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UTERINE FIBROIDS AND ENDOMETRIAL LESIONS (T. TULANDI, SECTION EDITOR)

Medical Treatment of Adenomyosis

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Abstract

Purpose of Review This article aims to offer a comprehensive review about current and investigational adenomyosis therapies and to address the gaps in our knowledge about the underlying pathogenic mechanisms to aid in the evolution of novel drugs.

Recent Findings Despite the growing tendency to explore new drugs which target the underlying pathophysiology of adenomyosis rather than the traditional suppressive and symptomatic therapies, research directed to adenomyosis medical treatment is strongly limited.

Summary Adenomyosis is a common benign gynecological disease for which the underlying pathophysiology is not entirely known. Despite it being silent in about one-third of patients, it presents with painful symptoms, bleeding, and infertility in the other two-thirds. Current imaging technique advancements, particularly TVS and MRI, have led to substantial improvements in adenomyosis diagnosis. Adenomyosis management should be customized to each patient, considering a variety of factors such as the patient's age, complaints, wishes, and fertility plans. Currently, hysterectomy is the definitive therapy for adenomyosis. There is still inadequate evidence to justify the use of conservative surgical approaches in adenomyosis treatment: uterine artery embolization (UAE), high-intensity focused ultrasound (HIFU), magnetic resonance-guided high intensity focused ultrasound (MRgHIFU), hysteroscopic endometrial resection, or endo-myometrial ablation represent alternative therapeutic modalities. Adenomyosis medical treatment is still subject to debate as the majority of the currently used drug are off-label with no guidelines to follow for appropriate management, which usually targets symptomatic relief. By improving comprehension of the underlying pathogenesis of adenomyosis, new therapeutic options have become available and could be potential alternatives for the currently available drugs, which by majority act by influencing sex hormones.

Keywords Adenomyosis · Medical treatment · COCs · Progestins · LNG-IUS · GnRH agonists

Introduction

Adenomyosis is a chronic, benign uterine pathology that affects approximately one-fifth of reproductive females and can be identified by the existence of the basal endometrial glands inside the myometrium [1]. The disease burdens both the individual and the healthcare system, where 82% of adenomyosis patients necessitate hysterectomy and up to 38% need chronic pain treatment [2]. It is no longer believed that adenomyosis is more common in women over 40 years since it is identified in 22% of infertile patients below 40 years who are undergoing ART treatment [3]. The underlying pathogenesis of adenomyosis is not fully recognized; however, the most common risk factors are old age, multiparity, previous cesarean section, or uterine surgery [1, 4]. Major theories for adenomyosis origin and pathogenesis include the involvement of the tissue injury and repair mechanism (TIAR) proposing that an injured

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endometrial-myometrial junction zone (JZ), which may be attributed to hyperestrogenism, causes endometrial basalis invagination into the myometrium [5]; the assumption that adenomyosis develops from epithelial-mesenchymal metaplasia of the displaced embryonic pluripotent stem cell remnants or the adult stem cells [6]; and the "from outside to inside invasion" theory which proposes that ectopic endometrial cells establish in the myometrium from posterior compartmental endometriosis. Interestingly, the existence of KRAS mutations in adenomyotic lesion is associated with the co-development of endometriosis [7, 8].

Adenomyosis is an estrogen-dependent disease and commonly related to conditions associated with hyperestrogenism like fibroids, endometrial hyperplasia, and endometriosis [1]. High-contrast MRI imaging indicated that adenomyosis occurs in 65% of endometriosis patients. Moreover, focal adenomyoma in the outer portion of the myometrium (FOAM) is commonly related to deep infiltrating endometriosis (DIE) [7]. Adenomyosis has been linked to endometrial progesterone resistance [9]. Additionally, adenomyosis has been associated with a process of chronic inflammation and increased oxidative stress with demonstrated increased levels of interleukins, neurotrophils, free radicals like nitric oxide, and increased macrophage activation in endometrium [10–12]. Neoangiogenic factors, matrix metalloproteinase enzymes, growth factors, and changes in the apoptosis can also have a role in adenomyosis development [4]. Affected uteri are usually enlarged with hypertrophic myometrial smooth muscle areas; thus, adenomyosis can be classified as a diffuse phenotype with a number of small lesions scattered all through the myometrium, a focal phenotype in which nodular endometrial tissue aggregates are encircled by normal myometrium, or an adenomyoma when the endometrial ectopic tissue is enclosed by hypertrophic myometrium [13]. However, a more structured categorization and detailed classification with universal acceptance that includes the association between specific subtypes and patient symptomatology is required [14].

Histopathological analysis of adenomyosis reveals that inside the myometrium, there exists ectopic basal endometrial tissue, surrounded by hypertrophic and hyperplastic smooth muscle, located at varying depths [15]. Multiple histological diagnostic criteria have been suggested, including affection of at least one-fourth of myometrial thickness, infiltration of about one-half: 2 low-power fields from the endometrial–myometrial junctional zone (JZ) and a minimal invasion depth of 0.1:0.4 cm [1]. Despite the fact that ~33% of adenomyosis patients are usually asymptomatic, they usually present clinically with incapacitating symptoms including infertility, abnormal uterine bleeding (in the PALMCOEIN FIGO, adenomyosis is classified as a distinct entity), and/or patterns of pelvic pain such as chronic pelvic pain (CPP), dysmenorrheal, and dyspareunia [1]. The relationship between adenomyosis and infertility is complex. In a recent cross-sectional study, infertility was not linked to diffuse adenomyosis. However, the presence of focal adenomyosis of the outer myometrium (FAOM) was revealed to be an independently associated factor of 1 ry infertility following a multinomial regression model, which included the women's age and correlated endometriosis or fibroid (adjusted odds ratio 1.9; 95% confidence interval 1.1–3.3) [16]. Figure 1 shows MRI images for different adenomyosis phenotypes and various concomitant pathologies.

