



Nonsurgical management of adenomyosis: an overview of current evidence

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Purpose of review

Adenomyosis is a condition where endometrium-like tissue spreads within the myometrium. Although its prevalence in the general population is not exactly known, its clinical manifestations are well established and include pelvic pain, dysmenorrhea (painful periods), heavy menstrual bleeding and subfertility [1]. Adenomyosis often coexists with other gynaecological conditions, such as endometriosis or fibroids, and may cloud the clinical presentation [2]. The aim of this article is to review current noninterventional, nonsurgical management modalities and wherever possible offer information that allows women to make safe and informed choices regarding their treatment options.

Recent findings

Recent studies support that medical strategies, including the Mirena coil, Dienogest and GnRH antagonists, are efficient in improving adenomyosis-associated symptoms. High-quality evidence is scarce and is needed to properly counsel women with this condition. Future research should prioritize overall pain, menstrual bleeding, quality of life and live birth as primary outcomes and assess women with different grades of adenomyosis.

Summary

This review provides the most current evidence with regards to the nonsurgical management of adenomyosis. In light of the paucity and low quality of existing data, high-quality trials are needed to definitely determine the impact of conservative and medical treatment on the clinical management of adenomyosis.

Keywords

adenomyosis, assisted reproduction technology, dysmenorrhea, IVF, medical management, nonsurgical management, pelvic pain, subfertility

INTRODUCTION

Adenomyosis is a benign gynaecological disorder characterized by aberrant development of endometrial glands and stroma within the myometrium, causing inflammation and neuroangiogenesis. The exact incidence of adenomyosis in the population is unknown but some studies have suggested it can be found in 1% of the general population [3] and in up to 20% of women attending the Gynaecology Clinic [4]. Up to 30% of women with adenomyosis are asymptomatic and symptoms commonly resolve after menopause [3,5]. Adenomyosis may be accompanied by other oestrogen-dependent benign disorders, such as endometriosis (70%), uterine fibroids (50%) or premalignant conditions, such as endometrial hyperplasia (35%) [6]. Furthermore, adenomyosis can be found in up to 24% of women with infertility [7] and it has a negative impact on both spontaneous conception, early pregnancy complications, and assisted reproductive outcomes [8].

MATERIALS AND METHODS

A literature review was undertaken and the MEDLINE and PubMed databases were searched for relevant studies published from April 2021 up to April 2022 (12 months), focusing on the noninterventional, nonsurgical management of adenomyosis using the following search terms alone or in combination: (adenomyosis), (pelvic pain), (dysmenorrhea). We also searched combination of (adenomyosis) AND (medical management) and (adenomyosis) AND

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KEY POINTS

- Adenomyosis remains an enigmatic condition with uncertain prevalence and a varied symptomatology spectrum.
- The Mirena IUS and Dienogest are effective in reducing uterine volume.
- GnRH antagonists are a promising strategy in managing patients with adenomyosis-associated symptoms.
- Further high-quality trials are needed to better inform women and clinicians about their options.

(nonsurgical management). A supplementary search was also performed with the additional terms of (adenomyosis) AND (fertility) or (ART), or (assisted reproduction technology), or (IVF).

Once different treatment modalities for adenomyosis were identified, then a supplementary search included adenomyosis and each management option individually.

Articles in English were selected. Information about the noninterventional, nonsurgical management of adenomyosis is included; as well as management of adenomyosis-related subfertility. Any surgical or radiological interventions, which required tertiary level hospital care were excluded.

RESULTS

The initial search strategy revealed 32 PubMed and 132 MEDLINE articles. Review of abstracts found 17 relevant articles, and once duplicate articles were excluded, a total of 11 unique articles were identified. References in these articles were individually searched for additional relevant articles within the designated period.

A summary of the included papers is included in Table 1.

Table 2 provides a synopsis of the pros and cons of each individual treatment modality described in this review.

MANAGEMENT OPTIONS

Conservative methods: lifestyle adjustments

Self-management strategies are commonly used in women with pelvic pain [9] and provide not only physical but also psychological benefits [10].

Yoga has been shown to be helpful in reducing chronic pelvic pain and improving quality of life in

women with endometriosis as well as pain where there is not a clear diagnosis [9].

On a systematic review by Armour *et al.* [9], regular exercise was associated with reduced menstrual pain severity in women with primary dysmenorrhea, although a more recent review indicated lack of good-quality data to make safe conclusions about its benefit in improving endometriosis-associated symptoms [11*].

