide sufficient evidence to determine the most effective and safe NSAID in this treatment scenario. Another Cochrane systematic review [21] investigated whether NSAIDs, besides their anti-inflammatory role, could also improve AUB. This review suggested that these drugs, without identifying a specific NSAID as more effective than others, may exert a hemostatic effect by reducing profuse bleeding. However, their effect is less pronounced compared with medications specifically intended for this purpose, such as tranexamic acid or aminocaproic acid, or hormonal treatments like the levonorgestrel-releasing intrauterine system (LNG-IUS) or danazol [22].

Therefore, NSAIDs could be considered for managing recurrent exacerbations of adenomyosis symptoms in women already receiving optimized hormonal treatment or in women seeking pregnancy who are not undergoing any treatment other than symptomatic relief.

2.2 Progestins

Decreased expression of progesterone receptors (PR) A and B has been observed in adenomyotic tissue, similar to endometriosis [23]. Progesterone induces antiproliferative activity by binding to its receptors [24]. The observed reduction in PR expression could partially explain the pathogenesis of adenomyosis and the poor response to progestins [25]. Although adenomyotic tissue has lower levels of PR, a good response to high-dose topical progesterone has been demonstrated [26]. However, to date, there is a scarcity of randomized controlled trials specifically focusing on the use of progestins in the treatment of adenomyosis. Despite their widespread use in patients with adenomyosis, the limited number of studies available contributes to the low level of scientific evidence supporting their efficacy in this context.

2.2.1 Levonorgestrel-Releasing Intrauterine System

The LNG-IUS is a highly effective and safe contraceptive approved for continuous use for up to 5 years. This drug is successfully used by several women for the treatment of AUB and for endometrial protection during continuous estrogen therapy after menopause. The LNG-IUS releases LNG directly to the endometrium, thereby reducing systemic exposure to this progestin [27, 28]. Studies have shown that the concentration of LNG achieved within the uterine cavity is 1000 times higher than that achieved in the bloodstream

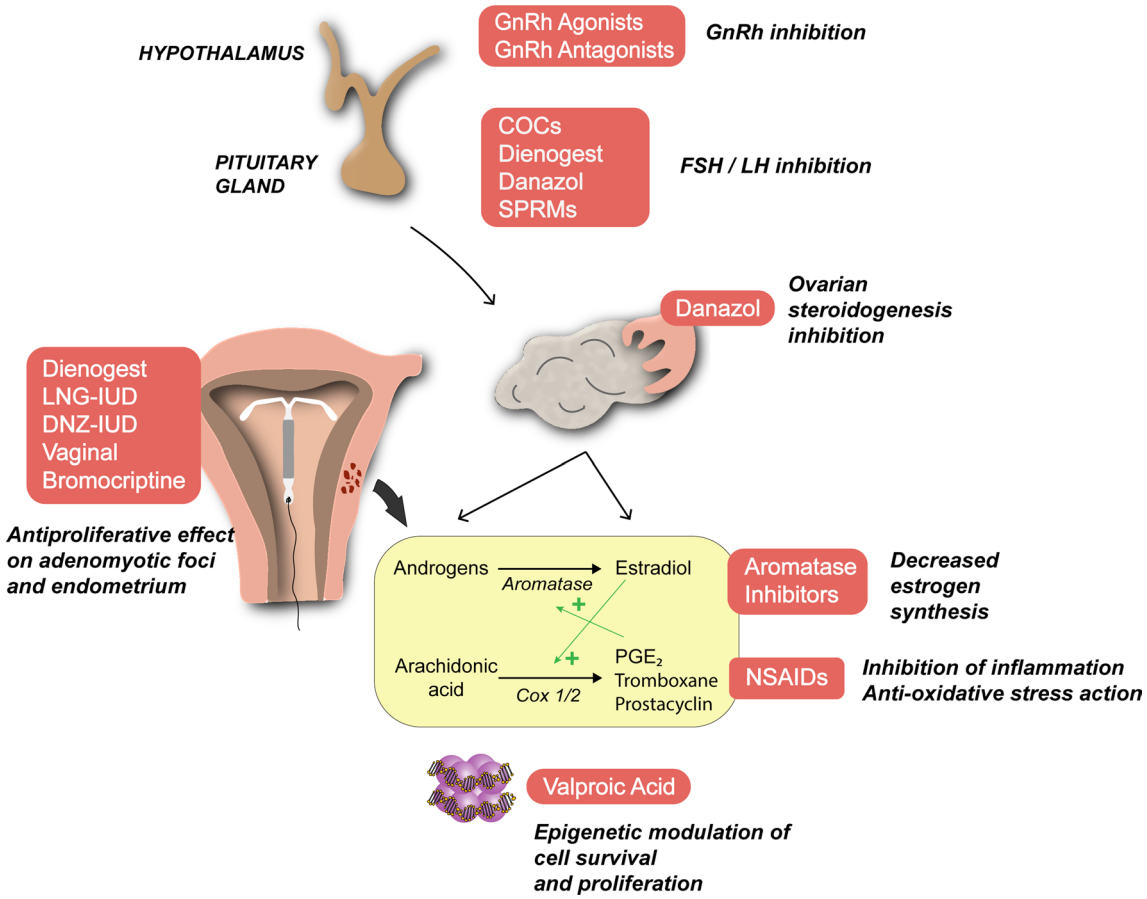

Fig. 1 The biological targets of the main drug classes available for treating symptoms related to adenomyosis

[29]. Additionally, once inserted, the device has a long-lasting effect, making it cost-effective.

