

Pharmacological Treatment for Symptomatic Adenomyosis: A Systematic Review

Tratamento farmacológico para adenomiose sintomática: revisão sistemática

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Abstract

Objective To assess the efficacy of non-surgical treatment for adenomyosis.

Data Sources A search was performed by two authors in the Pubmed, Scopus, and Scielo databases and in the grey literature from inception to March 2018, with no language restriction.

Selection of Studies We have included prospective randomized studies for treating symptomatic women with adenomyosis (abnormal uterine bleeding and/or pelvic pain) diagnosed by ultrasound or magnetic resonance imaging.

Data Collection Studies were primarily selected by title and abstract. The articles that were eligible for inclusion were evaluated in their entirety, and their data was extracted for further processing and analysis.

Data Synthesis From 567 retrieved records only 5 remained for analysis. The intervention groups were: levonorgestrel intrauterine system (LNG-IUS)(n = 2), dienogest (n = 2), and letrozole (n = 1). Levonorgestrel intrauterine system was effective to control bleeding when compared to hysterectomy or combined oral contraceptives (COCs). One study assessed chronic pelvic pain and reported that LNG-IUS was superior to COC to reduce symptoms. Regarding dienogest, it was efficient to reduce pelvic pain when compared to placebo or goserelin, but less effective to control bleeding than gonadotropin-releasing hormone (GnRH) analog. Letrozole was as efficient as GnRH analog to relieve dysmenorrhea and dyspareunia, but not for chronic pelvic pain. Reduction of uterine volume was seen with aromatase inhibitors, GnRH analog, and LNG-IUD.

Conclusion Levonorgestrel intrauterine system and dienogest have significantly improved the control of bleeding and pelvic pain, respectively, in women with adenomyosis. However, there is insufficient data from the retrieved studies to endorse each medication for this disease. Further randomized control tests (RCTs) are needed to address pharmacological treatment of adenomyosis.

Keywords

- ▶ adenomyosis
- ▶ abnormal menstrual bleeding
- ▶ pelvic pain
- ▶ systematic review
- ▶ medical treatment

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Resumo

Objetivo: Avaliar a eficácia de tratamento não cirúrgico para adenomiose.

Fontes de dados: Uma pesquisa foi realizada por dois autores nas bases de dados Pubmed, Scopus, Scielo e na literatura cinzenta desde o início de cada base de dados até março de 2018, sem restrição de idioma.

Seleção de estudos: Incluímos estudos prospectivos randomizados para tratamento de mulheres sintomáticas com adenomiose (sangramento uterino anormal e/ou dor pélvica) diagnosticadas por ultrassonografia ou ressonância magnética.

Coleta de dados: Os estudos foram selecionados principalmente por título e resumo. Os artigos que preencheram os critérios de inclusão foram avaliados na íntegra, e seus dados foram extraídos para posterior processamento e análise.

Síntese dos dados: De 567 registros recuperados, somente 5 permaneceram para análise. Os grupos de intervenção foram: sistema intrauterino de levonorgestrel (SIU-LNG) (n = 2), dienogest (n = 2), e letrozol (n = 1). O SIU-LNG foi efetivo no controle do sangramento quando comparado à histerectomia ou aos contraceptivos orais combinados (COCs). Um estudo avaliou a dor pélvica crônica e relatou que o SIU-LNG foi superior ao COC para reduzir os sintomas. Em relação ao dienogest, este foi eficiente em reduzir a dor pélvica quando comparado ao placebo ou à goserelina, mas foi menos eficaz no controle do sangramento do que o análogo do hormônio liberador de gonadotropina (GnRH). O letrozol foi tão eficiente quanto o análogo do GnRH para aliviar a dismenorreia e a dispareunia, mas não para a dor pélvica crônica. Redução do volume uterino foi observada com inibidores de aromatase, análogo de GnRH, e SIU-LNG.

Conclusão: O SIU-LNG e dienogest apresentaram bons resultados para o controle de sangramento e dor pélvica, respectivamente, em mulheres com adenomiose. No entanto, não há dados suficientes para endossar cada medicação para tratar essa doença. Futuros estudos randomizados são necessários para avaliar o tratamento farmacológico da adenomiose.

