Evaluation of endometriosis-associated pain and influence of conventional treatment: a systematic review

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Summary

Endometriosis is a chronic gynecological disease characterized by sustained painful symptoms that are responsible for a decline in the quality of life of sufferers. Conventional treatment includes surgical and pharmacological therapy aiming at reducing painful symptoms. This study aimed to evaluate pain levels in women with endometriosis, focusing on the influence of conventional treatment in controlling this variable. To do so, a literature search was conducted in the Medline/Pubmed databases, with 119 scientific articles found. After applying the inclusion and exclusion criteria, 27 were selected for reading and elaboration of this review. Thus, 9 studies evaluated the contribution of surgery, 17 the use of drugs to reduce pain levels in patients with endometriosis and one assessed surgical and medical treatment. The main results of these searches are presented and discussed in this revision. Surgery and the use of drugs provided reduced pain scores in patients with endometriosis but nevertheless exhibit disadvantages, such as risk of recurrence and side effects, respectively. Treatment of endometriosis is, therefore, a challenge for gynecologists and patients, as they must select the best therapeutic approach for this disease. However, improved quality of life in these patients has been obtained with the use of conventional treatment.

Keywords: endometriosis, pelvic pain, therapeutics, quality of life.

Introduction

Endometriosis is a gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity.[1] Treatment consists in relieving chronic pelvic pain (CPP) and recovering fertility, through medication and/or surgery.[2]

Patients with endometriosis display the following types of pain: CPP, dysmenorrhea, dyspareunia, dyschezia and dysuria.[1] CPP is defined as non-menstrual or non-cyclical pain, lasting at least six months, strong enough to interfere with daily activities and requiring medical or surgical treatment. Dysmenorrhea, also known as menstrual cramps, is pelvic pain occurring before or during a menstrual period. Pain during intercourse is called dyspareunia and pain when defecating and urinating are known as dyschezia and dysuria, respectively.

As the disease and the pain are chronic conditions, there is significant interference in the quality of life of these women, in their professional performance, and significant costs to health services.

Regarding professional activity, a multicenter study showed that symptoms of endometriosis have a negative impact on productivity at work, with the loss of approximately one working day per week.[3] Another study showed that 85% of patients with endometriosis perceived an evident decrease in the quality of their work, 19% reported being unable to work due to pain and 69% of patients reported that they continue to work despite the painful sensation.[4]

With respect to health expenditure, there is the need for surgery for definitive diagnosis of the disease or even to assess recurrences, as well as hospital admissions due to pain. According to a multicenter study carried out by Simoens et al.,[5] health care costs associated with endometriosis were mainly due to surgery (29%), monitoring tests (19%), hospitalization (18%) and medical appointments (16%). These high costs have been associated with severity of the endometriosis, the presence of pelvic pain, infertility, and a large number of years before diagnosis.[5]

Given the above, the symptoms of this painful gynecological condition interfere with the professional and personal life of patients and, therefore, control of this variable is essential in order to provide a better quality of life for such women. As such, this study aimed to evaluate the levels of pain in women with endometriosis, focusing on the influence of conventional treatment in controlling this variable.

Methods

A literature search was conducted in September 2013 in the Medline/PubMed databases without restriction by period, using the keywords "endometriosis" and "intensity of pain". PubMed was the database of choice for this systematic review as it is more comprehensive, used internationally in health care research and, therefore, provides the most complete indexing of scientific studies. 119 articles were found and 27 were retrieved and analyzed in full. The inclusion criteria for selection of the articles were: 1) those closely related to the theme, with selection based on titles and/or abstracts; 2) articles written in English or Portuguese; 3) the possibility of obtaining the full version of the article; 4) those that were original/research articles. In endometriosis, conventional treatment includes laparoscopic surgery and pharmacological treatment. The title and/or abstract of 27 articles presented information about the method of treatment used to control the symptoms of pain caused by endometriosis. Review articles or letters to the editor were excluded, as well as those without any relationship with the subject of the review, and those that did not offer access to the full article and those published in other foreign languages. The reference lists of articles identified in the electronic search were also reviewed in order to find potentially important studies for inclusion in this literature review. The selection of articles included in the review was carried out by a single examiner, following the previously defined criteria. Ten other references were also used to help compose the introduction and discussion of the results.

Results

After applying the pre-established inclusion and exclusion criteria, 27 studies that evaluated pain levels in patients with endometriosis were selected for the development of this literature review.[6-32]

Nine studies assessed the contribution of surgery to reduce pain levels in patients with endometriosis[7-9,11,14,16,21,25,29] and one assessed the combination of surgical and drug treatments (combined oral contraceptives – COC).[30] The individual values and frequency for each type of pain before and after the surgical procedure are presented in Tables 1 and 2. Also, Garry et al.[7] showed that of the 53 patients with dysmenorrhea, 43 reported improvement in this symptom 4 months after surgery, while 4 did not notice changes and 6 reported worsening after surgery. Non-menstrual pelvic pain was reported by 48 women, 34 of which reported an improvement after surgery, with four reporting no change and 10 feeling worse. Dyspareunia was reported by 41 patients, 32 of which reported improvement, while 5 and 4 patients reported no change and worsening of symptoms, respectively. Rectal pain was cited by 41 patients with 35 of them reporting improvement after surgery.