The use of LNG-IUS in the treatment of pelvic pain and AUB related to adenomyosis could be justified not only by the direct effect of LNG on adenomyotic foci but also by its modulatory action on altered endometrial factors. The local action of LNG, by down-regulating estrogen receptors, induces decidualization and atrophy of the ectopic endometrium, preventing further estrogenic stimulation [30].

Although there is limited specific literature on the treatment of adenomyosis with LNG-IUS, a few randomized trials have been conducted in this setting (Table 1). Currently, LNG-IUS is one of the most extensively investigated treatments and has shown to be effective in managing symptoms related to adenomyosis. This drug has been associated with improvements in quality of life comparable to those achieved with more invasive surgical techniques, high rates of symptom relief, and minimal local and systemic side effects.

A prospective randomized clinical trial conducted by Ozdegirmenci et al. [31] compared the effects of LNG-IUS with hysterectomy in 75 patients diagnosed with adenomyosis. The study concluded that LNG-IUS could be a promising alternative therapy to hysterectomy for women with adenomyosis; in particular, comparable improvements in hemoglobin levels were demonstrated between the two procedures during the first year, and LNG-IUS was found to have superior effects on psychological and social well-being.

Some Chinese authors [32] conducted a study of 94 patients with adenomyosis-associated dysmenorrhea to evaluate the long-term viability of LNG-IUS as an alternative treatment. Over the 3-year follow-up period, LNG-IUS was found to be effective in alleviating dysmenorrhea associated with adenomyosis. A multicenter, retrospective, observational study by Mansukhani et al. [33] assessed the efficacy and satisfaction of LNG-IUS in the treatment of AUB related to adenomyosis and/or uterine leiomyomas in 80 women. The study concluded that LNG-IUS appears to be a viable treatment option for AUB related to adenomyosis and/or uterine leiomyomas, with a high satisfaction rate reported among patients.

The use of LNG-IUS in combination or in comparison with other procedures has also been evaluated by some authors. Zheng et al. [34] recruited 43 patients with adenomyosis suffering from dysmenorrhea and menorrhagia to

Table 1 Studies evaluating the use of LNG-IUS for treating symptoms associated to adenomyosis

Study	Year	Study design	Population	Intervention	Main results
Ozdegirmenci et al. [30]	2011	Prospective randomized study	86 women with adenomyosis	LNG-IUS ($n = 43$);	Significant and comparable improvements in hemoglobin levels during the first year
				Hysterectomy ($n = 43$)	LNG-IUS associated to better effects on psychological and social life
Sheng et al. [31]	2009	Prospective non-randomized study	94 women with moderate or severe dysmenorrhea associated with adenomyosis	LNG-IUS	VAS for dysmenorrhea dropped significantly from 77.9 ± 14.7 to 11.8 ± 17.9 after 36 months
					The uterine volume decreased significantly from 113.8 ± 46.9 mL to 94.5 ± 40.1 mL at 6 months and to 87.7 ± 35.8 mL at 12 months
					The serum CA125 levels reduced significantly starting from 6 months after device insertion
					The most common side effects were weight gain (28.7%), simple ovarian cyst formation (22.3%), and lower abdominal pain (12.8%)
					At 36 months, the overall satisfaction rate of the treatment was 72.5%
Mansukhani et al. [32]	2013	Retrospective study	80 women with abnormal uterine bleeding ($n = 16$ with adenomyosis)	LNG-IUS	After 6 months 52.6% of patients with adenomyosis were asymptomatic
					26.3% of patients were in amenorrhea at 6 months and 31.6% at 12 months.
Zheng et al. [33]	2013	Prospective randomized study	43 women with dysmenorrhea and menorrhagia associated with adenomyosis	Transcervical resection of the endometrium (TCRE) plus LNG-IUS ($n = 20$);	Significant reduction in menstrual flow and pain in both groups
				LNG-IUS	The reduction in menstrual flow in group 1 was significantly greater than that of group 2 at 3, 6 and 12 months.
				($n = 20$)	No significant difference in the reduction of pain between the two groups.
Maia et al. [34]	2003	Retrospective	95 women with pelvic pain, menorrhagia, and pathologic diagnosis of adenomyosis	Hysteroscopic endometrial resection plus LNG- IUS ($n = 53$);	The rate of amenorrhea after 1 year was significantly higher in the LNG- IUS group.
				Hysteroscopic endometrial resection ($n = 42$)	Moreover, 19% of women in the control group had a second procedure to control bleeding compared with none in the LNG-IUS group

Table 1 (continued)

Study	Year	Study design	Population	Intervention	Main results
Shaaban et al. [35]	2015	Prospective randomized study	62 women with pain and menorrhagia associated with adenomyosis	LNG-IUS ($n = 31$);	Both treatments significantly reduced pain, number of bleeding days, uterine volume and doppler blood flow in the uterus; these effects were more significant in the LNG-IUS arm compared with the combined oral contraceptive arm
				30 µg ethinyl estradiol and 75 µg gestodinev ($n = 31$)	LNG-IUS is more effective than the combined oral contraceptives in reducing pain and menstrual blood loss
Cho et al. [36]	2008	Retrospective study	47 women with dysmenorrhea and menorrhagia associated with adenomyosis	LNG- IUS	Pain scores and PBAC scores dropped in 6 months and showed significant decrease after 36 months
					Significant decrease in mean uterine volume after 12 months (156.85 ± 49.79 mL to 118.64 ± 41.36 mL) and 24 months (128.84 ± 48.70 mL), no significant differences at 36 months
					The mean pulsatility indices of both uterine arteries significantly increased 12 months after insertion and decreased after 24 months without significance
					Significant increase of uterine volume, pain scores, and PBAC scores at 36 months compared with 12 months after insertion
Zhang et al. [37]	2013	Prospective study	21 women with adenomyosis whose uterine volumes were greater in size than at 12 weeks' gestation	Subcutaneus goserelin (GnRH-a) 1/month for 3–4 cycles plus LNG- IUS	Menstrual flow was significantly lower than baseline values (53.8 ± 11.7 versus 100) after 12 months from insertion
					The degree of dysmenorrhea was relieved 12 months after implantation (58.2 ± 11.5 versus 93.7 ± 0.2)
					Uterine volume was also below pre-GnRH-a levels after implantation (276.6 ± 32.1 versus 311.4 ± 32.3)
					LNG-IUS was expelled in three patients, giving an expulsion rate of 14%
Lee et al. [38]	2016	Retrospective study	171 women with dysmenorrhea and menorrhagia associated with adenomyosis	LNG-IUS	The treatment failure rate of large volume uterus (150 mL) with LNG-IUD was significantly higher than that of small volume uterus