Palavras-chave

- ▶ adenomiose
- ▶ sangramento menstrual anormal
- ▶ dor pélvica
- ▶ revisão sistemática
- ▶ tratamento médico

Introduction

Adenomyosis is a benign disorder in which basal endometrial glands and stroma are found in the myometrium with reactive hyperplasia of the surrounding smooth muscle myometrial cells.¹⁻⁵ It is a complex, gynecological condition with unknown incidence and etiology. Clinical symptoms are related to pain and bleeding, and they include dysmenorrhea, abnormal uterine bleeding, chronic pelvic pain (CPP), dyspareunia, and infertility; however, a third of women can be asymptomatic.⁶ Symptoms typically are reported to develop between the ages of 40 and 50 years; however, this may reflect the fact that the usual moment for diagnosing adenomyosis has been after performing a hysterectomy because of preoperative difficulty to establish the diagnosis. With improvement of diagnostic methods, like magnetic resonance imaging (MRI) and high-quality transvaginal ultrasound (TVUS), early diagnosis can be made with an accuracy of 80 to 90%.⁷⁻¹¹

Non-surgical treatment can be necessary or desirable for women who want to maintain the uterus for a future pregnancy, those with other comorbidities that pose a higher risk for surgery, or even those who are close to menopause and would not like to undergo a surgical procedure. There are systematic reviews about uterine artery embolization, fertility-sparing

treatment in patients with infertility, and local excision of adenomyosis.¹²⁻¹⁴ A published review about medical treatment for adenomyosis has presented their data narratively, since the author states that the aim was to discuss the medical approach to the management of adenomyosis symptoms, with no analysis of the risk of bias and methodological quality.¹⁵ Given the need for systematic reviews and quality assessment for analyzing these data, we sought to perform a systematic review of the effectiveness of non-surgical treatment for adenomyosis on uterine volume, pelvic pain, and menstrual bleeding, when compared with other surgical and non-surgical interventions.

Methods

Study Design, Data Search, Inclusion/Exclusion Criteria

The present review was recorded in the International Prospective Register of Systematic Reviews (PROSPERO)¹⁶ under the number CRD42017057896 and was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁷

Searches in the databases included articles from the following sources: Pubmed, Scopus, Scielo, and the grey

literature. Two authors (L. G. O. B. and T. A. A. M.) performed a distinct search using the following strategic combination of keywords: (“*medical treatment*” OR “*clinical treatment*” OR “*hormone treatment*” OR *goserelin* OR *leuprolide* OR *GnRH* OR “*GnRH analog*” OR “*GnRH antagonist*” OR *progesterone* OR *Dienogest* OR *desogestrel* OR *COC* OR “*oral contraceptive*” OR “*non-surgical treatment*” OR *levonorgestrel* OR *drug* OR *medroxyprogesterone* OR *mifepristone* OR *sprm* OR *ulipristal* OR *progestin* OR “*combined oral contraceptive*” OR *aromatase* OR *letrozole* OR *anastrozole* (*adenomyosis*)) NOT (*animals* OR *children*). All articles inserted in these databases were included up to March 2018.

We have included in this review prospective randomized and non-randomized studies with symptomatic women with image diagnosis (ultrasound [US] or MRI) suggestive of adenomyosis who were submitted to medical treatment versus any other comparator group. The main symptoms were: abnormal uterine bleeding, pain and/or changes in uterine volume. There were no restrictions regarding the language. We have excluded studies with no control group, with cross-sectional or case-control designs, case series, or retrospective studies.

Primary and Secondary Outcomes

Our primary outcomes were: menstrual bleeding through any kind of measurements, like hemoglobin (Hb) by laboratory test or number of pads/days by the number of protector changes per day according to women’s report; pelvic pain through the visual analogue scale (VAS); and reduction of uterine volume measured in milliliters or cubic centimeters by TVUS or MRI.

Quality of life was the secondary outcome, which was measured by questionnaires such as the World Health Organization Quality of Life (WHOQOL) short version or the Medical Outcomes Study (MOS).

Studies were primarily selected by title and abstract by the same authors that conducted the searches. Thus, articles that presented the eligibility criteria were evaluated in their entirety, and their data was extracted for further processing and analysis. Possible disagreements were discussed with a third author (C. L. B. P.) to obtain a consensus. The reviewers sought data that were not possible to obtain after reading the manuscript after an e-mail sent to the authors.

Statistical analysis

We tabulated mean difference (MD) and their standard deviations (SDs) between pre and posttreatments and their confidence intervals from continuous variables. In order to build forest plots, a mathematical calculation of error propagation was used, according to the author,¹⁸ to identify the SDs not described in some of the studies included in the present review after unanswered contact with the authors, once the publication did not mention these data. It was not possible to conduct a meta-analysis by the differences of the studies heterogeneity of the studies regarding the proposed treatments, because each study assessed a different treatment with or without a different comparator, and a single paired comparison was not present in more than one study. As the number of studies was scant, an indirect meta-

analysis was not considered either. Funnel plots (publication bias) were not elaborated due to the scant number of retrieved studies. The risk of bias in the studies was assessed using the Cochrane bias risk assessment tool,¹⁹ which classifies studies at risk of low, high, or unclear bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria²⁰ were used to build a summary of findings (SOF) table to evaluate the quality of the evidence.