Contradictory data exists between the results of assisted reproductive technology (ART) and adenomyosis as some reports claim that adenomyosis patients were associated with significantly lower clinical pregnancy rates and increased miscarriage rates following IVF/ICSI [17–21]; in contrast, another study showed that implantation rate was not greatly affected in asymptomatic adenomyosis patients during IVF treatment [22]. Adenomyosis may be related to increased risk for some adverse obstetrics outcomes such as increased risk of second-trimester abortion, pregnancy induced hypertension, prematurity, malpresentations, increased incidence for caesarean delivery, PPROM, abnormal placental position, IUGR, and post-partum hemorrhage [18].

Although many patients struggle perpetually until adenomyosis is diagnosed [4], recent advancements in imaging techniques have resulted in significant improvements in adenomyosis diagnosis. Particularly with early diagnosis, accuracy has now increased to 80–90% [23] since the Morphological Uterus Sonographic Assessment (MUSA) criteria provided a standardized, consistent reporting system of adenomyosis ultrasound findings [24, 25, 26••]. Hysteroscopy allows for direct inspection

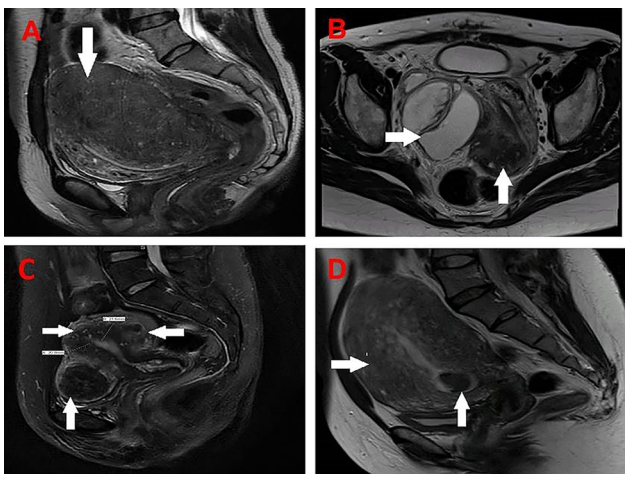

Fig. 1 MRI images for different adenomyosis phenotypes and various concomitant pathologies. **A** MRI image for posterior focal adenomyosis. **B** MRI image for concomitant focal adenomyosis and endometriosis. **C** MRI image for concomitant diffuse adenomyosis and fibroid. **D** MRI image for concomitant diffuse adenomyosis and uterine polyp

of uterine cavity as well as directed tissues sampling for histopathological examination with little risk [27], but the hysteroscopic appearance alone is of little value in diagnosing adenomyosis especially in cases of deep adenomyosis due to decreased specificity and sensitivity [28]. Uterine artery embolization (UAE), high-intensity focused ultrasound (HIFU), MRI guided HIFU (MRgHIFU), hysteroscopic endometrial resection, or endo-myometrial ablation represents alternative modalities for patients who need to preserve their uteri, who do not wish to perform a surgical intervention or those in whom surgery is contraindicated/risky [11, 12]. Surgical treatment for adenomyosis entails hysterectomy which is the most efficient option for symptomatic control and the definitive therapy in those who completed their families [29]. Conservative surgical approaches include adenomyomectomy, which have been evolved for patients to maintain their uteri and have yielded positive results [21]. However, there is still a lack of evidence to support conservative surgical use in adenomyosis treatment, as it is still technically difficult and related to higher risk of uterine rupture and/or recurrence of lesions after surgery. Moreover, there still exist frequent debates about their indications and the technical aspects [30]. Several techniques have been tried, such as the triple-flap technique described by Osada which could be employed for patients with diffuse and localized adenomyosis after appropriate counseling [31•]. The focus of this article will be on medical treatment of symptomatic adenomyosis.

Current Medical Treatment Options of Adenomyosis

Adenomyosis medical treatment is subject to debate as the majority of currently used drug are off-label with no guidelines to follow for appropriate management [32]. Considering the disease's devastating symptoms, negative impact on quality of life, high prevalence, and chronic course, the need for better long-term treatment options is required [33]. Adenomyosis medical treatment usually targets symptomatic relief in the form of pain alleviation and bleeding control, which is especially important for patients who want to restore or remain fertile [12]. Even though the majority of current treatment options influence sex steroid hormones and are primarily used as contraceptives or for the treatment of associated pathologies, the enhanced knowledge about the underlying pathogenesis paved the way for new therapeutic options which could be potential alternatives for the currently available drugs [34].

The mechanisms of action of the different medications used for the treatment of adenomyosis are detailed in Fig. 2.

Non-steroidal Anti-inflammatory Drugs

NSAIDs function by inhibiting cyclooxygenase (COX) enzymes, rate-limiting enzymes in prostaglandin production [35]. Although research on the specific use of NSAIDs in adenomyosis does not currently exist, they are frequently used as symptomatic treatment to alleviate pelvic pain and control heavy menstruation [33]. However, they are ineffective in approximately 18% of dysmenorrhea patients [36]. Commonly used NSAIDs are salicylic acid, indomethacin, ibuprofen, and mefenamic acid with no evidence on whether any individual NSAID is more efficacious than the other [35].