Other studies aimed at checking if there was a decrease in pain levels after surgery were performed by Fabbri et al.[14] and Jdrzejczak et al.[16] The first study used the McGill Pain Questionnaire (MPQ) in 55 women with severe endometriosis who underwent laparoscopy. The pain intensity ratio before surgery was 3, falling to 1 after surgery (6 months), that is, the intensity of the pain significantly decreased after laparoscopic treatment of endometriosis ($p<0.0005$). A significant reduction was also observed ($p<0.05$) on all individual pain indexes; however, 18.2% of those women showed no improvement in the symptoms of pain after laparoscopic surgery. Possible explanations for this include recurrence of the disease after surgery, incomplete excision of endometriotic lesions or pain unrelated to endometriosis. Jdrzejczak et al.[16] evaluated the effects of pre-sacral neurectomy in the treatment of CPP in 23 women, 16 of whom had endometriosis, while 7 did not. The symptoms of pain evaluated were dysmenorrhea, CPP and dyspareunia, with intensity determined by the visual analogue scale (VAS) before surgery, and 3 and 12 months postoperatively. The results show a significant improvement in pain symptoms after three months and this remained significant 12 months postoperatively. Furthermore, at the end of the study 79% of the patients reported general satisfaction in relation to pain relief.

The referred studies have shown that the severity of all kinds of pain was diminished after surgery, as well as the prevalence of such, thus demonstrating the effectiveness of surgery for pain relief, and consequently for the quality of life of women with endometriosis.

Seventeen studies published in the literature evaluated the use of drugs to treat pain associated with endometriosis.[6,10,12,13,15,17-20,22-24,26-28,31,32] The main results of these studies are summarized in Table 3.

TABLE 1 Pain scores before (pre-op) and after (post-op) laparoscopic surgery for endometriosis regarding the following pain symptoms: dysmenorrhea, pelvic pain, dyspareunia, dyschezia and dysuria.

	Garry et al.[7]		Abbott et al.[8]		Abbott et al.[9]						Lyons et al.[11]		Bassi et al.[21]	
	Pre-op	Post-op	Pre-op	Post-op	Late surgery Mean (SD)			Immediate surgery Mean (SD)			Pre-op	Post-op	Mean (SD)	Mean (SD)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Before	6 months	12 months	Before	6 months	12 months	Median (IQR)	Median (IQR)	Before surgery	After surgery
Dysmenorrhea	8 (7-9)	4 (1-7)	9 (7-9)	3.3 (2-7)	86.5 (16.7)	62.9 (27.4)	28.1 (32.8)	78.1 (23.7)	52.1 (25.6)	29.2 (26.9)	71 (43-85)	5 (0-10)	8.74 (1.84)	1.14 (2.06)
Pelvic pain	7 (3.5-8)	2 (0-6)	8 (6-9)	3 (0-5)	58.8 (28.1)	34.9 (31.5)	20.1 (24.2)	62.3 (24.4)	43.5 (29.3)	16.6 (22.2)	74 (48-85)	11 (0-18)	5.68 (3.45)	0.88 (1.78)
Dyspareunia	6 (0-9)	0 (0-4)	7 (5.5-9)	0 (0-4)	52.7 (36.5)	42.2 (37.1)	15.7 (24.9)	65.4 (26.2)	48.6 (31.3)	22.3 (29.9)	66 (0-98)	5 (0-8)	5.37 (3.67)	0.44 (1.15)
Dyschezia	4 (0-8)	0 (0-3.5)	7 (4-8)	2 (0-2)	50.8 (39.9)	32.7 (38.3)	22.1 (25.2)	44.6 (30.1)	30.1 (30.5)	25.1 (28.1)	48 (20-64)	20 (0-40)	5.62 (3.82)	0.65 (1.72)
Dysuria	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2.56 (3.77)	0.36 (1.34)

IQR: interquartile range; NA: not analyzed, SD: standard deviation.

TABLE 2 Frequency and pain scores before surgery (pre-op) and postoperatively (post-op) regarding the following pain symptoms: dysmenorrhea, chronic pelvic pain (CPP), dyspareunia, dysuria and dyschezia.

	Mabrouk et al.[25]		Setälä et al.[29]		Mabrouk et al.[30]	
	Frequency (mean VAS score)		Frequency (mean VAS)		Frequency (VAS score ± SD)	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Dysmenorrhea	99% (7±3)	23% (1±3)	100% (8.8)	82% (4.2)	77% (7±3)	23% (1±3)
CPP	63% (4±3)	18% (1±2)	82% (5.7)	54% (2.4)	57% (3±3)	15% (1±2)
Dyspareunia	76% (5±3)	23% (1±2)	82% (4.3)	31% (1.7)	77% (5±3)	26% (1±2)
Dysuria	34% (2±3)	6% (0±1)	50% (2.6)	14% (0.8)	39% (3±4)	5% (0±1)
Dyschezia	67% (5±4)	17% (1±2)	82% (5.7)	23% (1.2)	71% (5±4)	13% (1±2)

VAS: visual analog scale, SD: standard deviation.