Results

Study Selection and Characteristics

► **Figure 1** describes the flowchart regarding the studies that comprise the present review. From 567 records that were retrieved in this search, 5 were removed due to duplication, 562 were screened, and 11 were fully assessed for eligibility, but only 5 remained in the final model. ► **Table 1** displays all selected studies that comprised 288 women; a total of 267 women completed the treatment and were included in the final results. No studies have mentioned whether their results were interpreted by intention-to-treat or per protocol analysis.

In summary, three from the five studies were held in Egypt, four presented a randomized controlled design,^{21–25} and one was prospective, non-randomized.²⁴ One study was placebo-controlled,²⁵ and the others were pharmacological treatments versus surgery or other drugs for adenomyosis. Transvaginal ultrasound diagnosis was present in all studies, and MRI was added as an option to TVUS in two studies.^{21–24} The duration of treatment varied from 4 weeks to 12 months. The intervention x comparator groups were: levonorgestrel intrauterine system (LNG-IUS) versus hysterectomy²¹; LNG-IUS versus combined oral contraceptive (COC)²³; letrozole versus goserelin²²; dienogest versus triptorelin²⁴; dienogest versus placebo.²⁵ Some side effects of using pharmacological treatment were mentioned in all studies except one.²⁴ ► **Figure 2** condenses all forest plots from the analyzed outcomes. From our planned primary outcomes, almost all of them (4 of 5) were present.

Treatment with LNG-IUS

Two studies have assessed the use of LNG-IUS^{21,23} versus hysterectomy or combined oral contraceptive (COC), respectively. In the first study, the LNG-IUS was effective to control bleeding, with an improvement of hemoglobin levels, and reduction in the number of days with bleeding. In the second study, a reduction in the number of days with bleeding was observed. Compared to the other medical treatment using COC, the bleeding pattern was improved in both arms; in the case of LNG-IUS, the mean number of bleeding days per month decreased from 9.81 ± 1.82 days before recruitment to 2.63 ± 2.13 days after the 6th month of insertion ($p < 0.001$). In the COCs group, the number of bleeding days per month reduced from 9.97 ± 1.52 days to 5.52 ± 1.00 days ($p < 0.001$).

Pelvic pain was assessed in one study,²³ and the LNG-IUS was more efficient in the improvement of chronic pelvic pain than COC (6.23 ± 0.67 – 1.68 ± 1.25 - $p < 0.001$), as well as the reduction in uterine volume (10.23 ± 1.06 mL– 7.63 ± 0.49 mL, $p < 0.001$).