Combined Oral Contraceptives

The use of COCs in adenomyosis treatment is based on their ability to suppress ovarian hormones secretion with subsequent reduction in estrogen-induced prostaglandins production. In addition, they decrease the amount of withdrawal bleeding because of induced decidualization and decreased endometrial growth. Furthermore, COCs have the ability to inhibit aromatase expression decreasing the local estrogen production [33]. Most of data on COCs use are adapted from endometriosis studies, fibroids, or abnormal uterine bleeding treatment. In a RCT, the use of COCs (gestodene 75 mcg + ethinylestradiol 30 mcg) was proven to be effective in relieving pain, reducing bleeding associated with adenomyosis, and reducing uterine volume. However, this efficacy was inferior to that of LNG-IUS [38].

Progestins

Progestins have central and peripheral mechanisms of action, which involve their ability to induce decidualization and atrophy of both eutopic and ectopic endometrium. Additionally, by lowering serum levels of ovarian steroids by inhibiting LH surge [39]. However, progesterone resistance restricts their effectiveness [40].

Levonorgestrel Intrauterine System

Within its T-shape, the LNG-IUS device holds 52 mg of Levonorgestrel releasing 20 mg of Levonorgestrel each day over 5-year duration in the uterine cavity [41]. It exerts a suppressive effect through a high Levonorgestrel concentration in the endometrial cavity, which reduces the expression of glandular and stromal oestrogen and progesterone receptors. This causes glandular atrophy and stromal decidualization with establishment of amenorrhea in about 20% of its users within 12 months, which helps in alleviating pain and bleeding symptoms as well as reducing the lesion size [41]. Additionally, it reduces endometrial prostaglandin synthesis and decreases myometrial junctional zone thickness and uterine volume [33].