TABLE 3 Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Miller[6]	120 women with endometriosis	Leuprolide acetate	60 control group (treated with placebo) 60 treatment group (leuprolide acetate) Double-blind study	VAS (pain levels measured before the start of the study, 2 and 4 weeks after treatment)	Compared with the control women treated with a placebo, those treated with GnRHa exhibited a statistically ($p < 0.0001$) and clinically significant increase in pain levels, showing that this therapy is associated with an increase in pain associated with endometriosis.
Petta et al.[10]	82 women with endometriosis	LNG-IUS GnRHa	Final sample: 71 34 – LNG-IUS 37 – GnRHa	VAS (pain levels measured before and during the 6 months of treatment)	CPP decreased from the first month and continued to decline over the six months with the two forms of treatment, with no difference between groups ($p > 0.999$). In both groups, the women with stage III and IV endometriosis showed a faster improvement in VAS pain scores than those at stages I and II ($p < 0.002$). Both treatments were effective in reducing the CPP associated with endometriosis. The advantage of LNG-IUS is that it requires a single medical intervention for insertion into the womb every five years and may be the treatment of choice for women who do not want to become pregnant.
Remorgida et al.[12]	12 women with recto-vaginal endometriosis	Letrozole Norethisterone acetate	Letrozole and norethisterone acetate for 6 months	VAS (dysmenorrhea, deep dyspareunia and CPP). Pain symptoms were measured before starting the treatment, each month during treatment (6 months) and 3, 6 and 12 months after completion of treatment (follow-up)	100% of women with dysmenorrhea; 83.3% with deep dyspareunia and 83.3% with CPP. After completion of treatment, all symptoms of pain were significantly less intense than baseline (dysmenorrhea: 8.8±1.0 *versus* 3.7±2.2; dyspareunia: 7.6±1.5 *versus* 2.2±2.0 and CPP: 5.6±0.9 *versus* 2.4±1.6). Symptoms of pain returned rapidly after 3 months of follow-up and, after six months, no significant difference was observed in the intensity of dysmenorrhea, deep dyspareunia, and CPP compared to baseline values. Side effects reported by patients: weight gain (n=4), mood changes (n=4), weakness (n=3), bone and joint pain (n=3), vaginal bleeding (n=2), muscle pains (n=2), headache (n=2), depression (n=2), hot flashes (n=1), nausea (n=1), decreased libido (n=1). Due to the persistence of symptoms of pain, 41.7% of patients underwent surgery after an average (± standard deviation) of 7 (± 2.5) months after the end of medical treatment, that is, 5 patients had surgery during the follow-up. The combined use of letrozoleand norethisterone acetate quickly and effectively reduces the intensity of the symptoms of pain caused by recto-vaginal endometriosis without significant side effects, though pain symptoms returned quickly after stopping treatment.

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TABLE 3 (Cont.) Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Figueiredo and Nascimento[13]	10 women with endometriosis	LNG-IUS	10	VAS (pelvic pain before and after insertion of the LNG-IUS with 6 months of monitoring)	Before insertion of the LNG-IUS, the average pain score was 8.9 and, after insertion, there was a decrease over the year, reaching an average of 1.8 in 6 months. At the end of treatment, the average satisfaction score given by the patients was 9.8. This study showed that LNG-IUS was effective in reducing the pelvic pain associated with endometriosis.
Ferrero et al.[15]	82 patients with recto-vaginal endometriosis	Letrozole Norethisterone acetate	41 from the L group (letrozole, norethisterone acetate) 41 from the N group (isolated norethisterone acetate)	VAS (dysmenorrhea, deep dyspareunia assessed before, 3 and 6 months during treatment and 3, 6 and 12 months after completion of treatment)	Intensity of CPP and deep dyspareunia was significantly lower in the L group compared with the N group. At the end of treatment 63.4% of patients in the N group were more satisfied with the treatment compared to 56.1% in the L group (p=0.49). Adverse effects were more frequent in the L group than in the N group (p=0.02). The combined use of drugs was more effective in reducing painful symptoms; however, letrozole caused a high incidence of side effects, its cost is higher and it did not improve patient satisfaction or influence the recurrence of pain.
Walch et al.[17]	41 women with endometriosis	Implanon DMPA	21 – treated with implanon 20 – treated with DMPA	VAS (dysmenorrhea, non-menstrual pelvic pain and dyspareunia assessed before and after 3, 6, 9 and 12 months of treatment)	The level of patient satisfaction with treatment was similar in both groups (57% implanon *versus* 58% DMPA). During the period of 1 year of treatment, there was an improvement in pain intensity for both treatments. After 6 months, the mean decrease in pain was 68% in the group treated with Implanon and 53% in the DMPA group, but this difference was not statistically significant (p=0.36). The results showed that in relation to pain relief, the therapeutic efficacy of Implanon was not lower than DMPA, that is, both were effective in reducing the pain associated with endometriosis.
Indraccolo et al.[18]	4 patients with endometriosis and CPP	N-palmitoylethanolamide Polydatin	Palmitoylethanolamide and polydatin for 90 days Pilot study	VAS (CPP, deep dyspareunia, dyschezia, dysuria and dysmenorrhea) before and 1, 2 and 3 months after treatment	Preliminary results showed that the patients reported pain relief after one month of treatment. The palmitoylethanolamide/polydatin combination was effective in controlling CPP associated with endometriosis.