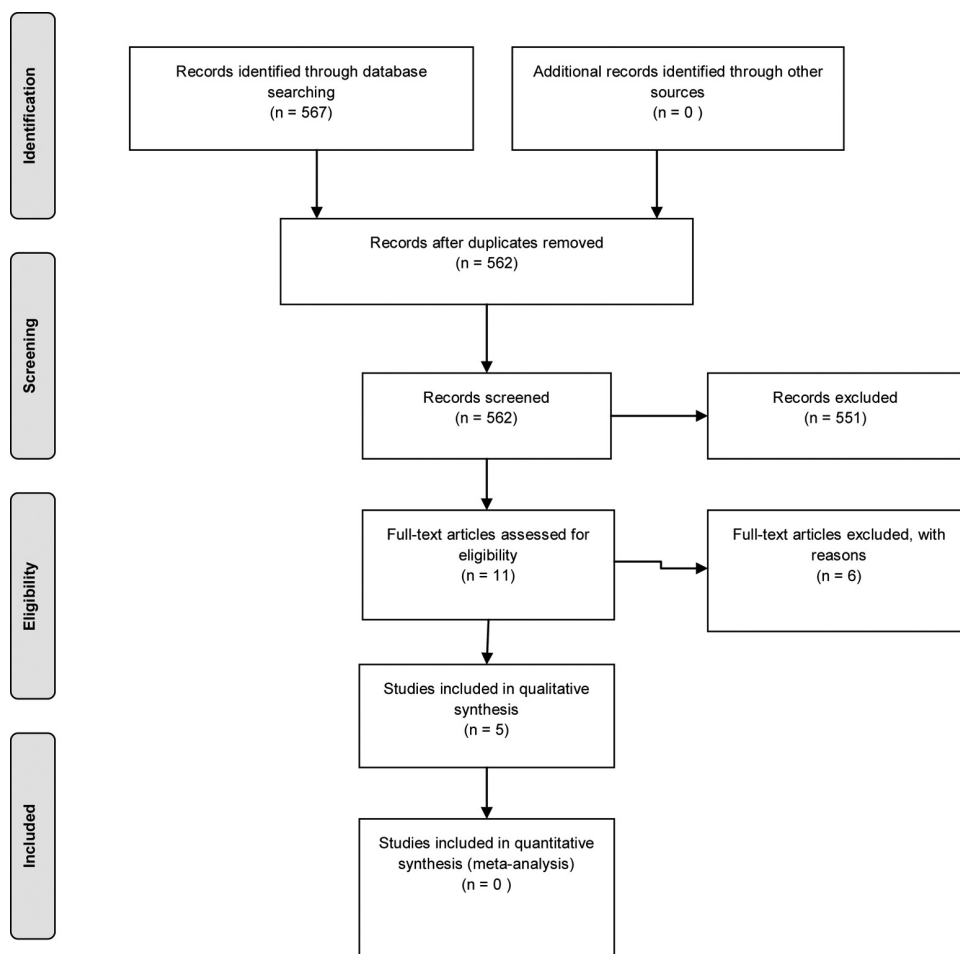


Fig. 1 Flow diagram describing the search and study inclusion processes.

Only one study assessed improvement of quality of life,²¹ with superior effects on psychological and social life with LNG-IUS when compared to hysterectomy. Women that used LNG-IUS presented adverse effects: headache (11.9%), breast tenderness (7.1%), acne (4.8%), and transient depressive episode (2.4%).

Treatment with an Aromatase Inhibitor (Letrozole)

Only one study²² evaluated letrozole in the treatment of adenomyosis compared to the GnRH analog goserelin. Letrozole was as efficient as goserelin to relieve dysmenorrhea ($p = 0.48$) and dyspareunia ($p = 0.70$), but the CPP control was statistically higher with goserelin ($p = 0.04$). Regarding the control of bleeding and the reduction of uterine volume, both medications presented similar response, but more side effects (hot flashes) were reported with goserelin (81.3%).

Treatment with Gonadotropin-releasing Hormone Agonist (GnRH Analog: Goserelin or Triptorelin Acetate)

Two studies evaluated the use of GnRH analog: one compared to an aromatase inhibitor (goserelin X letrozole),²² and the other compared to dienogest (triptorelin X dienogest).²⁴

The GnRH analog was more efficient than the aromatase inhibitor in controlling CPP ($p = 0.04$), but they were equally

efficient in the control of dysmenorrhea and dyspareunia. When compared to dienogest, the GnRH analog was more efficient in controlling dysmenorrhea at 16 weeks (30.6 ± 18.4 versus 0.0 , $p < 0.0001$) but equally efficient at reducing dyspareunia and CPP. Regarding bleeding control, the GnRH analog did not present a statistical difference when compared to letrozole; conversely, it was superior to dienogest. Finally, regarding the reduction of uterine volume, the GnRH analog and aromatase inhibitor were equivalents;¹⁸ however, when compared with dienogest, the GnRH analog was more efficient.²¹ One study evaluated side effects, having reported hot flashes in 81.3% of women treated with GnRH analog.²²

Treatment with dienogest

Two studies evaluated dienogest; one compared to GnRH analog (triptorelin)²⁴ and the other compared to placebo.²⁵ Dienogest was efficient in both studies to reduce pain complaints (dysmenorrhea, dyspareunia, and CPP). When dienogest was compared to the GnRH analog (triptorelin), both were similar to control dyspareunia (20.7 ± 16.5 versus 25.8 ± 19.1 , $p = 0.3899$) and CPP (21.7 ± 11.6 versus 24.5 ± 13.8 , p -value = 0.5076). There was a significant difference in the posttreatment dysmenorrhea between dienogest and triptorelin at 16 weeks, when the GnRH analog presented a better result (30.6 ± 18.4 versus 0.0 , $p < 0.0001$).