It is often challenging to evaluate the complex relationship between diet and benign gynaecological pelvic pain conditions and as such no definitive evidence exists to allow for formal recommendations on dietary changes [12].

It is speculated though that a diet modification trial, such as an anti-inflammatory diet, gluten-free diet or low FODMAP diet may be helpful in chronic pelvic pain management especially if there are co-existing visceral pain conditions affecting the bowel or bladder [13].

Pelvic physiotherapy is becoming a preferred treatment modality in the multidisciplinary and holistic approach to the management of chronic pelvic pain, with or without confirmed presence of pelvic benign disease [14]. However, a recent review has indicated scarcity of high-quality evidence supporting its use in reducing pelvic pain; highlighting that trigger point therapy might be a promising approach [15].

Nonhormonal medical options

Traditionally, mefenamic acid (MFA) and NSAIDs have been widely used in dysmenorrhea and endometriosis-associated pain but there are only a few randomized trials in endometriosis and none of them were performed in patients with adenomyosis [16].

The use of MFA and NSAIDs aim to reduce pain rather than alter pain sensitivity and other neuronal symptoms of dysmenorrhea [17]. Due to their anti-inflammatory action, NSAIDs have been investigated as an adjunct to assisted reproduction technology; however, there is no clear evidence that they provide any benefit [18].

Simple analgesics, such as Paracetamol are often used for chronic pelvic pain management. Chen *et al.* in a cross sectional study of 678 women with dysmenorrhea reported that only 50% of women taking Acetaminophen (Paracetamol) reported benefits. Disease severity and psychobehavioural aspects (anxiety/depression) were amongst the factors that affected perception of the effectiveness of dysmenorrhea treatment [19].

There is no evidence that neuromodulators, such as Amitriptyline and Gabapentin, are efficient

Table 1. Summary of reviewed current literature

Article	Key points	Country	Study design	Number of studies	Number of patients	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Stratopoulou CA, Dommez J, Dolmans MM. Conservative Management of Uterine Adenomyosis: Medical vs. Surgical Approach. <i>J Clin Med</i> 2021 Oct 22;10(21):4878. doi: 10.3390/jcm10214878. PMID: 34768397; PMCID: PMC8584979.	Medical treatment is the option of choice	NA	Review	Not reported	Not reported	Not reported	-	-
Dommez J, Stratopoulou CA, Dolmans MM. Uterine Adenomyosis: From Disease Pathogenesis to a New Medical Approach Using GnRH Antagonists. <i>Int J Environ Res Public Health</i> . 2021 Sep 22;18(19):9941. doi: 10.3390/ijerph18199941. PMID: 34639243; PMCID: PMC8508387.	GnRH antagonists are a promising treatment modality	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	-	-
Rafhinam KK, Abraham JJ, S HP, S A S, Sen M, George M, A P. Evaluation of pharmacological interventions in the management of adenomyosis: a systematic review. <i>Eur J Clin Pharmacol</i> 2022 Apr;78(4):531–545. doi: 10.1007/s00228-021-03256-0. Epub 2022 Jan 17. PMID: 35037089.	High-quality evidence is needed	NA	Review	27	4100	18–53	-	-
Ota I, Taniguchi F, Ota Y, Nagata H, Wada I, Nakaso T, Ikebuchi A, Sato E, Azuma Y, Harada T. A controlled clinical trial comparing potent progestins, LNG-IUS and dienogest, for the treatment of women with adenomyosis. <i>Reprod Med Biol</i> 2021 Sep 7;20(4):427–434. doi: 10.1002/rmb2.12408. PMID: 34646070; PMCID: PMC8499603.	LNG-IUS and DNG could be useful for long-term management of adenomyosis	Japan	Controlled clinical trial	NA	157	40–48	4	8
Sang CM, Shi QL, Kang YJ, Cui LM, Ding K, Liu XG, Zhao SP. [Pregnancy outcomes in patients with adenomyosis with fertility requirements: retrospective analysis of clinical data from real world]. <i>Zhonghua Fu Chan Ke Za Zhi</i> 2022 Apr 25;57(4):265–270. Chinese. doi: 10.3760/cma.j.cn112141-20210830-00475. PMID: 35484658.	Patients with adenomyosis have a high rate of miscarriage, and they should be included in the management of high-risk pregnant women	China	Retrospective cohort study	NA	231	31–42	3.7	11
Buggio L, Dridi D, Barbara G. Adenomyosis: Impact on Fertility and Obstetric Outcomes. <i>Reprod Sci</i> 2021 Nov;28(11):3081–3084. doi: 10.1007/s40302-021-00679-z. Epub 2021 Jul 6. PMID: 3423117	The available evidence supports the notion that adenomyosis negatively impacts fertility and pregnancy outcomes	NA	Review	Not reported	Not reported	Not reported	Not reported	Not reported

