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REVIEW ARTICLE

Current and Emerging Therapeutics for the Management of Endometriosis

Simone Ferrero[1,2] · **Fabio Barra**[1,2] · **Umberto Leone Roberti Maggiore**[1,2]

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Abstract

Endometriosis is a chronic benign disease that affects women of reproductive age. Medical therapy is often the first line of management for women with endometriosis in order to ameliorate symptoms or to prevent post-surgical disease recurrence. Currently, there are several medical options for the management of patients with endometriosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory conditions, being efficacious in relieving primary dysmenorrhea. Combined oral contraceptives (COCs) and progestins, available for multiple routes of administration, are effective first-line hormonal options. In fact, several randomized controlled trials (RCTs) demonstrated that they succeed in improving pain symptoms in the majority of patients, are well tolerated and not expensive. Second-line therapy is represented by gonadotropin-releasing hormone (GnRH) agonists. Even if these drugs are efficacious in treating women not responding to COCs or progestins, they are not orally available and have a less favorable tolerability profile (needing an appropriate add-back therapy). The use of danazol is limited by the large availability of other better-tolerated hormonal drugs. Because few data are available on long-term efficacy and safety of aromatase inhibitors they should be administered only in women with symptoms refractory to other conventional therapies in a clinical research setting. Promising preliminary data have emerged from multicenter Phase III trials on elagolix, a new oral GnRH antagonist but non-inferiority RCT data are required to compare elagolix with first-line therapies for endometriosis.

✉ Simone Ferrero
simone.ferrero@unige.it

[1] Academic Unit of Obstetrics and Gynecology, Ospedale Policlinico San Martino, Largo R. Benzi 10, 16132 Genoa, Italy

[2] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy

Key Points

Endometriosis is a chronic benign disease requiring long-term therapy that needs to balance clinical efficacy with a good safety profile. Medical therapy is often first-line for women with endometriosis to ameliorate symptoms or prevent post-surgical disease recurrence.

Combined oral contraceptives (COCs) and progestins, first-line medical therapies for endometriosis, are not only efficacious in improving pain symptoms in most patients but are also well tolerated and inexpensive.

Gonadotropin-releasing hormone (GnRH) agonists should be used in women not responding to first-line therapies or after surgical management. However, they are not orally available and are characterized by a high incidence of adverse events related to estrogen deficiency, (which may be limited by adding an appropriate add-back therapy).

Few data are available on long-term use of aromatase inhibitors, and the high rate of adverse effects limit their administration in clinical practice. Thus, these drugs should be administered only in patients with symptoms refractory to other conventional therapies in a clinical research setting.

Due to the high rate of androgen-related adverse effects and the marketing of GnRH agonists, the use of danazol is currently declining.

Promising preliminary results are available for oral elagolix, a new gonadotropin-releasing hormone antagonist (GnRH-ant), which is under investigation in multicenter Phase III trials.

1 Introduction

Endometriosis is a benign inflammatory disease affecting women of reproductive age, defined as the presence of endometrial glands and stroma outside the uterus. Endometriotic lesions may have various locations; they are found more frequently on the pelvic peritoneum, on the ovaries, in the rectovaginal septum, on the uterosacral ligaments, in the vesico-uterine fold, and more rarely in the bowel, diaphragm, umbilicus, pericardium and pleura [1].

The exact prevalence of endometriosis is unknown: differences in the reported prevalence of the disease vary by as much as 30–40 times. In part, these large variations can be explained by differences in the indications for surgery, or merely by the differing degrees of attention paid by surgeons to the accurate identification of endometriotic implants. A study of premenopausal women who requested a consultation with their general practitioner because of non-gynecological problems reported a prevalence of symptomatic endometriosis of 3.6% [2].

Although the exact pathogenesis is incompletely understood, it has been proposed that the retrograde menstruation of endometrial glands and stroma may be responsible for the implantation of endometrial implants in the peritoneal cavity. Other diffuse theories include celomic metaplasia, stem cell origin, and lymphatic and hematogenous spread. Moreover, it is known that genetic predisposition, hormonal and immunologic alternations play critical roles in the development of this chronic benign disease [1].

Although it may be asymptomatic, endometriosis often causes pain symptoms and infertility. Pain negatively influences quality of life (QoL), working efficiency, personal relations, and sexual life of patients. Transvaginal ultrasonography (TVS) is the gold standard technique for the diagnosis of deep endometriosis [3] and ovarian endometriomas [4]; magnetic resonance imaging (MRI) may be used when the gynecologists have no experience in the ultrasonographic diagnosis of endometriosis or when the findings of ultrasonography are unclear. In any case, the certain diagnosis of endometriosis is only obtained with the histological confirmation of endometrial stroma and glands [5].

The treatment of endometriosis involves conservative or radical surgery, or medical therapies. Although surgery aims to improve endometriosis-associated pain, QoL and sexual function [6], it can be technically demanding and it carries the risks of visceral, vascular and neurological complications. Moreover, pain may recur after surgery [7] or persist in case of incomplete excision of deep infiltrating endometriosis [8]. Medical therapy is often the first-line management for women with endometriosis to ameliorate women's symptoms or to prevent post-surgical disease recurrence. The currently available hormonal therapies for endometriosis decrease circulating estrogen levels and thus induce atrophy of endometriotic lesions and improvement of pain associated with the disease [9].

This review aims to summarize the therapies currently available for the treatment of endometriosis, highlighting the recent advances in the pharmacotherapy of this disease. A literature search was performed to find all the published studies evaluating clinical efficacy and safety of drugs for the treatment of endometriosis from inception until February 2018. The following electronic databases were used: Medline, PubMed, Embase, Science Citation Index via Web of Science and the Cochrane Library. The following search terms were used: 'endometriosis' in combination with 'medical therapy, 'non-steroidal anti-inflammatory drugs', 'estroprogestins', 'combined oral contraceptives, 'progestins, 'vaginal ring', 'gonadotropin-releasing hormone agonists,

'danazol', 'aromatase inhibitors' and 'gonadotropin-releasing hormone antagonists'. Current research registers (such as www.cliniclatrials.gov) were also considered. All pertinent articles were carefully evaluated, and their reference lists were examined to identify other manuscripts that could be included in the present review.

2 First-line Therapies

First-line therapies for the treatment of endometriosis-related pain include nonsteroidal anti-inflammatory drugs (NSAIDs), estroprogestins [in particular, combined oral contraceptives (COCs)], and progestins [9, 10] (Table 1).

2.1 NSAIDs

NSAIDs are widely used in the treatment of chronic inflammatory conditions and they are efficacious in relieving primary dysmenorrhea [11] (Table 1). The rationale for use of NSAIDs in endometriosis is based on their analgesic and anti-inflammatory effect. A double-blind randomized controlled trial (RCT) assigned 24 patients with moderate-to-very severe dysmenorrhea caused by endometriosis to be treated with naproxen (275 mg, 4 times per day) or placebo (4 times per day). Patients receiving naproxen experienced moderate or excellent pain relief significantly more often than those receiving placebo. In particular, complete or substantial pain relief was obtained with naproxen in 83% of patients suffering dysmenorrhea and in 41% with placebo [12]. In 2017, a Cochrane review concluded that there is a lack of high-quality evidence supporting the efficacy of NSAIDs in managing pain caused by endometriosis. In addition, there is no evidence that any individual NSAID is more effective than another [13]. Finally, women taking NSAIDs must be aware that these drugs may cause unintended adverse effects (AEs).

2.2 Estroprogestins

Estroprogestins (oral, vaginal ring or transdermal patch), either sequential or continuous, are commonly used to

Table 1 Main drug classes for the treatment of endometriosis

Drug	Characteristics	Levels of evidence
NSAIDs	First-line therapy	D
	Efficacious in improving moderate pain symptoms	
	Inexpensive	
	Does not block ovulation	
Estroprogestins	First-line therapy	A
	Inexpensive	
	Low rates of adverse effects	
	Multiple routes of administration	
Progestins	First-line therapy	A
	Inexpensive	
	Low rates of adverse effects	
	Multiple routes of administration	
GnRH agonists	Second-line therapy (efficacious in treating patients who did not respond to COCs or progestins)	A
	Subcutaneous administration	
	Expensive	
	High rate of adverse effects	
Danazol	Low popularity due to the androgenic adverse effects	A
	Inexpensive	
Aromatase inhibitors	Experimental use	B
	To be reserved only in women refractory to conventional therapies	
	Expensive	
	High rate of adverse effects	
GnRH antagonists	Investigational use (Phase III trials)	B
	Oral administration (elagolix)	

NSAID nonsteroidal anti-inflammatory drug, *GnRH* gonadotropin-releasing hormone

manage endometriosis-related dysmenorrhea and pain symptoms, even for some practical advantages, including contraception, long-term safety and control of menstrual cycle [14] (Table 1).