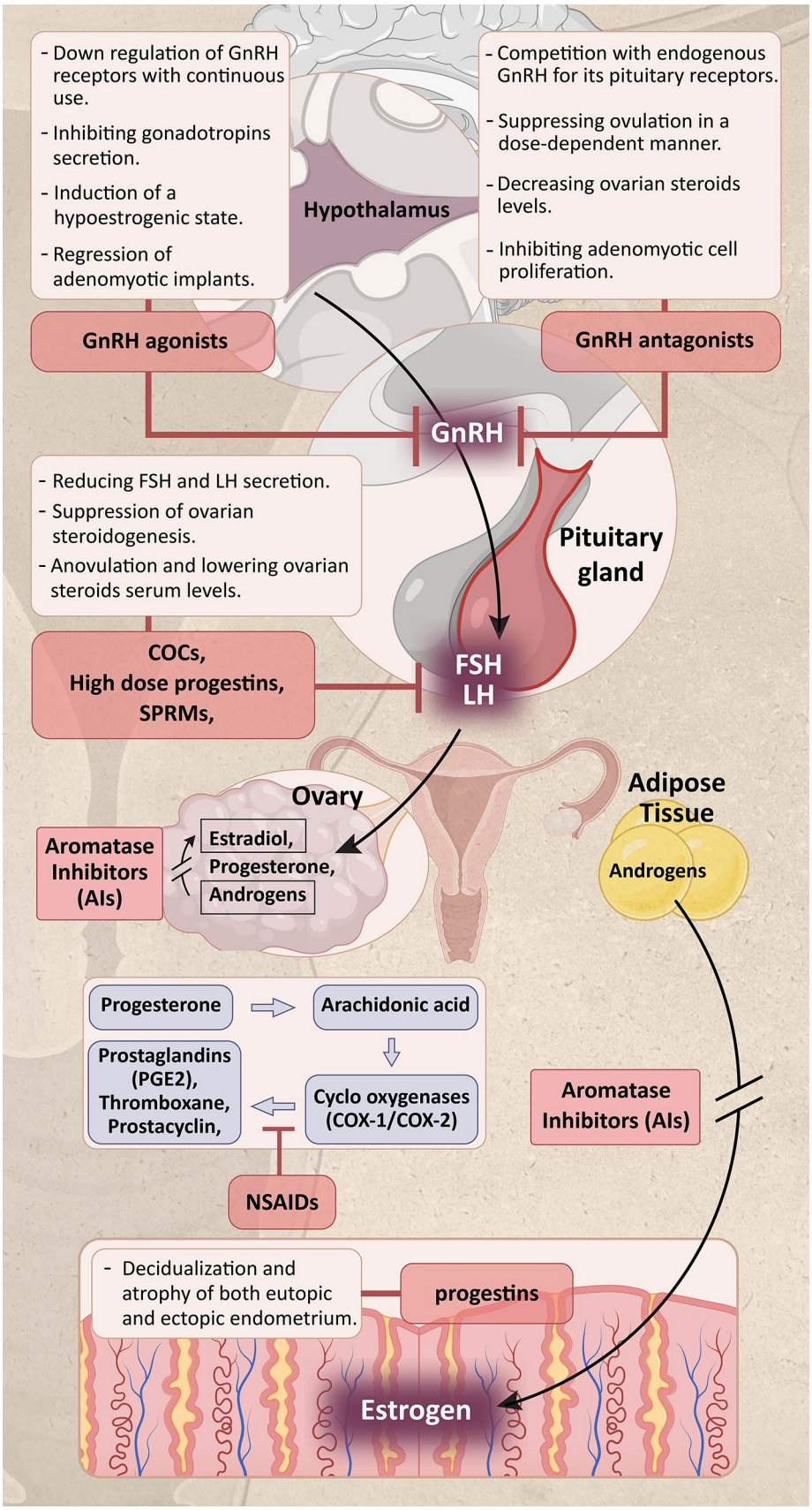

Fig. 2 Mechanisms of action of the different medications used for the treatment of adenomyosis. AIs aromatase inhibitors, COCs combined oral contraceptive pills, COX-1 cyclooxygenase-1, COX-2 cyclooxygenase-2, FSH follicle stimulating hormone, GnRH gonadotropin releasing hormone, LH luteinizing hormone, NSAIDs non-steroidal antiinflammatory drugs, PGE2 Prostaglandin E2, SPRMs selective progesterone receptor modulators

LNG-IUS is the most-studied medical treatment in adenomyosis (Table 1). With the largest RCT, including 86 adenomyosis patients demonstrating improvement in hemoglobin levels compared to hysterectomy patients, LNG-IUS appears to have the greatest impact on psychological and social well-being [42•]. It is recommended by the National Institute for Health and Care Excellence (NICE) as the first line of therapy for HMB in adenomyosis patients [43•]. LNG-IUS significantly improves adenomyosis symptomatology, laboratory results, decrease uterine size, and endometrial thickness [44, 45]. LNG-IUS could be a valuable option for decreasing recurrence after adenomyomectomy and maintaining the long-term therapeutic effects of HIFU in the long-term follow-up [46, 47]. The long-term benefits of LNG-IUS have been evaluated in a prospective longitudinal study including 1100 symptomatic adenomyosis patients, and the results revealed that all patients who completed 5 years of LNG-IUS treatment had significant improvements as regard dysmenorrhea, menstrual flow, hemoglobin level, uterine volume, and CA125 serum level in comparison to their baseline with side effects incidence being < 10% [48]. Efficacy of LNG-IUS in combination with major uterine wall resection and reconstruction of the uterus has been demonstrated in a study including 90 patients with severe adenomyosis. Results showed complete resolution of dysmenorrhea in all patients, restoration of uterine volume, and CA 125 serum levels to normal ranges without any recurrence noted during the follow-up [49]. LNG-IUS is a long-term, reversible, and cost-effective therapeutic option for adenomyosis, which provides numerous advantages including its accepted side effect profile as it delivers progesterone locally, so the systemic side effects are spared. Additionally, it avoids daily intake with subsequent fluctuating serum levels and poor compliance [50]. However, a limitation in LNG-IUS use among adenomyosis patients is the higher expulsion rate. This may be due to uterine cavity enlargement, heavy menstrual flow, abnormal uterine contractility, and concomitant pathologies like fibroids, insertion time, and technique [51].

Dienogest

DNG is a selective progestin that can inhibit ovulation and decrease the expression of nerve growth factors, as well as nerve fiber density [52]. The progestogen has been supported by the most evidence and achieved positive outcomes in endometriosis treatment [53]. It improves dysmenorrhea and excessive menstrual flow in adenomyosis patients efficiently [33]. The efficacy and tolerability of DNG were tested in two RCTs against LNG-IUS for 6 years and against COCs for treating symptomatic adenomyosis. DNG demonstrated efficacy in relieving pain, controlling heavy bleeding, decreasing the number of bleeding days, decreasing uterine size, and uterine artery blood flow with comparable BMD loss to LNG-IUS [54, 55]. However, it is associated with more adverse effects than COCs [54]. In a 4-month Phase III randomized, multicenter double-blind, placebo-controlled study in Japan, DNG's effectiveness and tolerability in adenomyosis pain treatment were investigated and results reported significant improvements in visual analogue scale and pain scores. Unfortunately, no decrease in uterine size has been reported. The most frequently reported adverse effect was abnormal vaginal bleeding, which occurred in nearly all patients, so DNG can be a good therapeutic option for adenomyosis related pain not associated with significant anemia or uterine enlargement [56]. DNG was able to prevent symptom recurrence when administered after GnRH treatment but it was not able to maintain uterine volume improvement, as it came back to pretreatment levels in many patients [57]. Long-term DNG therapy adequately alleviated pelvic pains, decreased the analgesic requirement, improved heavy bleeding, and enhanced quality of life with tolerable adverse effects and little effects on BMD [58–60]. Postoperative DNG was efficient in controlling adenomyosis associated pain and bleeding following microwave endometrial ablation [61]. Patients taking dienogest face the possibility of treatment discontinuation due to increased incidence of associated abnormal uterine bleeding, hot flushes, and depression [59].

NETA

NETA is an orally active synthetic progestin derived from 19-nor-testosterone, which is approved by FDA for endometriosis treatment [41]. It can be a safe, well-tolerated, and cost effective option for adenomyosis treatment but, there is no research assessing its effectiveness in comparison to other therapeutic options or studies assessing the impact on clinical symptoms and radiological features after treatment cessation [33]. Only one small retrospective study investigated the efficacy of NETA in 28 adenomyosis patients and revealed that low dose NETA can relief pain and control heavy bleeding [62].