GnRHa gonadotropin-releasing hormone agonist, *LNG-IUS* levonorgestrel intrauterine system, *TCRE* transcervical resection of the endometrium, *VAS* visual analogic scale, *PBAC* pictorial blood assessment chart

compare the effect of transcervical endometrial resection (TCRE) combined with LNG-IUS versus LNG-IUS alone in the treatment of adenomyosis. The results of their clinical trial concluded that TCRE combined with LNG-IUS for the treatment of adenomyosis is more effective in reducing menstrual flow than LNG-IUS alone. However, in terms of pain reduction, no superiority of the combined procedure over the single insertion was demonstrated. A Brazilian group [35] conducted a randomized observational study on 95 patients evaluating the efficacy of LNG-IUS after endometrial resection for the treatment of menorrhagia caused by adenomyosis. The study concluded that the insertion of LNG-IUS after endometrial resection is an effective treatment for menorrhagia caused by adenomyosis with a negligible number of adverse effects. In another randomized clinical trial by Shaaban et al. [36], the effectiveness of LNG-IUS was compared with a combined low-dose oral contraceptive (COC) in reducing pain and AUB in 62 women with adenomyosis. The authors found that LNG-IUS is more effective than COCs in reducing pain and menstrual bleeding. This effect could be related to decreased uterine volume and increased resistance to blood flow.

The impact of LNG-IUS on reducing the size of adenomyotic uteruses has been also investigated. Cho et al. [37] inserted an LNG-IUS in 47 patients diagnosed with adenomyosis to evaluate its long-term clinical effects. The study found that LNG-IUS is effective in reducing uterine volume with rapid improvement in vascularity and relief of symptoms. However, the decrease in uterine volume with LNG-IUS was not as rapid as expected, as it began to decrease 2 years after insertion. To evaluate the clinical outcomes of combining gonadotropin-releasing hormone agonists (GnRH-as) with LNG-IUS in patients with adenomyosis and significantly enlarged uterus, Zhang et al. [38] recruited 21 women diagnosed with adenomyosis and increased uterus size corresponding to week 12 of amenorrhea. The results indicated that combined treatment with GnRH-as and LNG-IUS was effective in reducing both symptoms and uterus size in patients with adenomyosis and an enlarged uterus. A study by a Korean scientific group [39] involving 171 patients with adenomyosis aimed to evaluate the relationship between uterine volume and LNG-IUS failure. The study reported a higher failure rate of LNG-IUS treatment in patients with adenomyosis who had changes in uterine volume. Specifically, the failure rate of LNG-IUS treatment was significantly higher in cases where the uterus volume was greater than 150 mL compared with cases with a smaller volume.

2.2.2 Dienogest

DNG is a fourth-generation progestin derived from 19-nortestosterone that binds to PR with high affinity. When taken continuously, DNG inhibits systemic gonadotropin secretion and has additional antiproliferative and local anti-inflammatory effects on endometrial tissue [40]. In 2009, DNG was initially approved for the treatment of endometriosis in the European Union [41]. Although there is limited literature on the use of DNG in the therapy of adenomyosis, it has shown potential indications for the treatment of this condition.

A randomized, double-blind, multicenter, placebo-controlled trial conducted by Osuga et al. [42] evaluated the efficacy and safety of DNG in 67 patients with symptomatic adenomyosis. The results showed that DNG is effective and well-tolerated in the treatment of painful symptoms associated with adenomyosis, as long as it is not associated with uterine enlargement or severe anemia. Nevertheless, it was also found that patients younger than 38 years old with pre-existing anemia may have reduced therapeutic compliance and may discontinue treatment [43]. Additionally, studies on the long-term treatment course with DNG have suggested that it is well tolerated, even up to menopause, and may be a viable treatment option to avoid hysterectomy [44, 45].

The efficacy and safety of DNG have also been compared with other progestins such as LNG-IUS or danazol, as well as with other hormonal treatments like GnRH-as. Ota et al. [26] conducted a randomized controlled trial involving 157 women with adenomyosis to evaluate the efficacy of LNG-IUS and DNG. The study concluded that both treatments could be effective in the long-term management of adenomyosis. Furthermore, in terms of the duration of uterine bleeding, DNG was found to be superior to LNG-IUS over a 6-year period. Similar conclusions were reached by Chinese authors [46] in a retrospective study comparing the effectiveness of LNG-IUS and DNG for the treatment of adenomyosis. Sasa et al. [47] compared the effectiveness and safety of low-dose DNG and low-dose danazol in 20 and 22 patients, respectively, for the management of endometriosis, including adenomyosis. The study concluded that both treatments were effective and safe for long-term management of these conditions. In a prospective comparative trial by Fawzy et al. [46], the efficacy of DNG was compared with GnRH-as in controlling symptoms due to adenomyosis. The study found that both treatments had equal efficacy in symptom control. However, GnRH-as treatment for 4 months resulted in better control of AUB and a more pronounced reduction in uterine volume.