A double blind, placebo-controlled, multicenter RCT investigated the efficacy of cyclic low-dose COC [ethinylestradiol, (EE) 0.035 mg and norethindrone acetate, (NETA) 1 mg; 51 women] and placebo (49 women) for treating endometriosis-related pain [15]. At four-months' follow-up, dysmenorrhea in the COC group was milder than in the placebo group; in contrast, the intensity of non-menstrual pelvic pain was not significantly decreased after treatment with COC or placebo. An open-label RCT, including 57 women with laparoscopically diagnosed endometriosis, compared 6-month treatment with low-dose cyclic COC [0.02 mg EE and 0.15 mg desogestrel (DSG), dose increased to 0.03 mg EE if spotting occurred; 28 women] and subcutaneous goserelin (3.6 mg every month; 29 women), a gonadotropin-releasing hormone agonist (GnRH-a) [16]. After 6 months' treatment, the intensity of deep dyspareunia significantly decreased in both groups, but the improvement was superior in patients treated with goserelin versus those receiving COCs. The intensity of non-menstrual pain decreased without differences between the two treatments. Patients receiving COCs experienced a significant reduction in the intensity of dysmenorrhea. At 6 months, after discontinuation of treatment, symptoms recurred without differences in intensity between the groups. Subsequently, another Italian RCT compared COCs [EE 0.02 mg and DSG 0.15 mg; 45 women) and cyproterone acetate (CPA), 12.5 mg/day; 45 women] showing no major between-group differences in the improvement of pain symptoms after 6 months of treatment [17]. In 2007, a RCT including 222 women with stage III-IV endometriosis compared a COC regimen with GnRH-a. Patients were randomly allocated to receive six months' continuous COC (EE 0.03 mg and gestodene 0.75 mg; 38 women), dietary therapy (vitamins, minerals salts, lactic ferments, fish oil; 35 women), placebo (110 women) or intramuscular triptorelin or leuprorelin (LEU), 3.75 mg every month; 39 women [18]. At the 12-month follow up, patients treated with COC or GnRH-a experienced less severe dysmenorrhea than those in the placebo or dietary groups. Moreover, hormonal suppression therapies and dietary supplementation were similarly effective in decreasing the intensity of non-menstrual pelvic pain and dyspareunia. Another two RCTs compared COC to GnRH-a in the treatment of endometriosis-associated pain [19, 20]. A multicenter RCT compared COC (EE 0.03 mg and gestodene 0.75 mg; 47 women) given for 12 months with triptorelin (3.75 mg intramuscular injection every month) given for 4 months followed by COC (EE 0.03 mg and gestodene 0.75 mg; 55 women) for 8 months. At the 12-month follow-up, both treatments caused significant reduction in dysmenorrhea and non-menstrual pain without inter-group differences [19]. A double-blind RCT evaluated the efficacy of a 48-week treatment with LEU (11.25 mg every 3 months) plus hormonal add-back therapy (5 mg NETA every day; 21 women) or with continuous COC (35 mg EE and 1 mg NETA; 26 women). Both treatments significantly decreased pain compared with baseline and there was no significant difference in the extent of pain relief between the two treatments [20]. A 24-week, open-label, RCT compared depot medroxyprogesterone acetate (DMPA 150-mg dose every 3 months; 42 women) and continuous COC (EE 0.03 mg and gestodene 0.075 mg daily; 42 women) demonstrating a significant decrease in pain severity in both groups at 24-week follow-up; however, dysmenorrhea was more severe in the COC group than in the DMPA group [21]. A recent patient preference study showed the effectiveness of a 91-day extended cycle COC in the treatment of endometriosis-related pain [22]. No RCT assessed the usefulness of vaginal ring and transdermal patch in treating endometriosis-related pain symptoms. A patient preference, prospective cohort study compared two sequential estrogen-progestin formulations delivered by vaginal ring [15 μg EE and 120 μg etonogestrel (ENG), every month; 123 women] and transdermal patch (0.60 mg EE and 6.0 mg 17-deacetylnorgestimate every month; 84 women) for the treatment of recurrent pelvic pain after conservative surgery for endometriosis. Although, pain symptoms were improved by both treatments, the ring was more effective than the patch [23]. The efficacy of the vaginal ring in patients with deep infiltrating endometriosis was subsequently confirmed in another patient preference study comparing continuous oral treatment with DSG (75 μg/day; 60 women) with combined sequential contraceptive vaginal ring (15 μg EE and 120 μg ENG every month; 83 women) [24].

2.3 Progestins

Progestins, which are synthetic progestogens, are available in various formulations (oral tablets, depot injections, implants, or releasing intrauterine systems), and are increasingly used as monotherapy for the treatment of women affected by endometriosis [10]. These compounds reduce the frequency and increase the amplitude of pulsatile gonadotropin-releasing hormone (GnRH) release, causing a decrease of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion. Suppressing the ovarian steroidogenesis, causing subsequent anovulation and reducing serum levels of ovarian steroids, they cause decidualization and acyclicity of both normal and ectopic endometrium [25] (Table 1).

NETA (17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate) is a synthetic, orally active progestin, derivative of 19-nor-testosterone. An open-label RCT including 90 patients with symptomatic rectovaginal endometriosis compared NETA (2.5 mg/day) with a COC regimen (EE

0.01 mg + CPA 3 mg). At 12-month follow-up, a similar percentage of women were satisfied or very satisfied in both the NETA group (73%) and in the COC group (62%). Moreover, both drugs were equally effective in controlling pain symptoms and in reducing the size of the endometriotic nodules. The most frequently reported AEs in the NETA group were weight gain (27%) and decreased libido (9%) [26]. A prospective study including 40 patients with colorectal endometriosis showed that NETA not only improves pain symptoms but it also decreases the severity of diarrhea, intestinal cramping and passage of mucus [27]. More recently, a patient-preference parallel cohort study including 154 patients compared continuous NETA (2.5 mg/day) to surgery for the treatment of endometriosis-related deep dyspareunia. In the surgery group, there was a marked improvement of dyspareunia, followed by partial recurrence of pain. In the NETA group, pain relief was more gradual but progressive throughout the whole study period. At 12-month follow-up, patients treated with NETA had a greater increase in intercourse frequency per month and had higher satisfaction with treatment (59 versus 43%) [28]. Subsequently, another patient preference, parallel cohort study compared NETA (2.5 mg/day) to laparoscopic surgery in the treatment of patients with persistent and recurrent severe deep dyspareunia, who had already undergone first-line surgery for endometriosis. At 1-year follow-up, surgery and NETA obtained similar improvements in sexual functioning, psychological well-being and health-related QoL [29]. Very recently, a long-term retrospective cohort study followed 103 women with symptomatic rectovaginal endometriosis treated with NETA (2.5 mg/day up to 5 mg/day) for 5 years. Sixty-eight percent of the patients who completed the study were satisfied or very satisfied with NETA. Intensity of chronic pelvic pain and deep dyspareunia significantly decreased during treatment. Moreover, a decrease in the volume of the endometriotic nodules was observed at MRI in 55.9% of the patients [30].