GnRH Agonists

GnRH agonists are group of synthetic GnRH derivatives with multiple formulations and preparations [63]. Their use in adenomyosis treatment is justified by their ability to inhibit ovarian hormone secretion by down-regulating GnRH receptors and inducing a hypoestrogenic state that is beneficial in reducing bleeding up to amenorrhea, relieving pain, and reducing uterine volume. Additionally, as they can induce apoptosis, they take direct antiproliferative action on adenomyotic lesions. Moreover, they can control the inflammation, inhibit angiogenesis and reduce nitrite/nitrate levels [64–66]. Various studies

Table 1 Studies assessing effectiveness of LNG-IUS in adenomyosis treatment

Author, Year	Study aim	Study design	Comment
Ota et al. (2021) [55]	To compare LNG-IUS vs. DNG	Controlled clinical trial	- LNG-IUS and DNG similarly improved pain scores, however after 3 months, DNG is a more efficacious treatment - Days of bleeding are effectively lessened by DNG - Both medications result in transient decrease in uterine size - BMD decrease is comparable with both drugs
Shaaban et al. (2015) [38]	To compare LNG-IUS vs. COCs	Prospective RCT	Both treatments alleviated pain and bleeding and decreased uterine size but the LNG-IUS group experienced more improvement
Ozdegirmenci et al. (2011) [42•]	To compare LNG-IUS vs. hysterectomy	Prospective RCT	- LNG-IUS & hysterectomy comparably increased hemoglobin concentrations - Both interventions enhanced health-related QOL, but LNG-IUS had a greater impact on psychological and social well-being
Costanzi et al. (2021) [45]	To assess the effectiveness of LNG-IUS in improving clinical symptoms and sonographic aspects of menometrorrhagia and dysmenorrheal in patients with and without adenomyosis	Prospective cohort study	- The size of the uterus in both cohorts decreased significantly after 6 months - Uterine morphology improved in adenomyosis cohort - The blood loss decreased significantly in both cohorts, specifically in adenomyotic patients - pain is relieved in both groups
Hai et al. (2021) [117]	To evaluate the effectiveness of transvaginal ultrasound-guided radiofrequency ablation (RFA) and LNG-IUS for adenomyosis treatment	Prospective study	3-year follow-up evaluations after treatment: - LNG-IUS expulsion was not documented -Dysmenorrhea and symptom severity scores effectively improved - The size of the uterus decreased by 55%
Xu et al.(2021) [46]	To investigate the effectiveness of LNG-IUS Vs. GnRH agonist in combination with HIFU in treating dysmenorrhea related to severe adenomyosis	Retrospective analysis	Alleviating dysmenorrhea is possible with HIFU alone in the short-term but when combined with LNG-IUS the therapeutic effect is maintained for long-term
Yang et al. (2019) [118]	To assess the effectiveness of HIFU in combination with GnRH agonist and the LNG-IUS in severe adenomyosis treatment	Prospective observational study	After the combined treatment: - Menorrhagia and painful menses significantly improved - The uterine volume and CA-125 were back to their normal levels
Liang et al. (2019) [119]	To study the outcome of LNG IUS as a pretreatment on IVF and vitrified–warmed ET outcomes in adenomyosis patients	Retrospective study	LNG-IUS use improved implantation rates and clinical pregnancy rates
Gupta et al. (2019) [120]	To estimate the effectiveness of LNG-IUS in the treatment of HMB and dysmenorrhea associated with adenomyosis	Observational study	- Dysmenorrhea, HMB, and hemoglobin levels are improved significantly -Uterine volume did not change significantly -Prolonged vaginal spotting and abdominal pain were common side effects - 1 patient demonstrated LNG-IUS expulsion -3 patients underwent hysterectomy -LNG-IUS overall success rate was 82.5%

Table 1 (continued)

