Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Pharmacological treatment of endometriosis: update from recent clinical trials

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Endometriosis is a chronic disease that causes pain and infertility. Combined oral contraceptives and progestins are commonly used for the treatment of endometriosis because they reduce the severity of pain symptoms in 60–70% of patients and are well tolerated. Gonadotropin-releasing hormone analogs and danazol may be administered to selected patients but their long-term use is limited owing to the high frequency of severe adverse effects. Aromatase inhibitors should be administered only to women who fail to improve after surgery and conventional hormonal therapy because they are not well tolerated. This article discusses the medical therapies available for the treatment of endometriosis-related pain symptoms; in addition, detailed information on the recent advances in the treatment of rectovaginal endometriosis, ovarian endometriomas and bowel endometriosis is presented.

Keywords: aromatase inhibitor • endometriosis • gonadotropin-releasing hormone analog • medical treatment • oral contraceptive pill • progestin

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Endometriosis is a chronic estrogen-dependent gynecological condition characterized by the presence of ectopic endometrial glands and stroma outside the uterine cavity. It affects at least 3.6% of women of reproductive age [1] and it is rarely observed in postmenopausal women who do not use hormonal therapies [2]. Women with endometriosis often suffer pain symptoms, such as dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia. In addition, endometriosis may cause infertility. These symptoms negatively affect patient's quality of life, work efficiency, sexual and social life [3–5].

Therapy for endometriosis consists of surgical excision of the lesions or medical treatments. Several studies demonstrated that the surgical excision of endometriotic nodules not only reduces the intensity of pain symptoms but also improves sexual function and quality of life [6–9]. However, in some patients, the resection of endometriotic lesions may be incomplete and pain symptoms may persist or quickly recur after surgery. Persistence or recurrence of symptoms is observed in 7–30% of women at 3 years from surgery and in 40–50% of patients at 5 years from surgery [10]. A 7-year follow-up study on the requirement for further surgery showed that the reoperation rate is 58% in women undergoing conservative laparoscopic excision of endometriosis [11]. Furthermore, the excision of deep endometriotic lesions may be associated with severe morbidity, particularly when intestinal, ureteral and vascular complications occur [12–14]. Therefore, medical therapies can be used either as an alternative to surgery or after surgical excision of endometriosis.

This article attempts to summarize the most recent advances in the pharmacological treatment of endometriosis. Particular attention will be given to the indications and limitations of medical treatment, the emerging drugs used in the treatment of endometriosis and the pharmacological treatment of particular locations of endometriotic lesions.

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Materials & methods

An electronic database search (EMBASE, MEDLINE, PubMed) was performed with the objective of identifying all studies published until June 2010 investigating the pharmacological treatments of endometriosis. Combinations of medical subject heading terms including 'aromatase inhibitors' (AIs), 'bowel/intestinal endometriosis', 'endometriomas', 'danazol', 'deep endometriosis', 'deeply infiltrating endometriosis', 'dysmenorrhea', 'dyspareunia', 'endometriosis', 'gonadotropin-releasing hormone analogs', 'medical therapy/treatment', 'oral contraceptive', 'pelvic pain', 'progestin', 'rectovaginal endometriosis', 'therapy/treatment' were used. All pertinent articles were retrieved and the relative reference lists were systematically reviewed in order to identify additional studies that could be included in the review. Moreover, review articles, books and monographs published on endometriosis were consulted and their reference lists were searched for any potential further study.

Principles of pharmacological treatment of endometriosis-related pain symptoms

Drugs suppressing ovarian function are the most efficacious pharmacological treatment used to reduce the intensity of pain symptoms caused by endometriosis. However, all these agents are contraceptives and, therefore, they cannot be administered to women wishing to conceive. Nonsteroidal anti-inflammatory drugs may represent an alternative to hormonal therapies in women wishing to conceive or in those with mild symptoms. Obviously, surgery is required in cases of obstructive uropathy, symptomatic bowel stenosis or when an ovarian mass with uncertain ultrasonographic appearance is present. Theoretically, all other patients with endometriosis may benefit from pharmacological therapy. Pharmacological treatment can be used: as an alternative to surgery in patients wishing to avoid or postpone laparoscopy; after surgery, in order to prevent the recurrence of endometriotic ovarian cysts; or in patients who have persistence or recurrence of pain symptoms after surgery. Clinicians should be aware that endometriosis is a chronic disease [15] and that pain typically recurs to a degree similar to that at baseline after discontinuation of endocrine therapies [16–20]. Therefore, hormonal therapies should be chronically administered to symptomatic women with endometriosis. Based on this long-term use, agents used to treat endometriosis should ideally be well tolerated by the patients in order to guarantee long-term compliance.