CPA (6-Chloro-17α-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione acetate) is a synthetic steroid with antiandrogenic and progestinic activity. An RCT including 23 patients with laparoscopically diagnosed endometriosis and pelvic pain investigated the efficacy of CPA (27 mg plus EE 0.035 mg/day) or danazol (600 mg/day) for 6 months to treat pelvic pain associated with endometriosis. Dysmenorrhea disappeared in all patients during treatment. 12 months after treatment discontinuation, dysmenorrhea recurred in 89% of the CPA group and in 92% of the danazol group. Non-cyclic pelvic pain improved markedly during treatment in both groups; 6 months after treatment withdrawal it recurred in four CPA subjects and four patients in the danazol group, whereas after 1 year, only one woman in the danazol group was free of this symptom. Deep dyspareunia was less affected by treatment, and 6 months later had recurred in all the women. At the completion of treatment, a second laparoscopy showed partial regression of endometriotic lesions in both groups, with no significant differences between them [31]. Another RCT (90 women) compared the efficacy and safety of low-dose CPA (12.5 mg/day) with a COC (EE 0.02 mg + DSG 0.15 mg) in the treatment of moderate or severe pain persisting after conservative surgery. At 6-month follow-up, a similar percentage of patients were satisfied or very satisfied with the treatment (73% with CPA and 67% with COC). Dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain scores significantly improved. Furthermore, improvements were observed in QoL, psychiatric profile, and sexual satisfaction in both study groups. Amenorrhea was reached in approximately 66% of women under CPA. The main AEs in the CPA group were bloating, decreased libido, depression, and headache [17].

DSG (3-Deketo-11-methylene-17α-ethynyl-18-methyl-19-nortestosterone) is a third-generation 19-nortestosterone derivative progestin [32]. In an RCT, continuous oral DSG (75 µg/day) was compared to COC (EE 20 µg + DSG 150 µg/day) for the treatment of 40 patients with stage I–II endometriosis. At 6-months' follow-up, pelvic pain improved with no differences between the two study groups. In the DSG group, breakthrough bleeding (20%) was the main AE reported [33]. A patient preference trial compared the contraceptive vaginal ring (EE 15 µg + ENG 120 µg; $n = 83$), administered cyclically, with oral DSG (75 µg/day; $n = 60$) for the treatment of symptomatic rectovaginal endometriosis infiltrating the rectum. At 12-month follow-up, the rate of satisfied patients was higher in the DSG group (61.7 versus 36.1%). Gastrointestinal symptoms, chronic pelvic pain, and deep dyspareunia improved more in patients receiving DSG. Moreover, the two treatments caused a similar reduction in the volume of the endometriotic nodules [24]. In another patient preference study, oral DSG (75 µg/day) and cyclic COC (EE 20 µg + DSG 150 µg) were administered to women with symptomatic rectovaginal endometriosis and migraine without aura. Both treatments were equally effective in decreasing endometriosis-related pain. The satisfaction rate was higher for patients receiving DSG (61.2 versus 37.8%), who also had a significant improvement in QoL. The severity and number of migraine attacks were significantly different between baseline and the end of treatment in the DSG group but not in COC group [34]. ENG (11-Methylene-17α-ethynyl-18-methyl-19-nortestosterone) is the derivative active form of DSG. It is available as single-rod progestin contraceptive sub-dermally placed in the inner upper arm for long-acting (3 years) reversible contraception in women. In an RCT, Walch et al., compared the efficacy of the ENG-subdermal implant ($n = 21$ patients) and depot medroxyprogesterone acetate (DMPA, $n = 20$) for the treatment of pain related to endometriosis. After 6-months of treatment, the mean reduction in pain was 68% in the ENG

subdermal implant group and 53% in the DMPA group. The overall degree of satisfied plus very satisfied subjects was almost identical in both groups, and, at 1-year follow-up, the improvement in the intensity of pain was equivalent in the two study groups. There was a higher withdrawal rate in the DMPA group (35%) compared to the ENG group (19%), and the main cause of discontinuation of treatment in the latter group was unbearable bleeding irregularities ($n = 2$) [35].

MPA is a 17-OH progesterone derivative. It is available as oral formulation or depot formulation, which can be administered intramuscularly (DMPA-M) and subcutaneously (DMPA-SC) every 3 months.

In two RCTs, Telimaa et al., demonstrated that the administration of MPA (100 mg/day) for 6 months is as effective as danazol for the treatment of pain both after diagnostic laparoscopy [36] and after surgical excision of endometriosis [37]. A prospective double-blind RCT compared MPA and GnRH-a for treating pain in 48 women with surgical diagnosis of endometriosis. Patients were treated for 6 months and followed-up for 1 year. There was a significant reduction in the severity of pain symptoms during the study, without any significant difference between the study groups [38]. These findings are in contrast to a prospective, double-blind RCT including 100 infertile women with endometriosis, which compared the efficacy of 3-month administration of MPA (50 mg/day) with placebo [39]. Moreover, in a Cochrane review on progestins for the treatment of endometriosis, it was observed that MPA (100 mg daily) appeared to be more effective in reducing all symptoms up to 12 months of follow-up (MD −0.70, 95% CI −8.61 to −5.39; $p < 0.00001$) when compared with placebo, although patients receiving MPA experienced more cases of acne and edema [25].

DMPA has been investigated in few clinical trials for the treatment of patients with endometriosis. In an RCT (80 women), Vercellini et al., compared DMPA-M (150 mg/3 months) to cyclic COC plus oral danazol (50 mg/day) for 1 year to treat endometriosis-related pelvic pain [40]. At the end of treatment, 72.5% of the women in the DMPA-M arm were satisfied or very satisfied compared with 57.5% in COC plus danazol arm ($p = 0.24$). Moreover, a significant decrease in all symptom scores was reported in both study arms with no significant differences. The main AEs in the DMPA-M group were menstrual pattern changes (breakthrough bleeding or spotting). An RCT compared a 3-year regimen of DMPA-M (150 mg/3 months) with the levonorgestrel-releasing intrauterine system (LNG-IUS) in 30 patients after conservative surgery for endometriosis. Both treatments were effective in the management of pain symptoms, and the only domains where no amelioration was observed were dyspareunia and urinary/bowel symptoms. At TVS, no recurrences of lesions were detected in either group. The dropout rate was higher in the DMPA-M group (53 versus 13%), and the two most common causes of discontinuation among the eight patients, that interrupted DMPA-M, were prolonged vaginal spotting ($n = 3$, 37.3%) and significant bone mineral density (BMD) loss over the lumbar spine ($n = 2$, 25%) [41].

In two large RCTs, Crosignani et al., and Schlaff et al., compared DMPA-SC (104 mg/0.65 mL) with LEU acetate (given every 3 months for 6 months). At 12-months' follow-up, DMPA-SC was statistically equivalent to GnRH-a in reducing pain symptoms. Moreover, significant improvements in QoL occurred in both treatment groups [42, 43]. Interestingly, in the study by Crosignani et al., patients who received DMPA-SC reported a significant amelioration in their sexual relationship after 6 months of treatment [42]. In both studies, after 6 months of treatment, although patients in both groups showed loss of BMD, it was significantly lower for women treated with the progestin; additionally, BMD in the DMPA-SC group returned to pretreatment levels at 12 months' follow-up. Patients receiving DMPA-SC experienced fewer symptoms caused by hypoestrogenism (such as headache and hot flushes) but more irregular bleeding (varying from light spotting to uterine hemorrhage). However, the discontinuation rate secondary to AEs was 2–5.4% in the DMPA-SC group and 1.4–6.7% in the LEU group [42, 43].

Evidence from clinical trials on DMPA for contraception [44] and for treating endometriosis [42, 43] demonstrates that a major source of concern regarding its continuous use is the loss of BMD [45]. Data are controversial with regard to the subsequent risk of fracture [46–48]. In 2004, the FDA published a 'black box warning', which suggested that physicians administer DMPA only if other methods are unsuitable or unacceptable, and limit the maximum use to 2 years [49].

Dienogest (DNG, 17α-Cyanomethyl-δ9-19-nortestosterone) is a fourth-generation selective progestin with minimal androgenic, estrogenic, glucocorticoid or mineralocorticoid activity [50]. After a single dose, DNG (2 mg) has high bioavailability (< 90%) [51]. Several RCTs have investigated the use of DNG for the treatment of endometriosis (Table 2) [52]. In a systematic review, DNG (2 mg/day) was superior to placebo and as effective as GnRH-a in reducing pelvic pain and growth of endometriotic implants [53]. Concerning the use of DNG as maintenance therapy after GnRH-a for the treatment of endometriosis-related pelvic pain, Kitawaki et al., in a prospective nonrandomized trial, showed that DNG prolongs the relief of pelvic pain while reducing the amount of irregular uterine bleeding [54].