2.3 Danazol

Danazol is an isoxazole derivative of the synthetic steroid ethisterone. It possesses direct effects on cell proliferation by inducing cell apoptosis and has been widely used in the treatment of endometriosis and adenomyosis [1, 48]. Danazol induces atrophy in lesions and indirectly improves

symptoms [49, 50]; this drug also has a suppressive effect on the autoimmune response present during adenomyosis [51]. Nevertheless, the use of danazol in the treatment of adenomyosis is limited due to serious side effects, especially when administered orally, and the need for restricted treatment duration and patient adherence. Therefore, the literature on the use of danazol for adenomyosis is scarce and often based on local delivery routes.

Animal studies suggest that danazol may act directly after administration with IUS and rings containing danazol on adenomyosis tissue, inhibiting DNA synthesis and inducing apoptosis [52].

Studies conducted by Igarashi et al. [53] involved the use of a danazol-IUS, observing that this approach was effective in reducing uterine size and allowing pregnancy in 66.6% of cases. Danazol-IUS showed also to obtain symptom resolution without systemic side effects [54].

To evaluate the clinical efficacy of vaginally administered danazol for the treatment of young women with menorrhagia and adenomyosis, an Italian academic group [55] conducted a prospective study. This study demonstrated that vaginally administered danazol was an effective medical treatment for these patients, due to the lack of systemic adverse effects. Therefore, it was proposed as an alternative treatment to more commonly used hormonal treatments or surgery. Other alternative routes of administration for danazol, such as the trans-cervical route, have also been studied. In a trans-cervical danazol treatment, various symptoms related to adenomyosis gradually improved starting from the fourth week after the start of injection [56].

It is important to note that the use of danazol in adenomyosis treatment should be carefully considered due to its potential for serious side effects, particularly when administered orally. Therefore, the choice of administration route and careful monitoring of patients are crucial to ensure both efficacy and safety.

2.4 Combined Oral Contraceptives

COCs are used off-label in the management of adenomyosis. They work by inducing a pseudo gestational state, leading to decidualization and subsequent atrophy of the endometrium and adenomyotic lesions [57, 58]. This results in amenorrhea, reduced menstrual volume, and relief from dysmenorrhea, providing benefits to patients with adenomyosis.

There is some evidence suggesting that COCs may also have an anti-inflammatory effect by inhibiting the action of COX in adenomyotic spots [59]. However, the literature on the use of COCs specifically for adenomyosis is limited.

In a prospective observational study by Alcade et al. [60], the influence of a COC containing 2 mg dienogest (DNG) and 30 µg ethinylestradiol on the quality of life (QoL) and sex life of patients with deep endometriosis with or without adenomyosis was evaluated. The study reported that patients' QoL and sex life were poorer compared with healthy controls, and the use of COCs significantly improved these outcomes. Other Egyptian authors [61] conducted a randomized controlled trial that demonstrated the effectiveness of COCs in treating symptoms related to adenomyosis. However, it was found that DNG was more effective than COCs in this regard, albeit with a higher incidence of side effects. Shaaban et al. [36] also conducted a randomized controlled trial, which showed that COCs can effectively reduce uterine volume and blood flow within the uterus, as well as alleviate symptoms of adenomyosis. However, COCs were found to be less effective than LNG-IUS in these aspects.

2.5 Gonadotropin-Releasing Hormone Agonists

GnRH-as can be used as second-line treatment for adenomyosis when progestins are not efficacious or not tolerated by the patients. GnRH is a hormone released by the hypothalamus that regulates reproductive function by stimulating the release of gonadotropins (FSH and LH) from the pituitary gland. Continuous administration of GnRH-as initially causes a flare-up effect but subsequently suppresses FSH and LH secretion, leading to the blockade of sex steroid production by the ovaries. GnRH-as can be used in the treatment of sex steroid-dependent diseases such as adenomyosis [62].

Clinical trials and solid evidence regarding the use of GnRH-as for adenomyosis are limited. However, some studies have provided insights into their effectiveness. For example, Grow et al. [63] presented a case report of adenomyosis treated with long-term GnRH-as therapy, which resulted in a reduction in uterine volume and relief from severe dysmenorrhea. In a nonblinded randomized study, a comparison was made between a 3-month treatment with aromatase inhibitors (AI) and GnRH-as in women with adenomyosis. Both treatment groups showed a significant reduction in uterine volume and adenomyotic focus after 12 weeks. However, the GnRH-as group experienced menopause-like symptoms such as hot flushes, while the AI-treated group did not report such symptoms. Additionally, pregnancy was achieved by women in the AI-treated group but not in the GnRH-as group. Improvement of symptoms was similar between the two groups, except for a greater reduction in chronic pelvic pain with GnRH-as treatment [64].

The administration of add-back therapy with GnRH-as in the prevention of induced menopausal symptoms remains unclear and requires further investigation. To address the issue of add-back therapy, Akira et al. [65] conducted a study using low-dose GnRH-as (nasal buserelin acetate 900 microg/day) in patients with adenomyosis. This approach maintained plasma estrogen levels at a level that did not

trigger menopause-related symptoms while still maintaining the therapeutic effect on adenomyosis. Although this study was conducted on a small sample size and more research is needed, it suggests a potential strategy for balancing the benefits of GnRH-as therapy while minimizing the impact of induced menopausal symptoms.

At the moment, the literature on GnRH-as for adenomyosis is limited, and more well-designed clinical trials are required to establish its efficacy, optimal dosing, and potential strategies to manage induced menopausal symptoms.