Currently, there is no evidence that pharmacological therapy may 'cure' endometriosis [21]. Hormonal therapies may reduce the size of endometriotic nodules [16,17,22,23], however, patients should be informed that endometriotic lesions are not expected to disappear during pharmacological treatment despite the improvement in pain symptoms [20,24,25].

Pharmacological treatment of endometriosis-related infertility

Pharmacological therapies commonly used to treat pain symptoms do not improve endometriosis-associated infertility. A prospective double-blind, randomized, placebo-controlled clinical trial investigated whether the postoperative treatment with pentoxifylline improves fertility [26]. A total of 80 infertile women with pain symptoms and laparoscopic diagnosis of endometriosis were randomized to receive either pentoxifylline (400 mg twice daily) or placebo. The 12-month overall pregnancy rate was 39.5 and 35.6% in the intervention and control groups, respectively (not significant) [26]. Therefore, there is no evidence that immunomodulation with pentoxifylline aids fertility [27]. The cyclical administration of dydrogesterone (at doses of 10–60 mg/day) should be considered in women with pain symptoms wishing to conceive [28]. In fact, this treatment prevents bleeding problems, has no androgenic adverse effects and does not inhibit ovulation [28]. In addition, a study including 300 women with endometriosis reported higher pregnancy rates in patients treated with dydrogesterone (50%) than in those treated with depot medroxyprogesterone acetate (35%) or placebo (30%) [29].

Some endocrine therapies may be useful before infertility treatments. A Cochrane review including three randomized controlled trials (165 women) demonstrated that the administration of gonadotropin-releasing hormone (GnRH) analogs for at least 3 months (up to 6 months) before assisted reproductive technologies increase the odds of clinical pregnancy by at least fourfold [30].

Conventional hormonal therapies in endometriosis

Hormonal therapies commonly used in the treatment of endometriosis are the combined oral contraceptive pill, progestins, GnRH analogs and danazol [31]. The combined oral contraceptive pill and progestins are commonly used for treating endometriosis-associated pain symptoms [31]. These agents determine a satisfactory improvement in pain symptoms in 60–70% of patients with endometriosis [23,32]. These drugs not only improve pain symptoms but are also well tolerated. Continuous combined oral contraceptives and progestins might be preferred in women with dysmenorrhea persisting during sequential therapy.

Various progestins have been used in the treatment of pain symptoms caused by endometriosis, such as medroxyprogesterone acetate, norethisterone acetate,

cyproterone acetate and the levonorgestrel-releasing intrauterine device. Among these compounds, norethisterone acetate (or norethindrone acetate), a derivative of 19-nortestosterone, may offer various advantages in the long-term treatment of endometriosis-related pain symptoms including a good control of uterine bleeding, a positive effect on calcium metabolism and limited effects on lipoprotein profile [21].

Several randomized controlled trials demonstrated the efficacy of GnRH analogs in the treatment of endometriosis-related pain symptoms when compared with placebo [33], danazol [34], gestrinone [35], medroxyprogesterone acetate [36] and the levonorgestrel-releasing intrauterine device [37]. However, the administration of GnRH analogs to premenopausal women is associated with several adverse effects determined by the hypoestrogenic state; they include hot flashes, insomnia, reduction in bone mineral density, vaginal dryness, decreased libido, depression, joint pain, mood swings and fatigue [38]. Combining GnRH analogs and a small amount of steroid hormones reduces the adverse effects without impairing the effectiveness of treatment [31]. Danazol is as affective as GnRH analogs in improving pain symptoms caused by endometriosis [34]. However, the long-term use of danazol causes severe androgenic adverse effects, such as weight gain, muscle cramps, atrophic breast changes, oily skin, acne, hirsutism, voice changes and lipid changes [39].

Emerging therapies in endometriosis

■ Aromatase inhibitors

Since the late 1990s, several studies have demonstrated that the aromatase P450 is expressed in both eutopic and ectopic endometrium of patients with endometriosis, while this enzyme is not detectable in eutopic endometrium obtained from healthy women and in endometriosis-free peritoneal tissue [40–42]. Based on these molecular observations, great attention has been given to the use of nonsteroidal type II AIs (anastrozole and letrozole) for the treatment of pain symptoms caused by endometriosis [43].