Table 1 (Continued)

Article	Key points	Country	Study design	Number of studies	Number of patients	Mean age of patients (years)	Standard deviation of age (years)	Age range of patients (years)
Moawad G, Kheil MH, Ayoubi JM, Klebanoff JS, Rahman S, Sharara FI. Adenomyosis and infertility. <i>J Assist Reprod Gener</i> 2022 May;39(5):1027-1031. doi: 10.1007/s10815-022-02476-2. Epub 2022 Mar 28. PMID: 35347501.	An association between adenomyosis and infertility seems to exist, and treatment could lead to improved fertility outcomes	NA	Review	Not reported	Not reported	Not reported	Not reported	Not reported
Tellum T, Omvedt M, Nafalin J, Hirsch M, Jurkovic D. A systematic review of outcome reporting and outcome measures in studies investigating uterine-sparing treatment for adenomyosis. <i>Hum Reprod Open</i> . 2021 Aug 7;2021(3):hoab030. doi: 10.1093/hropen/hoab030. PMID: 34466664; PMCID: PMC8398753.	The development and implementation of a core outcome set (COS) for interventional studies in adenomyosis could improve research quality	NA	Review	38	5175	NA	-	-
Cozzolino M, Tartaglia S, Pellegrini L, Troiano G, Rizzo G, Petraglia F. The Effect of Uterine Adenomyosis on IVF Outcomes: a Systematic Review and Meta-analysis. <i>Reprod Sci</i> . 2022 Jan 3. doi: 10.1007/s43032-021-00818-6. Epub ahead of print. PMID: 34981458.	Troiano Adenomyosis reduced the IVF clinical outcomes	NA	Review	6	1050	34-39	0.9-4.6	5
Lan J, Wu Y, Wu Z, Wu Y, Yang R, Liu Y, Lin H, Jiao X, Zhang Q. Ultra-Long GnRH Agonist Protocol During IVF/ICSI Improves Pregnancy Outcomes in Women With Adenomyosis: A Retrospective Cohort Study. <i>Front Endocrinol (Lausanne)</i> . 2021 May 31;12:609771. doi: 10.3389/fendo.2021.609771. PMID: 34135858; PMCID: PMC8202082.	IVF outcomes are improved with pretreatment downregulation with GnRh agonists	China	Retrospective cohort study	NA	328	33-37	4.08-4.12	4
Zheng J, Lai X, Zhu W, Huang Y, Chen C, Chen J. Effects of Acupuncture Combined with Rehabilitation on Chronic Pelvic Pain Syndrome in Females: A Meta-Analysis Running Head-Acupuncture Combined with Rehabilitation on Chronic Pelvic Pain. <i>J Healthc Eng</i> . 2022 Mar 15;2022:8770510. doi: 10.1155/2022/8770510. PMID: 35340243; PMCID: PMC8941541.	Acupuncture combined with rehabilitation is effective for CPPS in female individuals	China	Meta-analysis	14	1110	29-62	1.2-6.3	33

ING-IUS, Levonorgestrel-releasing intrauterine system.

Table 2. Synopsis of adenomyosis medical management

Method	Advantages	Disadvantages	Evidence
1. Conservative methods – lifestyle adjustments			
Physiotherapy Yoga Exercise Diet	Holistic approach Healthier lifestyle choices	Changes need to be maintained for prolonged periods of time to yield measurable effects	Low
2. Nonhormonal medical options			
NSAIDs/MFA Paracetamol	Readily accessible	Gastrointestinal side effects Ineffective treatment perception	Low/moderate
3. Hormonal medical methods			
Progestogens GnRH agonists	Long-term data for safety and efficacy	Progesterone resistance Menopausal side effects	Moderate
GnRH antagonists	Oral ingestion Dose-dependent effect No flare-up period	Lack of long-term data	Low/moderate
Ulipristal Acetate Danazol Aromatase inhibitors Bromocriptine	Alternatives to traditional hormonal methods requiring an individualized approach	Safety considerations Limited application and improvement	Low
4. Immunomodulators and microRNAs			
Immunomodulators MicroRNAs	Potential targeted medical therapy	Only on clinical research settings	Low
5. Alternative approaches			
Acupuncture Cannabis	Nonmedicinal approach	Cultural and ethical considerations	Low

in improving unexplained or adenomyosis-associated pelvic pain [20^a,21].