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TABLE 3 (Cont.) Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Ferrero et al.[19]	6 women with colorectal endometriosis	Letrozole Norethisterone acetate	Letrozole and norethisterone acetate for 6 months Pilot study	VAS (dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia, dyschezia and gastrointestinal symptoms) presence and intensity of symptoms assessed before starting treatment and after 3 and 6 months of treatment	Prevalence and mean intensity (standard deviation) of symptoms before and 3 and 6 months after treatment. Dysmenorrhea: 100% 7.6±1.8 NI NI Non-menstrual pelvic pain: 83% 6±1.1 3.2±0.5 2.2±0.4 Deep dyspareunia: 83% 5.1±1.9 1.7±1.2 1.2±1.0 Dyschezia: 67% 5.1±2.0 2.0±1.5 1.2±0.9 Intensity of symptoms decreased 3 months after treatment and even further after 6 months. 67% of patients reported being satisfied/very satisfied with respect to the overall assessment of the effects of the treatment on symptoms. 4 patients reported side effects of treatment but due to their mild severity, there was no interruption of treatment: bleeding (n=1), weight gain (n=1), joint pain (n=1), and decreased libido (n=1). The combined use of letrozole and norethisterone acetate reduces pain and gastrointestinal symptoms.
Ferrero et al.[20]	40 women with colorectal endometriosis	Norethisterone acetate	Norethisterone acetate for 12 months Initial sample: n=40 6 months: n=38 12 months: n=32	VAS (dysmenorrhea, CPP, deep dyspareunia, and dyschezia), and gastrointestinal symptoms measured before and after 6 and 12 months of treatment	85% dysmenorrhea, 73% CPP, 67% deep dyspareunia and 68% dyschezia. 60% of patients reported being satisfied/very satisfied with respect to the overall assessment of the effects of the treatment on symptoms at the end of treatment. 53% of patients reported improvement in gastrointestinal symptoms. The administration of norethisterone acetate promoted a significant improvement in the intensity of CPP, deep dyspareunia and dyschezia. Values expressed as a mean (± standard deviation) before the beginning of treatment and after 6 and 12 months. Dysmenorrhea: 6.8±1.9/not available/not available CPP: 5.5±1.3/4.1±1.8/3.5±1.6 Deep dyspareunia: 5.7±1.4/3.1±1.1/2.8±1.2 Dyschezia: 5.1±1.9/3.2±1.2/2.5±1.4

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TABLE 3 (Cont.) Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Ferrero et al.[22]	35 patients with recto-vaginal endometriosis	Letrozole Norethisterone acetate Triptorelin	17 from the N group (letrozole, norethisterone acetate) 18 from the T group (letrozole, triptorelin)	VAS and Multidimensional Categorical Classification Scale (dysmenorrhea, non-menstrual pelvic pain and deep dyspareunia assessed before, and after 3 and 6 months of treatment)	64.7% of patients in the N group reported being satisfied or very satisfied with the treatment compared with 22.2% from the T group. 77.8% of the T group patients reported adverse effects *versus* 35.3% from the N group. 44.4% of the T group patients stopped treatment due to adverse effects *versus* 5.9% from the N group. During treatment, the bone mineral density significantly decreased in the T group but not the N group. Pain intensity decreased significantly during treatment in both groups. This study demonstrated the effectiveness of the aromatase inhibitor in the treatment of pain associated with endometriosis.
Ferrero et al.[23]	15 women with recto-vaginal endometriosis	LNG-IUS Danazol	Vaginal danazol applied for 6 months	VAS and Multidimensional Categorical Classification Scale (symptoms evaluated: dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia and dyschezia) Intensity of the symptoms evaluated in three different situations: isolated use of LNG-IUS and after 3 and 6 months of treatment with vaginal danazol	Intensity of the symptoms of pain significantly decreased after administration of danazol for 3 months and continued to decrease even after 6 months of treatment. 80% of patients were satisfied with the treatment. Minimal adverse effects of LNG-IUS and vaginal danazol treatment: seborrhea, oily hair or acne (n=4), headache (n=3), weight gain > 3 kg (n=2) and vaginal irritation (n=2). Vaginal danazol reduced the severity of the painful symptoms related to endometriosis that persisted after insertion of LNG-IUS.
Guzick et al.[24]	47 women with endometriosis and CPP	Leuprolide Continuous oral contraceptives (COC)	21 – leuprolide 26 – continuous oral contraceptives	Biberoglu & Behrman/B & B and Numerical Scale measured before treatment, and after 4, 12, 24, 36 and 48 weeks of treatment	Both products were equally effective in treating the pelvic pain associated with endometriosis.
Mabrouk et al.[26]	106 women with endometriosis	COCs	75 – use of COCs 31 – non users of COCs	VAS (dysmenorrhea, dyspareunia, CPP and dyschezia)	The comparison of VAS scores between the two groups showed that during the preoperative period, dysmenorrhea and dyspareunia symptoms had higher VAS scores (p=0.02 and p=0.005, respectively) in the untreated group, with worsening of the intensity of the pain. The data suggest that therapy with combined oral contraceptive may have a role in limiting the progression of dysmenorrhea and dyspareunia associated with endometriosis.