In a 6-month multicenter double-blind RCT, efficacy and safety of DNG (2 mg/day) were evaluated in 255 Chinese patients with laparoscopically diagnosed endometriosis. At baseline, they had an endometriosis-associated pelvic pain score ≥ 30 mm on a 0–100 mm VAS. After the end of therapy, DNG obtained a higher reduction in this score than placebo (−24.54 mm; 95% CI −29.93 to −19.15; $p < 0.0001$).

Table 2 Randomized comparative trials of dienogest for the treatment of endometriosis

Author, year	Population	Regimen	Follow-up	Results	AE
Cosson, 2002 [114]	120 women with grade 2, 3, and 4 (≤70) endometriosis at initial laparoscopy	DNG (1 mg/day) or triptorelin (3.75 mg IM) every 4 weeks, for 16 weeks	12 months	Similar postoperative pain during treatment	AE reported in 87.7% of patients in the DNG group and 85.1% in triptorelin group
Harada, 2009 [76]	171 women with endometriosis	DNG (2 mg/day) or buserelin (900 µg/day, intranasally) every 4 weeks	6 months	Similar pain relief and improvement of QoL in both groups	DNG was associated with irregular genital bleeding more frequently and with fewer hot flushes
Strowitzki, 2010 [63]	252 women with confirmed endometriosis	DNG (2 mg/day) or LEU (3.5 mg depot IM) every 4 weeks, for 24 weeks	6 months	Similar pain relief in both groups; more improvement of QoL in DNG group	DNG was associated with more irregular genital bleeding, and less hypoestrogenic AEs
Lee, 2016 [61]	64 women with endometriosis after laparoscopic surgery	DNG (2 mg/day) or LEU (3.75 mg depot SC) plus add-back therapy (1.0 mg/day of E and 0.5 mg/day of NETA) every 4 weeks, for 24 weeks	No follow-up	Visual analogue scale pain score decreased significantly for both groups	Menstruation-like bleeding and spotting were significantly more common in DNG group than in LEU plus add–back group; BMD at the lumbar spine declined significantly in both treatment groups (−2.5% for LEU plus add-back and −2.3% for DNG)
Takaesu, 2016 [115]	111 women with endometriosis after laparoscopic surgery	DNG (2 mg/day) or goserelin (1.8 mg depot IM) every 4 weeks, for 24 weeks	24 months	No significant difference in the postoperative recurrence rate in both groups; Menstrual pain and chronic pelvic pain were significantly improved in both groups	Irregular vaginal bleeding occurred in 100% of patients in DNG group and 6% in goserelin group. Hot flush occurred in 11% of patients in DNG group and 94% in goserelin group. Headache was observed in 9% of patients in DNG group and 4% in goserelin group

AE adverse event, *DNG* dienogest, *E* estradiol, *IM* intramuscular, *NETA* norethindrone, *QoL* quality of life, *SC* subcutaneous, *VAS* visual analogue scale

Moreover, only 29.4% of patients who received DNG had AEs, the most common of which was vaginal hemorrhage (7.9%) [55]. Morotti et al., investigated the DNG efficacy for the treatment of women with rectovaginal endometriosis who had persisting pain symptoms during the administration of NETA. In this 24-week open-label prospective study, the authors evaluated the satisfaction of 25 patients after 6 months of DNG treatment. DNG obtained better results than NETA both in terms of pain relief and QoL improvement, which were evaluated with the Endometriosis Health Profile-30 (EHP-30) and Female Sexual Function Index (FSFI) questionnaires. Moreover, the endometriotic nodule volume did not significantly change during treatment [56]. DNG has also been investigated for the conservative treatment of bladder endometriosis [57]. In a recent pilot study including six women with bladder endometriotic lesions, 12-month DNG administration (2 mg/day) improved pain symptoms and urinary symptoms. Moreover, there was a significant decrease of size of bladder nodules at TVS after 3 and 12 months of treatment [58]. In a another prospective study, Leonardo-Pinto et al., evaluated the effectiveness of DNG for the treatment of 30 women with DIE, showing a significant improvement in pain, but without obtaining a reduction in lesions volume after 1 year of treatment [59]. Vercellini et al., using a before-after study design, compared NETA and DNG for the treatment of women with endometriosis. Both drugs caused pain relief and improvement of psychological status, sexual functioning, and health-related QoL. After 6 months, the proportion of satisfied plus very satisfied women was almost identical between the two study groups (71% in NETA group versus 72% in DNG group). After DNG implementation, the absolute risk reduction in the occurrence of any AE compared to NETA was 13.9% Thus, DNG was better tolerated than NETA, although the much higher cost limited its acceptance by the women [60]. Surprisingly, until now no RCT has compared DNG with COCs or other progestins, the first-line therapies most commonly used for the treatment of endometriosis [52].

The effect of DNG on BMD is controversial: in a comparative study, the administration of DNG (2 mg/day) or GnRH-a plus add-back therapy [NETA 0.5 mg/day or estradiol (E_2) 1 mg/day] for the treatment of endometriosis caused a decline in BMD at the lumbar spine in both treatment groups (−2.3% for DNG and −2.5% for GnRH-a plus add-back) [61]. These results are in line with those reported by Momoeda et al., which showed a significantly decrease (−1.6%) of lumbar spine BMD in 135 patients with endometriosis after 24 weeks' treatment with DNG [62]. In contrast, other authors reported no or minimal changes in BMD following a 6-month treatment with DNG [55, 63].

LNG (17α-Ethynyl-18-methyl-19-nortestosterone) is a synthetic second-generation progestin. This drug is six times more potent than progesterone, but also has strong androgenic properties. It is available as intrauterine releasing system [64]. A pilot-study including 11 women with symptoms caused by rectovaginal endometriosis demonstrated that the use of the LNG-IUS improved the severity of all pain symptoms, including deep dyspareunia and dyschezia, at 1-year follow-up. Moreover, it succeeded in decreasing the rectovaginal lesions size, evaluated by transrectal ultrasound and TVS [65]. Several RCTs have investigated the use of LNG-IUS for the treatment of endometriosis. Petta et al., compared the efficacy of LNG-IUS and depot GnRH-a (LEU 3.75 mg) in 82 women with endometriosis-related pain over a period of 6 months. At 6 months' follow-up, both treatments were similarly effective in improving chronic pelvic pain, demonstrating a 6-point decrease from baseline in the VAS pain score. At the end of the study, 13% ($n=5$) of patients receiving LNG-IUS and 14% ($n=6$) of those receiving LEU failed to reach a VAS pain score of <3. Furthermore, no difference was observed between groups with reference to improvement in QoL [66]. In a meta-analysis including five RCTs, the comparative evaluation of LNG-IUS and GnRH-a reported that both regimens succeed in reducing pain, as well as CA125 serum levels and the American Society of Reproductive Medicine staging scores of patients with endometriosis. Moreover, women who received the LNG-IUS experienced fewer hypo-estrogenic AEs than those receiving GnRH-a [67]. The long-term therapy with LNG-IUS has been evaluated in a retrospective study by Lockhat et al., in which LNG-IUS proved to be efficacious in improving symptoms throughout a 3-year study period [68]. These results are in line with those obtained in an RCT that compared the 36-month use of LNG-IUS with DMPA-M in 30 patients with moderate and severe endometriosis. Symptoms and recurrence were controlled by both therapies [41].

3 Second-line Therapies

If first-line therapies do not succeed in ameliorating women' pain symptoms, an accurate diagnostic workup is required prior to administering second-line therapies [14] (Table 1).

3.1 Gonadotropin-releasing Hormone Agonists

Second-line therapies include injectable depot formulations of GnRH-a. They are decapeptides that differ from the endogenous GnRH by the substitution of one or several amino acids. These drugs suppress estrogen ovarian production through the down-regulation of GnRH receptors at pituitary level, suppressing the production and release of gonadotropins. The hypoestrogenism and subsequent amenorrhea cause regression of endometriotic implants. In addition, secondary amenorrhea prevents new peritoneal seedlings. However, GnRH-a is responsible for several AEs,

e.g. alteration of lipid profile, depression, flushes, urogenital atrophying and loss of BMD. The intensity of these AEs can be decreased by administering "add-back" therapies (such as NETA or low-dose COCs) [69] (Table 1). Available GnRH-a include goserelin, LEU, nafarelin, buserelin, and triptorelin.