2.6 Gonadotropin-releasing hormone antagonists

Gonadotropin-releasing hormone antagonists (GnRH-ants) are peptide compounds that have a similar structure to the naturally produced GnRH in the body. They act by blocking the GnRH receptors in the pituitary gland, resulting in the immediate suppression of reproductive function by inhibiting the secretion of FSH and LH by the adenohypophysis. Currently, elagolix and linzagolix are being considered for the treatment of endometriosis and uterine leiomyomas. These medications have shown a dose-dependent and rapidly reversible effect on the pituitary-gonadal axis, leading to a significant reduction in dysmenorrhea and an improvement in the quality of life for patients [12, 66].

In recent times, there has been some exploration of the use of GnRH-ants in patients with adenomyosis. However, there is a scarcity of clinical studies in the literature, and the data regarding their efficacy in adenomyosis appears to be controversial. One case report described the treatment of an infertile patient with endometriosis and reduced ovarian reserve using elagolix. While elagolix effectively controlled severe pelvic pain associated with endometriosis, it surprisingly did not prevent the concomitant progression of adenomyosis [67]. As a result, the patient's treatment was switched to leuprolide acetate, which led to an improvement in the progression of adenomyosis. It should be noted that elagolix may not suppress adenomyosis as effectively as GnRH-as, particularly in infertile patients undergoing assisted reproductive technologies (ART). A study by Muneyyirci-Delale et al., demonstrated that elagolix, when used with add-back therapy, significantly reduces AUB in women with uterine fibroids and coexisting adenomyosis. However, there is a lack of data regarding the potential progression of adenomyosis lesions with this treatment [68]. More encouraging data on the use of linzagolix in adenomyosis are available from recent studies. A recent pilot study showed that a regimen of 200 mg of linzagolix once daily for 12 weeks, followed by 100 mg for another 12 weeks, reduced the volume of the adenomyotic uterus and improved associated symptoms [69]. Other studies have also reported similar results, demonstrating the efficacy of linzagolix treatment for patients with adenomyosis [70, 71].

The efficacy of relugolix on the reduction of uterine volume and clinical symptoms for the treatment of adenomyosis has been investigated in a retrospective cohort study of patients with fibroids and eventually concomitant adenomyosis. After treatment, uterine volume significantly decreased in patients with adenomyosis coexisting with fibroids in comparison with those with only fibroids (43% versus 27%; $p = 0.009$). Irrespective of the group, adenomyosis showed a significant reduction compared with uterine fibroids ($p < 0.001$). There was no statistically significant difference in the mitigation of symptoms (amenorrhea, pelvic pain, and anemia) between patients with adenomyosis coexisting with fibroids and those with only fibroids [72].

2.7 Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) have both agonist and antagonist activity against PRs [73]. They are used as an alternative therapeutic option for hormone-dependent diseases such as uterine leiomyomas and endometriosis when other treatments are not feasible or have failed [74–76]. SPRMs have been shown to reduce pain, decrease menstrual flow, inhibit cell proliferation, and suppress inflammation [73]. However, there is limited evidence regarding their use specifically in women with adenomyosis, as most studies have primarily focused on their effects on endometriosis or uterine leiomyomas [77].

Mifepristone, an SPRM, has demonstrated an influence on caspase 3 expression in adenomyosis tissue, leading to cell apoptosis [78]. Recent findings suggest that mifepristone, may be effective in treating dysmenorrhea caused by adenomyosis. In particular, this drug has demonstrated anti-inflammatory properties by reducing the secretion of IL-6 and TNF-α from endometrial cells and limiting mast cell infiltration and degranulation in both eutopic and ectopic endometrium [79].

In a randomized, double-blind controlled pilot study [79], the effect of ulipristal acetate (UPA), an SPRM, was evaluated in the treatment of AUB caused by adenomyosis. The study demonstrated that a daily dose of 10 mg of UPA for 12 weeks resulted in a significant reduction in dysmenorrhea and menstrual volume without reported adverse effects. Different results were evidenced in a preliminary report by Ferrero et al. [80], who showed an improvement of bleeding but a worsening of pain symptoms and uterine ultrasonographic characteristics in patients with adenomyosis under UPA therapy. Another study reported frequent adverse symptoms

and a higher rate of treatment discontinuation in women with adenomyosis or uterine leiomyomas [81]. Additionally, sporadic cases of liver injury and liver failure were reported during post-marketing experience, which decrease the UPA use worldwide [82, 83]. Therefore, healthcare professionals should provide comprehensive information about the potential incidence of adverse symptoms to women considering ulipristal acetate treatment.

2.8 Aromatase Inhibitors

Aromatase inhibitors (AIs) target the enzyme aromatase P450, which is responsible for converting androgens into estrogens. In women with endometriosis, adenomyosis, and leiomyomas, there is an abnormal expression of aromatase P450, which is stimulated by prostaglandin E2. This seems to lead to increased estrogen production and further expression of prostaglandin E2, contributing to inflammation within ectopic endometriosis implants [84]. Third-generation AIs, such as anastrozole or letrozole, selectively inhibit aromatase P450 and have been studied for the treatment of endometriosis, either as monotherapy or in combination with other hormonal drugs [85, 86].