Hormonal medical methods

Combined oral contraceptive pill

Although commonly used in the management of endometriosis-associated pain, the evidence regarding their potential benefit in patients with adenomyosis is inconclusive. We identified two studies that compared the combined oral contraceptive pill (COCP) to the Mirena coil and Dienogest for the clinical management of adenomyosis [22,23^{aa}]. Shaaban *et al.* [22] showed that the COCP was beneficial in improving pain; however, it was less efficient than the Mirena coil in both pain and uterine volume reduction. Patients should also be counselled that the long-term use of the COCP is associated with an increased risk of thromboembolic events [24].

Progesterone-only pill (POP) (Mirena coil, Dienogest).

Oral progestogens

Oral progestogens are a popular peer friendly first choice treatment of dysmenorrhea and adenomyosis-related menorrhagia that have been utilized for

many decades. They work via negative feedback pathways to suppress FSH and LH [25,26^a]. They possess antiproliferative and anti-inflammatory effects but progesterone resistance may limit their efficacy [27].

Mirena coil (Levonorgestrel-releasing intrauterine system)

Initially approved as a long-term contraceptive; the Levonorgestrel-releasing intrauterine system (LNG-IUS) has an evidence-based usage for the management of dysmenorrhea and menorrhagia [28]. LNG-IUS has been evaluated as an adenomyosis treatment alternative to hysterectomy. In one prospective randomized clinical trial, LNG-IUS increased the haemoglobin levels at the sixth month and first year of treatment to the comparable levels with hysterectomy [29]. It has been speculated that LNG-IUS therapeutic effects are diminished when adenomyosis is moderate or severe (full-thickness), and not limited or close to the uterine cavity [30–31].

Dienogest

Alleviation of both pain and bleeding were reported in a long-term study with Dienogest but not confirmed in cases of severe adenomyosis [32]. Hassanin *et al.* [23^{aa}] reported that Dienogest is more effective in treating adenomyosis-associated symptoms after 6 months when compared with the combined oral

contraceptive but with higher side effects. Even though studies have demonstrated lesion and uterine size reduction [33], there were limited improvements seen in the more clinically relevant outcomes of abnormal uterine bleeding and anaemia. This suggests that Dienogest may have a greater role amongst those with pressure or bulk symptoms than bleeding and should be clearly discussed with patients. Dienogest has also been shown to provide long down-regulation prior to IVF treatment for patients with endometriosis, which is equivalent to the GnRH analogues; however, this study did not include patients with adenomyosis [34].

Selective Progesterone Receptor Modulators: Ulipristal Acetate

Selective Progesterone Receptor Modulators (SPRMs), such as Ulipristal Acetate (UPA) induce reversible and benign endometrial changes known as progesterone receptor modulator-associated endometrial changes (PAECs) in the endomyometrial interface [26[■]]. Donnez and Donnez [35] reported more severe adenomyotic lesions after UPA therapy, with greater numbers and severity of cystic adenomyotic lesions; therefore, suggesting this as an ineffective management option.

A randomized controlled trial of UPA versus placebo reported on a transient improvement in adenomyosis-related bleeding and pain ($P < 0.01$) following a 12-week treatment but no significant difference at 6 months between the groups [36[■]]. MHRA has restricted the widespread use of UPA because of concerns about serious liver injury or even failure requiring liver transplantation [37]. Nevertheless, a retrospective South Korean cohort study demonstrated higher incidence of mild liver disease with UPA when compared with GnRH agonists but hepatic damage was very low [38].

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists (GnRH) agonists bind competitively to natural GnRH receptors with longer half-life than endogenous peptides. Their use in adenomyosis management relies on the decline of estradiol levels from ovarian downregulation and the antiproliferative effects in the myometrium [39].

Even though they have been used for decades for the treatment of endometriosis-associated pelvic pain, amenorrhoea and reduction in both uterine volume and junctional zone thickness [40], their considerable hypoestrogenic side effects (vasomotor symptoms and osteoporosis) do not allow for long-term management strategy in the majority of

patients [41]. It has been suggested that they may offer a short-term management option when combined with add-back hormonal replacement therapy (HRT) [42] or as a preparatory step before assisted reproduction technology (ART) [43]; however a recent review revealed that they do not improve ART outcomes [44].