In 2010, a Cochrane review evaluated GnRH-a at different doses, regimens and routes of administration in comparison with danazol, LNG-IUS, and placebo, for relieving endometriosis-associated pain symptoms [70]. 41 RCTs (4935 women) were included in this systematic review and meta-analysis. The authors concluded that GnRH-a are more efficacious in relieving pain symptoms than no treatment or placebo. No statistically significant difference between GnRH-a and danazol for dysmenorrhea was reported. There was a benefit in overall resolution of symptoms for GnRH-a compared with danazol. Furthermore, no statistically significant difference in the overall pain relief between GnRH-a and LNG was found. Limited evidence was identified on optimal dosage or duration of treatment with GnRH-a and no route of administration appeared better than another. No study comparing GnRH-a and analgesics is available.

Several studies compared GnRH-a with no treatment or placebo. In an RCT, Fedele et al., compared a 6-month treatment with intranasal buserelin acetate (1200 μg/day; 19 women) versus expectant management (16 women) in infertile patients with endometriosis. There was a significant benefit for buserelin compared with no treatment for the relief of the pain symptoms during the treatment and also for the 12 subsequent months [71]. Four RCTs investigated GnRH-a (LEU and triptorelin) versus placebo [72–75]. In 1998, a double blind RCT of 6 months' treatment followed by 12 months' follow-up evaluated the effect of triptorelin (3.75 mg every month; 24 women) versus placebo (25 women) on the symptoms of surgically verified endometriosis. Triptorelin decreased pain symptoms to a significantly higher degree than placebo [72]. A double blind, multicenter RCT involving 52 patients compared intramuscular LEU (3.75 mg every month; 28 women) versus placebo (24 women) in the treatment of pain associated with endometriosis. There was a significant improvement in dysmenorrhea and pelvic pain in the LEU group compared with the placebo group [73]. More recently, another double-blind, parallel, placebo-controlled RCT quantified the changes in endometriosis-associated pain and QoL during the stimulatory phase of GnRH-a therapy [75]. One-hundred and twenty women with endometriosis were randomized to receive a 1-month treatment with LEU (3.75 mg; 60 women) or placebo (60 women). Pain was measured at baseline and at 2 and 4 weeks. At 4-week follow up, patients treated with LEU had a significant temporary increase in pain severity compared with placebo-treated controls [75].

GnRH-a have been compared to almost all the available hormonal treatments commonly used for endometriosis-associated pain. Two Phase 3, multicenter, evaluator-blinded, comparator-controlled RCTs assigned patients to receive a 6-month treatment with subcutaneous DMPA (104 mg/0.65 mL every 3 months) or intramuscular LEU (11.25 mg every 3 months) and subsequently to have a 12-month post-treatment follow-up [42, 43]. The DMPA was equivalent to LEU in reducing pain symptoms at the end of treatment and after 12 months' follow-up [42, 43]. Two RCTs compared oral DNG to GnRH-a in women with endometriosis [63, 76]. In 2002, a Japanese Phase III, double blind, multicenter, RCT compared the efficacy and safety of a 24-week treatment with oral DNG (2 mg twice daily; 137 women) with intranasal buserelin acetate (300 μg/day three times daily; 134 women) [76]. The severity of symptoms during menstruation decreased significantly in both therapies at the end of the treatment without inter-group differences. The improvement in the severity of lower abdominal pain and lumbago from baseline to the end of treatment was similar in the two study groups [76]. A 24-week, multicenter, open-label, parallel-group, non-inferiority RCT compared oral DNG (2 mg/day; 124 women) and intramuscular LEU (3.75 mg every month; 128 women) [63]. Pelvic pain from baseline to the end of treatment significantly ameliorated in both study groups. DNG was non-inferior to LEU in improving pelvic pain. In addition, the rate of patients who had an improvement in pelvic pain was almost similar in the DNG (96.7%) and LEU groups (95.8%) after 24 weeks in comparison with baseline [63].

Three RCTs evaluated LNG-IUS versus GnRH-a [66, 77, 78]. An RCT compared the effect of a 6-month treatment with LNG-IUS (20 μg/day; 40 women) and LEU (3.75 mg every 3 months; 43 women) [66]. Pain symptoms significantly improved from the first month throughout the six months of therapy with both treatments, and no difference between the study groups was observed. In both treatment groups, women with stage III and IV endometriosis had a faster amelioration in the pain scores than women with stage I and II [66]. An open-label RCT evaluated the cardiovascular risk markers associated with endometriosis and the influence of the LNG-IUS (20 μg/day; 40 women) and LEU (3.75 mg every month; 43 women) on these risk markers as well as changes in pain symptoms after 6 months of treatment. After 6 months of treatment, a significant reduction in pain symptom severity was reported in both groups without any significant difference between the two drugs [77]. In another RCT, 40 women with surgically confirmed severe endometriosis were randomized to be treated for 24 weeks with LNG-IUS (20 μg/day; 20 women) or goserelin acetate (3.6 mg every month; 20 women). Both treatments had similar efficacy in the treatment of pelvic pain at the 12-month follow-up [78]. No RCT compared GnRH-a versus CPA or NETA for the treatment of endometriosis-associated pain. Vercellini et al., compared the efficacy of a

6-month treatment with low-dose cyclic COC (0.02 mg EE and 0.15 mg DSG, dose increased to 0.03 mg EE if spotting occurred; 28 women) versus subcutaneous goserelin (3.6 mg every month; 29 women) [16]. At 6 months, deep dyspareunia severity was significantly decreased in both groups, with goserelin superior to the COC. A significant improvement of non-menstrual pain without differences between treatments was reported. Patients using the COC had a significant improvement in dysmenorrhea. At the end of follow-up, symptoms similarly recurred without differences in intensity between the groups [16].

COC and GnRH-a were compared for the treatment of endometriosis-associated pain in other two RCTs [16–20]. A multicenter RCT compared COC (EE 0.03 mg and gestodene 0.75 mg; 47 women) administered for 12 months with intramuscular triptorelin (3.75 mg every month) given for 4 months followed by COC (EE 0.03 mg and gestodene 0.75 mg; 55 women) for 8 months. A significant improvement in dysmenorrhea and non-menstrual pain at 12-month follow-up was observed without inter-group differences with both therapies [19]. A double blind RCT compared the efficacy of a 48-week treatment with LEU (11.25 mg every 3 months) plus hormonal add-back therapy (5 mg NETA every day; 21 women) versus continuous COC (35 mg EE and 1 mg NETA; 26 women). Both LEU and continuous COC provided a significant improvement in pain from baseline without significant difference between the two groups [20]. A 2010 Cochrane review included 27 studies comparing GnRH-a versus danazol in patients with endometriosis; this review showed no significant difference between the two treatments in improving dysmenorrhea, deep dyspareunia and non-cyclic pelvic pain [70]. An RCT evaluated the efficacy of using either a combination of anastrozole (1 mg/day) and goserelin (3.6 mg every month; 40 women) for 6 months or goserelin alone (3.6 mg every month; 40 women) for 6 months after conservative surgery for severe endometriosis [79]. The combination of anastrozole plus goserelin was superior to goserelin alone in improving pain symptoms. In addition, there was a significant advantage in favor of goserelin plus anastrozole compared to goserelin only in terms of the time to detect symptom recurrence (> 24 versus 17 months). Three cases out of 40 recurred in the goserelin plus anastrozole arm (7.5%), whereas recurrences were observed in 14 cases out of 40 cases in the goserelin-only arm (35%) during the follow-up period of 24 months [79].

Three studies compared varying doses of GnRH-a used for the relief of pain symptoms in patients with endometriosis [80–82]. In detail, Adamson et al. [82] and Henzl et al. [81] compared 400 versus 800 µg nafarelin daily, whereas Minaguchi et al., [80] compared daily buserelin 300 versus 600 µg, 300 versus 900 µg as well as 600 versus 900 µg. All these studies demonstrated similar improvement in pain symptoms with the different treatment regimens [80–82].