Table 1 Characteristics of the included prospective studies

Author, Year	Country	Study aim	Diagnosis	Sample	Study design	Treatment	Follow-up	Evaluation method	Pain - results	Bleeding loss - results	Uterine volume - results	Quality of life	Other results	Side effects
Ozdegirmenci et al (2011) ²¹	Turkey	To compare LNG-IUS versus hysterectomy	US and MRI criteria	N = 86; 43 in each group	Prospective randomized clinical trial (do not register)	LNG- IUS (final participants n = 43); Hysterectomy (final participants n = 32)	6 and 12 months	1. Menstrual bleeding (number of pads/day and hemoglobin levels) 2. Quality of life (WHOQOL-brief)	Did not assess	LNG-IUS increased the Hb levels to comparable levels with hysterectomy	Did not assess	Both treatments have improved health-related quality of life, but LNG-IUS had a superior effect on psychological and social life		LNG-IUS: headache (11.9%), breast tenderness (7.1%), acne (4.8%), a transient depressive episode (2.4%). Hysterectomies: 1 (3.1%) post-operative infection
Badawy et al (2012) ²²	Egypt	To compare aromatase inhibitor (Letrozole 2.5 mg/d) versus GnRH analog (goserelin 3.6 mg)	US criteria	N = 32	Prospective randomized, non-blind controlled clinical trial (retrospectively registered)	Letrozole 2.5mg/d (final participants n=15) Goserelin 3.6mg/ month (final participants n = 16)	4, 8, and 12 weeks	1. Pain Pelvic pain, dysmenorrhea, dyspareunia (VAS) 2. Menstrual bleeding and sub-fertility (questionnaire, but it is not clear) 3. Uterine volume (TVUS)	Goserelin was more effective in relieving chronic pelvic pain ($p = 0.04$)	Goserelin was so efficient than letrozole in relieving menorrhagia and metrorrhagia	Reduction in uterine volumes, without difference between the two groups			Hot flashes (0% with letrozole, 81.3% with goserelin), Pregnancy (n = 2 with letrozole)
Shaaban et al (2015) ²³	Egypt	To compare LNG-IUS versus COC	US criteria	N = 62; 31 in each group	Prospective randomized clinical trial, registered	LNG-IUS (final participants n = 29) COC (35mcg of gestodene + 30 mcg of EE, 21/7) (final participants n = 28)	6 months	1. Pain (VAS) 2. Menstrual bleeding (menstrual diary, pads/day). 3. Uterine volume (TVUS and Doppler)	Both treatments reduced pains, however, the reduction was greater in the LNG-IUS group	Both treatments decreased the number of bleeding days, number of sanitary pads per day, but the reduction was greater with LNG-IUS	Both treatments decreased the uterine volume, but the reduction was greater with LNG-IUS		Uterine arteries and intramyometrial Doppler indices increase in both groups, but the increases were greater with LNG-IUS	LNG-IUS: expulsion (n = 1)

Table 1 (Continued)

Author, Year	Country	Study aim	Diagnosis	Sample	Study design	Treatment	Follow-up	Evaluation method	Pain - results	Bleeding loss - results	Uterine volume - results	Quality of life	Other results	Side effects
Fawzy and Mesbah (2015) ²⁴	Egypt	To compare dienogest versus triptorelin acetate	US criteria	N = 41; dienogest (n = 22); triptorelin acetate injection (n = 19)	Prospective non-randomized clinical trial (did not register)	Dienogest 2mg/day (final participants n = 19) Triptorelin acetate (final participants n = 18)	16 weeks	1. Pain, dysmenorrhea, dyspareunia and chronic pelvic pain (VAS) 2. Menstrual bleeding (3 levels of satisfied, blood cell count, ferritin) 3. Uterine volume (TVUS)	Both treatments reduced chronic pelvic pain and dyspareunia. Triptorelin was more effective in relieving dysmenorrhea	Triptorelin was more effective than dienogest (100 and 73.7% respectively) in controlling menstrual bleeding. Both treatments improved Hb levels and ferritin	Triptorelin was more effective in the reduction of uterine volume			Did not assess
Osuga et al (2017) ²⁵	Japan	To compare dienogest versus placebo	US and MRI criteria	N = 67	Randomized, double-blind, multicenter, placebo-controlled phase III study	Dienogest 2mg/day (final participants n = 34) Placebo (final participants n = 33)	16 weeks	1. Pain (pain severity score in order to access work and analgesics use and VAS) 2. Menstrual bleeding (Patient diary form, classified by the number of days and severity of bleeding). 3. Uterine volume (US and MRI) 4. Quality of life (MOS 36-item short-form health survey)	Dienogest reduced pelvic pain and other pain parameters	Dienogest presented a lower number of days with bleeding, and the most, was spotting or breakthrough, but the numbers were not statistically compared between the groups	Uterine volume reduction in both groups, but no difference between them	Bodily pain reduction (the item of quality of life)	Reduction of analgesics use score in the Dienogest group	Anemia and menstrual bleeding (placebo) and hot flash (dienogest)

Abbreviations: COC, combined oral contraceptive; GnRH, gonadotropin-releasing hormone; LVG-US, levonorgestrel intrauterine system; MOS, Medical Outcomes Study; MRI, magnetic resonance imaging; TVUS, transvaginal ultrasound; US, ultrasound; VAS, visual analogue scale; WHOQOL, World Health Organization Quality of Life.