Author, Year	Study aim	Study design	Comment
Li et al. (2018) [48]	To evaluate the long-term effects of using LNG-IUS in adenomyosis treatment	Prospective longitudinal study	- Uterine volume, hemoglobin level, PBAC score, verbal rating scale, the VAS and serum CA125 level are significantly improved - Minimal side effects were observed
Radzinsky et al. (2016) [121]	To determine the effectiveness of LNG-IUS in chronic pelvic pain treatment of due to adenomyosis and prevention of adenomyosis recurrence	Prospective continuing study	- Compared to baselines, pain scores pain and severe pelvic pain ratio improved significantly - The most encountered side effects were intermenstrual bleeding, headache and acne
Lee et al. (2016) [122]	To investigate the relationship between uterine volume and LNG-IUS failure in adenomyosis patients	Retrospective study	- LNG-IUS failure rate was related to uterine volume in adenomyosis patients - The uterine volume > 150 mL was significantly related to LNG-IUS failure
Miglani and Singh (2015) [123]	To evaluate effectiveness of LNG-IUS in patients with menorrhagia due to a variety of gynaecological diseases	Non-comparative longitudinal observational study	Over 2 years, there was a significant decrease in bleeding days and increase in hemoglobin levels
Ma et al. (2015) [124]	To assess efficiency of LNG-IUS in controlling heavy menstrual bleeding due to adenomyosis	Prospective, observational study	LNG-IUS is an efficient and safe option in improving menorrhagia, dysmenorrhea and enhancing QOL
Ekin et al. 2013[125]	To assess efficiency of LNG-IUS in improvement urinary incontinence in adenomyosis patients with menorrhagia and dysmenorrhea	Prospective, observational study	Urinary incontinence, obstructive and irritative urinary symptoms were improved in adenomyosis patients using LNG-IUS treatment for menorrhagia and dysmenorrhea
Zhang et al. (2013) [126]	To assess the clinical outcomes of GnRH agonist and LNG-IUS in patients with significantly enlarged uteruses due to adenomyosis	Prospective, observational study	- One year after LNG-IUS insertion, there was a relevant decrease in menstrual flow, painful menses, and uterine volume compared to baseline values - LNG-IUS expulsion rate is 14% -There were minimal side effects of LNG-IUS implantation combined with GnRH agonist
Bragheto et al. (2007) [127]	To evaluate the efficiency of LNG-IUS on adenomyotic lesions diagnosed and followed up by MRI	Prospective, observational study	- Junctional zone thickness significantly decreased without significant decrease in uterine volume between baseline and the 6-month evaluation - Pain score significantly improved at 3 and 6 months post insertion
Sheng et al. (2006) [128]	To assess the safety and effectiveness of LNG-IUS in adenomyosis associated dysmenorrhea	Prospective, observational study	- After 1 year, there were significant enhancements in mean VAS and VRS scores of dysmenorrhea and dyspareunia - 66% of patients were very satisfied or satisfied with the treatment
Laoag et al. (2003) [129]	To assess the impacts of LNG-IUS on VEGF and adrenomedullin (AM) expression in the endometrium of adenomyosis patients	Prospective observational study	Decreased expression of VEGF and increased expression of AM in the endometrial glands and stroma resulted after 3 months of from LNG-IUS treatment
Maia et al. (2003) [130]	To assess efficacy of LNG-IUS after endometrial resection	Randomized, observational study	The LNG-IUS group had higher amenorrhea rates after 12 months and 19% of patients in the control group had a subsequent intervention to improve bleeding compared to none in the LNG-IUS group

have proven the efficacy of different GnRH agonist preparations in controlling adenomyosis symptoms including abnormal bleeding, pelvic pain, and cramping menses. GnRH agonists in combination with LNG-IUS were effective in decreasing recurrence and extending recurrent free survival after adenomyomectomy in young patients [47]. There is a scarcity of information on the effect of adenomyosis treatment with GnRH agonists on future fertility [34]. GnRH agonist treatment has shown to achieve better pregnancy outcomes in adenomyosis mice model by improving endometrial receptivity through increasing the expression of Hoxa10, Hoxa11, integrin b3, and Lif mRNA and protein that shed light on the possible molecular mechanism of actions of GnRH agonist in adenomyosis treatment [67]. In a multicenter observational open-label study, treatment with intramuscular triptorelin 3.75 mg every 28 days yielded pregnancy in 24.9% of patients within 9 months after the treatment had ended [68]. Contradictory data exists about the role of GnRH agonist pretreatment in improving pregnancy outcomes in infertile adenomyosis patients undergoing ICSI and IVF treatment, with some studies advocating that pretreatment with GnRH agonist could be significantly beneficial in improving pregnancy outcomes during IVF and ICSI [19, 69, 70], while others claim that live birth rate does not improve with GnRH agonist pre-treatment before starting the long GnRH agonist protocol, nor does the cumulative live birth rate in infertile adenomyosis patients undergoing IVF/ICSI treatment [71]. Additionally, GnRH agonist pretreatment has not improve IVF outcomes in fresh embryo transfer (ET) cycles as controlled ovarian stimulation after GnRH agonist pretreatment results in increased estrogen concentrations which may reactivate the disease, meanwhile frozen embryo transfer (FET) after GnRH agonist treatment has better chance for achieving pregnancy [72, 73]. The combination of conservative adenomyosis surgery and GnRH agonist failed to achieve pregnancy in two-thirds of the patients with severe adenomyosis and more than 3 years of unexplained infertility in a small, long-term retrospective study [74]. Concerning issues regarding GnRH agonists include that with the start of administration of treatment, they stimulate pituitary FSH and LH secretions that may flare up symptoms like increased pain and excessive bleeding. Another issue is their hypoestrogenic side (e.g., hot flushes, mood swings, headache, and urogenital atrophy) which limit their long-term use and can cause treatment discontinuation. Moreover, they can cause relevant decrease in BMD which potentially increasing the risk of osteoporotic fractures. So, add-back therapy is recommended to control these hypoestrogenic side effects especially when GnRH agonists are used for long-term [63, 75].

GnRH Antagonists

A critical element in adenomyosis treatment is to control estrogen levels to maintain the effectiveness of treatment and concurrently minimize hypoestrogenic adverse effects. GnRH antagonists have the ability to inhibit estrogen secretion in a dose-dependent manner through gonadotropin secretion inhibition by acting as antagonists on GnRH receptors in the pituitary gland [76]. This decreases flare-up, that does occurs with GnRH agonists, which means no initial symptom aggravation and rapid reversibility upon treatment discontinuation [77]. Their encouraging results in endometriosis treatment make them a promising therapeutic option for adenomyosis [78]. GnRH antagonists can theoretically inhibit the growth of ectopic endometrial implantations in the myometrium, alleviate adenomyosis-related pain, and reduce uterine volume with lowered incidence of hypoestrogenism when dosages are adjusted [79]. Thus, there is no need for Add-back therapy at partial suppression doses, but it may be prescribed in full suppression doses. Elagolix (GnRH antagonist) accompanying add-back therapy efficiently improved menorrhagia in patients with uterine fibroids and concomitant adenomyosis in 2 identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials, indicating that elagolix efficiency was not impaired by adenomyosis being present [80]. Effectiveness of linzagolix (GnRH antagonist) at high full suppression dose after 3 months treatment in regard to controlling pain and bleeding symptoms, decreasing adenomyotic uterine volume as well as enhancing QoL, has been demonstrated in a recently published single-center, open-label exploratory pilot study in patients with diffuse adenomyosis with the results showing a reduction of 32% of the uterine volume after 6 months of treatment; these benefits have been maintained with 100 mg doses while decreasing the adverse effects [81]. A case report by Kavoussi et al. was the first report to demonstrate the ability of elagolix in decreasing the size of an adenomyoma as well as relieving pelvic pain in a 41-year-old patient who refused surgical treatment, NETA 5 mg daily continued to control hot flushes [82•]. More RCTs are required to investigate the efficacy and tolerability of GnRH antagonists in adenomyosis treatment.