Gonadotropin-releasing hormone antagonists

Recently oral GnRH antagonists are gaining momentum for the management of adenomyosis-related symptoms. They incompletely suppress FSH and luteinizing hormone (LH) in a dose-dependent fashion. They have a favourable therapeutic profile because of their water-soluble properties, oral absorption and lower side effects if supplied in low doses [26[■]]. Recent studies have demonstrated promising effectiveness in uterine volume reduction through lesion regression and associated adenomyosis symptoms decline [45[■],46[■]].

Moreover, from a fertility standpoint, GnRH antagonists do not radically suppress circulating LH and can easily be reversed when compared with GnRH agonists [47], thus, offering a great theoretical advantage for assisted reproduction techniques [48]; however, high-quality evidence supporting their use is outstanding.

Danazol

Danazol is an androgenic hormone used in the treatment of endometriosis-associated pain. In a retrospective study of 66 young women with dysmenorrhoea and/or abnormal uterine bleeding with sonographic evidence of adenomyosis, a 6-month treatment with vaginal danazol provided significant benefit in both pain and bleeding [49]. However, its side effect profile, including skin changes, weight gain and occasionally deepening of the voice [50], should be explained to patients before treatment initiation.

Aromatase inhibitors

European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend concomitant use of aromatase inhibitors and oral contraceptives, progestogens or GnRH agonists in patients with pain associated with drug-resistant and surgery-resistant rectovaginal endometriosis [51]. However, there is neither current evidence nor an international consensus on the use of aromatase inhibitors for adenomyosis management [46[■]]. Nevertheless, an older prospective study of

32 patients that compared effectiveness of letrozole to GnRH agonists for adenomyosis management has shown significant reduction in uterine volume post-treatment in both groups [52].

Bromocriptine

Bromocriptine is a dopamine agonist and prolactin inhibitor. A pilot study has reported improvement in adenomyosis-related pain and bleeding scores following vaginal bromocriptine. The same team showed a thinner maximal junctional zone at 6 months on ultrasound but results were not statistically significant on MRI [53].

IMMUNOMODULATORS AND MICRORNAS

AlAshqar *et al.* [54[■]] reviewed the role of inflammatory pathways in benign gynaecological conditions and the efficacy of novel immunomodulating agents. Pentoxifylline had a promising effect in reducing in-vitro production and pro-inflammatory actions of tumour necrosis factor alpha (TNF- α) as well as reducing postoperative pain across several studies but further high-quality trials showed no significant improvement [55].

There is not enough evidence currently to support regular use of anti-TNF- α agents to relieve pelvic pain in women [56].

Kotlyar *et al.* [57] reviewed a plethora of immunomodulators, such as antirheumatic drugs, cytokines, mTOR inhibitors, nucleotide inhibitors and microRNAs; however, their efficacy in humans is yet to be tested. It has been hypothesized that normalizing expression of endometrial microRNAs may encourage transcriptional regulation of their downstream pathways; hence provide a target area for novel treatment modality in the future [58,59].

ALTERNATIVE APPROACHES

Acupuncture

It has been speculated that traditional Chinese medicine in the form of acupuncture may have a role in the treatment of adenomyosis or relief of the clinical symptoms of adenomyosis [60], and further data are awaited in the near future [61].

Cannabis

In a cross-sectional survey of women with pelvic and perineal pain, dyspareunia or endometriosis, there was a 96% reported symptomatic improvement in symptoms with adjunct use of cannabis; including reduction in pain, cramping, muscle spasms,

anxiety, depression, sleep disturbances, anxiety, depression, sleep disturbances, libido and irritability. Moreover, a third of those women reported decreased number of clinical visits and number of phone calls or texts to their health provider [62[■]].

CONCLUSION

This review highlights the options for conservative medical management of adenomyosis-related symptoms. The usage of GnRH antagonists are gaining momentum in the conservative medical management with further research required for promising novel immunomodulating agents for this enigmatic condition. This avoids the morbidity of radiological interventions and surgical approaches that may also compromise further fertility potential of reproductive aged women with adenomyosis. This provides the patient with a holistic approach for symptomatic relief and quality-of-life improvement where surgery is not desired or suitable.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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