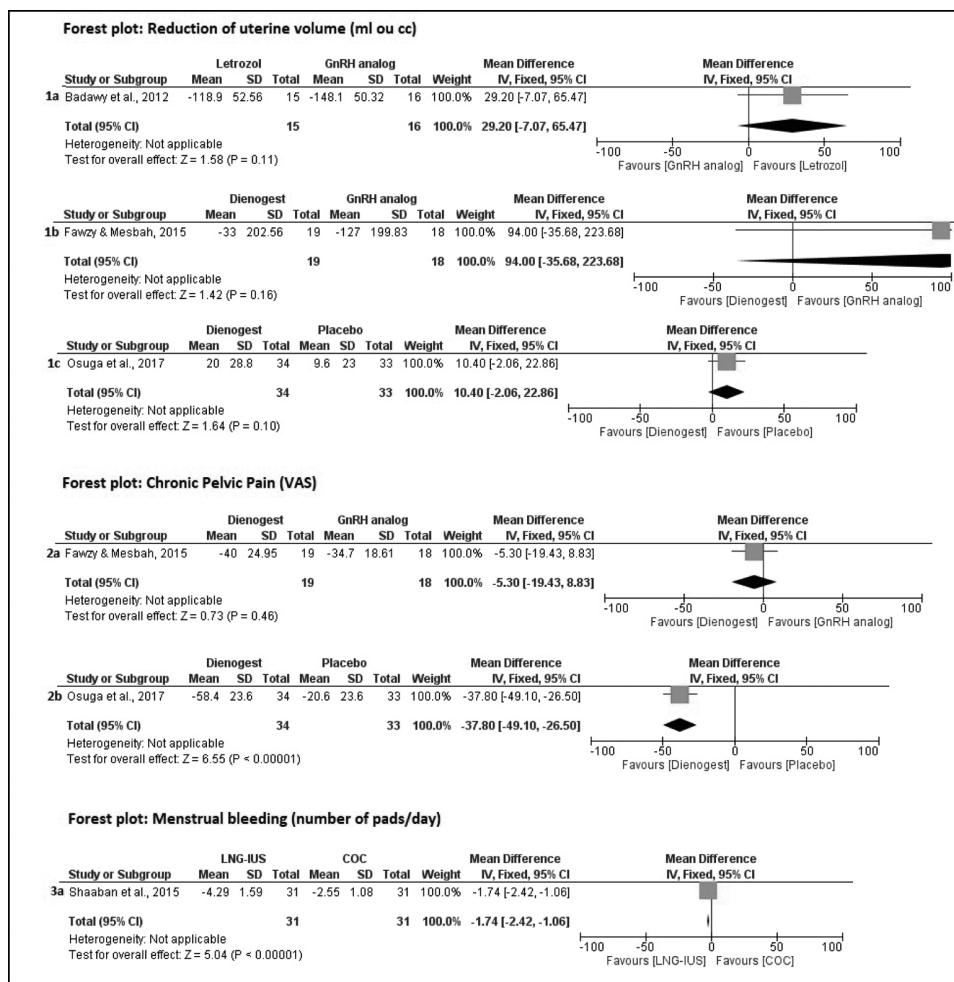


Fig. 2 Forest plot for the comparisons of the non-surgical treatments in the reduction of uterine volume, chronic pelvic pain, and menstrual bleeding.

Although bleeding control was reported by many women, dienogest maintained bleeding in 26.3% of women versus none from the GnRH group.²⁴ Similarly, uterine volume was reduced according to 2 studies in women who used dienogest, but this reduction was lower than that obtained with the study that used GnRH analog ($278 \pm 162 - 151 \pm 117$ ml - $p = 0.01$).²⁴ One of these studies²⁵ reported hot flushes (5.3%) as a side effect of the dienogest.

Treatment with Combined Oral Contraceptives

Only one study included one COC to treat adenomyosis,²³ containing 75 mcg of gestodene + 30 mcg of ethynylestradiol, that was taken for 21 days with 7 days without the pills (21/7), compared to LNG-IUS. The results showed a reduction of pain ($6.55 \pm 0.68 - 3.90 \pm 0.54$ - $p < 0.001$), decreased bleeding (numbers of days), and reduction of the uterine volume, but it was still less efficient than LNG-IUS for all evaluated parameters (pain - $6.23 \pm 0.67 - 1.68 \pm 1.25$ - $p < 0.001$).