Aromatase Inhibitors

Third-generation AIs (anastrazole, letrozole, vorozole, and exemestane) reduce local estrogen production by inducing a hypoestrogenic state by inhibiting aromatase P450, the key enzyme in conversion of androstenedione and testosterone to estrone and estradiol, respectively, and thus causes overexpression in adenomyotic and endometriotic tissues [33]. Anastrazole (AI) was given orally for 4 months combined with GnRH agonists in a patient with severe adenomyosis

who desired to maintain her fertility and was unresponsive to GnRH analogues and danazol and after 2 months of treatment, the uterine volume was reduced by 60%, and the patient had no AUB for 24 weeks after the AI was stopped [83]. Given their associated hypoestrogenic side effects and the associated ovarian cyst formation, they are typically used in combination with progestins [84]. Despite the fact that the use of AIs in endometriosis and adenomyosis treatment are off label, they appear to have a potential for adenomyosis treatment especially in resistant cases.

SPRMs

SPRMs are class of drugs that have the ability to interact with progesterone receptors in different tissues in various ways and depending on the expression of progesterone receptors in these tissues; they can act as pure antagonists, pure agonists, or partial antagonists/agonists. Moreover, SPRMs have revealed to inhibit the proliferation of endometrial epithelial and stromal cells in addition to their anti-inflammatory properties [85]; thus, they can be considered a beneficial therapeutic option for hormone-dependent disorders such as endometriosis, fibroids, and adenomyosis. Mifepristone (RU486), a predominantly progesterone antagonist SPRM, has been demonstrated to induce cell cycle arrest, induce cell apoptosis, and inhibit endometrial epithelial and stromal cell migration and invasion. Additionally, Mifepristone inhibits TNF α and IL-6 secretions from endometrial epithelial and stromal cells and mast cell infiltration and degranulation in ectopic and eutopic endometrium [85, 86]. Moreover, Mifepristone use is associated with significant improvement in painful menses and hemoglobin concentration in addition to reducing uterine volume and CA125 levels in adenomyosis patients [86, 87]. Ulipristal acetate (UPA) is another potent SPRM, which is approved as a fibroid treatment in Europe and Canada and as an emergency contraceptive in the US [88]. In a double-blind phase 2 randomized controlled pilot study, Ulipristal acetate demonstrated to be a promising treatment for pre-operative preparation to correct anemia. However, it cannot be used as a long-term therapeutic option to avoid surgery in adenomyosis patients due to concerns about liver toxicity with the long-term use [89]. In a retrospective study, a 3-month course of daily 5 mg UPA showed a significant improvement in pain and bleeding associated with adenomyosis with high rate of amenorrhea in a group of patients who also had fibroids. However, the retrospective nature and concomitant fibroid pathology limit this study [90]. There are many concerns around the use of UPA in adenomyosis treatment, such as non-physiological endometrial changes that were observed with UPA therapy called progesterone receptor modulator-associated endometrial changes (PAEC); fortunately, such deviations were reversible within 3 months of treatment discontinuation [91]. Moreover, a case report of a patient with severe and diffusing adenomyosis revealed paradoxical worsening of clinical and MRI findings with UPA treatment, which necessitated treatment withdrawal, in contrast to linzagolix treatment (GnRH antagonist) which produced significant clinical and radiological improvements [92]. These conclusions have been confirmed in adenomyosis patients treated with UPA due to an incorrect diagnosis of uterine fibroids and showed worsening of their painful symptoms as well as the ultrasonographic features indicative of adenomyosis [93•]. In another prospective pilot study, UPA treatment for 3 months caused intramyometrial adenomyotic lesions in 26.3% of cases in whom adenomyosis not diagnosed before treatment as well as worsening of the MRI findings in 80.0% of patients with pre-treatment MRI diagnosis of adenomyosis [94•]. These studies indicate that UPA may give the rise to adenomyosis or hasten its progression through its associated side effects [95]. Another safety concern, which limited its use in clinical practice, is the proposed severe liver injury, potentially requiring liver transplantation which led to its withdrawal from the market and it is no longer available [96].