Only one study assessed the efficacy of varying the length of treatment of GnRH-a for endometriosis-associated pain [83]. In this double-blind multicenter RCT, patients were assigned to 3 months' nafarelin (200 µg twice daily) followed by 3 months of placebo (91 women) or to 6 months nafarelin (200 µg twice daily; 88 women). Women were followed for 12 months after the interruption of treatment. Pain symptoms similarly decreased with both schedules. Symptoms recurred in both groups, and the severity in pain symptoms gradually worsened during the follow-up period but always remained below baseline in both groups. No significant difference in efficacy was reported between the study groups [83].

Four studies investigated the efficacy of GnRH-a varying the route of administration of the compounds [84–87]. Three trials evaluated intranasal buserelin versus subcutaneous daily administration [84–86], and one study compared intranasal nafarelin versus intramuscular LEU [87]. In the comparison between intranasal and subcutaneous administration, there was no evidence to suggest a statistically significant difference between the groups for pelvic pain, deep dyspareunia and dysmenorrhea. Similar findings were reported in the comparison between intranasal nafarelin and intramuscular LEU.

3.2 Danazol

Danazol is a derivative of the synthetic steroid ethisterone, which exhibits anti-gonadotropic, hypoestrogenic, hyperandrogenic effects inducing atrophy of the endometrium and of ectopic endometriotic implants, which can alleviate the symptoms of endometriosis. This drug was very popular for the treatment of patients with endometriosis during the 1970s and 1980s; however, its administration may be characterized by the occurrence of weight gain, acne, hirsutism and other androgenic AEs; also, with the marketing of GnRH-a, the use of danazol declined [88] (Table 1).

A double-blind, placebo-controlled RCT assessed the clinical efficacy and tolerance of danazol and MPA in the treatment of mild-moderate endometriosis [36]. After diagnostic laparoscopy, 59 patients were randomized to receive danazol (200 mg three times daily; 18 women), MPA (100 mg/day; 16 women) or placebo (17 women) for 6 months. A second laparoscopy was performed 6 months after the interruption of the medical treatment demonstrating total or partial resolution of peritoneal implants in 60% of patients receiving danazol and in 63% of those receiving MPA, while in the placebo group, resolution was observed in 18% of patients, and the size of the implants was increased in 23%. Pelvic pain, lower back pain and dyschezia significantly improved with danazol and MPA in comparison with placebo, but they did not differ from each other in these actions [36]. Another RCT investigated the efficacy of

postsurgical treatment with danazol in women with stage III or IV endometriosis [89]. Women were assigned to treatment with oral danazol (600 mg/day; 36 women) for 3 months after surgery and to no postoperative treatment (41 women). At the 6-month follow-up, 23% of patients on danazol and 31% without any treatment had moderate/severe pelvic pain recurrence; the respective cumulative pain recurrence rates at 12 months were 26 and 34% in the two study groups [89].

Several studies compared danazol versus other treatments. Fedele et al., compared a 6-month treatment with COC (CPA 7 mg plus EE 0.035 mg/day; 11 women) to danazol (600 mg/day; 12 women) in patients with laparoscopically diagnosed endometriosis [31]. At the end of treatment, a second laparoscopy was performed in those patients who agreed (four in the CPA, five in the danazol group), showing a partial regression of endometriotic lesions in both groups, with no significant differences between them. Dysmenorrhea disappeared in all patients during treatment. At the 6- and 12-month follow-up after treatment withdrawal, dysmenorrhea recurred in 66% of the CPA group and 58% of the danazol group, and in 89 and 92%, respectively. Non-cyclic pelvic pain improved during treatment in both groups; however, six months after treatment suspension, it recurred in four patients in both CPA and danazol groups; after 12 months, non-cyclic pelvic pain had recurred in all but one woman in the danazol group. Deep dyspareunia was less affected by both treatments and after 12 months it recurred in all women [31]. An RCT including infertile patients with laparoscopic diagnosis of endometriosis assessed a 6-month treatment with oral gestrinone (2.5 mg twice weekly; 20 women) versus oral danazol (600 mg/day; 19 women). Women were followed for at least 12 months after the end of the treatment; there was a significant decrease in the severity of pain symptoms during both treatments. Pain symptoms recurred during the follow-up in 57% of the gestrinone and 53% of the danazol group [90]. 27 studies evaluated the use of danazol versus GnRH-a in patients with endometriosis showing no significant difference between the two treatments in improving dysmenorrhea, deep dyspareunia and non-cyclic pelvic pain [70]. In 1988, a large RCT compared a 6-month treatment with oral danazol (800 mg/day; 80 women) or intranasal nafarelin (400 or 800 μg/day; 77 and 79 women, respectively) in 213 patients with endometriosis. Over 80% of the women in each treatment group had a decrease in the extent of disease. In addition, the percentage of patients who experienced severe pain symptoms decreased from 40% to 5–10%, while the percentage with no or minimal discomfort grew from 25 to 70% [81]. Wheeler et al., conducted a double-blind RCT including 270 patients from 22 centers [89]. Patients were randomized to a 24-week treatment with LEU (3.75 mg every month; 128 women) or oral danazol (800 mg/day; 125 women). At baseline there was no difference in dysmenorrhea, dyspareunia and pelvic pain between the study groups. After six months of treatment, pain symptoms similarly improved in both groups: a complete resolution of dysmenorrhea and pelvic pain was reported by 99 and 55% of patients on LEU and by 96 and 60% of patients on danazol, respectively. At the same follow-up, patients treated with danazol had higher improvement of dyspareunia than those treated with LEU [89]. An open-label RCT compared the efficacy of oral danazol (200 mg three times daily; 20 women) and intramuscular triptorelin (3.75 mg every 6 weeks; 20 women) for 6 months in the management of moderate and severe endometriosis. Both pain control and the revised American Fertility Society score at second-look laparoscopy showed no significant difference between the two medications [91]. An open-label, parallel group, RCT compared a COC (EE 0.02 mg and DSG 0.15 mg) plus oral danazol (50 mg/day for 21 days of each 28-day cycle; 40 women) versus intramuscular DMPA (150 mg every 3 months; 40 women) in the treatment of pain associated with endometriosis. At 1-year follow-up a significant improvement in all symptom scores was experienced in both study groups; dysmenorrhea was greater in women allocated to COC plus danazol because of the virtual absence of regular flow in patients receiving DMPA [40].

3.3 Aromatase Inhibitors

Aromatase P450 is the key enzyme responsible for the conversion of androgens into estrogens. It is expressed aberrantly in endometriosis and is stimulated by prostaglandin E_2, resulting in production of estrogen that promotes further prostaglandin E_2 expression and, thus, inflammation within endometriotic implants. Third-generation aromatase inhibitors (anastrozole and letrozole), which selectively inhibit the action of aromatase (Table 1), have been investigated for the treatment of endometriosis as monotherapy or in combination with other hormonally active drugs [92].

In a systematic review, Ferrero et al., identified 10 clinical studies on the administration of AIs for endometriosis (183 women). This review demonstrated that the continuous administration of two AIs, anastrozole and letrozole, was effective in reducing the severity of endometriosis-related pain symptoms and ameliorated women' QoL. However, the use of AIs was limited by the high incidence of AEs [93].

In an RCT, Soysal et al., compared the use of a 6-month treatment with anastrozole (1 mg/day) plus subcutaneous goserelin (3.6 mg every month; 40 women) versus subcutaneous goserelin alone (3.6 mg every month; 40 women) in patients who underwent after conservative surgery for severe endometriosis [79]. The combination of anastrozole plus goserelin was more efficacious in improving pain symptoms than goserelin alone. Furthermore, patients treated with goserelin plus anastrozole had a longer symptom recurrence period (> 24 versus 17 months). At 24 months' follow-up,

three women (7.5%) recurred in the goserelin plus anastrozole arm, while 14 women (35%) recurred in the goserelin-only arm [79]. Currently, a multicenter, double-blind, RCT Phase IIb study has compared the efficacy and safety of BAY98-7196, an intravaginal ring, which contains different doses of anastrozole (300–600–1050 μg/day) and LNG to placebo and LEU in patients with symptomatic endometriosis over a 12-week treatment (NCT02203331) period. Another ongoing randomized parallel Phase IV trial is studying the combinatory regimen of anastrozole plus LEU for the prevention of endometriosis recurrence in comparison with LEU as monotherapy (NCT01769781).