The use of AIs for adenomyosis has been investigated more recently. A case report described the successful management of a woman with severe adenomyosis who opted for conservative treatment using AIs in combination with GnRH-as [87]. Additionally, a study by Badawy et al., compared a 3-month treatment with letrozole (2.5 mg/day) with goserelin (3.6 mg/day), with no significant differences in the total uterine size between the post-treatment uterine volumes in the two groups. Total adenomyoma volume decreased by 40.9% and 49.1% at 12 weeks in patients receiving letrozole and goserelin, respectively ($p = 0.067$). The GnRH-a was more effective than letrozole in relieving chronic pelvic pain, dysmenorrhea, menorrhagia, metrorrhagia, and dyspareunia, but this difference was not significant. No woman receiving letrozole suffered from hot flashes, compared with 81.3% (13/16) women receiving the GnRH-a. Two patients receiving the AI became pregnant [64].

The literature reports two cases of endometrial cancer arising from adenomyosis during AI therapy after mastectomy [88]. However, it should be noted that larger case studies have not confirmed these findings.

2.9 Bromocriptine

Bromocriptine, a dopaminergic receptor agonist commonly used to treat hyperprolactinemia, may have therapeutic potential for women with adenomyosis. Studies in mice have shown that prolonged use of selective estrogen receptor modulators (SERMs) or inducing hyperprolactinemia can lead to the development of adenomyosis in certain strains of laboratory mice [89]. Although hyperprolactinemia has not been confirmed as a cause of adenomyosis in humans, bromocriptine could be beneficial in treating the condition.

In a pilot study, 23 women with diffuse adenomyosis were treated with vaginal bromocriptine to assess its impact on their symptoms [90]. Significant improvements were observed in AUB, dysmenorrhea, and quality of life following treatment with vaginal bromocriptine. Another study conducted by the same authors evaluated the effects of vaginal bromocriptine on MRI and vaginal ultrasound in patients with adenomyosis, particularly those with increased uterine size and wall asymmetry [91]. The results showed not only symptom improvement but also a reduction in uterine size and an improvement in uterine morphology.

2.10 Valproic Acid

Valproic acid, an anticonvulsant drug that acts as a specific inhibitor of histone deacetylase, has shown some potential efficacy in alleviating adenomyosis-related symptoms [92]. The increased expression of Class I histone deacetylase (HDAC) in adenomyotic tissue, correlated with the severity of dysmenorrhea, suggests its involvement in the development of the disease [93].

While valproic acid has been primarily used for epilepsy therapy [94], there have been limited studies indicating its effectiveness in treating adenomyosis-related symptoms.

Animal studies have shown that valproic acid not only reduces generalized hyperalgesia but also inhibits the invasion of endometriotic tissue into the myometrium and decreases myometrial contractions associated with dysmenorrhea [95, 96]. However, human studies on valproic acid's effects on adenomyosis are scarce and rely on limited patient follow-up experiences. Additionally, considering valproate's well-established teratogenicity and the fact that adenomyosis predominantly affects women of reproductive age [97], appropriate contraception strategies have to be employed when considering it as a long-term treatment option in the scientific setting.

A pilot study involving three patients with adenomyosis explored the off-label use of valproic acid to relieve dysmenorrhea [98]. The results demonstrated the complete disappearance of dysmenorrhea in all three patients after 3 months of treatment, along with an average one-third reduction in uterine size. In another study by Chinese authors [99], 12 patients with adenomyosis experiencing dysmenorrhea and enlarged uterus were treated with valproic acid for 3 months. The findings revealed complete resolution of dysmenorrhea, an average 26% reduction in uterus size 6 months after treatment, and a notable decrease in menstrual volume.

3 The Role of Medical Therapy in Infertility Related to Adenomyosis

It is already known that adenomyosis has adverse obstetric effects such as premature birth, preterm rupture of the membranes, and live birth rate [100]. Additionally, recent studies have shown that adenomyosis also negatively affects in vitro fertilization outcomes and may cause an increased risk of miscarriage. Anatomical factors such as the global enlargement of the uterus and its anatomical distortion by the presence of intramural adenomyoma can affect uterogamete and/or the embryo transport or the receptivity of the endometrium [101, 102]. Additionally, adenomyosis and endometriosis are highly comorbid conditions. Therefore, adenomyosis should be considered in the diagnosis and management of patients who are undergoing infertility treatment due to endometriosis.

While existing research on the medical treatment of adenomyosis focuses on AUB and dysmenorrhea, literature evaluating the medical treatment of adenomyosis-related infertility is very limited. Huang *et al.* conducted a retrospective study including nine adenomyosis patients with a history of unexplained infertility. All patients received a 6-month GnRH-a treatment following fertility-sparing surgery. They showed that the GnRH-a therapy had a positive effect on dysmenorrhea however the benefit on fertility was still questionable [103]. In a systematic review conducted by Rocha et al. in 2018, conservative treatments of adenomyosis-associated infertility were evaluated [102]. The authors reported a higher pooled spontaneous pregnancy rate after the administration of GnRH-as for 24 weeks following conservative surgery for adenomyosis. Cozzolino et al. [104] conducted a study among women with severe adenomyosis undergoing infertility treatment. They reported that in situations when long-term treatment ($\geq$ 3 months) with depot GnRH-as failed an additional treatment with an AI for 21 days could be beneficial prior to IVF treatment.

Intralipid comprises a sterile lipid emulsion composed of polyunsaturated fatty acids derived from soybean oil and egg yolk phospholipids. Lipid emulsions have been comprehensively documented to demonstrate a wide spectrum of immune-modulatory and anti-inflammatory effects, notably encompassing the suppression of natural killer (NK) cell activity [105]. Given that eutopic endometrium in individuals with adenomyosis often exhibits an inflammatory infiltrate characterized by elevated counts of macrophages and NK cells, the consideration of intralipid administration in the context of adenomyosis has been proposed [106]. In a retrospective cohort study involving 116 consecutive adenomyosis patients who underwent their initial transfer of a genetically screened euploid embryo, the administration of intralipid as an adjuvant treatment in conjunction with GnRH-a therapy (long downregulation) yielded markedly higher live birth rates (60%) in comparison to GnRH-a therapy alone (40%). This observed difference has been attributed to a twofold increase in the miscarriage rate observed in adenomyosis patients undergoing GnRH-a treatment without the inclusion of intralipid [107].