The efficacy of AIs in the treatment of endometriosis was shown for the first time in an open-label, nonrandomized study including ten patients who had pain symptoms that persisted after previous medical and surgical therapies [44]. The patients were treated with letrozole (2.5 mg/day), norethisterone acetate (2.5 mg/day), elemental calcium and vitamin D for 6 months. This treatment caused a significant decrease in the intensity of pain symptoms in 90% of the patients. These preliminary observations were confirmed in a subsequent prospective open-label trial [45]. A total of 18 women with pain symptoms caused by endometriosis received anastrozole (1 mg/day) and an oral contraceptive pill; of the 15 patients who completed the 6-month treatment, 14 had significant improvement in pain symptoms [45]. Subsequently, two open-label, prospective studies combining letrozole with either norethisterone acetate (2.5 mg/day) or desogestrel (75 µg/day) confirmed that AIs ameliorate pain symptoms in women with endometriosis; however, a recurrence of symptoms was noticed quickly after the interruption of treatment [19,20]. The major limitation of all the abovementioned studies is that AIs were administered in combination with drugs that downregulate gonadal estrogen biosynthesis and these agents are commonly used for the treatment of endometriosis (such as progestins or the oral contraceptive pill). Therefore, it was not possible to precisely discriminate the effects on pain symptoms determined by AIs and by drugs suppressing ovarian function (Table 1). In addition, all these studies had a small sample size. More recently, a prospective, open-label, nonrandomized patient preference trial including 82 women compared the effects on pain symptoms determined by a combination of letrozole and norethisterone acetate or norethisterone acetate alone [32]. The combination drug regimen was more effective in reducing pain and deep dyspareunia than norethisterone acetate alone; however, letrozole caused a higher incidence of adverse effects (in particular, joint pain and myalgia), cost more and did not improve patients' satisfaction or influence recurrence of pain after discontinuation of treatment.

In a recent study, AIs have been used to treat ovarian endometriomas. A total of five women with ovarian endometriomas received letrozole (2.5 mg/day), desogestrel (0.15 mg/day) and ethinyl estradiol (0.03 mg/day) for 6 months [46]. In all the patients, the size of the endometriomas significantly decreased within 3 months of initiation of therapy. One patient had complete regression of the endometrioma within 3 months of initiation of treatment; the remaining patients had complete regression of the endometriomas at the end of the 6 months of treatment. Interestingly, no recurrence of endometriomas was observed during the follow-up (up to 2 years from treatment) [46].

Only one randomized, placebo-controlled trial examined the usefulness of AIs in preventing the recurrence of endometriosis and associated symptoms after conservative surgery [47]. A total of 80 women were randomized to receive either anastrozole (1 mg/day) and goserelin (3.6 mg subcutaneous depot injections every 4 weeks) or goserelin alone for 6 months; all the patients received elemental calcium and vitamin D. This study demonstrated that letrozole plus goserelin reduced the proportion of women experiencing recurrence of pain at 24 months follow-up (8% with combination therapy vs 35% with goserelin alone).

Table 1. Studies evaluating the effectiveness of aromatase inhibitors in the treatment of endometriosis-related pain symptoms.

Length of treatment (months)	Type of study	Number of patients	Aromatase inhibitor	Drugs suppressing ovarian function	Ref.
6	Open-label, nonrandomized, prospective	10	Letrozole (2.5 mg/day orally)	Norethindrone acetate (2.5 mg/day)	[44]
6	Randomized, prospective	40	Anastrozole (1 mg/day orally)	Goserelin (depot injections of 3.6 mg/4 weeks)	[46]
6	Open-label, nonrandomized, prospective, multicenter	18	Anastrozole (1 mg/day orally)	Ethinyl estradiol (20 µg/day) and levonorgestrel (0.1 mg/day)	[45]
6	Open-label, nonrandomized, prospective	10	Anastrozole (0.25 mg/ day vaginally)	None	[18]
6	Open-label, nonrandomized, prospective	12	Letrozole (2.5 mg/day, orally)	Norethisterone acetate (2.5 mg/day)	[20]
6	Open-label, nonrandomized, prospective	12	Letrozole (2.5 mg/day, orally)	Desogestrel (75 µg/day)	[19]
6	Open-label, nonrandomized, patient-preference trial	41	Letrozole (2.5 mg/day, orally)	Norethisterone acetate (2.5 mg/day)	[32]

Case reports were not included in the table.