Risk of Bias and Methodological Quality

► **Figure 3** discusses the risk of bias from the retrieved studies. Osuga et al.²⁵ presented the lowest risk of bias when analyzing all criteria from this table. Almost all studies (except Osuga et al)²⁵ presented an unclear risk of bias for

allocation concealment and selective reporting. Blinding was only possible in two studies (Osuga et al,²⁵ and Ozdergimenci et al²¹). About the GRADE criteria (► **Table 2**), all variables presented a moderate certainty assessment, except menstrual bleeding (number of pads/day), comparing LNG-IUS versus COC for 6 months, that presented low certainty assessment. All studies presented serious imprecision due to the small number of events. Despite being sponsored by the pharmaceutical industry, the side effects of the Osuga et al study were reported, and, therefore, we do not consider that publication bias was low. Moreover, it was not possible to perform GRADE criteria for the study from Ozdergimenci et al due to inconsistencies, inaccuracy, and poor data description (it would not fit all the criteria for analyzing it).

Discussion

In the present systematic review, we have shown that the studied treatments (LNG-IUS, aromatase inhibitor [letrozole], GnRH agonist [goserelin and triptorelin], dienogest, and COC [75mcg of gestodene + 30 mcg of ethinyl estradiol]), were efficient for the control of the two most common symptoms of adenomyosis: heavy menstrual bleeding and dysmenorrhea/pelvic pain. Equally, regarding enlarged uterus, the treatments

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Badawy et al., 2012	+	?	-	-	+	?	?
Fawzy & Mesbah, 2015	-	?	-	-	+	?	?
Osuga et al., 2017	+	+	+	+	+	+	?
Ozdegirmenci et al., 2011	+	?	+	+	+	?	?
Shaaban et al., 2015	+	?	-	-	+	?	?

Fig. 3 Risk of bias summary ⊕ = high risk of bias; ? = uncertain risk of bias; ⊕ = low risk of bias.

promoted a reduction in the uterine volume. However, the number of retrieved studies is low and, according to the literature available up to this point, still not enough to endorse any of the analyzed treatments; the follow-up period of these studies was not long enough to permit a conclusion on how effective these treatments would be in the long term (only the LNG-IUS study presented a 12-month follow-up, which can be considered short to medium term). Unfortunately, we also noticed a lack of studies investigating the quality of life as a primary outcome; since most of the studies were concerned with objective outcomes (reduction of uterine volume, and number of days with abnormal bleeding); however, subjective improvement or patient satisfaction should also be considered.^{26,27} Moreover, the differences regarding intervention and comparator groups did not allow us to perform metanalysis or subgroup analysis.

The most frequent symptoms of adenomyosis are pelvic pain and abnormal uterine bleeding. Dysmenorrhea is present in 50 to 93% of women, while abnormal bleeding is present in 27 to 65%.²⁸ Despite the different comparators, it seems that the different pharmacological treatments evaluated, dienogest, COC, GnRH analog (triptorelin and goserelin), letrozole, and

LNG-IUS, were effective to reduce pelvic pain complaints and to reduce bleeding in women with adenomyosis. These results suggest that hormonal treatment improves the symptoms. The strengths of this review are: the inclusion of randomized controlled trials (RCTs) in a systematic review, and the quality assessment of these studies by the GRADE criteria. However, it is important to mention that our findings were limited by differences in the inclusion criteria of the studies, length of follow-up periods, different comparators, different scales used to measure blood volume loss or pelvic pain severity, which do not allow conclusions about delaying or avoiding surgical procedures. We have found another review in which the authors presented their data in a narrative format, citing the different available treatments. Also, in this publication, it is possible to visualize the difficulty of comparing treatments, limiting conclusions about pharmacological treatment.¹⁵ Therefore, the present study is the first systematic review evaluating the results from the pharmacological treatment in adenomyosis, with the intention to promote standardization of the methods and to fulfill gaps in the next prospective studies.

With the intention of standardizing future studies, in the present systematic review, we included below some

Table 2 Summary of findings table according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria

Study		Certainty assessment - Reduction in uterine volume (ml or cc)				Patients		Effects		Certainty	Importance
Study design	Bias risk	Inconsistency	Indirectness	Imprecision	Other considerations	Group 1	Group 2	Relative (95% CI)	Absolute(95% CI)		
Dienogest x Placebo (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	34	33	-	MD 10.4 higher (2.06 lower to 22.86 higher)	⊕⊕⊕⊕ MODERATE	
Letrozole x GnRH analog (12 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	15	16	-	MD 20.6 higher (0.09 lower to 41.29 higher)	⊕⊕⊕⊕ MODERATE	
Dienogest X GnRH analog (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	19	18	-	MD 94 higher (35.68 lower to 223.68 higher)	⊕⊕⊕⊕ MODERATE	
Certainty assessment – Chronic Pelvic Pain (VAS)											
Study	Study design	Bias risk	Inconsistency	Indirectness	Imprecision	Other considerations	Patients	Effects	Relative (95% CI)	Certainty	Importance
							Group 1	Group 2	Absolute(95% CI)		
Dienogest x Placebo (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	34	33	-	MD 37.8 lower (49.1 lower to 26.5 lower)	⊕⊕⊕⊕ MODERATE	
Dienogest x GnRH analog (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	19	18	-	MD 5.3 lower (19.43 lower to 8.83 higher)	⊕⊕⊕⊕ MODERATE	
Certainty assessment – Hemoglobin level (g/dL)											
Study	Study design	Bias risk	Inconsistency	Indirectness	Imprecision	Other considerations	Patients	Effects	Relative (95% CI)	Certainty	Importance
							Group 1	Group 2	Absolute(95% CI)		
Dienogest x GnRH analog (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	19	18	-	MD 1.2 lower (2.46 lower to 0.06 higher)	⊕⊕⊕⊕ MODERATE	
Dienogest x Placebo (16 weeks)											
1	Randomized trial	Not serious	Not serious	Serious ^a	Undetected	34	33	-	MD 0.4 higher (0.13 lower to 0.93 higher)	⊕⊕⊕⊕ MODERATE	
Certainty assessment – Menstrual bleeding (pad/day)											
Study	Study design	Bias risk	Inconsistency	Indirectness	Imprecision	Other considerations	Patients	Effects	Relative (95% CI)	Certainty	Importance
							Group 1	Group 2	Absolute(95% CI)		
LNG-IUS x COC (6 months)											
1	Randomized trial	Not serious	Not serious	Very serious ^a	Undetected	31	31	-	MD 1.74 lower (2.42 lower to 1.06 lower)	⊕⊕⊕⊕ LOW	

Abbreviations: CI, confidence interval; COC, combined oral contraceptive; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel intrauterine system; MD, mean difference^a; VAS, visual analogue scale. Total sample size of fewer than 400 patients.

suggestions that could be considered important to be included during any checklist for preparing a prospective study for women with symptomatic adenomyosis. More studies are needed to allow comparisons, conclusions on long-term efficacy, and side effects that limit its use.

Diagnosis

To use pelvic US (preferably transvaginal probe—TVUS and 3DTVUS—when available) or MRI for the diagnosis of adenomyosis,^{28,29} describing the presence or absence of at least the following criteria:

- globular uterus with regular contours (US or MRI);
- asymmetrical thickening of the myometrial walls (US or MRI);
- thickening of the junctional zone (JZ) ≥ 12 mm (MRI or, eventually, by US);
- greatest JZ thickness to total myometrium ratio > 40 to 50% (US or MRI);
- foci of high signal intensity running alongside the endometrium on T2 and sometimes also T1-weighted;
- images that persist on Fat-Sat (FS) (MRI);
- anechoic sub endometrial microcysts in the myometrium (around 2–4 mm in diameter) (US);
- description of association or not with leiomyoma.

Uterine Volume

- To perform the same imaging technique used for diagnosis, preferably at the same time that clinical complaints are re-evaluated, to correlate the results.

Symptoms (Pain and Bleeding)

- There is no specific questionnaire for adenomyosis
- To evaluate pain-related symptoms: pelvic pain, dysmenorrhea, and deep dyspareunia. The assessment criteria should include the VAS. When possible, make daily control diaries for each type of pain and register the frequency of pain.
- To evaluate bleeding symptoms through a scale with the number of days of bleeding and number of pads per 30-day (interval). We suggest using the Pictorial Blood Assessment Chart (PBAC) and serum levels of hemoglobin and ferritin.
- Both symptoms (pain and bleeding) should be evaluated at the initial time before treatment, and every 4 months (120 days).

Side Effects

- To describe in detail all possible and unpredictable side effects, especially when these were indicative of discontinuation of treatment, including the number of losses.
- To report cases of non-response to pharmacological treatment.

Quality of Life

- To use the 36-item short-form survey (SF-36) or the WHOQOL questionnaire.

Conclusion

Levonorgestrel intrauterine system and dienogest presented good results for controlling bleeding and pelvic pain, respectively, versus their comparators. However, there is insufficient data from the retrieved studies to endorse each medication for symptomatic adenomyosis. Future RCTs comparing pharmacological treatments for adenomyosis are needed to bolster the available data.

Contributions

All the authors participated actively in the study, as follows: Yela D. A., Benetti-Pinto C. L., and Brito L. G. O. were responsible for writing the protocol and the final manuscript. Teatin-Juliano C. R. and Mira T. A. A. collected the data and conducted a review of the literature.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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