Androgenic Derivatives

Danazol and Gestrinone are androgenic derivatives, which have antigonadotropic, hypoestrogenic, and hyperandrogenic properties [97]. They inhibit FSH and LH secretions, have anti-estrogen and anti-progestin activities on ectopic and eutopic endometrium, and have decreased sex hormone-binding globulin concentrations and higher free testosterone levels, so they can be treatment options for endometriosis and adenomyosis [97]. However, there exists little evidence on the systemic use of danazol in adenomyosis and endometriosis treatment due to the high prevalence of androgenic adverse effects [37]. Alternative routes (e.g., vaginal tablets, cervical injections, or Danazol loaded IUDs) have been evaluated in a number of studies with proven efficacy in controlling pain and bleeding symptoms, as well as decreasing uterine volume in adenomyosis patients as the local delivery system guarantees that the therapeutic tissue level is at its peak with fewer side effects due to decreased serum concentrations [98–100]. Moreover, there may be a beneficial impact on fertility after danazol IUD withdrawal [98].

Investigational/Future Medical Therapies

Valproic Acid

Class I histone deacetylase has been expressed increasingly in ectopic and eutopic endometrium in adenomyosis patients [101]. Valproic acid, which is used primarily as

an epilepsy treatment, is a specific and efficient histone deacetylase inhibitor, which has been revealed to be efficient in reducing dysmenorrhea and uterine bleeding as well as decreasing uterus size in a case series of adenomyosis patients [102, 103]. Additionally, research on murine adenomyosis models revealed the ability of valproic acid to reduce the uterine spasm, inhibit myometrial infiltration, and alleviate hyperalgesia [104, 105]. However, there are no clinical trials to assess the effectiveness of valproic acid in adenomyosis.

Anti-platelets

Anti-platelet use in adenomyosis treatment is supported by the theory that claims that adenomyosis is developed through an injury in the endometrial–myometrial junctional zone (JZ) in which platelets induce fibrosis [106]. In a unique animal study, it has been revealed that thromboxane A2 synthase inhibitor (an Anti-platelet therapy) is effective in decreasing uterine spasm, inhibiting myometrial infiltration, alleviating hyperalgesia as well as decreasing serum corticosteroid levels. Furthermore, a decrease in the expression of several proteins implicated in adenomyosis fibrogenesis was observed [107]. No human studies exist to assess the value of antiplatelet in adenomyosis treatment until now, so further research is required.

Dopamine Agonists

Dopamine agonists are group of drugs used primarily for hyperprolactinemia treatment and suppression of lactation. Despite the role of prolactin in adenomyosis pathogenesis not being sufficiently understood, it has been revealed that prolactin and its receptors are up regulated in adenomyotic tissue implying a link between the hormone and the disease. Thus, dopamine agonists, which are prolactin suppressors, can have a role in adenomyosis treatment [108]. Vaginal Bromocriptine (a Dopamine agonist), at a daily dose of 5 mg, has been demonstrated to be effective in controlling excessive bleeding, relieving pelvic pain and enhancement the QoL in a pilot study by Andersson et al. [109]. Moreover, thinning of the maximal JZ and decreased myometrial wall thickness was observed in 33% of patients who followed vaginal Bromocriptine treatment for 6 months [110]. However, there were no significant changes in other adenomyosis sonographic features such as the irregular endometrial-myometrial border, the presence of shadowing, striations cystic changes, or hyperechogenic islands. Additionally, no significant differences existed in JZ max on MRI scans after the treatment [110].

Oxytocin Antagonist

Upregulation of oxytocin receptors has been observed in the uteri of adenomyosis patients and has been linked to uterine spasm and cramping menses [111]. Epelsiban (selective oxytocin receptor antagonist) revealed safety and tolerability in adenomyosis treatment [112].

Ormeloxifene

Ormeloxifene is a benzopyran SERM that was initially introduced in India as a contraceptive [113]. It has been studied in a small short-term prospective study to evaluate its effectiveness in controlling adenomyosis pain and bleeding symptoms with encouraging results concerning safety and effectiveness [114]. However, the small cohort used limit this study, as well as its short duration and the study's patients only being followed up clinically.

Research Limitations

Our knowledge about adenomyosis' underlying pathophysiological processes contains significant gaps, and still very little research on this enigmatic disorder is available which hinders the development of more efficient therapies. Therefore, the extensive study of adenomyosis pathogenesis and signaling pathways is expected to pave the way for new therapeutic agents [115, 116]. More reliable, multi-center prospective RCTs to determine efficiency and tolerability of the drugs used in adenomyosis treatment are required to reach a point where precise approaches exist to alleviate and feasibly cure adenomyosis associated symptoms.

Conclusions

Medical treatment is critical in adenomyosis management, particularly in patients who require fertility preservation or are unfit for surgery. It should be individualized according to the patients' complaints and fertility plans, particularly given the growing number of nulliparous, younger patients with adenomyosis. Most of medical treatments are hormonal in nature, such as COCs, progestins, and GnRH agonists. However, more research is required to determine fertility outcomes and the long-term effects of these treatments. LNG-IUS seems to be the most efficient first-line of treatment according to its effectiveness in comparison to other treatments, its independent mode of administration, and its contraceptive nature. GnRH agonists have also shown advantages, though their hypoestrogenic adverse effects hinder their long-term use. However, these side effects can be

mitigated by the concurrent use of add-back therapy. Other promising agents include oral GnRH antagonists, SPRMs, AIs, dopamine agonists, and oxytocin antagonists. Given the lack of type I evidence for the majority of medical treatment options, multi-center prospective RCTs to demonstrate efficacy and tolerability are needed. Furthermore, the introduction of new treatment options is needed in light of recent research findings on the underlying pathogenic mechanisms of adenomyosis.

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Compliance with Ethical Standards

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• Of importance
•• Of major importance

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