On the basis of the available evidence, administration of AIs should be offered only to the small number of women who have severe pain despite previous surgical and hormonal therapies [43].

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRM) selectively inhibit endometrial proliferation and prostaglandin production in a tissue-specific manner, induce reversible amenorrhea without the systemic adverse effects caused by estrogen deprivation [48]. Therefore, these agents have been proposed for the treatment of endometriosis [49]. In a multicenter, randomized study, subjects with a laparoscopic diagnosis of endometriosis and pain symptoms were treated with asoprisnil 5 mg (n = 31), 10 mg (n = 33) and 25 mg (n = 32) or placebo (n = 34) for 12 weeks. All three asoprisnil doses significantly reduced the intensity of dysmenorrhea and nonmenstrual pelvic pain compared with placebo; adverse events were evenly distributed among treatment and placebo groups and were generally mild [50]. Unfortunately, to date, these interesting findings have not been reproduced by other studies.

Immunomodulatory agents

Experimental studies suggested that therapeutic manipulation of the immune system might play some beneficial role in the treatment of endometriosis [51]. However, only a few studies examined the effectiveness of immunomodulatory agents in improving endometriosis-related pain symptoms in humans.

A prospective double-blind, randomized, placebo-controlled clinical trial including 80 women investigated whether treatment with pentoxifylline (400 mg twice daily for 12 months) after laparoscopy reduces the recurrence of symptoms [26]. Recurrence of signs and symptoms was 14% in the intervention group and 15.6% in the placebo group (not significant); this finding suggests that pentoxifylline does not lessen the recurrence of endometriosis. Another randomized controlled study examined whether the administration of pentoxifylline (400 mg twice-daily for 3 months) improves pain scores at 2 and 3 months after conservative surgery for endometriosis [52]. The patients receiving pentoxifylline had significantly better visual analog scale (VAS) scores at 2 and 3 months after surgery and less frequently used analgesics than women receiving placebo [52]. More recently, a systematic review including four trials involving 334 participants showed that there is not enough evidence to support the use of pentoxifylline in the management of women with endometriosis in terms of relief of pain outcomes [27].

A randomized, double-blind, placebo-controlled pilot trial including 21 women examined whether the administration of the chimeric anti-TNF-α monoclonal antibody infliximab (three infusions at the dose 5 mg/kg) improves pain symptoms, volume of endometriotic lesions and their appearance at laparoscopy [53]. Pain severity, assessed by VAS scale, decreased during the treatment by 30% in both the placebo and infliximab groups; no significant differences between placebo and infliximab treatment could be identified. After

laparoscopic excision of endometriotic lesions, pain scores decreased in both groups to less than 20% of the initial value. On the basis of these preliminary findings, there is not enough evidence to support the use of anti-TNF-α drugs in the management of women with endometriosis for the relief of pelvic pain [54].

Pharmacological treatment of specific endometriotic lesions

Rectovaginal endometriosis

Several hormonal therapies have been proposed for the treatment of pain symptoms caused by rectovaginal endometriosis. A prospective study including 15 symptomatic women with rectovaginal endometriosis showed that the administration of GnRH analog for 6 months determines a significant improvement in pain symptoms; however, a quick recurrence of symptoms was observed after discontinuation of treatment [16]. A nonrandomized prospective study including 21 women with rectovaginal endometriosis showed that the administration of vaginal danazol (200 mg/day) for 12 months significantly decreases the intensity of dysmenorrhea, deep dyspareunia and chronic pelvic pain with minimal adverse effects [22]. Unfortunately, no follow-up of symptoms after discontinuation of vaginal therapy was provided. A prospective self-controlled clinical trial including 11 symptomatic women with rectovaginal endometriosis demonstrated that the insertion of the levonorgestrel-releasing intrauterine device significantly reduced the intensity of pain symptoms [17]. Moderate or severe dysmenorrhea disappeared by the third month of treatment in all the patients; in addition, significant improvements in chronic pelvic pain and deep dyspareunia were observed [17]. However, in some patients with endometriosis, the levonorgestrel-releasing intrauterine device fails to satisfactorily improve pain symptoms and 25–32% of patients request to remove the device after 6 months of therapy [55,56]. A recent pilot study including 13 women with rectovaginal endometriosis and pain symptoms persisting after the insertion of the levonorgestrel-releasing intrauterine device suggested that the administration of vaginal danazol (100 mg/day) reduces the intensity of pain symptoms increasing patients' satisfaction [57]. One randomized controlled trial including 90 women with rectovaginal endometriosis showed that both the oral contraceptive pill and norethisterone acetate (2.5 mg/day) significantly reduced the intensity of pain symptoms caused by rectovaginal endometriosis with minor adverse effects [23]. The efficacy and tolerability of low-dose norethisterone acetate in treating pain symptoms caused by rectovaginal endometriosis were subsequently confirmed in a patient preference trial [32]. Several studies showed that pain symptoms caused by rectovaginal endometriosis are improved by the administration of AIs [18,20,32]. A recent systematic review evaluated the available evidences on the efficacy of medical treatment of pain associated with rectovaginal endometriosis [21]. This review identified seven studies published on this topic between 2000 and 2009: five observational noncomparative studies [16–18,20,22], one patient preference cohort study [58] and one randomized controlled trial [23]. The systematic review, including 217 cases of medically treated rectovaginal endometriosis, demonstrated that 60–90% of the patients receiving hormonal therapies have considerable or complete relief from pain symptoms [21]. Although many women experienced adverse effects of variable severity, only a few women withdrew from the studies because of adverse effects. Available data do not suggest that one hormonal therapy is superior to the others in improving pain symptoms in women with rectovaginal endometriosis. Based on these data, the systematic review concluded that medical treatment determines a substantial reduction in the severity of pain symptoms related to the presence of rectovaginal endometriosis [21].