An open-label RCT compared the efficacy of letrozole (2.5 mg/day) in combination with either NETA (2.5 mg/day; 17 women) or triptorelin (11.25 mg/day every 3 months; 18 women) for 6 months for the treatment of pain symptoms caused by rectovaginal endometriosis. The severity of non-menstrual pelvic pain and deep dyspareunia significantly decreased during treatment in both study groups, though no statistical difference between the two groups was reported [94]. In another RCT, 144 infertile patients with endometriosis were randomly allocated to letrozole (2.5 mg/day for 2 months; 47 women; group 1), triptorelin (3.75 mg every month for 2 months; 40 patients; group 2) or no medication (57 women; group 3). At baseline, there was no difference in the prevalence of pain symptoms among the three groups. After 1 year of follow-up, recurrence rate of symptoms was 6.4% in group 1, 5% group 2 and 5.3% in group 3, without significant differences among the groups [95]. The combination of letrozole and NETA has also been investigated to treat ovarian endometriosis. In a prospective patient-preference study, the mean percentage reduction of their volume was greater in patients receiving the double regimen ($-74.4 \pm 4.2\%$ and $-46.8 \pm 3.8\%$, respectively, $p < 0.001$) than in those receiving only the progestin. However, in both groups, there was not a complete regression of ovarian endometriomas [96].

3.4 GnRHh Antagonists

GnRH antagonists (GnRH-ant) immediately decrease gonadotropin secretion by competing with endogenous GnRH for its pituitary receptors. No flare-up effect occurs, and the levels of gonadotropins are down-regulated leading to an immediate decrease in gonadal steroid blood levels. These characteristics of GnRH-ant avoid the flare of symptoms caused by GnRH-a and cause a more rapid onset of the therapeutic effect [97]. The down-regulation of gonadotropin release can be modulated by the receptor-related concentration of a GnRH-ant. Unlike GnRH-a, GnRH-ant causes a dose-dependent suppression of pituitary and ovarian hormones; in fact, while a partial suppression is achieved at lower doses, a full suppression is obtained at higher doses. The activity of GnRH-ant is completely reversible and normalization of gonadal function is expected a few days after cessation of their administration, when the native GnRH concentration exceeds the GnRH-ant concentration at the receptor [98] (Table 1).

Cetrorelix (CET) is a basic peptide that does not contain acid components. It is available for subcutaneous injections as sterile lyophilized powder for reconstitution with sterile water for injection. The impact of CET on endometriotic lesion was investigated in in vitro and in animal studies using GnRH-a as gold standard.

Taniguchi et al., compared the effects of CET and buserelin acetate on the proliferation of stromal cells obtained from the ovarian endometriomas linings and from eutopic endometrium. Both treatments decreased cell proliferation by reducing levels of tumor necrosis factor-α (TNF-α) in endometrial stromal cells, whereas ectopic endometriotic stromal cells did not respond to treatment. Moreover, neither hormonal treatment inhibited TNF-α–induced interleukin (IL)-8 production in endometriotic stromal cells [99]. An RCT study performed in the rat model compared the effects of CET and LEU on the peritoneal endometriotic implants. Both drugs significantly decreased the volume of the nodules, causing similar changes in their histological structure [100].

A study assessed the efficacy of CET subcutaneous injections (3 mg over a total period of 8 weeks) in 15 patients with laparoscopic diagnosis of endometriosis [101]. All patients were symptom free during treatment. The main reported AEs were headache (20.0%), and occasional bleeding (20.0%). Importantly, there was almost a complete lack of AEs related to estrogen withdrawal (such as mood changes, hot flushes, loss of libido, and vaginal dryness). In line with this observation, serum E_2 oscillated around a mean concentration of 50 pg/mL during therapy. At second-look laparoscopy, performed within one week after the last CET injection, showed regression of endometriosis in 60% of patients (9/15).

Elagolix is an oral short-acting, nonpeptide, GnRH-ant. Elagolix is well tolerated and rapidly bioavailable after oral administration [102]; it causes a rapid decline in serum gonadotropins and E_2 concentrations [103]. Daily (50–200 mg) or twice-daily (100 mg) administration for 7 days maintains low E_2 levels (17 ± 3 to 68 ± 46 pg/mL) in most subjects during late follicular phase, which are rapidly reversed after discontinuation [103].

An American Phase 2, multicenter, double-blind RCT study assessed the safety and efficacy of elagolix for treating endometriosis-associated pain [104]. One hundred and fifty-five women were randomized (1:1:1) to placebo, elagolix 150 mg, or elagolix 250 mg once daily for 12 weeks. At the end of week 12, patients on placebo were re-randomized to one of the elagolix treatment groups, while

patients on elagolix continued their treatment assignment for an additional 12 weeks. Patients who received elagolix continued to have regular menstrual cycles during treatment; however, their cycles were prolonged and the number of days with bleeding per cycle was reduced. Elagolix (150 and 250 mg) significantly improved dysmenorrhea and dyspareunia during the first 12 weeks of treatment. At week 12, the decreases in non-menstrual pelvic pain for both the elagolix treatment groups were numerically larger than for the placebo group but the difference was not statistically significant. The reductions in monthly mean pain scores were maintained through weeks 13–24. Elagolix had an acceptable safety profile. The most frequent AEs were headache (7.7–9.8%), nausea (5.8–9.8%), anxiety (5.8–5.9%), hot flushes of mild-to-moderate intensity, small changes in BMD, and little breakthrough bleeding and spotting [104]. Another American Phase 2, multicenter, double-blind, RCT study compared the effects of elagolix and DMPA-SC on BMD in 252 women with laparoscopic diagnosis of endometriosis suffering pain. Patients were randomized (1:1:1) to receive elagolix 150 mg every day, elagolix 75 mg twice a day, or DMPA-SC 104 mg/0.65 mL (subcutaneous injection at weeks 1 and 12) for 24 weeks; they were followed-up for 24 weeks after the completion of treatment. At the completion of treatment, dual-energy X-ray absorptiometry (DXA) showed that the three treatments caused minimal mean changes from baseline in BMD and in blood concentrations of N-telopeptide [105].

Recently, Taylor et al., reported the results of two similar, double-blind, Phase III RCTs (Elaris Endometriosis I, Elaris EM-I, and II, Elaris EM-II), which investigated the effects of two doses of elagolix (150 mg once daily and 200 mg twice daily) in the treatment of pain caused by moderate or severe endometriosis diagnosed by surgery. In this study, 872 premenopausal women were included. In Elaris EM-I, 46.4% of patients treated with elagolix 150 mg daily, 75.8% of those treated with elagolix 200 mg twice daily and 19.6% of those treated with placebo reported a clinically meaningful reduction in dysmenorrhea and a decreased or stable use of rescue analgesic agents. The percentage of women who had a clinically meaningful reduction in non-menstrual pelvic pain and decreased or stable use of rescue analgesic agents was 50.4% among those receiving elagolix 150 mg once daily, 54.5% among those receiving elagolix 200 mg twice daily, and 36.5% among those receiving placebo. In Elaris EM-II, 43.4% of patients treated with elagolix 150 mg daily, 72.4% of those treated with elagolix 200 mg twice daily and 22.7% of those treated with placebo reported a clinically meaningful reduction in dysmenorrhea and a decreased or stable use of rescue analgesic agents. The percentage of women who had a clinically meaningful reduction in chronic pelvic pain and decreased or stable use of rescue analgesic agents was 49.8% among those receiving elagolix 150 mg once daily, 57.8% among those receiving elagolix 200 mg twice daily, and 36.5% among those receiving placebo. The reductions in dysmenorrhea and non-menstrual pelvic pain were apparent at 1 month and were sustained at 6 months. More than 70% of women in each trial group reported at least one AE with a significant difference in frequency between those receiving the elagolix 200 mg twice daily and those receiving placebo. The three most frequent AEs were hot flushes (of mild or moderate severity), headache, and nausea.