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TABLE 3 (Cont.) Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Ferrari et al.[27]	26 women with colorectal endometriosis	Continuous oral contraceptives	26 patients on continuous oral contraceptives	VAS (dysmenorrhea, non-menstrual pelvic pain, dyspareunia and dyschezia with pain scores measured before and 12 months after administration of the drug)	The symptoms evaluated and their scores before and after treatment were: dysmenorrhea (90.4±9.9 *versus* 26.9±29.2), non-menstrual pelvic pain (65.0±27.3 *versus* 18.5±19.1), dyspareunia (63.1±22.8 *versus* 18.5±24.3) and pain on defecation (57.7±28.2 *versus* 13.1±17.6). The values are expressed as mean ± standard deviation and show that there was a significant decline in intensity of symptoms after 12 months of treatment ($p<0.01$). At the end of the study, 69% of patients were satisfied with the treatment. The following adverse effects were noted: 38% uterine bleeding, 23% moderate weight gain, 11% headache and 7% decreased libido, although none of the women discontinued treatment due to the effects.
Petraglia et al.[28]	168 women with endometriosis	Dienogest	Initial sample: 168 Final sample: 152	VAS (CPP – 65 weeks, that is, 53 weeks in the group treated with dienogest and 12 weeks in the placebo group)	The mean VAS score was significantly reduced by 43.2 mm (standard deviation ± 21.7) in the total period of 65 weeks of treatment (that is, the study group *versus* placebo group, $p<0.001$), meaning that a significant decrease pelvic pain was observed during continuous treatment with dienogest ($p<0.001$). Adverse effects related to medication were noted in 27/168 patients (16.1%) during the study, with the intensity of adverse events related to treatment ranging from mild to moderate in the majority of cases (92.5%). Only 4 patients (2.4%) discontinued treatment due to side effects. Long term treatment with dienogest was effective and the reduction of pelvic pain persisted for at least 24 weeks after the end of treatment.
Giugliano et al.[31]	47 patients with endometriosis	N-palmitoylethanolamide Trans-polydatin	47 patients divided into two groups according to the ED site 19 – Group A (ED of the rectovaginal septum) 28 – Group B (ED of the ovary)	VAS (dyspareunia, dyschezia, dysmenorrhea and CPP) before, 1, 2 and 3 months after treatment	Endometriotic pain intensity decreased significantly in both groups ($p<0.0001$). The efficacy of treatment was significant after 30 days. Pain intensity also decreased in both groups, except for dysmenorrhea, which was reduced faster in group B. The combination of N-palmitoylethanolamide and trans-polydatin reduced pain related to endometriosis, regardless of the site affected.

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TABLE 3 (Cont.) Main results of 17 studies that evaluated the effect of drugs on pain scores.

Study	Sample	Medication used	Number of patients treated	Information regarding pain (instrument used, types of pain, etc.)	Main results and/or conclusion
Morelli et al.[32]	63 women	GnRHa (leuprolide acetate)	15 – adenomyosis (group A) 48 – endometriosis (group B)	VAS (before and 3 months after administration of GnRHa)	Before using the drug, the scores were 72.5±18.5 *versus* 68.5±19.9 in groups A and B, respectively, and this difference was not statistically significant (p=0.48). After three months of treatment, the VAS scores decreased significantly in patients with adenomyosis (23.3±16.7 *vs.* 31.8±10.0 for groups A and B, respectively; p<0.05). The values are expressed as mean ± standard deviation. When comparing both groups, the reduction in CPP intensity, expressed as ΔVAS (difference between VAS scores prior to and after the use of GnRHa), was significantly higher in patients with adenomyosis compared to those with endometriosis (49.3±16 8 *versus* 36.7±15.6 for group A and B, respectively; p<0.001), showing greater effectiveness of GnRHa in the reduction of CPP in adenomyosis. In summary, a significant reduction in CPP intensity was observed in both groups (p<0.05), but was significantly higher in group A compared with B (p<0.001).

VAS: visual analogue scale, CPP: chronic pelvic pain, LNG-IUS: intrauterine system with levonorgestrel, DMPA: medroxyprogesterone acetate, GnRHa: gonadotropin-releasing hormone analogues, NI: not informed, COCs: combined oral contraceptives, ED: endometriosis.

Discussion

This study shows that the scientific literature is vast as to the number of scientific articles published on the prevalence and levels of pain in patients with endometriosis. The painful symptoms attributed to endometriosis include CPP, dysmenorrhea, dyspareunia, dyschezia and dysuria. Pain restricts and modifies the daily routine of these patients, directly affecting their quality of life. Despite the use of instruments to measure pain, such analysis is complex due to its subjective nature and the influence of factors such as personality, psychiatric disorders (depression) and psychosocial factors. The severity of pain may be related to the degree of depression and anxiety, present in 90% of women with endometriosis. Some authors indicate that depression is a direct consequence of pain, but there is no consensus on this temporal issue when defining which condition precedes the other. However, it is possible to affirm that the two conditions coexist, and that one worsens the experience of the other.[33] Whenever endometriosis patients exhibit depression, it is clinically important to assess the condition and start appropriate treatment as soon as possible. Depression, if left untreated, has a negative effect on the patient's ability to deal with the pain, daily functioning, and especially their quality of life. In addition, the impact of a chronic disease, such as endometriosis, associated with persistent painful symptoms, causes the patient to become isolated, damaging relationships given that women with endometriosis are labeled as "hypochondriac" and their circle of friends ends up getting tired of so many complaints. This favors the emergence of depressive symptoms.[33]