Ovarian endometriomas

Long-term administration of oral contraceptive, progestins and GnRH analogs may reduce the size of ovarian endometriotic cysts; however, these lesions do not disappear during treatment and their size returns to baseline values after discontinuation of treatment [59–61]. Recent studies suggested that hormonal therapies might reduce endometriomas recurrence after surgery. In a prospective study, 70 women who underwent laparoscopic excision of endometriomas were randomized to receive low-dose cyclic oral contraceptive for 6 months or no treatment [62]. After a mean follow-up of 22 months, there were two (6.1%) endometrioma recurrences in the 33 patients who received postoperative oral contraceptives versus 1 (2.9%) recurrence in the 35 patients in the control group (not significant) [62]. Another study showed that, 30 months after surgery, the proportion of women free from endometriomas was 94% in patients who used a low-dose monophasic oral contraceptive pill during the entire follow-up period versus 51% in women who never used the hormonal therapy after surgery [63]. Interestingly, this study showed that the protective effect of the hormonal therapy rapidly tend to diminish after discontinuation of treatment [63]. These observations were confirmed by other investigations. One study including 239 women reported that, at 24 months of follow-up, the rate of endometrioma recurrence was 29% in untreated patients, 14.7% in patients treated with cyclic oral contraceptive pill and 8.2% in women treated with continuous oral contraceptive pill [64]. A retrospective cohort study including 87 women who underwent laparoscopic excision of ovarian

endometriomas demonstrated that endometrioma recurrence at 24-month follow-up was significantly lower in women who used the oral contraceptive pill during the entire follow-up period (2.9%) than in the other patients (35.8%) [65]. Based on these observations, the oral contraceptive pill should be administered to all women undergoing surgical excision of endometriomas who do not wish to conceive after surgery.

Bowel endometriosis

Bowel endometriosis affects 3.8–37% of women with endometriosis [12]. Nowadays, imaging techniques (e.g., transvaginal ultrasonography, MRI and multidetector computerized tomography enteroclysis) allow a noninvasive diagnosis of intestinal endometriosis [66]. Although several studies demonstrated that the surgical excision of intestinal endometriosis improves abdominal pain, intestinal symptoms and quality of life [12,67,68], some patients may wish to avoid or postpone surgery because of the potential complications associated with this type of surgery. Recent studies evaluated the effects of hormonal therapies in the treatment of pain and intestinal symptoms caused by bowel endometriosis [69–71]. A prospective study including 40 patients with symptomatic colorectal endometriosis evaluated the effects of norethisterone acetate (2.5 mg/day for 12 months) on pain and intestinal symptoms [69]. This study demonstrated that, at the completion of treatment, 60% of the patients were either satisfied or very satisfied with the therapy. The administration of norethisterone acetate induced a significant improvement not only in pain symptoms but also in several intestinal complaints, such as constipation during the menstrual cycle, diarrhea, intestinal cramping, passage of mucus and cyclical rectal bleeding. Interestingly, at completion of the 12-month treatment, 40% of patients wished to continue the therapy with norethisterone acetate [69]. Subsequently, another study showed that the suppression of ovarian function by triptorelin improved pain and intestinal symptoms in women with colorectal endometriosis [70]. More recently, a pilot study reported similar results in six women with bowel endometriosis treated with an AI (letrozole 2.5 mg/day) and norethisterone acetate (2.5 mg/day) continuously for 6 months [71]. Obviously, not all women with intestinal endometriosis can be treated with hormonal therapies; patients with endometriotic nodules associated with a stenosis of the bowel lumen of 60% or greater should undergo surgery because of the potential risk of bowel occlusion. Importantly, all patients with intestinal endometriosis receiving hormonal therapies should be aware that the disease may progress during treatment despite the improvement in symptoms. The case of a patient who had an endometriotic serosal sigmoid nodule, which, after 41 months of continuous oral contraceptive pill enlarged and reached the intestinal submucosa requiring bowel resection has recently been reported [25].