Another study from China by Liang et al., evaluated the effect of LNG-IUS on pregnancy rates of women with adenomyosis who were undergoing IVF treatment with a frozen embryo transfer cycle. When these women were treated with LNG-IUS prior to embryo transfer, higher pregnancy rates were reported in comparison with the controls [108]. However, these results are yet to be validated by randomized controlled trials. Additionally, the benefits of NSAIDs and/or oral contraceptives on the fertility of adenomyosis patients have also not been reported in the literature [109].

4 Discussion

To date, there is no approved medical therapy for adenomyosis, and the evidence for deciding which medical treatment is preferred is severely limited, partly because of the complexity of diagnosis, partly because of the prevalence of concomitant gynecological conditions, such as endometriosis and uterine leiomyomas, which often may influence the response to medical therapy, sometimes necessitating recourse to surgical approach. The concomitant prevalence of endometriosis in patients with adenomyosis is well-documented, with a significant number of individuals exhibiting both conditions simultaneously [110]. This overlapping occurrence poses challenges in the management of symptoms and treatment decisions. However, it has been observed that medical therapies targeting adenomyosis can also provide beneficial effects on symptoms related to endometriosis.

Currently, the available literature focuses mainly on the treatment of AUB, dysmenorrhea, and the attempt to restore the original volume of the enlarged uterus in cases of adenomyosis. Data evaluating fertility outcomes and the impact the disease may play on sex life and QoL in general after treatment are scarce and not supported by robust evidence. Nevertheless, scientific research evaluating new drugs for adenomyosis is active, as evidenced by the various ongoing trials in this field (Table 2).

Therapy with NSAIDs may only be useful as a support in the case of mild symptoms or re-exacerbation of symptoms during hormone therapy; however, if these drugs are effective in treating menstrual pain, no data are present related to the superiority of one NSAID in comparison with another; additionally, NSAIDs seems to be less effective than hormonal treatment or tranexamic acid on treating AUB associated to adenomyosis [20, 21].

Table 2 Ongoing trials on medical therapies for the treatment of adenomyosis

NCT number	Conditions	Study design	Interventions	Outcome measures
NCT05151016	Patients with adenomyosis	Randomized interventional study	Study Group: mifepristone 10 mg oral tablets, daily for 24 weeks	Change from baseline in pain on the visual analogue scale at week 24
			Control Group: Triptorelin Acetate 3.75 mg subcutaneous injection, every 28 days for 24 weeks	Pictorial blood loss assessment chart
				Change from baseline in uterine size at week 24
				Change from baseline in hemoglobin at week 24
				Change from baseline in CA125 at week 24
NCT03654144	Patients with adenomyosis	Randomized interventional study	Study Group: Dienogest oral tablet	Mean pain score
			Control Group: Combined Oral Contraceptive	
NCT03421639	Patients with adenomyosis Patients who underwent recurrent implantation failure	Randomized interventional study	Study group: oral anastrazole 1 mg/day oral tablet plus leuprolide 3.75 mg/monthly for 12 weeks	Pregnancy after embryo transfer Uterine volume reduction
			Control Group: leuprolide acetate 3.75 mg subcutaneous injection, every 28 days for 12 weeks	
NCT03037944	Patients with adenomyosis	Randomized interventional study	Group A: LNG- IUS 60 mg	Measurement of pain by an appropriate pain measurement score
			Group B: ethinyl estradiol 0.03 mg plus drospirenone 3 mg oral tablets, daily for 24 weeks.	Number of bleeding days
NCT02556411	Patients with adenomyosis	Randomized interventional study	Study group: LNG 0.10 mg plus ethinylestradiol 0.02 mg oral tablets, daily	Change of pelvic pain as measured by visual analogue scale Quality of sexual life
			Control group: LNG-IUS 13.5 mg.	

LNG-IUS levonorgestrel intrauterine system

LNG-IUS appears to be an effective first-line therapy for treating adenomyosis, which succeeds in improving symptoms and in decreasing the uterine size of patients affected [31–33]. The low incidence of adverse effects and the long duration of action, once this progestin-releasing device is inserted into the uterine cavity, make it one of the treatments of choice in cases of adenomyosis, reducing the need for surgical interventions. Several studies have investigated the efficacy of DNG in the treatment of adenomyosis and have reported promising results [42], with efficacy levels comparable to those of LNG-IUS, according to some authors [26]. Unfortunately, both in the case of LNG-IUS and particularly in the case of DNG, the limited number of studies available prevents us from attaining a high level of scientific evidence to provide definitive treatment recommendations in this context.

By reducing estrogen levels, danazol helps alleviate symptoms associated with adenomyosis such as pelvic pain and AUB. However, the use of danazol in adenomyosis therapy is limited due to its androgenic side effects, including weight gain, acne, and voice changes. These side effects can significantly impact patients' quality of life and may lead to noncompliance with treatment. However, if administered vaginally [55] or trans-cervically [56], it would seem to be able to guarantee good results in terms of remission of symptoms and restoration of uterine size. Furthermore, the availability of other hormonal options, such as progestins, with better tolerability profiles has led to a decrease in the use of danazol in adenomyosis therapy. At the best of our knowledge, no specific trials have been developed on the role of other progestins, such as desogestrel [DSG] and etonogestrel [ETG]-subdermal

implant, for treating patients with adenomyosis; however, it could be argued that these drugs could exert a similar benefit on pain symptoms owing to suppression of the hypothalamic–pituitary–ovarian axis and a less hypoestrogenic effect. In general, a potential disadvantage of progestins in women desiring contraception is that only few of them (DSG, ETG-subdermal implant and LNG-IUS) are approved as contraceptives.