In relation to the instruments for measuring pain, the VAS has prevailed as the most frequently applied questionnaire for analysis of endometriotic pain. It is a one-dimensional instrument that quantifies pain according to intensity. It consists of a line of 10 or 100 cm, which contains the number 0 on the left and the number 10 or 100 at the other end. Patients are advised to mark the position that reflects the degree of pain, with 0 being no pain and 10 or 100 considered the worst pain experienced.[15,27]

One way to reduce the painful symptoms in patients with endometriosis is to use conventional treatment including surgery and/or medication.

The data presented in Tables 1 and 2 show that surgical treatment for endometriosis was effective in relieving dysmenorrhea, dyspareunia, pelvic pain, dyschezia and dysuria. These studies show that laparoscopic excision reduces pain levels after surgery, ranging from 4 months,[7] to 6 months,[25,30] 12 months[9,11,21,29] and 2-5 years.[8]

Surgical treatment for endometriosis consists of excision of endometriotic lesions by laparoscopy. Laparotomy can also be used in the treatment of this disease; however, laparoscopy is more widely employed because it is minimally invasive compared to the first, and has the following advantages: less blood loss, shorter postoperative recovery time, less postoperative pain and early hospital discharge.[2] A recent review addressed the surgical treatment of endometriosis in terms of improvement in pain and infertility. The authors conclude that surgical treatment seems to be the definitive therapy for women with exacerbated painful symptoms.[34]

According to Nácul and Spritzer,[2] pharmacological treatments for pain associated with endometriosis include estro-progesterone combinations (birth control), isolated progestins (norethindrone acetate, dienogest, medroxyprogesterone acetate – DMPA, intrauterine systems with levonorgestrel – LNG-IUS), gonadotropin releasing hormone analogues (GnRHa – nafarelin acetate, leuprolide acetate, triptorelin), danazol and gestrinone and aromatase inhibitors (letrozole and anastrozole). The costs and side effects of these drugs differ significantly. Of the 17 studies that evaluated the influence of medication on decreasing pain levels, seven evaluated one drug alone[6,13,20,26-28,32] and 10 evaluated drugs in combination.[10,12,15,17-19,22-24,31] Thus, 3 studies employed contraceptives;[24,26,27] 10 used isolated progestins;[10,12,13,15,17,19,20,22,23,28] 5 used GnRHa,[6,10,22,24,32] one used danazol[23] and 4 used aromatase inhibitors.[12,15,19,22] The use of aromatase inhibitors for the treatment of endometriosis and its associated symptoms is justified by the fact that endometriotic tissue over-expresses aromatase, an enzyme key for the production of estrogen, noting that endometriosis is an estrogen-dependent gynecological condition. However, they exhibit poor tolerability and high costs compared to more conventional therapies.[35] Among the therapeutic options for treatment of endometriotic pain, estrogen-progestin combinations are the 1st line therapy, with progestins as 1st or 2nd line therapy, and GnRHa and danazol/gestrinone as 2nd and 3rd line treatments, respectively.[2] An interesting finding in relation to GnRHa (triptorelin) was reported by Ferrero et al.[22] who also evaluated the effect of letrozole (aromatase inhibitor) and norethisterone acetate (isolated progestin). In their study, about 80% of patients who received letrozole and triptorelin reported side effects and 45% discontinued treatment as a result. Side effects of GnRHa include dry vagina, decreased libido, depression, irritability, fatigue and bone mineral loss, which limits its use.[2] Danazol is another drug that has limited use due to adverse androgen-

ic effects, such as changes in lipid profile, weight gain, edema, acne, vaginal dryness, hot flashes, liver toxicity, breast atrophy, voice alteration, hirsutism, and oily skin; however, vaginal use has shown satisfactory results.[23] Accordingly, while indicating a drug for treatment of pain associated with endometriosis, one must consider the adverse effects and investigate the patient's satisfaction with the treatment. It is also recommended to inform women with endometriosis of the benefits, limitations and costs of each drug. In relation to dienogest (DNG), a scientific paper recently published presented the results of nine studies using DNG, short and long term, in the treatment of endometriosis. This drug proved to be effective in reducing pain symptoms associated with endometriosis.[36]

In addition to the clinical treatments that reduce estrogenic activity, as presented above, drugs that reduce inflammation are also used in endometriosis (non-steroidal anti-inflammatory drugs – NSAIDs). Two studies have evaluated the combination of N-palmitoyl ethanolamine and transpolydatin/polydatin, drugs that act on inflammation, in the treatment of pain associated with endometriosis.[18,31] Polydatin is a resveratrol glycoside that has antioxidant activities. Therefore, the combination of these drugs work on the inflammatory processes and oxidative stress involved in the development of endometriosis.