Future perspective

In the past, pharmacological treatment has often been considered an alternative to surgery. Nowadays, it is well accepted that endometriosis is a chronic disease and, thus, requires a chronic treatment. Although surgery has a key role in the treatment of pain symptoms caused by endometriosis, patients typically require a chronic pharmacological treatment of pain symptoms.

Since pharmacotherapies should often be administered for years, not only improvement of symptoms but also occurrence of adverse effects should be considered when prescribing treatments for endometriosis. To date, limited information is available on the risk of progression of endometriosis during long-term hormonal treatment. In women with rectovaginal endometriosis, a long-term pharmacological treatment may decrease the severity of symptoms but it may not prevent intestinal infiltration or ureteral compression and hydronephrosis. In women with bowel endometriosis, the nodules may enlarge determining subocclusive symptoms and the need for surgical treatment. Therefore, all women receiving long-term pharmacological treatment should be informed of the potential risk of endometriosis progression [25]. At the same time, the progression of endometriosis should be carefully monitored in these patients. In the next 5–10 years, investigators should determine the imaging techniques and timing of follow-up of patients receiving pharmacological treatment.

Improving the understanding of the pathogenesis of endometriosis at the molecular and cellular levels may allow development of new pharmacological therapies for endometriosis [51]. The observation that aromatase P450 is aberrantly expressed in eutopic endometriomas and ectopic lesions of women with endometriosis [40–42] prompted the use of AIs in the treatment of endometriosis. Similarly, the observation that angiogenesis is a prerequisite for the development of endometriosis encouraged the use of angiostatic drugs in the treatment of endometriosis in animal models [72]. In the future, identification of new molecules involved in the pathogenesis of endometriosis may allow new therapies for the treatment of this disease to be proposed.

Nowadays, pharmacological therapies are administered simply of the basis of the diagnosis of endometriosis or, at best, because on the presence of specific endometriotic lesions (e.g., ovarian endometriomas or rectovaginal nodules). Little information is available on the risk of each patient to have a recurrence of

endometriosis after surgery or to have a progression of the disease during treatment. Future studies should aim to determine the risk of recurrence or progression of endometriosis in each woman. In the future, molecular studies performed on endometriotic lesions (such as proteomics investigations) may allow prediction of which women have a higher risk of recurrence or progression of the disease [73] and, thus, require chronic treatment.

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Executive summary

- Endometriosis is a chronic disease and, therefore, pharmacological treatment should aim to improve pain symptoms with minimal adverse effects.
- Combined oral contraceptive and progestins significantly reduce the severity of pain symptoms caused by deep endometriosis and are well tolerated; therefore, they should be considered the first-line treatment for endometriosis.
- Aromatase inhibitors efficaciously reduce the severity of pain symptoms caused by endometriosis but they cause adverse effects of variable severity; these agents should be administered only to women who fail to improve after surgery and conventional hormonal therapy.
- Administration of combined oral contraceptives after surgical excision of ovarian endometriomas significantly reduces the risk of endometriomas recurrence.
- Norethisterone acetate, letrozole and gonadotropin-releasing hormone analog significantly improve intestinal symptoms caused by colorectal endometriosis.
- The administration of gonadotropin-releasing hormone analogs for at least 3 months (up to 6 months) before assisted reproductive technologies increase the odds of clinical pregnancy by at least fourfold.
- Limited information is available on the risk of progression of endometriosis during long-term hormonal treatment.
- Better understanding of the pathogenesis of endometriosis may allow identification of new therapies for the treatment of this disease.

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