COCs can be offered to young patients who do not desire to place LNG-IUS, and who do not tolerate the (often common) side effects occurring under oral progestin therapy, or who also requires contraception. Although successful in controlling dysmenorrhea and AUB due to adenomyosis, patients should be made aware of the possibility that treatment with COCs may be less effective than treatment with progestins, as previously reported [36].

GnRH-as have demonstrated effectiveness in managing symptoms related to adenomyosis, although at the moment they should be considered as second-line therapy for patients with adenomyosis. In fact, the use of GnRH-as is limited by its hypogonadal effects, and adherence to treatment without clear guidelines on add-back therapy is challenging for many women [65]. Nevertheless, the use of GnRH-as has been also employed prior to fertility treatments to improve the chances of pregnancy in infertile women with adenomyosis [111].

After being studied for the treatment of endometriosis [112, 113], new research is demanding to study the effectiveness and safety of GnRH-ants for treating adenomyosis. The principal purported advantages of GnRH-ants in the context of these hormonal-dependent diseases encompass dose-dependent estrogen suppression, spanning from partial suppression at lower doses to near-complete suppression at higher doses. However, GnRH-ants could maintain sufficient circulating estrogen levels for limiting vasomotor symptoms, vaginal atrophy, and loss of bone mineral density; additionally, they are characterized by immediate suppression of gonadotropins, circumventing the flare-up effect and by swift reversibility, with a return to normal hormone secretion following the cessation of treatment; lastly, they have oral administration for enhanced convenience. However, it is important to note that customizing the extent of hypoestrogenism may correlate with the degree of clinical response. In other words, reducing side effects may be linked to an incomplete alleviation of pain. Existing data suggests that lower dosages of GnRH-ants, particularly those tailored to maintain favorable estrogen levels to preserve bone density, may not provide comprehensive pain relief for individuals with endometriosis. It is worth noting that a similar scenario could also apply to adenomyosis, especially considering that in the majority of trials observing adenomyosis, there is a significant coexistence of endometriosis and adenomyosis in the enrolled patients [70, 71]. Nevertheless, more evidence is needed for drawing a conclusion on the role of GnRH-ants for treating adenomyosis, in particular, investigating the impact of a long-term regimen and the concomitant necessity of adopting an add-back therapy.

In light of the limited findings on the role of medical options for infertility and adenomyosis, the use of GnRH-as or progestins (oral or LNG-IUS) for 3 to 6 months prior to embryo transfer could be an option for patients who are undergoing IVF treatment with a frozen embryo transfer cycle. Additionally, considering the recent advancements in GnRH-ants, characterized by different dosages and biological activities, these agents might become increasingly significant in the treatment of adenomyosis-related infertility in the future.

The important point being made is that relying solely on GnRH-as or -ants to suppress ovarian estrogen production may not be sufficient to completely quiesce adenomyosis because of this local estrogen production by aromatase in the adenomyotic tissue itself [84]. To address this issue, the use of AIs has been investigated, showing efficacy for the improvement of AUB and pelvic pain associated with adenomyosis [64]. Nevertheless, the role of AIs in the management of adenomyosis requires further research, as previous data on their use consists in small nonrandomized trials. Additionally, the potential risk of endometrial cancer associated with AI use warrants careful consideration and requires clarification through additional investigations [88]. AIs could theoretically complement GnRH-as or GnRH-ants by further reducing the available estrogen, not only from the ovaries but also from the local enzymatic activity within the adenomyotic tissue. Although the combination of AIs and GnRH-as has been extensively investigated as adjuvant hormonal therapy for breast cancer [114], no data on adenomyosis are present in the current literature.

SPRMs have a controversial role in the management of adenomyosis, as data evaluating their role in this setting are limited. UPA has been evaluated in a few studies, reporting comprehensive data on symptom control [78]. However, there are international alerts suggesting a risk of serious liver problems associated with its use. Mifepristone, with its anti-inflammatory effect, may reduce symptoms and disease progression [79]; however, evidence related to this drug is very limited and larger patient numbers are needed to determine its actual efficacy.

Similar to endometriosis [115], the development, maintenance, and progression of adenomyosis are due to a variety of altered mechanisms including cell proliferation, immune function, apoptosis, invasion capacity, and angiogenesis. The growing knowledge of different molecular pathways involved in endometriosis development paved the way for the investigation of new drugs. Among them, in the future, modulation of prolactin [90, 91] and studies on the epigenetics of

adenomyosis [92] could provide new nonsteroidal therapeutic options for the treatment of adenomyosis. A significant factor contributing to the failure of numerous nonhormonal drug research, nonreaching late stage of scientific investigation in humans, is the lack of comprehension of the natural progression of ectopic endometrium, which is implied in the pathogenesis of adenomyosis and endometriosis [116, 117]. This often arises from the utilization of animal models that inadequately replicate the essential characteristics of human conditions.

In conclusion, adenomyosis remains a challenging condition to manage due to the lack of approved medical therapies and limited high-quality evidence supporting treatment decisions. The available literature primarily focuses on addressing symptoms such as AUB and dysmenorrhea, as well as reducing the size of the enlarged uterus. Future research should aim to elucidate the optimal therapeutic strategies for adenomyosis, explore novel nonsteroidal treatment options, and expand our understanding of the disease's impact on fertility and quality of life.

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