The studies presented above show that the pharmacological and surgical treatments for relief of pain associated with endometriosis are effective. Most clinical treatments lead to stabilization or regression of lesions, which usually recur after the medication is stopped, as well as recurrence of the disease after surgery.[34] There has been predominance in the use of medication to control the pain associated with endometriosis. This is in the premise established by the American Society for Reproductive Medicine (ASRM) which has established that "endometriosis should be viewed as a chronic disease that requires a life-long pain management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures".[37] Despite the side effects of drugs and their cost, surgery is an invasive procedure with a risk of complications. Thus, surgery is indicated to confirm the diagnosis and to manage the patients that do not respond to medical treatment.[34] Given the above, the choice of ideal treatment for endometriosis is complex. The data herein presented show that both treatments helped to relieve the pain associated with endometriosis and, consequently, they promoted an improvement in the quality of life of women with this gynecological disease.

Conclusion

Endometriosis is a gynecological disease that has as its main characteristic pain that compromises the sexual, social and professional life of women affected. Thus, painful symptoms have been linked to deterioration in the quality of life of such patients. Treatment for this disease, therefore, focuses on pain relief.

The data herein presented show that patients with endometriosis exhibit high levels of pain. Surgery and the use of drugs provided reduced pain scores in patients with endometriosis, but nevertheless exhibit disadvantages, such as risk of recurrence and side effects, respectively. Treatment of endometriosis is, therefore, a challenge for gynecologists and patients, as they must select the best therapeutic approach for this disease. However, improved quality of life in these patients has been obtained with the use of conventional treatment.

Resumo

Avaliação da dor associada à endometriose e influência do tratamento convencional: uma revisão sistemática

A endometriose é uma doença ginecológica crônica caracterizada por quadros álgicos constantes responsáveis pela redução da qualidade de vida das portadoras. O tratamento convencional, que inclui o cirúrgico e farmacológico, tem por finalidade reduzir os sintomas de dor. Este estudo teve por objetivo avaliar os níveis de dor nas mulheres com endometriose, com enfoque na influência do tratamento convencional no controle dessa variável. Para isso, foi realizada uma pesquisa bibliográfica no Medline/PubMed e foram encontrados 119 artigos científicos, sendo que, após a aplicação dos critérios de inclusão e exclusão, 27 foram selecionados para leitura e elaboração desta revisão. Desse modo, nove estudos avaliaram a contribuição da cirurgia; dezessete, o uso de medicamentos para redução nos níveis de dor em pacientes com endometriose; e um, o tratamento cirúrgico e medicamentoso. Os principais resultados dessas pesquisas estão apresentados e discutidos nesta revisão. A cirurgia e o uso de medicamentos proporcionaram redução nos escores de dor nas pacientes com endometriose, no entanto, exibem desvantagens como risco de recorrência e efeitos colaterais, respectivamente. Assim, o tratamento para endometriose é um desafio para ginecologistas e pacientes, uma vez que é necessário selecionar a melhor abordagem terapêutica para essa doença. Entretanto, melhora na qualidade de vida das pacientes foi obtida com o emprego do tratamento convencional.

Palavras-chave: endometriose, dor pélvica, terapêutica, qualidade de vida.