Insomnia, mood swings, and night sweats were also reported more commonly with patients treated with elagolix than by those receiving placebo. Furthermore, patients treated with elagolix had higher HDL cholesterol, LDL cholesterol level and triglyceride levels and greater decreases from baseline in BMD compared with patients treated with placebo [106]. Currently, two ongoing Phase III trials, are evaluating the safety and efficacy of both elagolix alone and elagolix plus E_2 and NETA over 24 months of treatment for the management of moderate-to-severe pain in premenopausal women with endometriosis (NCT03343067 and NCT03213457).

Relugolix (TAK-385) is a new non-peptide, orally selective GnRH-ant. After having demonstrated the continuous and reversible suppression of the hypothalamic-pituitary-gonadal axis [107], it has been tested in clinical trials. A Phase II open-label placebo-controlled study published in the abstract form compared the safety and efficacy of relugolix and LEU in 397 women with endometriosis-associated pain. Relugolix was administered at three doses (10, 20 and 40 mg) orally once daily for 24 weeks. Relugolix and LEU were equally effective in treating pain symptoms. Moreover, the incidences of AEs, such as metrorrhagia, menorrhagia, and hot flush, experienced in the relugolix 40 mg group were similar to those observed in the LEU group. Dose-dependent BMD loss was observed in the relugolix 40 mg group, which was consistent with that observed in the LEU group. E_2 levels decreased with increasing dose of relugolix and were maintained below the postmenopausal levels throughout the 24-week relugolix 40 mg treatment period [108]. A double-blind RCT Phase III trial is testing the efficacy and safety of relugolix (40 mg, once-daily) co-administered with either 12 or 24 weeks of low-dose E_2 (1.0 mg) and NETA (0.5 mg), compared with placebo in women with endometriosis-associated pain (NCT03204318).

Among other novel drugs, a prospective, dose-finding, double-blind, RCT Phase IIb study is testing the efficacy and safety of OBE2109, a novel GnRH-ant, for the treatment of 330 women with moderate-to-severe endometriosis-associated pain (NCT02778399); the results are awaited.

4 Discussion

Endometriosis is a chronic disease requiring long-term therapy that needs to balance clinical efficacy (preventing recurrence, controlling pain symptoms) with acceptable toxicity. Currently, there are numerous medical options for the management of patients with endometriosis. The most appropriate treatment choice is based on multiple factors including patient age, patient preference, reproductive plans, pain severity, and degree of disease.

Almost all currently available therapies for endometriosis are suppressive and not curative. In fact, although they are associated with the temporary relief of women's symptoms, at discontinuation of the treatment their recurrence is common [16, 31]. Moreover, current treatment approaches for endometriosis-associated pain, excepting NSAIDs, are contraceptive. Thus, these therapies are not suitable for women wishing to become pregnant.

Estroprogestins (administered orally, as transdermal patch or as vaginal ring) and progestins (administered orally, as depot injections, as implants, or through the LNG-IUS) allow treating most patients with endometriosis with a satisfactory improvement of pain symptoms, minimal AEs, long-term safety as well as low cost.

COCs are available in different formulations, and their contraceptive activity may be useful for women who do not desire to conceive. Continuous treatment with COCs should be preferred in patients suffering severe menstrual-related symptoms [9].

If COCs have been used for decades as first-line treatment for endometriosis, progestins are increasingly and successfully employed as monotherapy [10]. Progestins have a lower increase in the thrombotic risk compared with COCs and are better tolerated by patients suffering migraine [34]. A potential disadvantage for their administration in women desiring contraception is that only three of them (DSG, ENG-subdermal implant and LNG-IUS) are licensed as contraceptive agents. The two progestins supported by the largest available evidence for the treatment of endometriosis are NETA and DNG, both approved by the US FDA [109]. Notwithstanding the strong rationale supporting the use of COCs and progestins, between one-fourth and one-third of patients treated with these compounds do not respond to these therapies [9].

GnRH-a are prescribed when first-line therapies are ineffective in improving pain symptoms, are not tolerated or are contraindicated. The current recommendation is to perform an accurate diagnostic work-up for evaluating endometriosis prior to administering second-line hormonal treatments. Evidence from the literature demonstrates that all GnRH-a (nafarelin, LEU, buserelin, goserelin or triptorelin) may be efficacious for the treatment of endometriosis-associated pain in patients resistant to first-line therapies. However, there is still controversy over their optimal schedules in terms of dosages and duration of treatment, and there is limited evidence on the different routes of administration of these compounds supporting that the efficacy may be independent from the way GnRH-a are taken. New studies on these topics are needed. It is important to underline that the long-term use of GnRH-a is limited by the incidence of hypoestrogenism-related AEs (particularly BMD loss); therefore, a treatment longer than 6 months with GnRH-a should be combined with add-back therapy.

Although danazol is effective in treating endometriosis-associated pain symptoms, its use is limited by the occurrence of weight gain, acne, hirsutism and other androgenic side effects (which nevertheless may be limited by performing carefully monitored clinical care) and by the large availability of other efficacious and better-tolerated drugs [88].

There is paucity of evidence on the use of AIs (anastrozole and letrozole) to treat patients with endometriosis. Most studies investigating AIs include a limited number of patients and a relatively short period of therapy (mainly 6 months). Moreover, the reported bothersome AEs, such as hot flushing, myalgia, arthralgia, seem to limit their long-term clinical use. Thus, their administration for endometriosis is off-label and therefore should be limited to women with symptoms resistant to other therapies and in the setting of clinical research [93].

In the last few years, great attention has been given to the use of GnRH-ant. They produce a dose-dependent hypoestrogenic environment by direct pituitary gonadotropin suppression, inhibiting endometriotic cell proliferation and invasion but maintaining sufficient circulating E_2 levels to avoid vasomotor symptoms, vaginal atrophy, and loss of BMD. Recently, two recent large multicenter, RCTs demonstrated the benefits of elagolix in the treatment of endometriosis-associated pain [106]. However, the appropriate dose of elagolix remains to be established [110]. While a higher dose (200 mg twice daily) of elagolix was slightly more efficacious in treating pain, it caused more BMD loss, this being a relevant limitation for its long-term use. Future studies should assess whether the administration of an add-back therapy (similarly to that done with GnRH-a) may allow extending the use of elagolix without reducing its efficacy. An ongoing RCT is evaluating the safety and efficacy of elagolix combined with add-back therapy (E_2/NETA) in the management of women with moderate-to-severe endometriosis-associated pain (NCT03213457). Moreover, further RCTs are needed to compare elagolix to first-line therapies (COCs and progestins).

Although this topic is controversial, cost analyses of endometriosis in patients presenting with chronic pelvic pain suggest that diagnosis and initial treatment with

medical therapies may be less expensive than using a surgical approach [111]. Also, regarding cost, wide consensus exists on the indication of COCs and progestins as first-line cost-effective options for treating patients with endometriosis not undergoing directly surgical management. As there are not sufficient robust data demonstrating the superiority of one progestin compound over the other, NETA may be an effective choice considering the extremely favorable cost-effectiveness profile. Although DNG seems to be better tolerated than NETA, the much higher cost limits its acceptance by patients. Thus, we deem that the switch to DNG may be a suitable option in particular subpopulations of patients who do not tolerate NETA or whose disease is resistant to its action (preferring to avoid or postpone surgery) [56]. Compared with COCs or progestins, therapy with GnRH-a is undeniably more expensive. Nevertheless, it can represent a cost-effective option for the prevention of recurrence in patients with severe endometriosis after conservative surgery [112]. Updated cost-effective analyses evaluating the main drug classes for treating endometriosis are lacking in the literature. For this reason, new studies on this topic are needed to draw conclusions.

Overall, development, maintenance and progression of endometriotic lesions depend on a variety of altered mechanisms including cell proliferation, immune function, apoptosis, invasion capacity and angiogenesis. The growing understanding of the physiopathologic mechanism responsible for the development of this benign chronic disease paved the way for the investigation of efficacious alternative medical opportunities. New therapies or schedules of treatment are emerging with intriguing findings from scientific research [113]; however, a careful evaluation of their long-lasting efficacy, tolerance and safety is necessary before they can support or even displace current available first- and second-line therapies.

Compliance with Ethical Standards

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