References

1. Bulun SE. Endometriosis. Review. N Engl J Med. 2009; 360(3):268-79.
2. Nácul AP, Spritzer PM. Aspectos atuais do diagnóstico e tratamento da endometriose. Rev Bras Ginecol Obstet. 2010; 32(6):298-307.
3. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011; 96(2):366-73.
4. Fourquet J, Gao X, Zavala D, Orengo JC, Abac S, Ruiz A, et al. Patients' report on how endometriosis affects health, work, and daily life. Fertil Steril. 2010; 93(7):2424-8.
5. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod. 2012; 27(5):1292-9.
6. Miller JD. Quantification of endometriosis-associated pain and quality of life during the stimulatory phase of gonadotropin-releasing hormone agonist therapy: a double-blind, randomized, placebo-controlled trial. Am J Obstet Gynecol. 2000; 182(6):1483-8.
7. Garry R, Clayton R, Hawe J. The effect of endometriosis and its radical laparoscopic excision on quality of life indicators. BJOG. 2000; 107(1):44-54.
8. Abbott JA, Hawe J, Clayton RD, Garry R. The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. Hum Reprod. 2003; 18(9):1922-7.
9. Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. Fertil Steril. 2004; 82(4):878-84.
10. Petta CA, Ferriani RA, Abrão MS, Hassan D, Rosa E Silva JC, Podgaec S, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005; 20(7):1993-8.
11. Lyons SD, Chew SS, Thomson AJ, Lenart M, Camaris C, Vancaillie TG, et al. Clinical and quality-of-life outcomes after fertility-sparing laparoscopic surgery with bowel resection for severe endometriosis. J Minim Invasive Gynecol. 2006; 13(5):436-41.
12. Remorgida V, Abbamonte HL, Ragni N, Fulcheri E, Ferrero S. Letrozole and norethisterone acetate in rectovaginal endometriosis. Fertil Steril. 2007; 88(3):724-6.
13. Figueiredo J, Nascimento R. Avaliação da qualidade de vida de pacientes portadoras de endometriose após inserção do sistema intra-uterino liberador de levonorgestrel (SIU-LNg). ACM Arq Catarin Med. 2008; 37(4):20-6.
14. Fabbri E, Villa G, Mabrouk M, Guerrini M, Montanari G, Paradisi R, et al. McGill Pain Questionnaire: a multi-dimensional verbal scale assessing postoperative changes in pain symptoms associated with severe endometriosis. J Obstet Gynaecol Res. 2009; 35(4):753-60.
15. Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Hum Reprod. 2009; 24(12):3033-41.
16. Jedrzejczak P, Sokalska A, Spaczyński RZ, Duleba AJ, Pawelczyk L. Effects of presacral neurectomy on pelvic pain in women with and without endometriosis. Ginekol Pol. 2009; 80(3):172-8.
17. Walch K, Unfried G, Huber J, Kurz C, van Trotsenburg M, Pernicka E, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis--a pilot study. Contraception. 2009; 79(1):29-34.
18. Indraccolo U, Barbieri F. Effect of palmitoylethanolamide-polydatin combination on chronic pelvic pain associated with endometriosis: preliminary observations. Eur J Obstet Gynecol Reprod Biol. 2010; 150(1):76-9.
19. Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Seracchioli R, et al. Letrozole and norethisterone acetate in colorectal endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010; 150(2):199-202.
20. Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Hum Reprod. 2010; 25(1):94-100.
21. Bassi MA, Podgaec S, Dias Jr JA, D'Amico Filho N, Petta CA, Abrão MS. Quality of life after segmental resection of the rectosigmoid by laparoscopy in patients with deep infiltrating endometriosis with bowel involvement. J Minim Invasive Gynecol. 2011; 18(6):730-3.
22. Ferrero S, Venturini PL, Gillott DJ, Remorgida V. Letrozole and norethisterone acetate versus letrozole and triptorelin in the treatment of endometriosis related pain symptoms: a randomized controlled trial. Reprod Biol Endocrinol. 2011; 9:88.
23. Ferrero S, Tramalloni D, Venturini PL, Remorgida V. Vaginal danazol for women with rectovaginal endometriosis and pain symptoms persisting after insertion of a levonorgestrel-releasing intrauterine device. Int J Gynaecol Obstet. 2011; 113(2):116-9.
24. Guzick DS, Huang LS, Broadman BA, Nealon M, Hornstein MD. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil Steril. 2011; 95(5):1568-73.
25. Mabrouk M, Montanari G, Guerrini M, Villa G, Solfrini S, Vicenzi C, et al. Does laparoscopic management of deep infiltrating endometriosis improve quality of life? A prospective study. Health Qual Life Outcomes. 2011; 9:98.
26. Mabrouk M, Frascà C, Geraci E, Montanari G, Ferrini G, Raimondo D, et al. Combined oral contraceptive therapy in women with posterior deep infiltrating endometriosis. J Minim Invasive Gynecol. 2011; 18(4):470-4.
27. Ferrari S, Persico P, Di Puppo F, Vigano P, Tandoi I, Garavaglia E, et al. Continuous low-dose oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic ultrasonography. Acta Obstet Gynecol Scand. 2012; 91(6):699-703.
28. Petraglia F, Hornung D, Seitz C, Faustmann T, Gerlinger C, Luisi S, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2012; 285(1):167-73.
29. Setälä M, Härkki P, Matomäki J, Mäkinen J, Kössi J. Sexual functioning, quality of life and pelvic pain 12 months after endometriosis surgery including vaginal resection. Acta Obstet Gynecol Scand. 2012; 91(6):692-8.
30. Mabrouk M, Montanari G, Di Donato N, Del Forno S, Frascà C, Geraci E, et al. What is the impact on sexual function of laparoscopic treatment and subsequent combined oral contraceptive therapy in women with deep infiltrating endometriosis? J Sex Med. 2012; 9(3):770-8.
31. Giugliano E, Cagnazzo E, Soave I, Lo Monte G, Wenger JM, Marci R. The adjuvant use of N-palmitoylethanolamine and transpolydatin in the treatment of endometriotic pain. Eur J Obstet Gynecol Reprod Biol. 2013; 168(2):209-13.
32. Morelli M, Rocca ML, Venturella R, Mocciaro R, Zullo F. Improvement in chronic pelvic pain after gonadotropin releasing hormone analogue (GnRH-a) administration in premenopausal women suffering from adenomyosis or endometriosis: a retrospective study. Gynecol Endocrinol. 2013;29(4):305-8.
33. Lorençatto C, Vieira MJN, Pinto CLB, Petta CA. Avaliação da frequência de depressão em pacientes com endometriose e dor pélvica. Rev Assoc Med Bras. 2002; 48(3):217-21.
34. Kondo W, Zomer MT, Amaral VF. Tratamento cirúrgico da endometriose baseado em evidências. Femina. 2011; 39(3):143-8.
35. Nothnick WB. The emerging use of aromatase inhibitors for endometriosis treatment. Reprod Biol Endocrinol. 2011; 9:87. Review.
36. Bahamondes L, Camargos AF. Dienogest: uma nova opção terapêutica em endometriose. Femina. 2012; 40(3):155-9.
37. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014; 101(4):927-35.